Contemporary Approaches to Renal Vessels Disorders

Updates and Management Strategies

Adrian Covic
Alexandru Burlacu
Editors

Springer

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This endeavor is lovingly dedicated to our beloved wives, whose unwavering support and encouragement have been our greatest strength, and to our precious children, who inspire us every day.

Adrian Covic and Alexandru Burlacu

Foreword

Arterial hypertension is a major risk factor for cardiovascular mortality, with an extremely high prevalence among patients with renal disease. The presence of hypertension accelerates the progression of renal damage, while renal disease itself can lead to hypertension, creating a harmful vicious cycle. Both conditions synergize to promote the development and progression of cardiovascular disease.

Despite clear evidence, the role of renal vasculature in these processes is often underestimated and poorly understood. Beyond the activation of the renin–angiotensin system and the autonomic nervous system, recent research has uncovered new biochemical and molecular mechanisms underlying kidney damage in hypertension. Damage to the renal microcirculation has been associated with increased oxidative stress, endothelial dysfunction, and a chronic state of subclinical infection. Understanding these mechanisms, which underlie hypertensive nephroangiosclerosis, has led to new research to control these factors.

In addition to microcirculation, diseases and abnormalities of the renal large arterial and venous vessels can lead to pathological conditions that threaten systemic health. Significant advances have been made in the early identification and treatment of these conditions. The approach to atherosclerotic nephrovascular disease has evolved, emphasizing the optimization of pharmacologic intervention and reserving revascularization for selected cases, in line with personalized medicine principles based on the clinical condition of individual patients.

Kidney transplantation and its associated renal vascular issues are also critical topics. Kidney transplantation is often considered the treatment of choice for eligible patients with kidney failure, offering numerous advantages over dialysis, such as decreased mortality risk, longer life expectancy, and improved quality of life. However, vascular complications in renal transplantation, including transplant renal artery stenosis, thrombosis, and biopsy-induced vascular injuries, remain relatively common and can lead to allograft damage. Understanding these complications and the perioperative vascular considerations is essential for improving patient outcomes and graft survival.

Finally, recent guidelines from hypertension scientific societies have renewed the importance of renal denervation techniques for treating resistant forms of

hypertension, based on the latest randomized trials. Additionally, new evidence suggests that renal denervation may provide benefits beyond treating resistant hypertension, impacting renal, arrhythmic, and metabolic diseases.

This book, coordinated by two experts in the field, Prof. Adrian Covic and Prof. Alexandru Burlacu, addresses all these topics, providing a comprehensive overview of subjects that are often insufficiently known and considered. It aims to be a valuable resource of knowledge and clinical intervention, not only for nephrologists but also for cardiologists and physicians dealing with metabolic diseases.

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Contents

Introduction 1
Alexandru Burlacu and Adrian Covic

The Renal Vascular System: Anatomical Considerations and Clinical Applications 3
Cristina Furnica, Raluca Ozana Chistol, Elena Sapte, and Grigore Tinica

Renal Vascular Anomalies 31
Cristian Mornos and Adrian-Sebastian Zus

Contrast Induced Acute Kidney Injury 45
Simona Mihaela Hogas and Adrian Covic

Renal Artery and Vein Thrombosis 61
Bogdan Obrișcă and Gener Ismail

Renovascular Disease: Updated Management Protocols 87
Philip A. Kalra, Áine DeBhailis, and Darren Green

Arterial Hypertension and Renal Vessels 101
Laura Vasiliu, Anca Diaconu, Radu Sascau, and Cristian Statescu

Renal Artery Denervation: Evidence, Guidelines, and Major Trials 113
Paula Cristina Morariu, Alexandru Florinel Oancea, and Mariana Floria

Beyond Blood Pressure: Expanding the Use of Renal Denervation in Diverse Pathologies 127
Alexandru Burlacu and Crischentian Brinza

Kidney Transplantation and Renal Vascular Issues 147
Titus Andrian, Luminita Voroneanu, and Adrian Covic

Introduction

Alexandru Burlacu and Adrian Covic

Abstract Advancements in nephrology have significantly enhanced the understanding of the renal vascular system and its pivotal role in health and disease. This book presents a comprehensive exploration of renal vascular physiology, pathologies, diagnostic techniques, and therapeutic interventions, aiming to provide an essential resource for healthcare professionals and researchers.

Keywords Nephrology · Renal vascular system · Renal vascular physiology · Diagnostic techniques · Therapeutic interventions · Hypertension · Hypertensive renal damage · Endothelial dysfunction · Imaging · Renal disease

Advancements in nephrology have significantly enhanced the understanding of the renal vascular system and its pivotal role in health and disease. This book presents a comprehensive exploration of renal vascular physiology, pathologies, diagnostic techniques, and therapeutic interventions, aiming to provide an essential resource for healthcare professionals and researchers.

Hypertension remains one of the most prevalent and challenging health issues worldwide. The interplay between hypertension and renal vasculature involves several complex mechanisms, including the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). Hypertensive renal damage often results in conditions like nephrosclerosis and glomerular injury, which, in

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turn, can worsen systemic blood pressure control. We investigated the latest research on endothelial dysfunction, oxidative stress, and inflammation as key factors in the progression of hypertensive renal damage, providing insights into novel therapeutic targets and treatment strategies.

Renal vascular anomalies, such as renal artery aneurysms and arteriovenous fistulas, present significant diagnostic and therapeutic challenges. In the present book, we analyzed advanced imaging techniques, which have greatly improved the accuracy and early detection of these anomalies. Additionally, the shift from traditional surgical methods to minimally invasive procedures, such as endovascular stenting and coil embolization, is thoroughly examined, highlighting their benefits in reduced risk and quicker recovery times.

The management of renovascular diseases has evolved with significant advancements in pharmacological and interventional therapies. Drugs targeting the RAAS and SNS have proven effective in controlling hypertension and slowing the progression of renal disease. This work reviews the efficacy of these pharmacological interventions, as well as the latest interventional techniques, including renal artery stenting and embolization, which offer less invasive alternatives to traditional surgery. The advancements have not only improved patient outcomes but also provided new avenues for treatment in cases where conventional methods are less effective.

Also, we provided an in-depth look at the latest diagnostic tools and techniques that have revolutionized the field. High-resolution imaging modalities, such as CT and MR angiography, allow for detailed visualization of the renal vasculature, enabling early and precise detection of anomalies. The clinical implications of these advancements are discussed, with case studies illustrating their practical applications in diagnosing and managing renal vascular diseases.

Ongoing research in renal vascular biology continues to uncover new insights into the mechanisms underlying renal vascular diseases. Genetic studies are shedding light on hereditary factors that contribute to these conditions, while advancements in molecular biology are identifying new biomarkers for early detection and monitoring. We analyzed the potential of personalized medicine, which tailors therapeutic approaches based on individual genetic profiles, promising more effective and customized treatments. Emerging technologies and innovative research further advance our understanding and management of renal vascular health.

The exploration of the renal vascular system presented in this book aims to enhance our awareness of its complexities and its interplay with systemic health. By integrating current knowledge with innovative research and clinical practices, this book provides a comprehensive resource for healthcare professionals and researchers dedicated to improving patient outcomes in renal vascular health. Through continued investigation and the application of advanced therapeutic strategies, the future of renal vascular medicine holds significant promise for addressing the challenges of tomorrow.

The Renal Vascular System: Anatomical Considerations and Clinical Applications

Cristina Furnica, Raluca Ozana Chistol, Elena Sapte, and Grigore Tinica

Abstract The kidneys play a significant role in influencing overall body circulation and maintaining homeostasis. The renal circulation possesses distinctive anatomical and functional characteristics, and various congenital and acquired conditions can significantly affect it, potentially impacting all body systems and posing life-threatening risks. This chapter provides an overview of the key aspects of renal vascularization, covering its development, gross and microscopic anatomy, and concluding with a summary of major conditions affecting renal vascularization.

Keywords Renal vascularization · Vasculogenesis · Gross anatomy · Imaging · Clinical anatomy

Introduction

The kidneys are specialized organs characterized by high vascularity specifically designed to fulfil the following functions:

- homeostasis of extracellular and intracellular fluid volumes;
- ensure normal plasma concentrations;
- excretion of metabolic waste;

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- metabolic reabsorption;
- H^+ and HCO_3 absorption and excretion, thereby regulating acido-base balance.

The kidneys have a distinct and complex structure and organization into renal corpuscles, tubules, and renal collectors allowing them to receive about 20–25% of the cardiac output, which equates to 1.0–1.2 L per minute [1].

The vascular structure of the kidney ensures the maximum blood flow per unit weight of the organ. Consequently, any diseases affecting the kidney's blood vessels can disrupt its normal function, leading to significant health risks and potentially life-threatening outcomes.

The study of kidney vascularization involves analysing the branching pattern of the renal artery, which underpins the vascular organization of the renal parenchyma. The renal parenchyma is split into two primary arterial territories, anterior and posterior, which are further segmented to aid in partial nephrectomies. The branching pattern of the renal artery includes dorsal and ventral branches, further dividing into segmental branches, lobar branches, interlobar arteries, arcuate arteries, interlobular arteries, afferent arterioles, efferent arterioles, and interlobular cortical capillary networks. Cortical venules branch off from these capillary networks, radiating and draining into the *vasa recta*. Additionally, there are capillary networks associated with the medulla, which drain into the renal veins.

The arterial model within the kidney is terminal, indicating limited or no anastomosis between the interlobar, arcuate, or interlobular arterioles. The kidney's vascular structure includes significant arteriovenous shunting, and multiple capillary networks are intricately arranged. Occlusion of one of these arteries results in the infarction of the afferent renal parenchyma, often referred to as a white infarct.

Renal Vasculogenesis

The development of the renal vasculature coincides with the formation of the kidneys during the third week of gestational age. The kidneys originate from the intermediate mesoderm and undergo three sequential phases of growth: *the pronephros*, *mesonephros*, and *metanephros*. The *pronephros* emerges at the third week of gestation and consists of simple tubules and regresses by the fifth week. Around the fourth week of gestation, the *mesonephros* is observed in the thoracolumbar region, below the pronephros, contains primitive glomeruli that function at this stage and is supplied by the urogenital *rete arteriosum* or mesonephric arteries. These arteries arise from the dorsal aorta, between the lower cervical and midlumbar spine, and supply the gonads, kidneys, and adrenal glands. As the mesonephros gradually regresses around the eighth week of gestation, the mesonephric arteries degenerate, except for a single persistent branch that evolves into the main renal artery. If more than one mesonephric artery persists per kidney, it leads to the formation of supernumerary renal arteries [2]. The *metanephros* appears in the fifth week of gestation and becomes functional by the 12th week secondary to the contact of the

metanephric blastema with the ureteric bud derived from the mesonephric duct. The metanephros forms the definitive kidney.

Between the sixth and ninth weeks of gestation, the kidneys initiate renal ascent from the pelvic region to the level of T12-L1 intervertebral disk, inferior to the adrenal glands. As they migrate upward, the kidneys undergo a medial rotation along their long axes, while the mesonephric arteries supplying them at the lower end degenerate. If the migration process is disrupted or incomplete, it can lead to the development of a pelvic or ectopic kidney. In such cases, the kidneys may retain the foetal vascular supply and exhibit variant vascular anatomy.

During embryonic development, the renal venous drainage is established by a network of veins known as the aortic collar consisting of vesseles that develop around the aorta. The dorsal arch results from anastomoses between supracardinal and subcardinal veins, while the intersubcardinal anastomosis forms the ventral arch. In normal development, the dorsal arch of the aortic collar regresses, and the ventral arch persists, becoming the renal vein. In the case of a retroaortic renal vein, the ventral arch regresses, and the dorsal arch persists, forming the left renal vein. On the other hand, a circumaortic renal vein can develop if both the ventral and dorsal arches persist.

The metanephric mesenchyme is responsible for the embryonic origin of the epithelial nephron, facilitating various developmental processes such as the growth, branching, and differentiation of the ureteric bud. Additionally, it plays a crucial role in the transformation of the condensing mesenchyme into a mesenchymal epithelial state.

The development of the renal vascular system involves three distinct interconnected processes:

- *vasculogenesis*—creation of new blood vessels through differentiation and assembly of endothelial tubes, followed by the recruitment of vascular smooth muscle cells originating from surrounding mesenchymal precursors, particularly Foxd1-positive stromal cells;
- *angiogenesis*—generation of new vessels from existing ones, encompassing the proliferation, migration, and sprouting of differentiated endothelial cells together with recruitment of vascular smooth muscle cells. Major renal vessels typically originate from vascular plexus branches of the aorta and vena cava, the smaller vessels differentiating and connecting to larger ones;
- *hemovasculogenesis*—simultaneous formation of blood precursors and blood vessels. It occurs under pathological conditions such as myeloproliferative disorders and haemolytic anaemias, where extramedullary haematopoiesis takes place. Studies suggest that hemovasculogenesis in the kidney primarily happens through hemogenic endothelial cells [3];
- *lymphangiogenesis*—development of lymphatic vessels. Several genes, including lymphatic vessel endothelial hyaluronanreceptor 1 (LYVE-1), vascular growth factor receptor 3 (VEGF-3), podoplanin, and prospero-related homeobox gene 1 (Prox-1), are implicated in this process.

In the formation of functional nephrons, each arteriolar tip must connect to a glomerulus. This necessitates spatial and temporal regulation of the differentiation, migration, the assembly of vascular cells ensuring synchronized connection of arterioles with their associated nephrons. Pericytes interact with endothelial cells through both direct physical contact and secretion of molecules such as VEGF. During angiogenesis, for the proper proliferation, migration, and remodelling of endothelial cells (EC), pericytes need to detach from the expanding vessels [3].

Under the influence of Foxd1-positive cells, which are stromal progenitors expressing the fork head transcription factor 1, mural cells and vascular development occur in the outer layer of the developing kidney.

Tbx18 is a transcription factor belonging to the Tbox family is expressed in a specific subset of the metanephric mesenchyme surrounding the ureteric stalk and throughout the mesenchyme surrounding the developing ureter. Its expression is essential for the proper development of both the ureter and the kidney [4].

Renin is an enzyme traditionally associated with the regulation of blood pressure and the maintenance of overall homeostasis. Renin-producing cells are typically found in the juxtaglomerular (JG) area of the afferent arterioles. These cells sense changes in perfusion pressure and release renin accordingly. Renin plays a crucial role in the renin-angiotensin system, where it cleaves its substrate, angiotensinogen, leading to the formation of angiotensin II. Angiotensin II has potent effects on vasoconstriction and the regulation of fluid and electrolyte balance. Interestingly, renin cells are not only involved in blood pressure regulation but are essential for the normal development of the kidney and its vasculature. Unlike in adults where renin cells are restricted to the JG area, during embryonic development, renin cells have a wider distribution throughout the kidney. As the intrarenal arteries and arterioles mature, these renin cells progressively differentiate into vascular smooth muscle cells. Disruptions to the renin-angiotensin system (RAS) during pregnancy due to exposure to medications that interfere with this system like Angiotensin Converting Enzyme (ACE) inhibitors or Angiotensin Receptor Blockers (ARB), can lead to severe malformations of the renal parenchyma and vasculature. Furthermore, genetic mutations in the genes involved in the renin-angiotensin system can cause vascular abnormalities and a severe disorder known as renal tubular dysgenesis and characterized by potentially life-threatening oligohydramnios and lung hypoplasia [5].

Wnt7b is a secreted ligand of the Wnt family and controls the elongation of the renal medulla through oriented cell division and the elongation of the loop of Henle through proliferation. Recent studies have shown that Wnt7b, acting through the developing ureteric bud, regulates the proliferation of both mural and endothelial cells in the medullary peritubular capillaries [6].

The **glomerular vasculature** is a specialized network of fenestrated capillaries formed by endothelial cells and their associated perivascular cells, known as mesangial cells. Critical for filtration, the glomerular capillary wall comprises three layers: the capillary endothelium, the glomerular basement membrane, and the podocytes. Any defects in these components can disrupt the glomerular filtration barrier, leading to proteinuria.

Before the development of blood vessels in the embryonic kidney, progenitors of the glomerular endothelium, podocytes, and mesangial cells are already present. The initial phase of glomerular development involves the creation of an epithelial vesicle, which subsequently invaginates to form a vascular cleft, referred to as the S-shape body. This is where endothelial and mesangial progenitors enter the developing glomerulus.

VEGFA (vascular endothelial growth factor A), secreted by developing podocytes, acts on endothelial precursors, which in turn express VEGF receptors. This interaction triggers endothelial cell differentiation and proliferation, leading to the formation of a single primordial capillary loop. Maturation of these loops occurs through intussusception and branching remodelling, a process requiring apoptosis of mesangial and endothelial cells for the successful formation of mature capillary loops [7].

The main regulators of the development of renal vascularization are:

- **Vascular Endothelial Growth Factor** (VEGF) and its receptors—regulate vascular growth and maturation. There are five members of the VEGF family (VEGFA-D and Placental GF) that interact with three types of receptors (VEGFR1–3) that have tyrosine kinase activity and span the cell membrane. VEGF is produced by different kinds of cells, such as platelets, macrophages, renal podocytes and mesangial cells, keratinocytes and cancer cells. VEGF can act on the same cells that produce it or on nearby cells. Vascular endothelial cells have VEGFR1 and VEGFR2 on their surface and respond to VEGFA, which is a powerful stimulator of blood vessel formation and function. VEGFA is vital for the movement and growth of endothelial cells and for their association with other cells that support the blood vessels. VEGFR3 is found in lymphatic endothelial cells and in blood vessel endothelial cells during early development [8]. VEGFA expression by the podocytes and its receptors in the endothelial precursors is essential for the normal formation of blood vessels in the glomerulus and a functional glomerular filtration barrier in the developing nephron. If VEGFA in podocytes (or the VEGFR2 in glomerular endothelial cells) is conditionally deleted, it causes hydrops fetalis and kidney failure with perinatal death and abnormal glomeruli with fewer, poorly developed endothelial cells. Conversely, overexpression of VEGF in podocytes also leads to renal failure due to glomerulopathy with collapsed capillary tufts. VEGF also affects branching morphogenesis of the ureteric bud, not just the development of the vasculature in the developing kidney [8].
- **NOTCH signalling pathway**—crucial role in regulating the expression of VEGFRs. Notch activation increases VEGFR1 expression while inhibiting VEGFR2 and VEGFR3 expression. Meanwhile, VEGFA directly activates the NOTCH pathway in vascular development. During early development in the metanephric kidney, VEGFA and its receptors are expressed before the vasculogenesis. As nephrogenesis progresses, VEGFA is expressed in the developing epithelial structures, including podocytes, while its receptors are mainly found in endothelial cells [9];

- **Transforming Growth Factor β (TGFβ)**—controls various cellular activities such as cell growth, proliferation, differentiation, and apoptosis in both autocrine and paracrine manners. TGFβ and its receptors expressed in endothelial and vascular smooth muscle cells, play a role in both normal and abnormal processes [10]. TGFβ is essential for the growth of endothelial and vascular smooth muscle cells, and controls directly the components of the endothelial basement membrane and the extracellular matrix formation. Moreover, TGFβ, through PDGF-β, stimulates the proliferation, recruitment, and differentiation of pericytes and vascular smooth muscle cells;
- **Platelet-derived growth factor (PDGF)**—plays a vital role in cell proliferation and migration, its isoforms (PDGF-A to PDGF-D) being expressed in various renal compartments, including the mesangium, interstitium, vasculature, and tubules. PDGF-B, produced by endothelial cells, is crucial for the recruitment, proliferation, and maturation of pericytes and smooth muscle cells being essential for proper vascular development. The absence of PDGF-B or its receptor, PDGFRβ, leads to severe vascular malformations characterized by impaired vascular smooth muscle differentiation, dilated and leaky vessels, and embryonic haemorrhages, ultimately causing death. PDGF is prominently involved in renal diseases, particularly in mesangial cell proliferation. PDGF-B secreted by glomerular endothelial cells interacts with PDGFRβ expressed in mesangial precursors, stimulating the formation of the glomerular mesangium. The deletion of PDGF-B or its receptor in the developing kidney results in significant glomerular defects, including mesangial cell development failure and the formation of aneurysmatic glomeruli. Conversely, overexpression of PDGF-B triggers mesangioproliferative disorder and renal fibrosis [11];
- **Angiopoietin (Ang 1 and 2)-Tie pathway**—plays a vital role in angiogenesis, vascular remodelling, and the maintenance of vascular function in both embryonic and postnatal stages. Ang1 serves as an essential ligand for Tie2 being expressed in mesenchymal cells surrounding developing vasculature, as well as in differentiated mural cells like pericytes, vascular smooth muscle cells, fibroblasts, and monocytes. Ang1 promotes vessel stability and inhibits fibrosis. Ang2, predominantly expressed by endothelial cells, exhibits context-dependent autocrine functions. During early development, Ang1 plays a crucial role in vascular morphogenesis, and later in life, it potentially functions to prevent kidney damage in response to injury or microvascular stress, such as during diabetic nephropathy [12];
- **Stromal cell-derived factor 1** (SDF1)—chemoattractant cytokine that, by interacting with its receptors CXCR4 and CXCR7, plays a crucial role in organogenesis, regeneration, and tumorigenesis. During embryonic kidney development, SDF1 is expressed in stromal cells surrounding developing nephrons and blood vessels, as well as in podocytes [13];
- **Ephrins and their receptors**—play a regulatory role in arterial and venous specification and contribute to the maintenance of angiogenesis and stem cell differentiation in postnatal life. There are eight ephrin ligands (ephrinA1–5 and

ephrinB1–3) that bind to nine ephrinA receptors as well as five EphBs (EphB1–4 and EphB6), respectively. Within the kidney, the absence of ephrinB2 in smooth muscle cells and pericytes results in the dilation of poorly organized glomerular capillaries. There is also a postulation that ephrins may be involved in the pathogenesis of congenital anomalies of the kidney and urinary tract [13];

- **Sphingosine 1-phosphate (S1P)**—functions as a signalling molecule that promotes vascular stability and is broken down by the S1P lyase enzyme. S1P through its S1PR1 receptor is essential for the proper morphogenesis of the kidney vasculature, including glomerular capillary development, arterial VSMC coating, and lymphatic vessel development [14];
- **MicroRNAs**—act as epigenetic posttranscriptional regulators and are essential for the development of nephrons, the maturation of renal tubules, and the homeostasis and function of podocytes. They also play a significant role in the normal development of the renal vasculature.

Normal Vascular Renal Architecture

Renal Arteries

Origin

Usually, a single one-sided renal artery emerges from the abdominal aorta, situated between the origins of the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA), corresponding to the L1-L2 intervertebral disk. The left renal artery originates slightly below the right renal artery. Because of the anatomical position of the abdominal aorta, the right renal artery is longer than the left one and passes behind the inferior vena cava (IVC) to reach the hilum of the right kidney. Occasionally, there are two or more additional renal arteries, known as polar arteries.

Course

From their origin, the renal arteries take an oblique and downward course, traversing the diaphragmatic pillars, the greater and lesser psoas muscles, and then running anterior to the renal pelvis before entering the medial aspect of the renal hilum.

In approximately two-thirds of cases [15], an arterial trunk bifurcates into anterior and posterior branches (Table 1). The anterior branch promptly divides into ascending and descending branches: the superior branch is angled obliquely anteriorly and superiorly, vanishing in the most cranial part of the kidney. The inferior branch is angled obliquely inferiorly and anteriorly, traversing the anterior surface of the renal vein and reaching the inferior renal pole. Meanwhile, the posterior branch forms a loop in an antero-posterior direction, extending caudally on the

Table 1 Renal arteries branches

Collateral branches	Terminal branches
• Inferior adrenal artery; • Branches for the lumbar lymph nodes; • Superior ureteral artery; • Capsuloadipose arteries; • Inferior phrenic artery	At the level of the hilum, the renal artery divides into two branches: • Anterior (prepyelic) branch, which emits 3–4 prepyelic branches; • Posterior (retropyelic) branch, which loops above the renal pelvis, with a caudal retrosinusal vertical course, up to the level of the renal hilum.

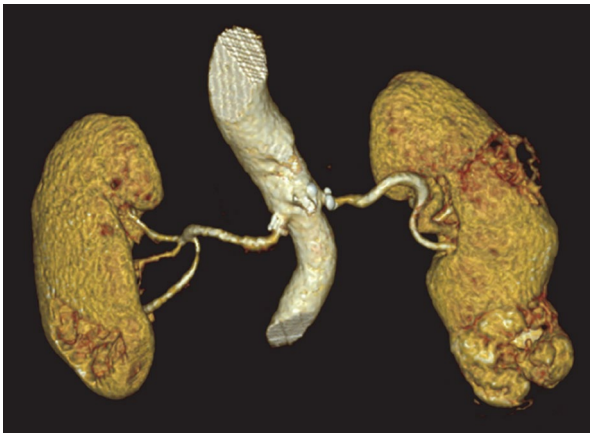

Fig. 1 The branching pattern of the renal artery when reaching the hilum—volume rendered reconstruction of CT angiography (Cardiovascular Diseases Institute Iasi)

posterior pelvic surface, lying on the posterior crest of the renal hilum, and disappearing into the deep side of the renal sinus (Fig. 1).

Within the renal hilum, each renal artery branches into two to four *segmental arteries*. These segmental arteries further divide to form *interlobar arteries*, which run along the outer border of each renal pyramid, extending from the medulla–cortex boundary to the cortical parenchyma. Outside the medullary pyramids, these 4–6 interlobar arteries are also known as *lobar arteries*.

At the base of the Malpighian pyramids, the *peripyramidal arteries* are oriented obliquely, giving rise to transverse recurved branches called *arcuate arteries* (*arteriae arciformes*). These arcuate arteries anastomose with each other, forming a large network that covers the pyramids, called the suprapyramidal arteries or simple *arterial pyramidal network*. This network penetrates the Ferrein pyramids.

The concave side of each arcuate artery does not give rise to any branches. However, numerous small branches emerge from its convex side, extending directly and radially towards the fibrous renal capsule at a 90-degree angle. These branches are known as *interlobular arteries*. This branching pattern, described by Hyrtl in 1877, explains the terminal type of renal blood supply [16].

The interlobular arteries further divide into 5–6 *afferent arterioles*, which form a tangled network of capillaries known as the glomerulus. The *efferent arterioles* exit the glomerulus and form a peritubular network that supplies blood to the nephron

tubules in the outer 2/3 of the renal cortex. The inner 1/3 of the cortex and the medullary zone receive blood from a different set of straight arteries called *vasa recta*. This arrangement ensures that the high blood pressure within the glomeruli is maintained to facilitate filtration. The efferent arterioles, carrying blood away from the glomeruli, form a second capillary bed with lower blood pressure than the glomerulus. This network of capillaries eventually connects to venules at its distal end.

Relations

Within the renal pedicle, the renal vein lies anteriorly, while the renal pelvis occupies the posterior position. At its origin, the renal artery approaches the aortorenal ganglion that receives the lesser splanchnic nerve and gives rise to the renal plexus with a perirenal distribution. The left renal artery follows a transverse course towards the left renal hilum, with the left renal vein and the body of the pancreas situated anteriorly. Superiorly, it relates to the splenic vein and the splenomesenteric trunk. In contrast, the right renal artery describes an inferior oblique course towards the right renal hilum, extending 1 cm further than the left artery. Anteriorly, it relates to the inferior vena cava (IVC), the right renal vein, the head of the pancreas, and the second part of the duodenum (DII). The psoas muscles and the diaphragmatic pillars are situated posteriorly to both renal arteries.

The boundary between the two terminal renal arteries (prepyelic and retropyelic) territories runs 5 mm posterior to the convex margin of the kidney (*Hyrtl's line*). This line marks a relatively bloodless area on the posterior and lateral surface of the kidney that serves as the site for nephrotomy.

Intrahilarly, the prepyelic and retropyelic arteries branch into *five segmental arteries* to vascularize the five segments of the kidney:

- Apical (superior) segment—receives the homonymous artery (*arteria segmenti superioris*), branch of the prepyelic artery, for the anteromedial region of the upper pole;
- Anterosuperior segment—receives the artery of the anterosuperior segment (*arteria segmenti anterosuperioris*) branch of the prepyelic artery, for the rest of the upper pole and the central anterosuperior region;
- Anteroinferior segment—located between the anterosuperior and caudal segments, receives by the corresponding artery (*arteria segmenti anteroinferioris*), also branch of the prepyelic artery;
- Caudal (inferior) segment—receives the corresponding artery (*arteria segmenti inferioris*), branch of the prepyelic artery, the anteromedial aspect of the lower pole;
- Posterior segment—retropyelic location, vascularized by its own artery (*arteria segmenti posterioris*), the continuation of the retropyelic artery.

Inside the renal sinus, segmental arteries give rise to approximately 100 *interlobar arteries* (*aa. interlobares reni*). These arteries penetrate the renal columns (4-5-6 around each pyramid) along the lateral faces of the pyramids, extending from their

papillary zones towards the bases. At right angles to the interlobar arteries, the *arcuate arteries* (*aa. arcuatae*) emerge and do not form anastomoses with each other. *Interlobular arteries* (*aa. interlobulares*) branch abundantly and abruptly from the arcuate arteries, do not anastomose, pass radially through the renal cortex between medullary stripes and reach the fibrous capsule. In some cases, they even perforate the capsule, forming anastomoses with perirenal arteries [17].

From the interlobular arteries, *afferent glomerular arterioles* branch off and enter the renal corpuscle, forming the *renal glomerulus*. The renal glomerulus connects to the efferent glomerular arteriole, which continues into the corpuscle at the vascular pole and terminates in a dense capillary network surrounding the renal tubules. *Efferent arterioles* supply the cortical renal tubules. Juxtamedullary glomeruli, on the other hand, contribute to the vascularization of the underlying cortex and medulla. Efferent arterioles from juxtamedullary glomeruli destined for the medulla travel directly downwards in a "*raindrop*" pattern, forming the *straight arterioles* (*arteriolae rectae*). The medulla contains its own unique vascular network, with a reduced blood flow compared to the cortex. This network includes straight arterioles that originate from the arcuate arteries, sometimes from the interlobular arteries (Ludwig's artery), or even from afferent or efferent arterioles [18].

The kidney consists of lobes, also known as pyramids, organized into two rows: ventral and dorsal. The ventral row of pyramids and the upper section of the dorsal row receive blood supply from the prepyelic branches of the renal artery. The rest of the dorsal row, excluding the upper part, is irrigated by the retropyelic branch. There are instances where the territories intersect in the contact area, which means that branches from the ventral system cross over branches from the dorsal system, and parts of the dorsal pyramids receive blood supply from ventral branches. This alters the concept of an avascular (paucivascular) zone, as proposed by Hyrtl. The avascular zone is defined by the absence of major terminal branches in the contact area. Due to the architectural variability of the kidney, defining the avascular zone is challenging. It is traditionally described as the plane that is 5–10 mm posterior to the kidney's lateral edge. Nephrotomy is performed along this plane for the removal of kidney stones [19].

Accessory or *polar renal arteries* are additional blood vessels that supply the kidney, originating from various sources, including the abdominal aorta, gonadal artery, internal iliac artery, external iliac artery, common iliac artery, middle sacral artery, or inferior phrenic artery. The *upper polar artery* typically branches from the inferior phrenic artery, while the *lower polar arteries* more frequently arise from the aorta.

Arterial Anatomical Variants

The renal arterial system can exhibit variations such as supernumerary renal arteries, accessory and aberrant in nature, and prehilar (early) branching.

Prehilar branching refers to the branching of the renal artery within 15–20 mm from the origin for the left and behind the IVC for the right. This variant is seen in approximately 5–10% of individuals and interferes with renal transplantation [18].

Supernumerary renal arteries, accessory or aberrant, are the most prevalent arterial variant, occurring in up to 30% of individuals.

Accessory renal arteries typically arise between T11 and L4 directly from the aorta. In some instances, they may originate from the common iliac arteries (Fig. 2). These arteries enter the kidney through the renal hilum and supply the superior and inferior renal poles, their calibre being often like the main renal arteries [20]. Their presence imposes comprehensive imaging of the renal arterial anatomy, particularly in cases of kidney donation [21].

Aberrant or polar renal arteries differ from accessory arteries by their entrance into the kidney through the renal capsule, rather than the renal hilum. They typically supply a single renal pole.

The presence of supernumerary renal arteries has been linked to several pathological conditions, including focal renal infarctions, secondary hypertension, and, in rare instances, type II endovascular leaks in case of endovascular treatment of aortic aneurysms. Additionally, the presence of more than two renal arteries may pose a relative contraindication to renal donation. Generally, if an individual has three renal arteries with one being a small-calibre polar artery supplying the upper pole, the kidney can still be donated because the polar artery can be safely sacrificed without compromising graft function. Prehilar branching may disqualify a volunteer from renal donation, as the donor renal artery typically needs to be at least 1 cm long to facilitate the main renal artery donor-recipient anastomosis.

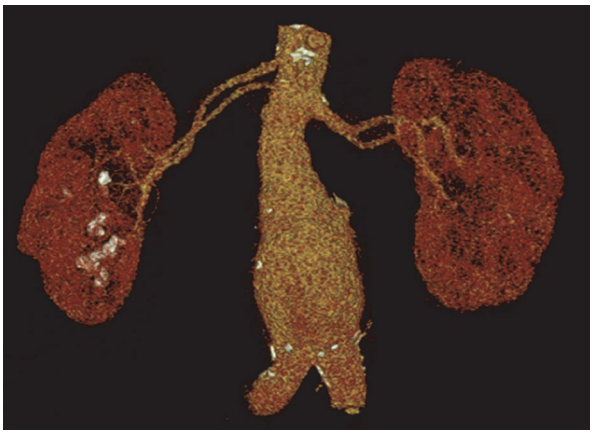

Fig. 2 Accessory right renal artery in a patient with aneurysmal dilatation of the infrarenal abdominal aorta and right nephrolithiasis—volume rendered reconstruction of CT angiography (Cardiovascular Diseases Institute Iasi)

Renal Veins

Unlike the arterial circulation, the venous drainage of the kidney is not a linear system. It exhibits a rich network of collateral vessels, enabling blood to flow between different venous territories.

The *interlobular veins* and *arcuate veins* collect blood from the renal cortex and converge to form *interlobar veins*. These interlobar veins drain into the *lobar veins*, which unite to form the main renal vein at the level of L1-L2. The main renal vein lies anterior to the main renal artery.

Traditionally, the left renal vein travels horizontally between the aorta and superior mesenteric artery, eventually joining the inferior vena cava (IVC). In addition, the left renal vein receives blood from the left gonadal vein and left adrenal vein.

The *right renal, gonadal, and adrenal veins*, unlike the left renal vein, drain directly into the IVC. The venous drainage of the renal parenchyma is organized into a continuous suprapyramidal venous arch, encompassing *descending arcuate veins* (*venae arcuatae*) and *ascending straight venules* (*venulae rectae*). The descending veins, also known as *interlobular veins* (*venae interlobulares*), originate from the renal surface and fibrous capsule, where they join *stellate venules* (*venulae stellatae*) or Verheyen's stars. These stellate veins are deep in the cortex, not directly subcapsular, and are thought to be remnants of the fetal renal venous system. From their origin, the interlobular veins descend vertically through the cortex alongside interlobular arteries, collecting blood from the peritubular capillary plexus. Near the base of the renal pyramids, they curve and transition into the *arcuate veins*. The arcuate veins follow the paths of their corresponding arteries, intertwining at the renal columns and descending deeper into the medulla. Venous blood from the peritubular capillary network and the subcapsular peripheral venous network drains into the interlobular veins, which eventually terminate in the arcuate veins located at the base of the Malpighian pyramids. The suprapyramidal venous arcade lies at the corticomedullary junction. These arcades, along with the interlobular veins that drain into them, form a continuous network oriented in the frontal plane, extending between the ventral and dorsal rows of the pyramids. Corresponding to the renal columns, the interlobular veins bend and descend within the columns, the *interlobar veins*. These voluminous veins collect tributaries from the Bertin's columns and reach the renal sinus. At the level of the calices, the interlobar veins unite, forming the venous branches of the sinus. Upon exiting the sinus, the interlobular veins encircle the renal papillae and small calices, creating anastomotic rings. These pericaliceal rings anastomose, forming anterior and posterior anastomoses of the renal pelvis. The median (anastomotic) vein of Hauck arises between the ventral and dorsal rows of calices. From these anastomoses, pre- and retropyelic venous branches depart, and converge to form a single renal vein. These branches exhibit varying courses, with some situated in front of and others behind the arterial branches. The branches of the renal sinus unite to form the renal vein. The renal veins (*v. renalis*) exit the renal hilum and drain into the IVC [15].

The left renal vein exhibits a horizontal course, longer and wider than its right counterpart. It traverses anteriorly to the aorta through the aortomesenteric fork (located between the aorta and superior mesenteric artery), alongside the third part of the duodenum (DIII) and the uncinate process of the pancreas. The left renal vein ultimately empties into the left side of the IVC. It also receives the left gonadal and left adrenal veins as tributaries.

The right renal vein is shorter and narrower than its left counterpart. It drains directly into the right side of the IVC and receives few collateral veins that form an extrarenal venous arch near the adipose capsule of the right kidney. This arch communicates with the veins of the colon and the veins of the posterior abdominal wall, establishing portocaval anastomoses.

Renal venous anatomical variations encompass supernumerary, circumaortic, and retroaortic renal veins. Accurate pre-surgical identification of the number of renal veins is crucial for potential kidney donors. *Supernumerary renal* veins are the most prevalent venous variants, occurring in 15–30% of individuals, primarily on the right side [16]. Delayed venous confluence refers to the coalescence of renal vein branches within 15 mm from the left lateral margin of the aorta on the left side and within 15 mm from the anastomosis with the inferior vena cava on the right side. Preoperative knowledge of delayed left venous confluence enables laparoscopic surgeons to anticipate the need for two venous transections if they cannot secure control around the short main renal vein segment. *Circumaortic renal veins*, the most common left renal vein variant, are observed in up to 17% of patients. In this instance, the left renal vein bifurcates into ventral and dorsal limbs that encircle the aorta before draining into the IVC [22]. Recognizing a circumaortic renal vein is particularly crucial for IVC filter placement, as the filter must be inserted inferior to the most distal portion of the lowest limb. It is also essential to identify this variant before aortic surgery, retroperitoneal resection, and kidney donation [23]. Less commonly, *retroaortic left renal veins* are detected in up to 3% of individuals [24]. These veins course between the aorta and vertebrae. The left renal vein may become entrapped and compressed, leading to posterior nutcracker syndrome.

Lymphatic Drainage

The lymphatic vessels of the kidney follow the path of the blood vessels through the Bertin columns, forming larger lymphatic trunks that intertwine to create a subcapsular lymphatic plexus and a lymphatic plexus of the adipose capsule. These lymphatic vessels connect to vessels of the ureter and the renal pelvis at the medial edge of the kidney.

On the left side, the initial lymphatic station comprises the left lateral paraaortic, retro- and preaortic lymph nodes. Occasionally, an accessory lymphatic drainage is observed originating from the left kidney, directing lymph towards the retrocrural lymph nodes or directly into the thoracic duct, above the diaphragm.

On the right side, lymph flows into the interaortic, para-, pre- and retrocaval lymph nodes. Occasionally, lymphatic drainage towards the retrocrural or left lateral paraaortic lymph nodes is observed on the right side [16].

The nephron is the structural and functional unit of the kidney. Each kidney contains an estimated 1–1.3 million nephrons, which connect to collecting ducts. These collecting ducts receive urine from multiple nephrons and eventually merge before opening into the minor calyces. The nephron and the collecting duct form together the uriniferous tubule, responsible for the filtration, reabsorption, and secretion of urine. The nephron is a long, convoluted tube measuring approximately 55 mm in length in the human kidney. It begins at one end with Bowman's capsule, a highly modified cup-shaped structure that envelops a tuft of capillaries called the glomerulus. This arrangement forms a renal corpuscle, which is the primary site of filtration. The visceral layer of Bowman's capsule contacts directly the glomerular capillaries, while the parietal layer encloses an approximately spherical urinary space.

The *renal corpuscle*'s Bowman's capsule has a parietal layer that seamlessly transitions into the walls of the proximal convoluted tubule (PCT). The cells of the visceral layer, known as podocytes, presents a complex structure with a cell body with numerous primary and secondary foot processes enveloping the blood vessels. The podocyte foot processes located on a shared basal lamina almost entirely envelop the capillary surfaces, leaving small gaps. Blood plasma is filtered from the capillary lumen to the urinary space through the combined capillary endothelium-podocyte complex. The endothelium present large fenestrations (50–100 nm) that cover 20% of the capillary surface and prevent cells from exiting but allow plasma to flow freely. The shared basal lamina of podocytes and endothelium forms the initial, less fine filtration barrier, blocking molecules larger than 70 kD. The thin diaphragms that cover the slit openings between the podocyte processes form a more selective filter [25]. These slits are made up of elongated proteins that originate from the surface of the adjacent foot process cell membranes and meet in the centre of the slit, forming a zipper-like configuration. The junction width between two adjacent podocytes varies between 20 and 50 nm, possibly due to the glomerulus perfusion pressures. Podocyte processes are mobile (they contain actin and myosin) and interconnected by the slit diaphragm and to the basal lamina. The slit diaphragm molecular complex is linked with the actin cytoskeleton. Changes in the composition and/or arrangement of these complexes are observed in various forms of human and experimental diseases [26].

The *proximal convoluted tubule* (PCT) originates at the urinary pole of Bowman's capsule and follows a winding path, ending with a straight segment that connects to the loop of Henle. PCT cells are tall and have a distinctive pink cytoplasm, long apical microvilli for enhanced surface area, and extensive basal invaginations for active transport processes. Numerous large mitochondri are located between these basal invaginations. The lateral borders of adjacent PCT cells are extensively interdigitated, increasing the surface area for efficient transport.

The *loop of Henle* is smaller in diameter than the PCT and has two distinct limbs—the descending and ascending limbs—that run in opposite directions. Some

loops of Henle have a wider segment before entering the distal tubule. The distal convoluted tubule (DCT) is further divided into straight and convoluted segments. Traditionally, the straight portions of the PCT and DCT were considered part of the loop of Henle (thick ascending and descending limbs), but recent studies suggest that they are more closely related to the PCT and DCT, respectively. The unique arrangement of the loop of Henle's descending and ascending limbs, along with their specific transport and permeability properties, allows them to function as "*countercurrent multipliers*." This process creates a concentration gradient of extracellular fluid tonicity in the renal medulla, playing a crucial role in regulating urine osmolarity and final volume.

The *distal convoluted tubule* (DCT) reconnects with its originating glomerulus and links to the collecting tubule, collecting urine from multiple nephrons and presenting an open end. The epithelium of the DCT, loops of Henle, and collecting ducts vary in thickness and have clearly defined cell borders. Some have a limited number of surface microvilli. Generally, these tubes either perform less active transport than the PCT or are involved solely in passive water movements.

The *collecting ducts* are lined with principal cells and intercalated cells. The outline of these cells is more pronounced than that of the PCT or DCT cells. Principal cells are responsive to aldosterone. Mesangial cells, known as Polkissen or Lacis cells, are situated between capillaries, beneath the basal lamina, and outside the capillary lumen. There is no basal lamina separating mesangial and endothelial cells. Mesangial cells are phagocytic and may intervene in maintaining the basal lamina. Abnormalities in mesangial cells are observed in several diseases that result in blocked and/or misshapen glomeruli.

The *juxtaglomerular (JG) complex* consists of the JG apparatus (located in the wall of the afferent arteriole), the *macula densa* (a specialized area of the DCT), and a group of mesangial cells. The JG cells are modified smooth muscle cells that secrete renin.

The *macula densa* is composed of tall cuboidal cells in the wall of the DCT that monitor sodium levels in the tubular fluid.

Vascularization of the Adipose Capsule

The renal adipose capsule encompasses an arterial and venous arch formed by the anastomosis of numerous blood vessels.

The arterial blood supply, known as capsulo-adipose arteries, originates from the renal artery. It sends anterior and posterior branches that extend to the adipose capsule, traversing over the surfaces of the kidney. These branches join the interlobular arteries that penetrate the fibrous capsule and connect with the perirenal arch. Within the adipose capsule, these branches anastomose with thinner accessory branches of the inferior phrenic, testicular, or ovarian arteries, superior mesenteric artery, lumbar arteries, and/or adrenal arteries. These connections play a crucial role in establishing complementary collateral circulation in the event of renal artery obstruction.

The adipose capsule presents a robust venous network centred around an extrarenal venous arch that runs parallel to the kidney's lateral margin. This arch serves as a blood diversion zone by connecting to neighbouring venous territories. The venous network of the adipose capsule intertwines with the renal veins and veins of surrounding organs. Connections with the renal veins occur through the renal vein trunk and the intrarenal venous network, via structures that penetrate the fibrous capsule. Some veins transport blood from the perirenal network to the stellate veins, while others convey it from cortical venules to the perirenal network. Connections between the adipose capsule's veins and veins of neighbouring organs can be found on the anterior surface of the kidney, where they communicate with the veins of the colon, and on the posterior surface, connecting with the veins of the posterior abdominal wall and nerves (subcostal, iliohypogastric, and ilioinguinal).

The extrarenal arch communicates cranially with the adrenal veins and caudally with the ureteral and gonadal (testicular or ovarian) veins. The practical implication of these venous connections lies in their ability to expand and provide an alternative pathway for renal blood flow in the event of a blockage in the renal vein. From a practical standpoint, the anastomoses between the extrarenal vein and the caudal lumbar veins, as well as the cranial azygos vein, are crucial as they can compensate for an obliterated renal vein [27].

Vascularization of the Renal Pelvis and Calices

The arterial network of the renal pelvis originates from small branches of the renal artery and branches within the renal sinus. These vessels supply blood to the walls of the renal pelvis, the surrounding connective tissue, and the adipose tissue within the renal sinus. Within the thickness of the pelvic wall, these arteries branch repeatedly into smaller vessels that rapidly transform into capillaries and form a three-dimensional network with distinct characteristics in the submucosal and muscular layers. At the point where the calices transition into the pelvis, the network undergoes a transformation, with larger loops forming in the submucosa's deepest portion and flattening towards the mucosa. These deeper loops drain into veins that traverse the muscular layer and join the tributaries of the nearby renal vein. These deeper venous networks, which lie within the submucosa's depth, explain the occurrence of haemorrhages in the pelvic wall and certain forms of pyelovenous reflux. The pelvic wall also contains arteries with a helical course that penetrate the renal parenchyma and extend into the submucosa, where they branch into capillaries.

Autoregulation of Renal Blood Flow

Under homeostatic conditions, renal blood flow remains stable within a Mean Arterial Pressure (MAP) range of 75–160 mmHg. This regulation is primarily ensured by the myogenic response, which accounts for 50% of the total autoregulatory response and is characterized by a standard vasculoconstrictive response of the vascular smooth muscle to wall stretch [28]. Tubuloglomerular feedback contributes to 35% of the regulation and is a negative feedback loop that reduces renal blood flow in response to an increase in sodium delivery to the tubule. This process is mediated by ATP and adenosine secreted by macula densa cells, leading to afferent arteriolar vasoconstriction. Mechanisms involving angiotensin-II and Nitric Oxide (NO) account for less than 15% of the regulation [28]. Sympathetic autoregulation typically maintains a stable renal blood flow across a broad range of systemic sympathetic conditions. The Glomerular Filtration Rate (GFR) is less affected (disproportionate to blood flow) because the efferent arterioles constrict more than the afferent arterioles in response to a sympathetic stimulus.

Imaging Features of Renal Vascularization

Standard non-angiographic CT and MRI scans are not suitable for precise assessment of the renal vasculature due to flow artifacts and inadequate contrast enhancement. To accurately evaluate the renal arteries and veins using imaging studies, one must have a thorough understanding of normal renal vascular anatomy, be familiar with common variations in renal vascular anatomy, and be able to recognize both intrinsic and extrinsic vascular pathologies that can affect the kidney. Identifying the vascular nature of these pathological conditions is essential for guiding further investigations and determining appropriate treatment strategies.

Ultrasonography

Doppler ultrasonography (US) is commonly employed as the primary imaging modality for assessing both native and transplanted kidneys, offering a combination of anatomical and functional insights. Doppler US has a variety of applications, including evaluating renal artery stenosis (RAS), detecting renal vein thrombosis, identifying pseudoaneurysms and true aneurysms, diagnosing vascular complications related to transplanted kidneys, assessing the cause of acute renal failure suspected to be vascular in origin, and examining kidney blood flow in cases of aortic dissection (Fig. 3).

A comprehensive renal vascular Doppler examination involves assessing the patency and waveform features of the main renal artery and vein, of the arcuate and

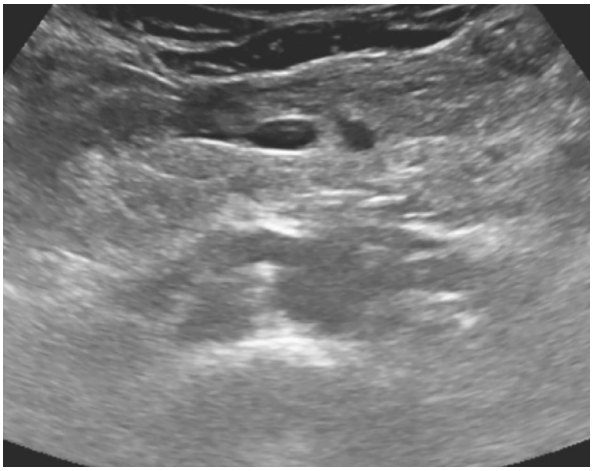

Fig. 3 Renal arteries emerging from the abdominal aorta—ultrasound aspect (Cardiovascular Diseases Institute Iasi)

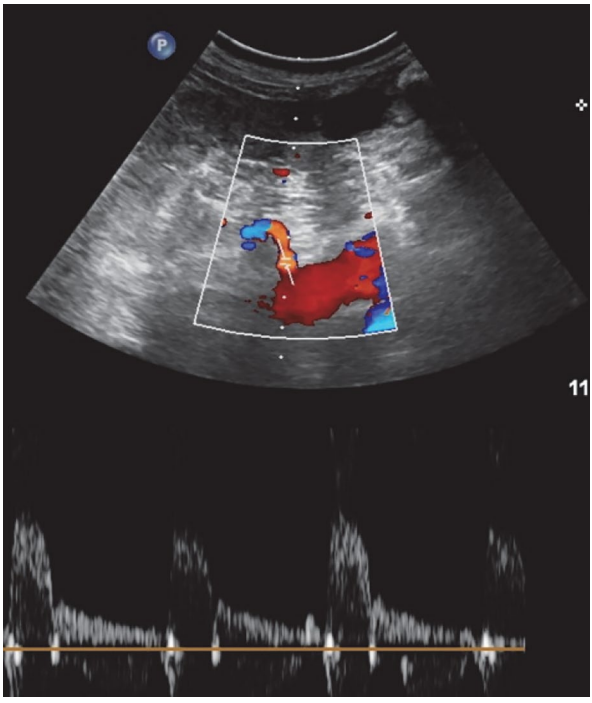

Fig. 4 Doppler assessment of renal arteries in a hypertensive patient—normal waveform (Cardiovascular Diseases Institute Iasi)

interlobar arteries located in the upper, middle, and lower poles of the kidney, and the associated resistive index (RI). The RI is a calculated value that reflects the resistance to blood flow within the kidney. It is determined using the following formula: RI = (peak systolic velocity—end-diastolic velocity)/peak systolic velocity. In healthy adults, the RI typically falls within the range of 0.6–0.7 (Fig. 4).

The RI serves as an indicator of blood flow resistance within an organ. Elevated RI values are associated with obstructions to blood flow, such as those determined by renal vein thrombosis, urinary obstruction due to hydronephrosis, renal parenchymal disorders and renal extrinsic compressions. As resistance to blood flow intensifies, a progressive reduction in blood flow occurs, eventually leading to absent flow and, in some cases, retrograde flow during the diastolic phase of the heartbeat. Conversely, reduced RI values are observed unilaterally in moderate to severe renal artery stenosis (RAS) or bilaterally in aortic coarctation. However, in advanced untreated RAS, RI values tend to increase as the affected vessel loses its elasticity.

CT Angiography and MR Angiography

Computed tomography angiography (CTA) and *magnetic resonance angiography* (MRA) are cutting-edge imaging modalities that utilize high-resolution images captured during a carefully timed arterial phase. Advanced multidetector CT systems can acquire thin slices (less than 1 mm) that can be reconstructed into diverse planes, including curved planar and volume rendering reconstructions. Precise timing of the angiographic phase is typically accomplished through bolus-tracking algorithms, where the radiologist identifies a region of interest (ROI) within the abdominal aorta and the scan commences automatically when the attenuation measurement (in Hounsfield units) within the ROI reaches a predetermined threshold level, typically 100 HU. This strategy reliably ensures precise timing of the angiographic phase and is largely unaffected by the patient's circulatory status or cardiovascular function (Fig. 5).

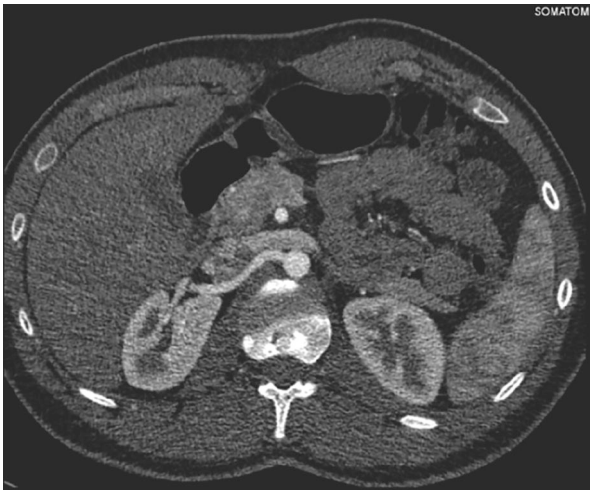

Fig. 5 Normal right renal artery—CT angiography (Cardiovascular Diseases Institute Iasi)

In case of MRA, to produce high-resolution images, three-dimensional (3D) volumetric acquisition methods are employed, utilizing large matrix sizes, and partitioning the section thickness using a section-select gradient. To accelerate 3D imaging acquisition, various techniques are employed, such as volume interpolation, keyhole imaging, and view sharing. Angiographic phase timing can be achieved using empirical triggering, test bolus, fluoroscopic triggering, or automatic bolus tracking [29].

Both CTA and MRA encounter the challenge of venous contamination, where contrast medium in neighbouring veins can obscure the visualization of arteries. Therefore, precise timing of the angiographic phase is essential for adequate imaging. For individuals with impaired renal function or iodine allergy, MRA using group II gadolinium-based contrast agents may be a more suitable option. Nephrogenic systemic fibrosis (NSF), a potential complication of gadolinium enhanced MRA in patients with stage 4 and 5 chronic kidney disease, arises from the toxicity of unbound gadolinium ions. The risk of NSF is reduced with group II gadolinium-based contrast agents and has been reported to be less than 0.07% in this patient population [29].

Renal Artery Angiography/Angioplasty

When interventional treatment is being considered, conventional angiography is the preferred diagnostic method. Although CTA or MRA can be used as screening tools in hypertensive patients, conventional angiography remains the study of choice when renal artery stenosis or renal vascular malformation are strongly suspected. This is because it enables stent placement and embolization of vascular tumours at the same time as the diagnostic procedure.

Clinical Anatomy

Renal artery stenosis (RAS) is the most prevalent cause of secondary hypertension mostly determined by atherosclerosis. It can also complicate renal transplantation when occurring at the site of the main renal artery anastomosis. Medical imaging offers a range of tools for excluding and grading RAS in renovascular hypertension. For patients with normal renal function, abdominal CTA (100% sensitivity, 98% specificity) or MRA (97% sensitivity, 85% specificity) are the recommended first-line imaging modality [30]. In patients with renal dysfunction, Doppler US is the first-line investigation with 85% sensitivity, 84% specificity [29]. The reduced sensitivity and specificity of Doppler US compared to CTA and MRA are attributable to the depth and small calibre of the renal arteries and its dependence on patient and operator factors. Catheter angiography was traditionally considered the gold standard for diagnosing RAS but is now reserved for therapeutic interventions

(angioplasty) in patients with already diagnosed RAS through MRA, CTA or Doppler US. Endovascular treatment is indicated in suitable clinical settings for patients with moderate or severe stenosis [31] (Fig. 6).

Fibromuscular dysplasia (FMD) is a disease that affects the vascular system, specifically small and medium-sized arteries such as the renal, internal carotid, mesenteric, and iliac arteries. It's not related to atherosclerosis and is characterized by the thickening of arterial walls due to fibroplasia. This condition is more prevalent in women between their 40s and 50s. FMD is often a bilateral condition categorized into three types based on the layer of the arterial wall that undergoes fibroblastic changes: the tunica media (involved in over 80% of cases), the tunica intima (involved in about 10% of cases), and the adventitia, which is seldom affected. FMD is the second leading cause of secondary hypertension due to Renin-Angiotensin System (RAS) and it usually affects the middle to distal parts of the renal arteries, unlike atherosclerotic disease which impacts the proximal part. In CTA, MRA, and catheter angiography, FMD presents a unique "*string-of-beads*" appearance because of multiple stenoses and dilatations. The preferred treatment is percutaneous balloon angioplasty, possibly combined with stent placement. Surgery is only considered for cases where multiple branches of the same vessel are involved or for macroaneurysms that pose a risk of rupture and therefore need to be removed [32, 33].

True renal artery aneurysms are quite uncommon, with a prevalence of only 0.1% [29]. They typically occur at the point where the main renal artery bifurcates. Although they usually don't cause symptoms, they can sometimes lead to serious

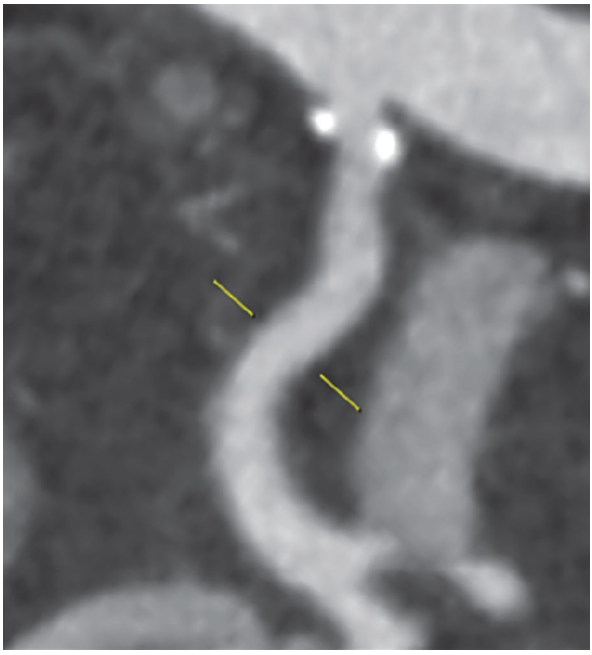

Fig. 6 Calcified atherosclerotic plaques at the origin of the right renal artery—curved planar reconstruction of CT angiography (Cardiovascular Diseases Institute Iasi)

complications such as arterial thrombosis, embolism, or rupture. The most frequent causes of true renal artery aneurysms are FMD and atherosclerosis. It is recommended to treat renal artery aneurysms that are larger than 2.0 cm, those discovered during pregnancy, or those that cause symptoms such as pain, haematuria, hypertension that doesn't respond to medication, thromboembolism, dissection, or rupture [29, 34] (Fig. 7).

Pseudoaneurysms are generally associated with atherosclerotic lesions, trauma, renal transplantation, infections, and vasculitis that lead to a breach in the arterial wall with blood leakage into a contained sac lined by adventitia or surrounding soft tissues.

Both aneurysms and pseudoaneurysms can be detected by Doppler US based on the typical *yin-yang sign* due to the swirling motion of the blood in the sac. Additionally, the feeding vessel shows *to-and-fro motion* with a high degree of turbulence. At CTA and MRA, aneurysms and pseudoaneurysms are seen as focal dilatations or outpouchings from the renal arteries.

Small, medium, and large vessels vasculitis typically affect renal vascularization—antineutrophil cytoplasmic antibodies (ANCAs)-associated vasculitis including granulomatosis with polyangiitis in case of small vessels, polyarteritis nodosa for medium-sized vessels and Takayasu arteritis or giant cell arteritis for large vessels. Small-vessel vasculitis has not distinctive imaging findings, microaneurysms being difficult to identify at CTA or MRA due to limited resolution. Medium-sized vessel vasculitis associated to polyarteritis nodosa is a necrotizing vasculitis more commonly found in men with hepatitis B between the fifth and seventh decades of life. Microaneurysms of the distal interlobar and arcuate arteries are the most typical imaging features [33].

Renal vein compression (*nutcracker) syndrome* recognizes two entities, anterior and posterior nutcracker syndrome. Nutcracker syndrome typically presents with flank pain or haematuria, caused by the rupture of small venous collaterals that form due to increased pressure in the renal vein and drain into the collecting system. The

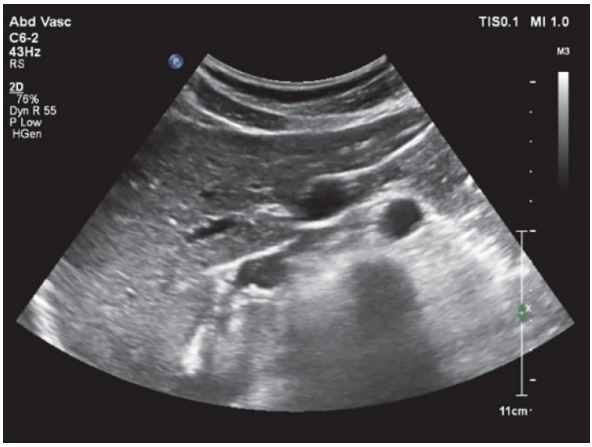

Fig. 7 Right renal artery aneurysm in a young female patient—ultrasound aspect (Cardiovascular Diseases Institute Iasi)

syndrome is slightly more common in women in their 20s and 30s. In the past, conventional venography was used to diagnose nutcracker syndrome. However, Doppler US is now the primary diagnostic tool. The diagnosis is based on measuring the ratio of the inner diameter at the renal hilum to the inner diameter at the site of stenosis and assessing blood flow velocity in both supine and standing positions. If the inner diameter ratio is at least 3 when supine and at least 5 when standing, accompanied by an increase in velocity of 100 cm/s between the two positions, it is considered diagnostic of nutcracker syndrome.

On CT scan, an angle between the superior mesenteric artery and aorta <35° is associated with anterior nutcracker syndrome. Kim et al. evaluated the diagnostic validity of various CT criteria for anterior nutcracker syndrome and found that the "*beak sign*"—characterized by focal narrowing of the left renal vein at the aortomesenteric junction and left renal vein diameter were the most reliable indicators [35].

Treatment approaches for nutcracker syndrome are tailored to the severity of symptoms and may range from conservative management to minimally invasive procedures and surgical interventions in severe cases (renal vein transposition or bypass).

Iatrogenic, blunt, or penetrating trauma can cause life-threatening injuries to the renal vasculature such as pseudoaneurysms, perinephric hematomas, arterial dissections, arteriovenous fistulas (AVF), and arterial or venous thrombosis.

The 2018 revision of the ***American Association for the Surgery of Trauma (AAST)*** renal injury scale incorporates imaging criteria based on CT scans for classifying traumatic injuries:

- vascular injury is defined as the presence of a pseudoaneurysm or AVF—focal collection of contrast material that decreases in attenuation at delayed imaging;
- active bleeding is defined as contrast material that increases in size or attenuation in the delayed phase;
- grades I and II injuries do not involve the renal vasculature;
- grade III injury is characterized by renal vascular injury with active bleeding confined within Gerota's fascia;
- grade IV injury involves active bleeding extending beyond Gerota's fascia into the retroperitoneum or peritoneum. It also includes segmental renal artery or renal vein injury and segmental infarction due to thrombosis;
- grade V injury represents devascularization of the kidney due to hilar injury with major renal artery or vein laceration [36].

Benign and malignant vascular or perivascular tumours such as leiomyoma, leiomyosarcoma, angiosarcoma, haemangioma, and perivascular epithelioid cell tumour (PEComa) can affect the renal vasculature.

Leiomyomas are uncommon benign tumours of mesenchymal origin that can develop from smooth muscle cells located in renal veins, the renal capsule, or the muscularis of the renal pelvis. Despite not having recognized invasive characteristics, they can expand along the vessel wall and into the lumen, leading to obstruction and thrombosis downstream.

Leiomyosarcomas, which account for 7% of all soft-tissue sarcomas, usually develop from the renal veins and grow outwardly (exophytically). However, they can also have a varying intraluminal component and extend into the IVC [37]. They are invasive malignant tumours that often invade the adjacent renal parenchyma and retroperitoneal structures.

Renal haemangiomas (capillary or cavernous) are rare benign vascular renal tumours found in the renal pelvis or medulla. Most patients are asymptomatic, but larger haemangiomas can cause recurrent haematuria. The imaging features of renal haemangioma are similar to those of the hepatic haemangioma: centripetal fill-in of contrast medium following that of the blood pool and peripheral nodular arterial enhancement at CT and MRI investigations, high signal intensity on T2-weighted images [29, 38].

Renal angiomyolipomas (AMLs) belong to the category of PEComas, encompass smooth muscle, fatty, and vascular elements and are the most prevalent benign solid renal tumor. 80% of cases are sporadic, but 20% are associated with syndromes, predominantly tuberous sclerosis complex [39]. Due to their vascular component, AMLs carry a risk of pseudoaneurysm formation and spontaneous life-threatening haemorrhage, particularly in larger lesions. Elective endovascular treatment may be considered when these high-risk features are identified.

Renal vein extension is a typical feature of renal neoplasms, particularly renal cell carcinoma (RCC). Accurate documentation of invasion into the renal vein or IVC is vital for staging according to the eighth edition of the TNM staging system by the American Joint Committee on Cancer (AJCC). Tumour thrombus can be differentiated from bland thrombus by features such as enhancement, renal vein expansion, and presence of microscopic fat with CT and MRI imaging, uptake on fluorodeoxyglucose (FDG) with PET, diffusion restriction with MRI imaging (Fig. 6).

The extent of vascular tumour invasion determines the surgical approach. For intrahepatic IVC involvement, a hepatobiliary consultation is necessary, while cardiac surgery expertise is required when IVC invasion extends above the diaphragm (Fig. 8).

Renal arteriovenous shunts are rare abnormal connections between arteries and veins, affecting approximately 0.04% of the population [29, 40]. While some individuals may remain asymptomatic, these shunts can cause significant health problems, including high blood pressure, haematuria, heart failure when large and multiple, and even life-threatening bleeding. Two main types of AV shunts exist: AVMs and AVFs.

Arteriovenous malformations (AVMs) are inborn conditions characterized by an unusual connection between arteries and veins through a nidus, a complex network of vessels. AVM patients often suffer from haematuria due to the rupture of veins into the renal calyces. AVMs can be divided into two types: cavernous AVMs, which have a single feeding artery, and cirsoid AVMs, which have multiple feeding arteries. Colour Doppler US is highly effective in detecting AVMs, showing a prominent aliasing artifact on Doppler spectral tracing. AVMs display high-velocity flow with spectral broadening (turbulence) and low RI. On CTA and MRA, AVMs may appear

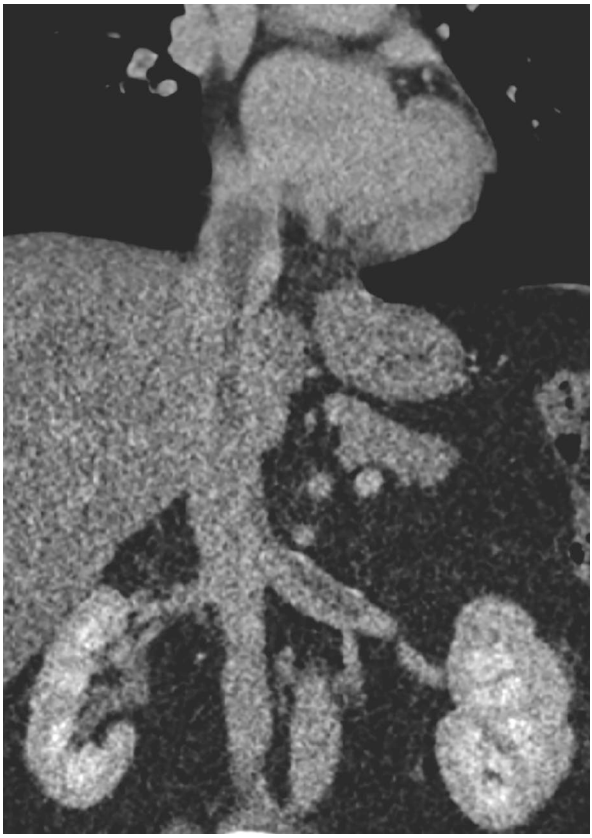

Fig. 8 Thrombosis of the left renal vein extending to the inferior vena cava and the right atrium—CT aspect (Cardiovascular Diseases Institute Iasi)

subtle, looking like an abnormal cluster of small vascular channels. The preferred treatment for AVMs is endovascular embolization.

Arteriovenous fistulas (AVFs), on the other hand, are characterized by a direct link between an artery and a vein, without an intervening capillary bed. AVFs are typically acquired lesions, either traumatic or non-traumatic. Traumatic AVFs can result from percutaneous biopsy, penetrating or blunt trauma, while non-traumatic AVFs can develop secondary to tumour invasion. Most renal AVFs are incidentally detected during a colour Doppler examination, appearing as a focus of aliasing artifact. Spectral tracing of AVFs reveals an increased peak systolic velocity, spectral broadening, decreased resistive index, and arterialization of the draining vein. Small renal AVFs can be difficult to identify on CTA and MRA, which typically show an abnormal arteriovenous communication with an early-draining venous channel. Like AVMs, the treatment of choice for AVFs is also endovascular embolization.

Conclusions

Routine evaluation of the renal vasculature during imaging should be a standard practice for all practitioners. A thorough understanding of renal vascular anatomy and common anatomical variations is crucial not only for assessing potential renal donors but also for preventing bleeding during percutaneous biopsies. Moreover, atypical vascular patterns have been associated with extrarenal pathological conditions. Identifying and accurately characterizing intrinsic renal vascular disorders, neoplasms that involve the renal vasculature, and vascular malformations can expedite further investigations and guide appropriate patient management.

References

1. Martini FH, Nath JL, Bartholomew EF. Fundamentals of anatomy & physiology. 11th ed. Harlow: Pearson; 2017.
2. Sadler TW. Langman's medical embryology. 14th ed. Baltimore: Wolters Kluwer; 2018.
3. Zweyer M. Embryology of the kidney. In: Quaia E, editor. Radiological imaging of the kidney. Medical radiology. Berlin/Heidelberg: Springer; 2010.
4. Schoenwolf GC. Larsen's human embryology. 5th ed. Philadelphia: Elsevier; 2014.
5. McAninch JW, Lue TF. Smith and Tanagho's general urology. 18th ed. New York: McGraw-Hill Education LLC; 2020.
6. Roker LA, Nemri K, Yu J. Wnt7b signaling from the ureteric bud epithelium regulates medullary capillary development. J Am Soc Nephrol. 2017;28(1):250–9. https://doi.org/10.1681/ASN.2015111205.
7. Gu X, Zhang S, Zhang T. Abnormal crosstalk between endothelial cells and podocytes mediates tyrosine kinase inhibitor (TKI)-induced nephrotoxicity. Cells. 2021;10(4):869. https://doi.org/10.3390/cells10040869.
8. Kim BS, Goligorsky MS. Role of VEGF in kidney development, microvascular maintenance and pathophysiology of renal disease. Korean J Intern Med. 2003;18(2):65–75. https://doi.org/10.3904/kjim.2003.18.2.65.
9. Sirin Y, Susztak K. Notch in the kidney: development and disease. J Pathol. 2012;226(2):394–403. https://doi.org/10.1002/path.2967.
10. Sureshbabu A, Muhsin SA, Choi ME. TGF-β signaling in the kidney: profibrotic and protective effects. Am J Physiol Renal Physiol. 2016;310(7):F596–606.
11. Buhl EM, Djudjaj S, Babickova J, Klinkhammer BM, Folestad E, Borkham-Kamphorst E, Weiskirchen R, Hudkins K, Alpers CE, Eriksson U, Floege J, Boor P. The role of PDGF-D in healthy and fibrotic kidneys. Kidney Int. 2016;89(4):848–61. https://doi.org/10.1016/j.kint.2015.12.037.
12. Kim W. The role of angiopoietin-1 in kidney disease. Electrolyte Blood Press. 2008;6(1):22–6. https://doi.org/10.5049/EBP.2008.6.1.22.
13. Chai OH, Song CH, Park SK, Kim W, Cho ES. Molecular regulation of kidney development. Anat Cell Biol. 2013;46(1):19–31. https://doi.org/10.5115/acb.2013.46.1.19.
14. Patel SR, Dressler GR. The genetics and epigenetics of kidney development. Semin Nephrol. 2013;33(4):314–26. https://doi.org/10.1016/j.semnephrol.2013.05.004.
15. Standring S. Gray's anatomy. The anatomical basis of clinical practice. 42nd ed. Amsterdam: Elsevier; 2020.
16. Aristotle S, Sundarapandian FC. Anatomical study of variations in the blood supply of kidneys. J Clin Diagn Res. 2013;7(8):1555–7. https://doi.org/10.7860/JCDR/2013/6230.3203.

17. Ryan S, McNicholas M, Eustace SJ. Anatomy for diagnostic imaging. 3rd ed. Edinburgh: Saunders; 2011.
18. Sinnatamby CS. Last's anatomy regional and applied. 12th ed. Edinburgh: Elsevier; 2011.
19. Zagoria R. Genitourinary radiology: radiology requisites series. 2nd ed. St. Louis: Mosby; 2004.
20. Young AH, Thompson P. Abnormalities of the renal arteries, with remarks on their development and morphology. J Anat Physiol. 1903;38(Pt 1):1–14.1.
21. Cho Y, Yoon SP. Bilateral inferior renal polar arteries with a high origin from the abdominal aorta. Folia Morphol (Warsz). 2021;80(1):215–8. https://doi.org/10.5603/FM.a2020.0040.
22. Beckmann CF, Abrams HL. Circumaortic venous ring: incidence and significance. AJR Am J Roentgenol. 1979;132(4):561–5. https://doi.org/10.2214/ajr.132.4.561.
23. Haładaj R, Polguj M, Wysiadecki G, Żytkowski A, Topol M. Circumaortic left renal vein (circumaortic renal collar) associated with the presence of vascular anomalies: a case series and review of literature. Folia Morphol (Warsz). 2019;78(2):437–43. https://doi.org/10.5603/FM.a2018.0090.
24. Hostiuc S, Rusu MC, Negoi I, Dorobanțu B, Grigoriu M. Anatomical variants of renal veins: a meta-analysis of prevalence. Sci Rep. 2019;9(1):10802. https://doi.org/10.1038/s41598-019-47280-8.
25. Dudek RW. High-yield kidney. Baltimore: Lippincott Williams & Wilkins; 2006.
26. Assady S, Wanner N, Skorecki KL, Huber TB. New insights into podocyte biology in glomerular health and disease. J Am Soc Nephrol. 2017;28(6):1707–15. https://doi.org/10.1681/ASN.2017010027.
27. Kabalin JN. Surgical anatomy of the retroperitoneum, kidneys and ureters. In: Walsh PC, Retik AB, Vaughan Jr ED, Wein AJ, editors. Campbell's urology. 8th ed. Philadelphia: WB Saunders; 2002. p. 3–40.
28. Dalal R, Bruss ZS, Sehdev JS. Physiology, renal blood flow and filtration. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482248/.
29. Leckie A, Tao MJ, Narayanasamy S, Khalili K, Schieda N, Krishna S. The renal vasculature: what the radiologist needs to know. Radiographics. 2021;41(5):1531–48. https://doi.org/10.1148/rg.2021200174.
30. Expert Panels on Urologic Imaging and Vascular Imaging, Harvin HJ, Verma N, Nikolaidis P, Hanley M, Dogra VS, Goldfarb S, Gore JL, Savage SJ, Steigner ML, Strax R, Taffel MT, Wong-You-Cheong JJ, Yoo DC, Remer EM, Dill KE, Lockhart ME. ACR appropriateness criteria® renovascular hypertension. J Am Coll Radiol. 2017;14(11S):S540–9. https://doi.org/10.1016/j.jacr.2017.08.040.
31. Nair R, Vaqar S. Renovascular hypertension. [Updated 2023 May 22]. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551587/.
32. Baradhi KM, Bream P. Fibromuscular dysplasia. 2023 Jul 10. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2024. PMID: 29630256.
33. Maritati F, Iannuzzella F, Pavia MP, Pasquali S, Vaglio A. Kidney involvement in medium- and large-vessel vasculitis. J Nephrol. 2016;29(4):495–505. https://doi.org/10.1007/s40620-016-0303-8.
34. González J, Esteban M, Andrés G, Linares E, Martínez-Salamanca JI. Renal artery aneurysms. Curr Urol Rep. 2014;15(1):376. https://doi.org/10.1007/s11934-013-0376-z.
35. Kim KW, Cho JY, Kim SH, Yoon JH, Kim DS, Chung JW, Park JH. Diagnostic value of computed tomographic findings of nutcracker syndrome: correlation with renal venography and renocaval pressure gradients. Eur J Radiol. 2011;80(3):648–54. https://doi.org/10.1016/j.ejrad.2010.08.044.
36. Chien LC, Vakil M, Nguyen J, Chahine A, Archer-Arroyo K, Hanna TN, Herr KD. The American Association for the Surgery of Trauma Organ Injury Scale 2018 update for computed tomography-based grading of renal trauma: a primer for the emergency radiologist. Emerg Radiol. 2020;27(1):63–73. https://doi.org/10.1007/s10140-019-01721-z.

37. Khetrapal S, Bhargava A, Jetley S, Rana S, Jairajpuri Z. Renal leiomyoma: an uncommon differential diagnosis of renal masses with a clinical relevance. J Clin Diagn Res. 2014;8(10):FD08–9. https://doi.org/10.7860/JCDR/2014/9434.4993.
38. Costa Neto TF, Renteria JM, Di Biase FG. Renal hemangioma. Int Braz J Urol. 2004;30(3):216–8. https://doi.org/10.1590/s1677-55382004000300008.
39. Shamam YM, Leslie SW. Renal angiomyolipoma. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK585104/.
40. Maruno M, Kiyosue H, Tanoue S, Hongo N, Matsumoto S, Mori H, Sagara Y, Kashiwagi J. Renal arteriovenous shunts: clinical features, imaging appearance, and transcatheter embolization based on angioarchitecture. Radiographics. 2016;36(2):580–95. https://doi.org/10.1148/rg.2016150124.

Renal Vascular Anomalies

Cristian Mornos and Adrian-Sebastian Zus

Abstract Renal vascular anomalies encompass both congenital and acquired abnormalities of the renal vasculature, including renal artery aneurysms and renal arteriovenous fistulas. Renal aneurysms are slow-growing but rupture has high mortality. Traditional surgical excision has been progressively replaced by minimally invasive closing techniques using stents, coils and other materials, with good results and reduced risks, even in cases with complex anatomy. Arteriovenous fistulas can lead to heart failure and are becoming more frequent secondary to an increase in renal interventions, such as needle biopsies. Interventional closure is challenging because of increased flow, but success rate is extremely high, with few cases requiring surgical repair.

Keywords Renal aneurysm · Renal fistula · Renal endovascular repair · Renal coil embolization · Amplatzer plug · Renal vascular intervention

Renal Artery Aneurysms

General Information

By definition, aneurysms are vascular dilatations with a diameter 1.5–2 times greater than the proximal and distal vascular diameter. The aneurysm wall contains all three layers of the vascular wall. Renal artery aneurysms are rare (0.1%–1–1.3% of the population), more common in women, especially those of reproductive age, due to a higher incidence of fibromuscular dysplasia. They are more frequent on the right renal artery, with 29% of cases being bilateral. Risk factors for their occurrence include, in addition to fibrodysplasia, Ehlers-Danlos syndrome, Marfan syndrome, atheromatosis of the renal arteries, Takayasu syndrome, Behcet's disease,

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granulomatosis with polyangiitis, trauma, and infections. Neurofibromatosis type I, a genetic disease associated with renal artery stenosis, can rarely cause aneurysms at this level.

They grow slowly and are associated with high mortality in case of rupture (between 10% and 80%), with the risk being higher in women in the third trimester of pregnancy due to increased intravascular volume, uterine compression, and vascular changes induced by pregnancy. Most often, they are asymptomatic and discovered incidentally, with an increased frequency as the rate of non-invasive vascular imaging (CT and MR angiography) usage grows. When symptomatic, they manifest through macroscopic hematuria, ileus, flank, or back pain due to renal infarction or compression caused by the aneurysm on adjacent structures (for example, hydronephrosis due to compression of the renal pelvis or ureter). Acute pain may be a sign of rupture and represents an emergency, with the clinical manifestation being hemorrhagic shock. Untreated, they can complicate, in addition to rupture, with dissection, distal embolization (causing renal infarcts), arterial hypertension, kidney failure.

Classification

Depending on morphology and location, they are classified into: saccular, fusiform, dissecting, and intrarenal. Another classification used is Rundback's—type I: saccular aneurysm of the renal artery or of a major branch, type II: fusiform aneurysm at the level of an arterial bifurcation, type III: intraparenchymal aneurysms (Fig. 1). A rare sub-type of type I aneurysm is the hilar aneurysm, where the aneurysm is found in the distal portion of the renal artery, close to the renal parenchyma.

Treatment

Initially, treatment indications were considered based on various factors: a diameter exceeding 2 cm, women of reproductive age, persistent flank pain, hematuria, refractory hypertension, thromboembolism, dissection, and rupture. However, due to the very slow growth of renal aneurysms, an intervention indication is currently considered for asymptomatic ones with a diameter exceeding 3 cm, or a diameter under 3 cm accompanied by conditions such as hypertension, pregnancy, women in the reproductive period, impaired renal function, flank pain, dissected aneurysms causing stenosis, single kidney, intrarenal thromboembolism, or renal infarcts.

The standard treatment used to be vascular reconstructive surgery, either open or ex-vivo, involving nephrectomy and autotransplantation. However, this approach carries risks of cerebrovascular complications, challenging recovery, and, in case of failure, potential loss of the kidney (up to 5.5% in the case of ex-vivo reconstruction). Surgical techniques include aneurysmorrhaphy, direct suturing,

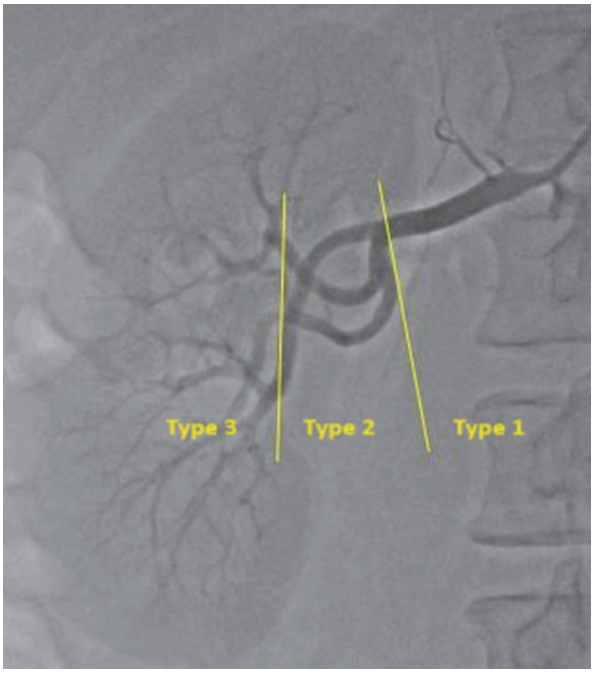

Fig. 1 Rundback's classification of renal artery aneurysms

aneurysmectomy, and end-to-end anastomosis, or extra-anatomic bypass using saphenous vein, internal iliac artery, or synthetic graft. Isolated cases have been treated using robot-assisted surgery. Another option is the transplantation of the affected kidney to another patient, benefiting both the donor and the recipient.

Multiple transcatheter interventional techniques offer treatment alternatives even in cases with complex anatomy. The arterial approach can be femoral, brachial, or radial, with intravenous or intra-arterial heparin used to achieve an activated clotting time (ACT) 2–3 times the normal value. Periprocedural monitoring of blood pressure and renal function (glomerular filtration rate) is performed.

Type I Aneurysms

Covering the Aneurysm with a Graft-Stent

The stents utilized in these procedures are coated with polytetrafluoroethylene (PTFE), with or without a heparinized bioactive surface, or incorporate an autologous saphenous vein graft on a nitinol support. It is essential to maintain a minimum distance of 15 mm between the ostium and the aneurysm to ensure a suitable landing zone for the proximal edge of the stent.

In cases where the aneurysm is situated distally, the stent can be positioned with its distal edge at the level of the bifurcation of the renal artery into the main branches,

accompanied by the placement of coils in the aneurysmal sac. This technique offers the advantage of simultaneously addressing arterial stenoses and excluding the aneurysm. However, it is not applicable to type II aneurysms (due to involvement of the main branches, with the risk of covering an important side branch) or type III (difficulty in navigating smaller, tortuous branches). Additionally, the presence of atherosclerosis, which increases vascular stiffness, may pose technical challenges during the intervention. Given its long-term occlusion rate of 17%, this approach may not be the preferred treatment for the younger population.

Embolization with Metallic Coils

It can be employed in all types of aneurysms, proving technically simpler in cases with a narrow neck and more challenging in those with a wide neck or complexity involving efferent branches. This method stands as the most frequently utilized interventional technique.

Type II Aneurysms

Type II aneurysms present a challenge owing to their anatomical complexity determined by location. Aneurysms with a wide neck (>4 mm) pose increased difficulty in treatment due to the instability of coils, which may protrude into the vessel, resulting in a low rate of aneurysm occlusion. Consequently, surgical intervention remains a viable option in these cases. Various interventional techniques for Type II aneurysms include:

(a) Flow-diverter stents

The primary objective of flow-diverter stents is to ensure laminar blood flow, contrasting with the turbulent flow typically observed in an aneurysm. Their woven structure facilitates the diversion of flow toward the real lumen of the artery, resulting in a deceleration of the flow from the aneurysm. This has a dual effect of reducing pressure at this level, consequently decreasing the risk of rupture, and fostering aneurysmal thrombosis. Over time, the stent mesh becomes covered by the endothelium, effectively excluding the aneurysm from the blood flow.

Initially employed predominantly in cerebrovascular interventions, these stents have recently demonstrated success in visceral circulation. The reported success rate in renal procedures has reached 100%, albeit based on a limited number of cases. However, challenges may arise if vascular reconstructive surgery becomes necessary subsequent to the placement of such a stent. The rigidity of these materials renders them unsuitable for navigation in smaller branches associated with type III aneurysms. Therefore, careful consideration of the specific anatomical context is essential when contemplating the use of flow-diverter stents in therapeutic interventions.

(b) Remodeling techniques

These techniques can be applied in both type I and type II aneurysms with complex anatomy, utilizing uncovered stents and coils. The procedure involves placing a metallic stent over the mouth of the aneurysm. A microcatheter is then introduced through the stent mesh, allowing the release of coils inside the aneurysmal sac. Alternatively, coils can be initially placed and subsequently covered with a stent.

The "waffle-cone" method, successfully employed in interventional neuroradiology, can be adapted for complex renal aneurysms with a wide neck. This method entails placing a stent with its distal edge at the base of the aneurysm, followed by introducing coils into the aneurysm body. This approach avoids extensive manipulation of the aneurysm beyond its neck, thereby reducing the risk of vascular complications.

Remodeling techniques can also be achieved without using stents. A balloon can be employed to facilitate the positioning of coils in the aneurysm. Alternatively, a protective coil can be placed in the mouth of the aneurysm while micro-coils are introduced through a microcatheter. The initial coil acts as a barrier against the migration of micro-coils and is withdrawn at the conclusion of the procedure. Fusiform aneurysms involving the branches of the renal artery necessitate interdisciplinary discussion for optimal management, taking into consideration the unique challenges posed by their anatomical characteristics.

Type III Aneurysms

Superselective embolization of segmental branches can be performed using coils or liquid chemicals (such as Onyx™ or Histoacryl™) delivered through microcatheters. This embolization results in infarction of the corresponding renal parenchyma, which can manifest clinically as symptomatic or asymptomatic. Aneurysm treatment options include "packing" (filling the aneurysm with coils), trapping (placing coils both proximally and distally to the neck of the aneurysm), or blocking the entryway (obstructing the artery feeding the aneurysm). Better outcomes have been reported with the "packing" technique.

In cases of complex type III aneurysms, a combination of stent-grafts and chemical embolization or coils and chemical embolization can be employed, with favorable results reported in isolated cases. To prevent local release of renin, infarction of the entire renal area affected by the aneurysm is recommended. The goal is to preserve as many segmental branches as possible.

In instances where anatomical complexity poses challenges, surgical resolution may be the only viable option. For example, a distal aneurysm with five emerging branches was successfully treated by excising the kidney, performing an incision and arteriorrhaphy of the aneurysm, and reimplanting it in the iliac fossa. This involved anastomosis of the renal artery and vein to the respective iliac artery and vein. Surgical interventions of this nature become necessary in scenarios where the

complexity of the aneurysm anatomy requires a more comprehensive and direct approach.

Results and Follow-Up

The reported success rate of these procedures is up to 100%. Beyond technical success, several authors have observed a reduction in blood pressure values in patients with secondary arterial hypertension, sometimes to the extent of discontinuing medication. Additionally, an improvement in renal function has been noted. However, in rare cases, secondary arterial hypertension may worsen after the intervention. Following the procedure, a standard recommendation involves double antiplatelet therapy for a duration of 1 year, followed by lifelong antiplatelet monotherapy. In some cases, postprocedural parenteral anticoagulant treatment may be continued for up to 3 days without an associated increase in the risk of bleeding.

Prior to discharge, imaging control is advised using CT or MR angiography, or invasive arteriography. CT angiography may have the drawback of artifacts caused by the materials used during the intervention. Subsequent imaging reevaluations are typically scheduled at 1 month, 6 months, and then annually. In addition to imaging, renal function is monitored by measuring serum creatinine and calculating the glomerular filtration rate. Given that 29% of renal aneurysm cases are bilateral, imaging follow-up provides the added benefit of detecting contralateral occurrences. However, the long-term success rate for endovascular interventions is not definitively known due to their relatively recent implementation, emphasizing the importance of ongoing research and monitoring for a comprehensive understanding of outcomes over time.

Complications and Contraindications

Major periprocedural complications encompass myocardial infarction and renal failure necessitating dialysis. On the other hand, minor complications include:

- Renal infarcts—15%;
- Complications at the puncture site (infection, pseudoaneurysm);
- Urinary infections;
- Transitory renal failure;
- Abdominal abscesses;
- Stent restenosis;
- Renal by-pass thrombosis;
- Renal artery thrombosis (treated by intraoperative thrombolysis and/or additional stenting);

- Postembolization syndrome (leukocytosis, fever, abdominal pain, nausea, and vomiting)—8%;
- Coil migration—1.2%;
- Aneurysm reperfusion;
- Aneurysmal sac expansion;
- Renal artery dissection;
- Perforation;
- Stent infection with pseudoaneurysm.

Patients undergoing endovascular techniques generally experience a shorter intervention duration, reduced blood loss, shorter time spent in intensive care, and a briefer hospital stay compared to those treated surgically. Some studies suggest a higher rate of complications, including death, in patients receiving endovascular treatment. However, this may be attributed to the specific profile of patients selected for interventional therapies, often presenting with more comorbidities such as a history of coronary artery disease, myocardial infarction, cardiac arrhythmias, and renal failure. Given the risk of up to 5% for secondary nephrectomy due to technical complications in surgical correction cases, interventional therapies are preferred for patients with a single kidney.

Contraindications to interventional treatment include infections of the target vessel, impaired renal function, allergy to contrast substances, and hemodynamic instability in the context of an acute rupture, where emergency surgical intervention is warranted. As cases of late aneurysm reperfusion have been reported, long-term follow-up is deemed necessary for patients treated by endovascular techniques.

Renal Arteriovenous Fistulas

General Information

An arteriovenous fistula is defined as a direct communication between an artery and a vein, bypassing the capillary network. The frequency of acquired arteriovenous fistulas is increasing due to the rising number of interventions on the kidney, with multiple causative factors implicated. Up to 18% of renal biopsies can result in the formation of an arteriovenous fistula, which carries a higher risk of rupture and can be associated with the development of pseudoaneurysms.

In the general population, the incidence is low (0.04%). Congenital fistulas, along with idiopathic ones (occurring in the absence of predisposing factors), are collectively termed "spontaneous." Typically, both are large with high flow, increasing the risk of incomplete closure or migration of embolized material during endovascular treatment.

Fistulas may sometimes be associated with renal artery or venous aneurysms. Pressure and flow overload on the thin venous wall can weaken it, leading to subsequent atrophy and dilation, forming a venous aneurysm. Another proposed

mechanism for the formation of these venous aneurysms is chronic venous hypertension secondary to the compression of the left renal vein between the inferior mesenteric artery and the aorta.

Similar to aneurysms, arteriovenous fistulas are more common on the right side, being twice as frequent in women. They can be asymptomatic, discovered incidentally, or manifest in middle-aged or elderly individuals through heart failure due to the hyperdynamic state, predominantly diastolic arterial hypertension, flank pain, abdominal tumoral formation, and hematuria. Auscultation may reveal a paraumbilical systolic murmur. The clinical course is generally slow; however, acute cases can occur secondary to renal biopsy punctures.

According to Cho et al.'s classification, renal fistulas are classified as type I shunts, involving up to three arterial components that empty into the proximal portion of a single venous component.

A positive diagnosis of arteriovenous fistula is typically established through imaging modalities. Renal ultrasound often reveals an anechoic image that may resemble a renal cyst, but Doppler flow can confirm its vascular nature. Additional imaging with CT (Fig. 2) or MR investigation can provide a more detailed description, including a dilated afferent vessel, early opacification of the efferent venous system due to increased flow, and the potential location of the fistula, aiding in treatment planning. In some cases, cortical renal infarcts resulting from distal embolization of thrombotic material formed in the varicose veins associated with the fistula can also be identified through imaging. These diagnostic findings collectively

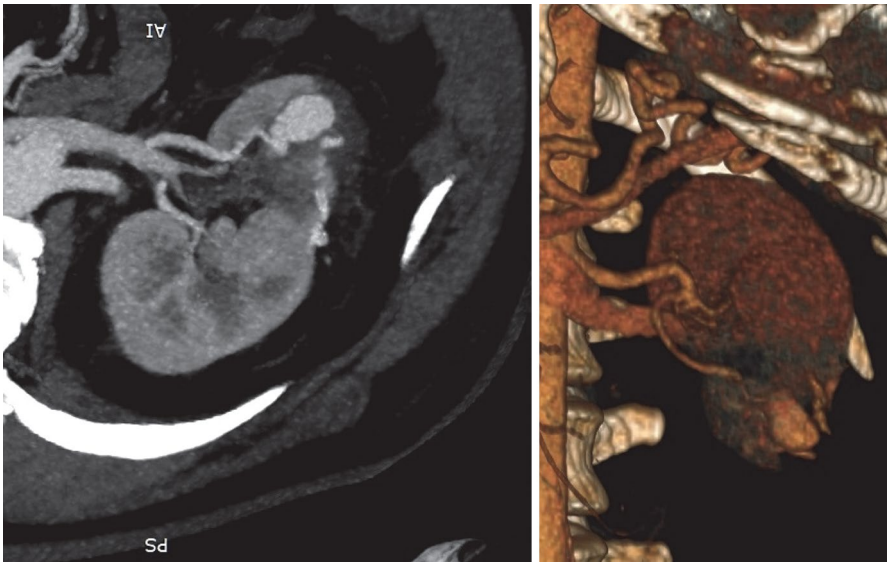

Fig. 2 CT angiography and 3D reconstruction of arteriovenous fistula in a tumor-infiltrated left kidney, courtesy of Prof. dr. Cumpănaş Alin Adrian—Timişoara County Emergency Hospital Romania

contribute to a comprehensive understanding of the arteriovenous fistula and guide appropriate therapeutic interventions.

Classification

From an ethiopathogenic point of view, there are the following types:

- Acquired (70%)—secondary to biopsies, nephrostomy, or surgical interventions on the kidney. Other causes are renal trauma, tumors, fibrodysplasia, arterial dissections, and inflammatory processes. The incriminated mechanism is presumed to be erosion of the venous wall by an arterial aneurysm;
- Congenital (25%)—usually presented as multiple varicose vessels;
- Idiopathic (3–5%)—present with hematuria and a single dilated afferent vessel.

Treatment

The primary goal of any intervention for renal arteriovenous fistulas is to achieve complete and permanent closure of the afferent artery while preserving renal function. Traditionally, surgery was the first option for treatment, but increasingly, endovascular management is preferred. Interventional treatment offers advantages such as a high success rate, fewer complications, shorter hospitalization time, and reduced costs. Moreover, the preservation of renal function tends to be better with selective occlusion of the specific arterial branch involved in the fistula, a task that can be more challenging with surgical approaches. Reported success rates for interventions in patient series are close to 100%.

The techniques involved in endovascular treatment include obtaining vascular access through brachial or femoral arterial approaches, followed by cannulation of the renal artery using various types of catheters. In cases of embolization, superselective cannulation of a distal arterial branch is achieved using microcatheters. In selected cases, a retrograde venous approach may also be utilized.

When the risk of incomplete occlusion or embolization of materials is deemed very high, surgery may be preferred over endovascular treatment. Surgical options include suturing the shunt, performing partial nephrectomy, or, in extreme cases, total nephrectomy, especially when dealing with multiple shunts. In cases of uncomplicated fistulas, watchful-waiting for spontaneous resolution can be considered. A stepwise or hybrid approach involves placing a balloon in the responsible renal artery, inflating it to temporarily stop blood flow, stabilizing the patient until a curative intervention, whether endovascular or surgical, is performed. This approach ensures a comprehensive and tailored strategy based on the specific characteristics of each case.

Interventional options for renal arteriovenous fistulas are tailored based on the angioarchitecture of the fistula and may include:

- *Embolization using coils or gels*. Some coils have "whiskers" made of synthetic fibers that promote local thrombosis. To counteract the problem of material migration due to increased flow, various solutions have been proposed:
  - coils larger than the embolized vessel,
  - detachable balloons,
  - Swan-Ganz catheter placed distally to slow down the blood flow (with the risk of not being able to remove it in case of using gels that act as glue),
  - Fogarty catheter placed proximally, with advancement through its lumen of a microcatheter through which the coils are placed distally,
  - "fixing" stent (Wallstent™).
- *Covered stents* exclude the fistula from circulation, but require favorable anatomy, with proximal and distal landing zone.
- *The Amplatzer™ devices* are a series of medical devices initially designed for structural cardiac procedures and subsequently adapted for peripheral applications. There are currently four models (I-IV), each with specific indications depending on the characteristics of the target vessel. The common feature among these devices is a self-expanding nitinol plug integrated into a delivery system. These devices serve dual purposes: they can be utilized to prevent the embolization of closure materials during various vascular interventions, and can also be used as a permanent closure solution, involving the placement of a plug in the arterial and/or venous branch of a fistula, with or without additional coils.
- *other vascular closure devices and vascular plugs*.

Results and Follow-Up

The success rate of interventions is reported to be 100% technically (with rare instances requiring reintervention) and over 96% clinically, indicating an improvement in symptoms. Post-procedurally, the puncture site is monitored, and the occlusion of the fistula is verified using ultrasound, CT, or MR angiography. Early recurrence within the first few days and late recurrence can occur due to the migration of embolized materials, prompting ultrasound screening before discharge and at 3, 6, and 12 months.

Renal function and cardiovascular parameters are crucial for short and long-term follow-up, aiming to preserve renal function while improving symptoms of heart failure, which may be noticeable as early as days after the procedure. A CT angiography at 6 months can be valuable to confirm the position of the device and assess renal architecture. Some authors recommend a double antiplatelet regimen during the first 3 months after the implantation of an Amplatzer device.

Complications

Coils, adhesive gels, and other vascular closure devices have the potential to migrate due to the high blood flow, increasing the risk of embolization into the renal venous or pulmonary circulation. Thrombosis of distal renal veins may occur if these materials partially obstruct the vessels. Improper placement of an Amplatzer device can lead to acute renal ischemia by obstructing arterial flow to the renal parenchyma, resulting in renal infarct or ischemia. When the affected branches are small, the functional impact is typically minimal. Additionally, local ischemic complications may arise from the closure of secondary branches during the placement of a covered stent over them.

Postembolization syndrome, characterized by fever, leukocytosis, and abdominal symptoms, occurs relatively frequently but is self-limiting. Although the recurrence of the fistula is rare, it can manifest days, months, or, exceptionally, years later. Other complications are akin to those encountered in renal aneurysm closure procedures.

Bibliography

1. Ye P, Wu H, Chen Y, Li Y, Cai C, Lv P. Endovascular therapy for distal hilar renal artery aneurysm: a case report and literature review. J Int Med Res. 2022;50(1) https://doi.org/10.1177/03000605211069282.
2. Ghosh S, Dutta SK. Endovascular interventions in management of renal artery aneurysm. Br J Radiol. 2021;94(1124):20201151. https://doi.org/10.1259/bjr.20201151.
3. Chui JN, Wang K, Puttaswamy V. Ex vivo repair and autotransplantation for a complex renal artery aneurysm. J Surg Case Rep. 2023;2023(7):rjad425. https://doi.org/10.1093/jscr/rjad425.
4. Buck DB, Curran T, McCallum JC, Darling J, Mamtani R, van Herwaarden JA, Moll FL, Schermerhorn ML. Management and outcomes of isolated renal artery aneurysms in the endovascular era. J Vasc Surg. 2016;63(1):77–81. https://doi.org/10.1016/j.jvs.2015.07.094. Epub 2015 Sep 18. PMID: 26386509; PMCID: PMC4698072.
5. Choksi H, Singla A, Yoon P, Pang T, Vicaretti M, Yao J, Lee T, Yuen L, Laurence J, Lau H, Pleass H. Outcomes of endovascular, open surgical and autotransplantation techniques for renal artery aneurysm repair: a systematic review and meta-analysis. ANZ J Surg. 2023;93(10):2303–13. https://doi.org/10.1111/ans.18628. Epub 2023 Jul 31. PMID: 37522385.
6. Dezfouli SA, Ramouz A, Demirel S, Chang DH, Mehrabi A, Böckler D. Multimodal repair of renal artery aneurysm—10-year single center experience. Ann Vasc Surg. 2022;82:303–13. https://doi.org/10.1016/j.avsg.2021.10.049. Epub 2021 Nov 14. PMID: 34785341.
7. AlSheikh S. Renal artery aneurysm induced by neurofibromatosis type 1: a case report and review of the endovascular interventions for this rare vasculopathy. Medicine (Baltimore). 2023;102(27):e34216. https://doi.org/10.1097/MD.0000000000034216. PMID: 37417633; PMCID: PMC10328702.
8. Li S, Li F, Liu Z, Zeng R, Ye W, Shao J, Zheng Y. Blood pressure and renal outcomes after renal artery aneurysm intervention: single-center experience and review of literature. Front Cardiovasc Med. 2023;10:1127154. https://doi.org/10.3389/fcvm.2023.1127154. PMID: 37153466; PMCID: PMC10160466.
9. Laurin T, Borghese O, Branchereau J, Karam G, Brisard L, Corvec TL, Chaillou P, Desal H, Bourcier R, Maurel B. Single centre experience in open and endovascular treatment of renal

artery aneurysms. Ann Vasc Surg. 2022;79:17–24. https://doi.org/10.1016/j.avsg.2021.07.024. Epub 2021 Oct 10. PMID: 34644627.
10. Grandhomme J, Lejay A, Gogeneata I, Steinmetz L, Georg Y, Chakfé N, Thaveau F. Robotic surgery for in situ renal artery aneurysm repair: technical note and literature review about a mini- invasive alternative. Ann Vasc Surg. 2021;74:526.e7–526.e12. https://doi.org/10.1016/j.avsg.2021.03.014. Epub 2021 Apr 6. PMID: 33836224.
11. Steuer J, Bergqvist D, Björck M. Surgical renovascular reconstruction for renal artery stenosis and aneurysm: long-term durability and survival. Eur J Vasc Endovasc Surg. 2019;57(4):562–8. https://doi.org/10.1016/j.ejvs.2018.09.014. Epub 2018 Oct 18. PMID: 30343992.
12. Kawase T, Inoue Y, Matsuo J, Omura A, Seike Y, Uehara K, Sasaki H, Matsuda H. Results of surgical repair of hilar renal artery aneurysm to preserve renal blood flow. Ann Vasc Dis. 2020;13(3):281–5. https://doi.org/10.3400/avd.oa.20-00020. PMID: 33384731; PMCID: PMC7751073.
13. Reis PEO, Abrão GP, Roever L. Endovascular treatment of wide-neck saccular renal artery aneurysm with waffle-cone technique. J Vasc Bras. 2021;20:e20200116. https://doi.org/10.1590/1677-5449.200116. PMID: 34093681; PMCID: PMC8147879.
14. Castellano D, Boghi A, Comelli C, Di Maggio L, Savio D. Use of a 4 mm Amplatzer Vascular Plug II in the treatment of a renal arteriovenous fistula: a case report. CVIR Endovasc. 2021;4(1):40. https://doi.org/10.1186/s42155-021-00229-3. PMID: 33988781; PMCID: PMC8121712.
15. Nagpal P, Bathla G, Saboo SS, Khandelwal A, Goyal A, Rybicki FJ, Steigner ML. Giant idiopathic renal arteriovenous fistula managed by coils and amplatzer device: case report and literature review. World J Clin Cases. 2016;4(11):364–8. https://doi.org/10.12998/wjcc.v4.i11.364. PMID: 27900325; PMCID: PMC5112356.
16. Catelli A, Loiudice G, Corvino A, Castaldo A, Bracale UM, Quarantelli M, Venetucci P. Amplatzer vascular plug IV in the treatment of high flow renal arteriovenous fistula: case considerations. Radiol Case Rep. 2020;15(9):1442–5. https://doi.org/10.1016/j.radcr.2020.05.060. PMID: 32642014; PMCID: PMC7334554.
17. Perkov D, Novačić K, Novosel L, Knežević N. Percutaneous embolization of idiopathic renal arteriovenous fistula using Amplatzer vascular plug II. Int Urol Nephrol. 2013;45(1):61–8. https://doi.org/10.1007/s11255-012-0358-y. Epub 2012 Dec 25. PMID: 23266863.
18. Jiang Q, Wu J, Zou S, Jin J, Ji X, Qu L. Endovascular therapy of a giant renal artery aneurysm combined with high-flow renal arteriovenous fistula using a patent ductus arteriosus occluder. Ann Vasc Surg. 2019; https://doi.org/10.1016/j.avsg.2018.12.075.
19. Balasubramanian K, Keshava SN, Lenin A, Mukha R. Endovascular management of a patient with massive renal arteriovenous fistula: challenges and tricks. BMJ Case Rep. 2021;14(2):e236358. https://doi.org/10.1136/bcr-2020-236358. PMID: 33526517; PMCID: PMC7853036.
20. Cho SK, Do YS, Shin SW, Kim DI, Kim YW, Park KB, Kim EJ, Ahn HJ, Choo SW, Choo IW. Arteriovenous malformations of the body and extremities: analysis of therapeutic outcomes and approaches according to a modified angiographic classification. J Endovasc Ther. 2006;13(4):527–38. https://doi.org/10.1583/05-1769.1. PMID: 16928170.
21. Burch B, Tucker S. Successful embolization of a renal arteriovenous fistula; a feared kidney biopsy complication. Radiol Case Rep. 2021;16(11):3182–5. https://doi.org/10.1016/j.radcr.2021.07.085. PMID: 34484515; PMCID: PMC8403705.
22. Rhee YH, Busch L, Sansone R, Ertas N, Floros N, Schelzig H, Mulorz J, Wagenhäuser MU. Endovascular occlusion of a renal arteriovenous fistula with renal vein aneurysm formation for rupture prevention. Case Rep Vasc Med. 2019;2019:8530641. https://doi.org/10.1155/2019/8530641. PMID: 31915564; PMCID: PMC6930724.
23. Guo H, Wang C, Yang M, Tong X, Wang J, Guan H, Song L, Zou Y. Management of iatrogenic renal arteriovenous fistula and renal arterial pseudoaneurysm by transarterial embolization: a single center analysis and outcomes. Medicine (Baltimore). 2017;96(40):e8187. https://doi.org/10.1097/MD.0000000000008187. PMID: 28984770; PMCID: PMC5738006.

24. Schwing J, Piveteau A, Ernandez T, Hansen-Pham C, Toso C, Hadaya K. Renal arteriovenous fistula in a renal transplant recipient: a case report and literature review. Transplant Direct. 2019;6(1):e513. https://doi.org/10.1097/TXD.0000000000000958. PMID: 32047841; PMCID: PMC6964933.
25. Becker LS, Hinrichs JB. Fogarty-assisted transcatheter embolization of a large renal high-flow arteriovenous fistula. CVIR Endovasc. 2022;5(1):19. https://doi.org/10.1186/s42155-022-00295-1. PMID: 35389109; PMCID: PMC8991269.
26. Huy NT, Nguyen PT, Tran NT, Hoa T, Duc NM. Percutaneous intervention for giant renal extrarenal aneurysm and arteriovenous fistula. Radiol Case Rep. 2022;17(12):4526–31. https://doi.org/10.1016/j.radcr.2022.09.019. PMID: 36193275; PMCID: PMC9526015.
27. Osawa T, Watarai Y, Morita K, Kakizaki H, Nonomura K. Surgery for giant high-flow renal arteriovenous fistula: experience in one institution. BJU Int. 2006;97(4):794–8. https://doi.org/10.1111/j.1464-410X.2006.06108.x. PMID: 16536776.

Contrast Induced Acute Kidney Injury

Simona Mihaela Hogas and Adrian Covic

Abstract Contrast-induced acute kidney injury (CI-AKI) is a significant concern in patients undergoing interventional cardiac procedures involving the use of contrast media. While the risk of CI-AKI remains a topic of debate, studies have shown conflicting results regarding the nephrotoxic effects of contrast-enhanced scans compared to unenhanced scans. The physico-chemical characteristics of contrast media play a crucial role in its nephrotoxicity, with tubular epithelial cells being particularly vulnerable to damage. Diagnostic strategies for CI-AKI involve monitoring serum creatinine levels post-contrast administration, although discrepancies in clinical definitions and management approaches exist. Recommendations emphasize the importance of optimizing contrast doses for imaging quality while considering individual patient factors to minimize the risk of kidney injury. Further research is needed to clarify the mechanisms underlying CI-AKI and develop effective prevention strategies in high-risk patient populations undergoing vascular imaging procedures.

Keywords Kidney injury · Contrast-induced acute kidney injury · Interventional cardiac procedures · Contrast-associated kidney injury · Contrast medium

Introduction

Vascular imaging reclaimed an essential place in diagnostic strategies nowadays. Ultrasound, computed tomography (CT) angiography, magnetic resonance angiography (MRA), and traditional angiography are the most common techniques required for a certain diagnostic.

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Iodine contrast is mandatory in angiographic imaging and interventional cardiac procedures. Because of an increasing number of coronary angiography and coronary interventional procedures, the increasing use of contrast media, and the increasing number of invasive cardiac procedures being performed in high-risk patients with chronic kidney disease, and kidney failure due to contrast-induced nephropathy remains a rising pathology. A sudden change in kidney function is a common complication of coronary angiography, and percutaneous coronary intervention, primarily because of contrast-induced acute kidney injury.

Definition

The terminology describing kidney injury following exposure to contrast medium (CM) has undergone important changes. The current American College of Radiology (ACR) Committee on Drugs and Contrast Media guidelines, propose the term contrast-associated acute kidney injury (CA-AKI), previously referred to as post-contrast acute kidney injury (PC-AKI), as a broad descriptor for a decline in kidney function occurring within 48 h after the intravascular administration of iodinated contrast medium. CA-AKI is a descriptive diagnosis, regarding the specific cause of acute kidney injury (AKI). Conversely, the term contrast-induced acute kidney injury (CI-AKI), formerly known as contrast-induced nephropathy (CIN), is suggested as a causal diagnosis specifically attributing AKI to CM [1] (Table 1).

Table 1 A concise overview of the guidelines terminology.

However, pinpointing the cause of CA-AKI is challenging due to various patient and procedure-related factors influencing kidney function, such as hemodynamic instability resulting from catheter manipulation. The terminology previously used in clinical studies has been inconsistent, making it challenging to distinguish CI-AKI from CA-AKI in most studies, primarily due to the absence of a suitable control group. The incidence of CI-AKI might have encompassed cases of CA-AKI, although CI-AKI is considered a subgroup of CA-AKI.

Table 1 Definitions/terminology [1]

Term	Definition
Acute kidney injury (AKI)	Increase in creatinine >26 μmol/L in 48 h, OR increase by >50%, in 7 prior days OR urine output <.5 mL/kg/h for 6–12 h
Chronic kidney disease (CKD)	Abnormalities of kidney structure or function, present for >3 months
Contrast associated acute kidney injury (CA-AKI)	AKI after a contrast procedure, includes CI-AKI and other causes of AKI: acute tubular necrosis or acute interstitial nephritis
Post contrast acute kidney injury (PC-AKI)	AKI following a contrast procedure same as CA-AKI in definition
Contrast induced nephropathy (CIN)	Increase in creatinine of 44 μmol/L or 25% from baseline after contrast
Contrast induced acute kidney injury (CI-AKI)	AKI after a contrast procedure, which can be attributed to contrast-induced kidney damage

Kidney dysfunction in contrast induced nephropathy (CIN) is typically reversible, with the decline in kidney function occurring 2–3 days after contrast exposure and returning to baseline levels within 1–2 weeks. Diagnostic criteria for CIN have evolved similarly to those for AKI, independent of etiology.

For an extended period, the universally accepted definition of CI-AKI was a rise in creatinine level of ≥0.5 mg/dl (44 μmol/l) or ≥25% from baseline within 2–5 days after exposure to contrast. However, the Kidney Disease Improving Global Outcomes (KDIGO) has introduced an updated definition, now widely adopted. According to KDIGO, CI-AKI was characterized by a creatinine level with 0.3 mg/dl (26.5 μmol/l) higher after 48 h of contrast media exposure or an increase of at least 1.5 times the baseline value within 7 days [2, 3].

The European Renal Best Practice working group, the Contrast Media Safety Committee (CMSC) of the European Society of Urogenital Radiology (ESUR), and the ACR Committee on Drugs and Contrast Media all advocate for the use of the KDIGO definition for CIN. The CMSC proposed events within 48–72 h after contrast exposure as a practical definition [4].

Pathophysiology

Contrast-induced nephropathy is the third leading cause of iatrogenic acute kidney injury, the incidence ranges from 3.3% to 14.5%. The commonest cause is hypoperfusion of the kidneys causing either prerenal injury or acute tubular necrosis. Moreover, the number and the type of risk factors directly affect the incidence of renal impairment [5].

The pathophysiology of CIN remains poorly defined and poorly understood. Related mechanisms include changes in renal blood flow leading to ischemic and hypoxic damage to the renal medulla, and the production of oxygen free radicals that damage the tubular epithelium. Furthermore, contrast agents exert direct nephrotoxic effects on tubular epithelial cells, leading to osmotic nephrosis and reduced oxygen output.

Contrast-associated acute kidney injury (CA-AKI), also recognized as post-contrast acute kidney injury (PC-AKI), is a broad term denoting a sudden decline in renal function occurring within 48 h following the intravascular administration of iodinated contrast medium. The occurrence of CA-AKI may not necessarily be linked to the contrast medium as the cause of the deterioration. Contrast-induced acute kidney injury (CI-AKI), previously known as contrast-induced nephropathy (CIN), specifically refers to AKI resulting from the administration of iodinated contrast medium; hence, CI-AKI is a subset of CA-AKI [1].

The underlying causes of CI-AKI are not fully comprehended. Nonetheless, several potential mechanisms have been suggested, including: (1) alterations in kidney hemodynamics leading to reduced renal blood flow (RBF); (2) direct injury to tubular cells caused by iodine; (3) medullary hypoxia accompanied by impaired

microcirculation; (4) involvement of intracellular signaling pathways leading to cell death; and (5) inflammation [6] (Fig. 1).

Intravenous iodinated contrast agents have been demonstrated to induce renal hemodynamic changes with a biphasic effect on renal blood flow (RBF). Initially, there is vasodilation of afferent arterioles, leading to a transient increase in RBF. Subsequently, prolonged vasoconstriction occurs, causing a decrease in RBF. Vasoconstriction is attributed to the action of various vasoactive substances such as angiotensin II, endothelin, adenosine, and an increase in intracellular [Ca^{2+}] in vascular smooth muscle cells. Simultaneously, there is a decrease in nitric oxide, prostaglandin PGE1, and PGE2 production. For instance, adenosine induces afferent arteriolar vasoconstriction and efferent arteriolar vasodilation, compromising glomerular filtration rate (GFR) and leading to AKI. This forms the rationale for using theophylline, which antagonizes the effects of adenosine [6].

Iodine induces direct harm to membrane proteins, resulting in the compromise of cell membrane integrity. This suggests a potential direct injury to kidney tubules which generate reactive oxygen species (ROS). Kidney tubular epithelial cells exhibit apoptosis with the loss of cellular membrane proteins, cytochrome C release from mitochondria, and pathological vacuolization in proximal tubular cells. Antioxidants in animal studies have shown preventive effects against nephrotoxicity induced by contrast media, forming the basis for using antioxidants like N-acetylcysteine and ascorbic acid in humans to prevent CI-AKI. Additionally, $NaHCO_3$ has been demonstrated to act as an antioxidant and prevent nephrotoxicity [6, 8].

Renal medullary hypoxia stands out as a crucial mechanism for CI-AKI. Normally, the renal medulla functions under low O_2 tension (30 mmHg), in contrast to the cortex where O_2 tension is high. Contrast media significantly reduce outer

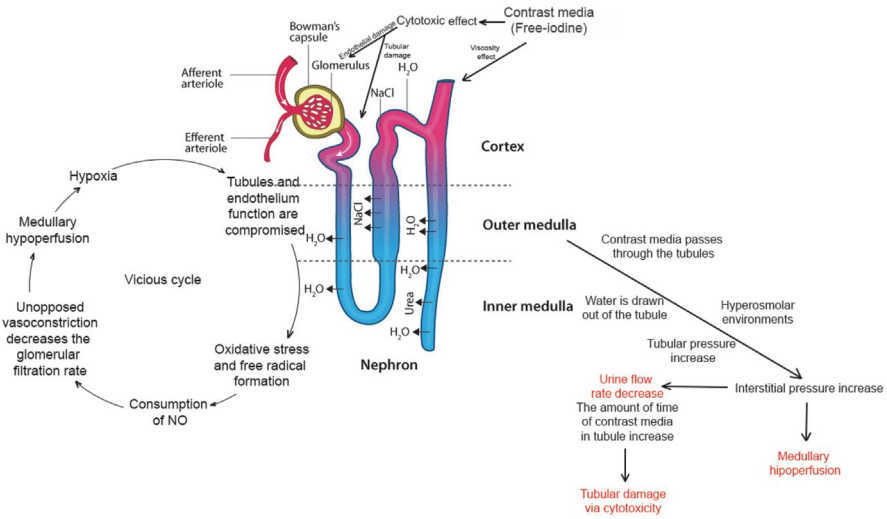

Fig. 1 The pathophysiology of contrast-induced acute kidney injury [7]

medullary O_2 tension to as low as 10 mmHg. The medullary portion (thick ascending limb of Henle's loop) of the nephron segment demands high O_2 tension due to active transport mechanisms. Furthermore, contrast media increase viscosity in both tubular fluid and vasa recta, leading to red blood cell aggregation. These changes result in reduced blood supply and O_2 to the medulla, causing medullary hypoxia. Stimulated ROS generation leads to membrane injury and DNA damage. Impaired mitochondrial enzyme activity contributes to intracellular energy depletion, cell necrosis and apoptosis [6].

All iodinated contrast media, regardless of osmolality, elevate intraluminal pressure through water reabsorption into the kidney tubular lumen, increasing hydrostatic pressure. This elevated pressure induces vasa recta constriction, ultimately resulting in medullary hypoxia and CI-AKI.

High-osmolality contrast media induce osmotic diuresis by triggering the release of atrial natriuretic peptide. The excessive delivery of NaCl to the macula densa activates the tubule-glomerular feedback mechanism through adenosine, leading to constriction of the afferent arteriole and a subsequent decrease GFR.

Histopathological alterations in the tubular epithelium occur in both experimental animals and human subjects when exposed to contrast media. Following injection, iodinated contrast medium stays within the intravascular compartment, unbound to albumin, enabling it to undergo free filtration at the glomerulus. After filtration, the contrast medium is not reabsorbed by the tubules and instead accumulates during the reabsorption of water and solutes. This concentrated medium exposes tubular epithelial cells to potential damage. The characteristic feature of contrast media is the vacuolization of proximal tubular epithelial cells [9].

Diagnostic

Diagnosing contrast-associated acute kidney injury (CA-AKI) involves evaluating serum creatinine levels after the administration of iodinated contrast media (ICM). Nevertheless, it's crucial to highlight that the definitions employed in clinical research may not necessarily align with specific symptom thresholds or necessitate alterations in management.

Conducting routine creatinine measurements in this context presents logistical challenges, potentially causing unnecessary anxiety for patients and leading to additional healthcare resource utilization without clear benefits. Therefore, regular creatinine testing should be reserved for individuals with an extremely high risk of CA-AKI. For patients who have undergone intra-arterial ICM administration and have an estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m^2, a follow-up serum creatinine measurement is recommended within 48–72 h. Routine testing for AKI is generally deemed unnecessary for the majority of patients due to the perceived low risk. Nonetheless, individuals identified as at-risk should be counseled to seek medical attention if they encounter heightened shortness of breath,

peripheral edema, or a significant reduction in urine output in the days following the procedure. Such symptoms may prompt additional kidney function testing [1].

Several factors related to the patient and the procedure contribute to the development of CI-AKI. These factors encompass baseline kidney disease, advanced age, diabetes mellitus, anemia, and the patient's status on presentation (cardiogenic shock, congestive heart failure, acute coronary syndrome etc.). Advanced chronic kidney disease (CKD), characterized by an estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73 m^2, stands out as the most potent patient-related risk factor, leading to a potential threefold increase in the risk of CI-AKI. Indeed, there is a proportional relationship between lower renal function and a higher risk of kidney injury [10]. While diabetes mellitus has long been considered an important predictor of CI-AKI due to the prevalent occurrence of kidney disease among diabetic patients, the Iohexol Cooperative Study (1995), a randomized trial involving 1196 patients, revealed that diabetes was not independently associated with CI-AKI risk [11, 12].

The perception of contrast-induced acute kidney injury (CI-AKI) has shifted, over de past four decades, from being widely acknowledged as a common complication to being scrutinized as a potential medical 'myth.'

In a significant study dating back to 1983, contrast media was identified as the third most frequent cause of AKI in hospital settings, following hypovolemia and major surgery [13]. Unfortunately, this study, characterized as a small case series, exclusively involved admitted inpatients, lacked a control group of patients not exposed to contrast, and focused on high-osmolar contrast media, which is no longer in use. In a 2006 study analyzing 3081 articles published between 1996 and 2004 with keywords like "contrast" and "kidney failure," only 40 (1.3%) investigated patients receiving intravenous contrast, and merely two included control groups of patients not exposed to contrast media [14]. Another study involving over 32,000 hospitalized patients demonstrated that fluctuations in creatinine levels are relatively common, with around 27% of inpatients experiencing a 25% or greater rise in creatinine even in the absence of intravenous contrast administration [15].

In such studies, a control group is vital for assessing the baseline incidence of AKI, which is expected in unwell patients undergoing computed tomography (CT) examinations for various indications, such as sepsis or hypoperfusion. Some patients may develop AKI due to their underlying diseases or other concurrent causes, including ischemic acute tubular necrosis resulting from renal hypoperfusion, drug-induced acute interstitial nephritis, and atheroembolic renal disease [16].

Subsequent studies utilizing advanced statistical methods to control for confounding variables, such as propensity score-matched analyses, have not yielded evidence supporting genuine Contrast-Induced Acute Kidney Injury (CI-AKI), as described below.

These investigations reveal that the incidence of AKI associated with contrast-enhanced CT scans is no higher than that observed with unenhanced CT scans [17–19]. It's crucial to emphasize that negative findings in propensity score studies should not be construed as conclusive proof that 'CI-AKI is a myth.' However, these results do suggest that the true incidence of CI-AKI is considerably lower than

previously believed. It's important to acknowledge that propensity scoring addresses known biases and covariates within an administrative database, leaving unknown biases and confounders unaccounted for, as would be addressed in a randomized clinical trial (RCT). Despite the substantial sample sizes in these studies (n > 10k), the count of patients with significantly impaired kidney function (e.g., estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m^2), those facing the greatest risk of CI-AKI, remained limited, and uncertainty continues within this population. Contradictorily, certain studies have indicated a reduced risk of acute kidney injury (AKI) in contrast-enhanced scans compared to unenhanced scans. This phenomenon is attributed to selection bias rather than any nephroprotective effect of the contrast [17, 18]. In Davenport et al.'s study, a slightly elevated risk of AKI was noted particularly in the subgroup with eGFR ≤ 30 mL/min/1.73 m^2; however, this observation has not been consistently duplicated in subsequent studies [19].

To sum up, the claim that contrast is the definitive cause of AKI lacks conclusive evidence, and the likelihood of contrast-induced AKI is probably minimal. Nevertheless, existing evidence does not endorse the notion of complete absence of risk. The potential risk becomes notably pertinent in individuals with profound underlying chronic kidney disease (CKD) having an eGFR ≤ 30 mL/min/1.73 m^2, those experiencing AKI, and/or those exposed to a substantial volume of contrast, particularly via the arterial route. Furthermore, the discourse on AKI following contrast predominantly concerns the manifestation of AKI defined by a modest increase in creatinine, and the risk of severe AKI necessitating renal replacement therapy (RRT) is notably diminished [1].

Prevention and Treatment

The KDIGO Clinical Practice Guideline for Acute Kidney Injury provides several key recommendations for preventing contrast-associated acute kidney injury (CI-AKI) [2]. Here are some of the recommendations outlined in the guideline:

1. Assessment of the population at risk for CI-AKI: It is crucial to identify individuals who are at a higher risk of developing CI-AKI, particularly those with pre-existing conditions such as chronic kidney disease (CKD) and diabetes, as they are more vulnerable to kidney injury following contrast media exposure.
2. Nonpharmacological prevention strategies for CI-AKI: These strategies may include measures such as adequate hydration before and after contrast administration, as well as the use of iso-osmolar or low-osmolar contrast agents to reduce the risk of kidney injury.
3. Pharmacological prevention strategies for CI-AKI: Pharmacological interventions like the administration of agents such as N-acetylcysteine or sodium bicarbonate may be considered in certain high-risk patients to prevent CI-AKI.
4. Effects of hemodialysis or hemofiltration in CI-AKI: In cases where CI-AKI has already occurred and renal function needs to be supported, the guidelines discuss

the potential role of hemodialysis or hemofiltration as treatment options for managing CI-AKI.

The objectives of screening are to identify individuals prone to avoidable decline in kidney function associated with the use of ICM. Since the release of the 2012 guidelines from the Canadian Association of Radiologists, recent research has significantly revised our assessments of the risks linked to ICM usage. Key predictors of CA-AKI include the presence of CKD and AKI from other origins. Risk stratification aligns with the Kidney Disease Improving Global Outcomes (KDIGO) staging. Comorbidities like diabetes, exposure to nephrotoxic substances, hypovolemia, and congestive heart failure (CHF) are correlated with CA-AKI. Also, having a solitary kidney, including a transplant kidney, aids in identifying patients more prone to CKD, but none of these factors have demonstrated independence from eGFR. Patients with normal kidney function or stable mild to moderate CKD are deemed to have negligible risk, irrespective of other considerations. Only those with severe CKD (eGFR $\leq$ 30 mL/min/1.73 m^2) and individuals with pre-existing AKI are susceptible to CA-AKI. The screening process should efficiently direct most low-risk patients to undergo a medically necessary contrast-enhanced CT scan without unnecessary expense or delay. Additionally, screening should identify those at elevated risk for a more thorough screening and prevention regimen involving three targeted interventions: (1) assessing kidney function using eGFR, (2) determining whether ICM or an alternative imaging approach is optimal for addressing the clinical question, and (3) considering prophylactic strategies for at-risk patients requiring ICM [1].

Higher doses and repeated administration of contrast have been linked to an increased risk of Contrast-Associated Acute Kidney Injury (CA-AKI). However, the observed incidence might be influenced by confounding factors, such as indication bias. Complex procedures in high-risk patients may necessitate higher contrast doses, especially in certain cardiac interventions. Extrapolating this to routine clinical doses in lower-risk scenarios could lead to suboptimal scans without significant safety benefits. The reduction of intravenous (IV) contrast doses for CT examinations is not recommended, as it may compromise parenchymal enhancement and deviate from established high-quality protocols. The working group recommends administering the suitable intravenous (IV) dose for optimal CT imaging in all patients. Regarding intra-arterial (IA) interventions, a practical approach is proposed, utilizing the required dose to attain diagnostic and therapeutic objectives. However, it is advisable to cautiously decrease the dose in situations where adjunctive imaging and lower doses offer minimal benefit or can be postponed, such as ventriculography following cardiac catheterization [1].

The physico-chemical characteristics of contrast media also contribute to its nephrotoxicity. In the past, ionic and high-osmolar contrast media with osmolality exceeding 1200 mOsm/L were utilized. The development of safer contrast agents has contributed to reducing the risk of contrast-associated AKI. Newer agents have lower nephrotoxicity profiles, leading to a decreased incidence of AKI. However, modern non-ionic, low-osmolar (typically ~600 mOsm/L), and iso-osmolar contrast media have replaced them globally. A meta-analysis of data from 31

randomized controlled trials (RCTs) provides convincing evidence that low-osmolar contrast media have a lower risk of CA-AKI compared to high-osmolar contrast media [20].

Regarding low vs. iso-osmolar contrast media, the literature presents mixed findings. Initial RCTs favored iso-osmolar contrast, but subsequent RCTs and meta-analyses yielded conflicting and heterogeneous results. A 2017 systematic review with 10 RCTs found no added benefit with iso-osmolar contrast media compared to low-osmolar (RR.72, 95% CI 0.50–1.04) [21]. In summary, there is little difference in AKI events between iso-osmolar and low-osmolar contrast in high-risk settings, resulting in a negligible difference in low-risk settings (venous contrast) for clinically meaningful outcomes. Therefore, the choice between low- and iso-osmolar contrast media should be based on other considerations, such as cost and availability.

Adequate hydration before and after contrast medium administration is crucial in preventing CA-AKI [1] (Table 2). Intravenous isotonic saline is commonly used to maintain renal perfusion and promote contrast medium excretion, reducing the risk of kidney injury. In the realm of both nonpharmacological and pharmacological approaches to prevent contrast-associated acute kidney injury (CI-AKI), fluid administration emerges as a pivotal component. Highlighting insights from the KDIGO Clinical Practice Guideline for Acute Kidney Injury, here are key considerations surrounding fluid administration in the prevention of CI-AKI [2]:

1. Enabling extracellular volume expansion during radiocontrast media administration serves as a potential countermeasure against intrarenal hemodynamic shifts and the direct tubulotoxic effects implicated in CI-AKI.
2. The neurohumoral effects of volume expansion can play a role in mitigating radiocontrast-induced medullary hypoxia. This is achieved by suppressing vaso-

Table 2 Summary of the literature with volume expansion and hydration [1]

Trial	Study Details	Main Findings
Mueller et al. [22]	N = 1620, undergoing coronary angioplasty compared *.9% saline vs .45% saline + 5% glucose*	.9% saline superior to .45% saline +5% glucose (events 5/685 vs 14/698)
Merten et al. [23]	N = 119, undergoing any contrast procedure (venous or arterial) compared *sodium bicarbonate (mixed in 5% dextrose) vs .9% saline*	Bicarb superior to saline (events 1/60 vs 8/59)
Nijssen et al. [24]	N = 660, receiving contrast (arterial or venous) compared *.9% saline vs no prophylaxis*	No difference (events 8/296 in hydrations vs 8/307 in control
Weisbord et al. [25]	N = 4993, receiving arterial contrast compared *.9% saline versus 1.26% sodium bicarbonate*	No difference (events 110/2511 in bicarb vs 116/2482 in saline)
Timal et al. [26]	N = 523, receiving venous contrast compared *1.26% sodium bicarbonate vs no prophylaxis*	No difference (7/262 in no prophylaxis vs 4/261 in bicarbonate)

pressin, inhibiting the renin-angiotensin axis, and enhancing the synthesis of vasodilatory renal prostaglandins.

3. Volume expansion contributes to the direct reduction of cellular damage by diluting the contrast medium, particularly within the medullary tubular segments. Additionally, it has the potential to diminish the impact of contrast media on increasing tubular fluid viscosity. Studies have linked intravascular volume expansion through fluid administration with a reduced incidence of CI-AKI, underscoring the critical role of adequate hydration in high-risk patient populations.
4. For CI-AKI prevention, diverse fluids have been evaluated, encompassing hypotonic saline (0.45%), isotonic saline (0.9%), and isotonic sodium bicarbonate. The selection of fluid should be guided by individual patient factors and considerations of risk. Optimizing prevention strategies for CI-AKI involves monitoring fluid balance and tailoring fluid administration based on individual patient characteristics and the procedural context. This adaptive approach ensures a more effective and personalized preventive strategy.

In essence, robust evidence indicates that, for individuals with eGFR >30 mL/min/1.73 m^2 undergoing elective intravascular contrast media (ICM) administration, there is minimal benefit from intravenous (IV) hydration compared to no hydration. There is inadequate evidence to either substantiate or challenge the current routine of administering hydration (intravenous or oral) at or below an eGFR of 30 mL/min/1.73 m^2 in contrast to withholding hydration. Furthermore, there is evidence of limited quality indicating that oral hydration might be as efficacious as intravenous (IV) hydration. The application of hydration for preventing contrast-associated acute kidney injury (CA-AKI) in high-risk patients (those with severe chronic kidney disease and an eGFR $\leq$ 30 mL/min/1.73 m^2) lacks enough evidence to warrant a decisive recommendation. As a result, the working group opts not to provide a specific recommendation, enabling institutions to choose practices aligning with their local contexts [1].

Recognizing the logistical challenges associated with organizing IV hydration in certain patients, the working group acknowledges that, if volume expansion is being considered, both oral and IV hydration may be employed for CA-AKI prophylaxis in these patients, acknowledging the low certainty regarding the benefit of this approach. Concerning the choice of IV hydration, bicarbonate-based fluid does not offer any additional advantages over the use of normal saline for volume repletion around contrast administration. Given that 0.9% saline is more accessible and easier to administer, it is the preferred option, although bicarbonate-based fluids may be considered equivalent if local factors, protocols, or convenience support this choice [1].

N-acetylcysteine (NAC) serves as a mucolytic and functions as an antioxidant by replenishing glutathione. Initially, there was a rationale for exploring NAC in the context of contrast-induced acute kidney injury (CI-AKI) due to the belief that reactive oxygen species played a role in its pathogenesis. Furthermore, NAC has the ability to enhance nitric oxide (NO) release and diminish angiotensin production by

inhibiting angiotensin-converting enzymes (ACEs). These actions directly or indirectly impact the microcirculation of the renal cortex and medulla, ultimately mitigating the renal vasoconstriction induced by contrast media. The initial small randomized controlled trial (RCT) yielded positive results, prompting widespread use of NAC, given its ease of administration. However, subsequent trials presented mixed outcomes. Initial reports indicated benefits at a dose of 600 mg administered orally twice daily, starting 2 days before the procedure [27], but, subsequent trials, involving both higher doses and intravenous administration, have yielded conflicting results across nearly 40 clinical trials and 13 meta-analyses. Notably, the use of NAC is generally well-tolerated without significant adverse effects, except for potential anaphylactoid reactions associated with high-dose intravenous administration. As such, its use is not commonly contraindicated [28]. Over the last decade, two large RCTs, involving over 7000 patients collectively, have conclusively demonstrated that NAC does not offer protection against the development of CI-AKI. Intriguing recent evidence even suggests that NAC might influence creatinine measurement rather than impacting the physiology of nephrotoxicity. As a result, there is robust evidence opposing the prophylactic use of NAC for CI-AKI [1]. The divergence in findings among these studies might be attributed to variations in CA-AKI definitions, the diverse baseline health conditions, and initial creatinine values within the study population.

Additionally, other antioxidants, including sildenafil, tadalafil [29], recombinant klotho [30], and febuxostat [31], have demonstrated a capacity to diminish the risk of contrast medium-induced nephropathy in animal experiments. Future clinical studies are warranted to delve into the potential renal protective effects of these drugs.

Clinical trials have also explored the use of statins in preventing contrast-associated acute kidney injury (CA-AKI), primarily in the context of coronary angiography and percutaneous coronary interventions. The exact mechanism by which statins could provide kidney protection is not well-defined, except for their pleiotropic effects. The majority of randomized controlled trials (RCTs) investigating statins are centered around coronary angiography. It can be contended that individuals with pre-existing cardiovascular disease undergoing these procedures should already be prescribed statins for cardiovascular protection. Given that patients at an increased risk of AKI after contrast, especially those with eGFR $\leq$ 30 mL/min/1.73 m^2, are also at a heightened cardiovascular risk, the working group acknowledges that although the evidence supporting statins for AKI prevention in this context may not be robust, there is no evidence of harm. Therefore, statins may be used for cardiovascular prevention in this population. However, the use of statins solely for the prophylaxis of CA-AKI is not recommended [1].

Using renal replacement therapy (RRT) such as hemodialysis or hemofiltration as a preventive measure is paradoxical, as the primary goal of preventing contrast-associated acute kidney injury (CA-AKI) is to avoid the need for dialysis and its associated morbidities. From a physiological perspective, intravenously injected iodinated contrast media (ICM) rapidly reaches the kidneys within a few cardiac cycles. Attempting to remove circulating contrast through extracorporeal means, such as RRT, is unlikely to yield any beneficial effects. It's important to note that

RRT can artificially lower serum creatinine levels, leading to a misleading improvement in outcomes when assessed based on changes in serum creatinine in some trials.

Discussions

Contrast-Induced Acute Kidney Injury (CI-AKI) has been a topic of extensive study, with a historical perception shift from a common complication to a nuanced understanding. While iodinated contrast media (ICM) administration has been associated with AKI, recent research challenges the notion of a direct causal relationship. Patient-specific factors, including baseline kidney function, age, and comorbidities, play crucial roles in CI-AKI risk assessment. Despite the development of risk prediction models, uncertainty remains, particularly in patients with severely reduced kidney function. The assertion that contrast is the sole cause of AKI is unproven, and current evidence suggests a very low risk, especially in patients with normal renal function. Pre-procedural hydration strategies, individualized based on risk factors, emerge as a key preventive measure. Additionally, while certain agents like statins and N-acetylcysteine have been explored, the evidence for their prophylactic use remains inconclusive. Monitoring and personalized hydration protocols are crucial in optimizing prevention strategies. The decision for prophylactic renal replacement therapy lacks support due to the absence of clear benefits and potential complications.

A retrospective study performed in Iceland between 2008 and 2015 on patients after coronary angiograms with or without angioplasty; the authors demonstrated an interaction between contrast agent dose and existing renal function, with a significant risk of AKI only at higher doses in patients with a normal eGFR [32]. In a retrospective study of 544 consecutive cardiac catheterization patients with end-stage liver disease (ESLD), Bhandari et al. [33] analyzed 179 cases after coronary angiography and found CI-AKI in 23% of patients.

The concomitant use of nephrotoxic drugs, non-steroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors, drugs that are used in more than 60% of patients undergoing imaging procedures, was also found to increase the incidence of CI-AKI [34]. Chronic kidney disease, diabetes and the dose of contrast agent are the main risk factors [35].

Conclusions

While vascular imaging plays a critical role in the diagnosis and management of various cardiovascular conditions, the risk of contrast-induced nephropathy necessitates a careful approach to the use of contrast agents. Adequate patient selection, hydration, minimizing contrast volume, and consideration of alternative imaging modalities are essential strategies to mitigate the risk of CIN. As healthcare

professionals, it is our responsibility to quantify the benefits of diagnostic imaging against the potential risks, ensuring the safety of our patients.

Prevention of CIN is a critical component of patient management during procedures requiring contrast media. Strategies include the identification of at-risk patients through a thorough medical history and baseline renal function assessment. Hydration before and after the procedure is fundamental, as it helps to dilute the contrast media and maintain renal perfusion. The use of isotonic saline or sodium bicarbonate solutions has been recommended in various guidelines. Additionally, minimizing the contrast volume and using non-ionic, low-osmolarity contrast agents have been shown to reduce the risk of CIN. In high-risk patients, prophylactic medications such as N-acetylcysteine or the use of alternative imaging modalities that do not require iodinated contrast may be considered.

In conclusion, CI-AKI is a complex interplay of factors, and preventive measures should be tailored to individual risk profiles, emphasizing the need for ongoing research to refine our understanding and improve clinical outcomes.

Bibliography

1. Macdonald DB, Hurrell C, Costa AF, McInnes MDF, O'Malley ME, Barrett B, Brown PA, Clark EG, Hadjivassiliou A, Kirkpatrick IDC, Rempel JL, Jeon PM, Hiremath S. Canadian Association of Radiologists guidance on contrast associated acute kidney injury. Can Assoc Radiol J. 2022;73(3):499–514.
2. KDIGO. KDIGO clinical practice guideline for acute kidney injury. Off J Int Soc Nephrol. 2012;2(1):69–89.
3. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179–84.
4. van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin MF, Bertolotto M, Clement O, Heinz-Peer G, Stacul F, Webb JAW, Thomsen HS. Post-contrast acute kidney injury—part 1: definition, clinical features, incidence, role of contrast medium and risk factors: recommendations for updated ESUR Contrast Medium Safety Committee guidelines. Eur Radiol. 2018;28(7):2845–55.
5. Barrios López A, García Martínez F, Rodríguez JI, Montero-San-Martín B, Gómez Rioja R, Diez J, Martín-Hervás C. Incidence of contrast-induced nephropathy after a computed tomography scan. Radiologia (Engl Ed). 2021;63(4):307–13.
6. Chaudhari H, Mahendrakar S, Baskin SE, Reddi AS. Contrast-induced acute kidney injury: evidence in support of its existence and a review of its pathogenesis and management. Int J Nephrol Renovasc Dis. 2022;15:253–66.
7. Bansal S, Patel RN. Pathophysiology of contrast-induced acute kidney injury. Interv Cardiol Clin. 2020;9(3):293–8.
8. Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. Eur Heart J. 2012;33(16):2007–15.
9. Kiss N, Hamar P. Histopathological evaluation of contrast-induced acute kidney injury rodent models. Biomed Res Int. 2016;2016:3763250.
10. McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, Tumlin J, CIN Consensus Working Panel. Risk prediction of contrast-induced nephropathy. Am J Cardiol. 2006;98(6A):27K–36K.

11. Rudnick MR, Goldfarb S, Wexler L, Ludbrook PA, Murphy MJ, Halpern EF, Hill JA, Winniford M, Cohen MB, VanFossen DB. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. Kidney Int. 1995;47(1):254–61.
12. Chandiramani R, Cao D, Nicolas J, Mehran R. Contrast-induced acute kidney injury. Cardiovasc Interv Ther. 2020;35(3):209–17.
13. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med. 1983;74(2):243–8.
14. Rao QA, Newhouse JH. Risk of nephropathy after intravenous administration of contrast material: a critical literature analysis. Radiology. 2006;239(2):392–7.
15. Newhouse JH, Kho D, Rao QA, Starren J. Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity. AJR Am J Roentgenol. 2008;191(2):376–82.
16. Hiremath S, Velez JCQ. Preventing a nonexistent entity: the curious case of contrast and acute kidney injury. Curr Opin Nephrol Hypertens. 2020;29(1):152–60.
17. McDonald RJ, McDonald JS, Bida JP, Carter RE, Fleming CJ, Misra S, Williamson EE, Kallmes DF. Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? Radiology. 2013;267(1):106–18.
18. Wilhelm-Leen E, Montez-Rath ME, Chertow G. Estimating the risk of radiocontrast-associated nephropathy. J Am Soc Nephrol. 2017;28(2):653–9.
19. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. Radiology. 2013;268(3):719–28.
20. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology. 1993;188(1):171–8.
21. Pandya B, Chalhoub JM, Parikh V, Gaddam S, Spagnola J, El-Sayegh S, Bogin M, Kandov R, Lafferty J, Bangalore S. Contrast media use in patients with chronic kidney disease undergoing coronary angiography: a systematic review and meta-analysis of randomized trials. Int J Cardiol. 2017;228:137–44.
22. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med. 2002;162(3):329–36.
23. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA 3rd, Rittase RA, James Norton H, Kennedy TP. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA. 2004;291(19):2328–34.
24. Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, van Ommen V, Wildberger JE. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrastinduced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet. 2017;389(10076):1312–22.
25. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin S-S, Conner TA, Chertow GM, Bhatt DL, Shunk K, Parikh CR, McFalls EO, Brophy M, Ferguson R, Wu H, Androsenko M, Myles J, Kaufman J, Palevsky PM, PRESERVE Trial Group. Outcomes after angiography with sodium bicarbonate and acetylcysteine. N Engl J Med. 2018;378(7):603–14.
26. Timal RJ, Kooiman J, Sijpkens YWJ, de Vries J-PPM, Verberk-Jonkers IJAM, Brulez HFH, van Buren M, van der Molen AJ, Cannegieter SC, Putter H, van den Hout WB, Wouter Jukema J, Rabelink TJ, Huisman MV. Effect of no prehydration vs sodium bicarbonate prehydration prior to contrast-enhanced computed tomography in the prevention of postcontrast acute kidney injury in adults with chronic kidney disease: the Kompas randomized clinical trial. JAMA Intern Med. 2020;180(4):533–41.

27. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med. 2000;343(3):180–4.
28. Mullasari A, Victor SM. Update on contrast induced nephropathy. E J ESC Counc Cardiol Pract. 2014;13(4):1–3.
29. Iordache AM, Docea AO, Buga AM, Zlatian O, Ciurea ME, Rogoveanu OC, Burada F, Sosoi S, Mitrut R, Mamoulakis C, Albulescu D, Vasile RC, Tsatsakis A, Calina D. Sildenafil and tadalafil reduce the risk of contrast-induced nephropathy by modulating the oxidant/antioxidant balance in a murine model. Food Chem Toxicol. 2020;135:111038.
30. Oh HJ, Oh H, Nam BY, You JS, Ryu DR, Kang SW, Chung YE. The protective effect of klotho against contrast-associated acute kidney injury via the antioxidative effect. Am J Physiol Renal Physiol. 2019;317(4):F881–9.
31. Yang KJ, Kim JH, Chang YK, Park CW, Kim SY, Hong YA. Inhibition of xanthine oxidoreductase protects against contrast-induced renal tubular injury by activating adenosine monophosphate-activated protein kinase. Free Radic Biol Med. 2019;145:209–20.
32. Helgason D, Long TE, Helgadottir S, Palsson R, Sigurdsson GH, Gudbjartsson T, Indridason OS, Gudmundsdottir IJ, Sigurdsson MI. Acute kidney injury following coronary angiography: a nationwide study of incidence, risk factors and long-term outcomes. J Nephrol. 2018;31(5):721–30.
33. Bhandari P, Shah Z, Patel K, Patel R. Contrast-induced acute kidney injury following coronary angiography in patients with end-stage liver disease. J Community Hosp Intern Med Perspect. 2019;9(5):403–9.
34. Neyra JA, Shah S, Mooney R, Jacobsen G, Yee J, Novak JE. Contrast-induced acute kidney injury following coronary angiography: a cohort study of hospitalized patients with or without chronic kidney disease. Nephrol Dial Transplant. 2013;28(6):1463–71.
35. Alamartine E, Phayphet M, Thibaudin D, Barral FG, Veyret C. Contrast medium-induced acute renal failure and cholesterol embolism after radiological procedures: incidence, risk factors, and compliance with recommendations. Eur J Intern Med. 2003;14(7):421–31.
36. Vlachopanos G, Schizas D, Hasemaki N, Georgalis A. Pathophysiology of contrast-induced acute kidney injury (CIAKI). Curr Pharm Des. 2019;25(44):4642–7.
37. Goulden R, Rowe BH, Abrahamowicz M, Strumpf E, Tamblyn R. Association of intravenous radiocontrast with kidney function: a regression discontinuity analysis. JAMA Intern Med. 2021;181(6):767–74.
38. Aycock RD, Westafer LM, Boxen JL, Majlesi N, Schoenfeld EM, Bannuru RR. Acute kidney injury after computed tomography: a meta-analysis. Ann Emerg Med. 2018;71(1):44–53.e4.

Renal Artery and Vein Thrombosis

Bogdan Obrișcă and Gener Ismail

Abstract Macrovascular disorders of the kidney are rare causes of kidney injury, yet their incidence is underestimated due to the non-specific clinical presentation that may mimic other, more common, intraabdominal disorders. Accordingly, renal artery and vein thrombosis are frequently misdiagnosed or diagnosed late in clinical practice, posing the risk of irreversible loss of renal parenchyma. In addition, there is a lack of consensus and adequate guidelines, hence the treatment approach relies on the experience driven from case series or individual case reports. Nonetheless, a thorough multidisciplinary approach is essential to identify the underlying etiology and guide patient management. This chapter aims to provide an overview of the vascular complications of the main renal artery and vein.

Keywords Renal artery · Thrombosis · Occlusion · Renal infarction · Renal vein · Renal artery thrombosis · Renal vein thrombosis

Renal Artery Thrombosis

Introduction and Epidemiology

Renal artery occlusion is associated with an abrupt reduction of flow in the main renal arteries and/or its segmental branches with consequent renal infarction and it is an uncommon cause of acute kidney injury, though likely underdiagnosed due to nonspecific clinical features [1, 2].

The true incidence and prevalence of renal artery occlusion are unknown, with the current data being biased by the type of population included. Accordingly, the

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incidence in autopsy series has been reported to be approximately 0.5–1.5% [3]. Contrary, the incidence of renal infarction documented by emergency department visits has been reported to be 0.004–0.007%, likely an underestimation due to non-specific clinical presentation that may mimic other, more common, disorders [4]. By comparison, in a series of 186 consecutive cases of renal infarction diagnosed over 15 years at a Hypertensive Unit of a tertiary center that adopted a multidisciplinary diagnostic approach, the reported incidence and prevalence were 0.07% and 1%, respectively [5].

Etiology

Renal artery occlusion can be attributed to embolic or thrombotic, traumatic or non-traumatic, systemic or local causes, and has many etiologies that are outlined in Table 1 [1].

While several approaches to the classification of renal artery occlusion can be employed, the one proposed by Bourgault et al may be regarded as optimal since it is related to the underlying pathophysiological mechanism and may further guide therapy (Table 2) [6]. Accordingly, the etiology of renal artery occlusion can be subdivided into a cardiac origin, renal endothelial injury origin, hypercoagulable state origin and idiopathic origin [6].

The prevalence of etiologies varies significantly across studies in relation to the type of population included. Several studies have outlined that atrial fibrillation is the most common etiology being documented in up to 40% of cases of renal infarction, possibly an overestimation given that some studies included only patients with atrial fibrillation [9, 10]. Contrary, a study that enrolled 29,862 Danish patients with a discharge diagnosis of incident atrial fibrillation reported an incidence of renal thromboembolism of only 2% [11]. Nonetheless, an adequate etiologic work-up performed in a multidisciplinary approach is essential, as has been shown that adequate screening of other vascular beds may help identify additional cases of renal artery lesions previously misclassified as idiopathic [5].

Nevertheless, it is worth outlining that several clinical scenarios have been excluded from the abovementioned studies, such as iatrogenic renal artery injuries or vascular complications in kidney transplant recipients.

Renal infarction after endovascular procedures has been reported with variable frequency. Kramer et al, in a retrospective study that enrolled 99 patients followed for at least 12 months after endovascular aortic aneurysm repair, identified a low prevalence of renal infarction (8.3%) that was not associated with suprarenal endograft fixation and did not lead to an increased risk of persistent renal function impairment [12]. By contrary, in a larger study (663 patients with endovascular abdominal aortic aneurysm repair), Bockler et al identified a renal infarction rate of 11.9%, with a three-fold higher risk in those with suprarenal fixation [13]. Among these patients, 21.5% had a worsening of renal function due to renal artery occlusion, with two patients eventually requiring renal replacement therapy. Embolism

Table 1 Causes of renal artery occlusion [1, 2]

Thrombotic origin	Thromboembolic origin
Endothelial injury	*Cardiac origin*
Atherosclerotic disease	Atrial fibrillation
Fibromuscular dysplasia	Endocarditis
Renal artery aneurysm	Myocardial infarction
Extension of an aortic dissection	Cardiomyopathy
Dissecting hematoma	Septal defects with paradoxical embolism
Systemic vasculitis/autoimmune disorders	*Aortic or renal artery origin*
• Polyarteritis nodosum	Atherosclerosis
• Takayasu arteritis	*Surgical procedures (iatrogenic)*
• Kawasaki disease	Cardiac valve repair
• Thromboangiitis obliterans	Endovascular stenting
• Behcet disease	Angiography
• ANCA-associated vasculitis	
• Systemic lupus erythematosus	
• Henoch-Schoenlein purpura	
Syphilis	
Drug abuse (e.g. cocaine)	
Ehlers-Danlos syndrome	
Hypercoagulability	
Antiphospholipid syndrome	
Nephrotic syndrome	
Inherited thrombophilia	
Heparin-induced thrombocytopenia	
Malignancy	
Trauma	
Blunt trauma	
Penetrating injury	
Surgical procedures (iatrogenic)	
Endovascular stenting	
Renal transplantation	
Angiography	

during deployment, graft misplacement and occlusion of undiagnosed pole arteries are among the highlighted mechanisms attributed to renal infarction after abdominal aortic aneurysm graft-stenting. However, the increasing use of distal protective devices in the setting of endovascular procedures may significantly improve outcomes and decrease the rate of distal embolization [14].

In terms of vascular complications post-transplantation, in a study of 1200 consecutive living-donor renal transplant recipients, 2.8% of patients had vascular complications with only five cases (0.4%) of renal artery thrombosis. In these patients, renal artery thrombosis occurred after a mean 8 ± 11.5 days after renal

Table 2 Prevalence of the mechanism of renal artery occlusion across different studies

Study	Number of pts.	Etiology/Mechanism	Prevalence
Faucon et al.[a] [5]	186	Embolic	9.1%
		Renal artery lesion	81.2%
		Thrombophilia	5.9%
		Idiopathic	3.8%
Bourgault et al.[a] [6]	94	Embolic	24.5%
		Renal artery lesion	30.8%
		Thrombophilia	16%
		Idiopathic	28.7%
Oh et al.[a] [7]	438	Embolic	55.7%
		Renal artery lesion	7.5%
		Thrombophilia	6.6%
		Idiopathic	30.1%
Bae et al. [8]	100	Embolic	56%
		Renal artery lesion	10%
		Thrombophilia	6%
		Idiopathic	28%

[a]Excluded patients with iatrogenic renal artery occlusion or post-renal transplantation

transplantation, with four patients necessitating graft nephrectomy and only one patient having a preservation of graft function by arterial thrombectomy [15].

In addition, acute renal artery thrombosis has been rarely reported after blunt abdominal trauma. An incidence of 0.1% of complete unilateral renal artery occlusion has been identified in a study conducted in two centers with an average annual rate of approximately 1600 blunt trauma patients admitted, with an extensive literature review identifying approximately 400 reported cases [16–18].

Hypercoagulable states (e.g., nephrotic syndrome, antiphospholipid syndrome) are more frequently associated with venous thromboembolic events rather than renal artery thrombosis. Despite being rare, renal artery thrombosis has been reported in patients with antiphospholipid antibody syndrome and in patients with systemic lupus erythematosus without antiphospholipid antibodies [19–21]. In a study that evaluated 215 patients with antiphospholipid syndrome by abdominal CT, 42 patients were identified to have abdominal thrombotic or ischemic events, of whom 22 patients had renal infarction [22]. Similarly, arterial thrombosis has been described in patients with nephrotic syndrome [23]. In a case series of 35 patients with nephrotic syndrome and arterial thrombosis, 10 patients had documented renal artery thrombosis [24].

Pathophysiology

While for the majority of cases a complex interplay of traditional risk factors for cardiovascular events has been proposed to mediate the pathogenesis of acute renal artery occlusion, several other particular situations need to be outlined [1]. Among the currently accepted risk factors for an increased risk of vascular events are: age, male gender, smoking, hyperlipidemia, hypertension, obesity, hyperhomocysteinemia, diabetes mellitus and chronic kidney disease [6]. These may explain the cases of acute renal artery thrombosis associated with endothelial dysfunction in the context of systemic atherosclerosis as well as those with a cardioembolic source of renal artery occlusion. Accordingly, several studies have identified a higher frequency of hypertension, diabetes mellitus, cardiovascular disorders, valvular heart disease or arrhythmias in patients with a cardiogenic cause of renal infarction, while smoking was more prevalent in patients with a preexisting renal artery lesion [5, 6]. Nonetheless, vascular wall inflammation may also mediate the loss of the arterial endothelial surface integrity and result in renal artery thrombosis as has been described in large and/or medium size vessel vasculitis (e.g., Takayasu arteritis) [2].

The prothrombotic state associated with antiphospholipid syndrome is explained by a direct interference of antiphospholipid antibodies with regulatory proteins of the clotting pathway (e.g., inhibitory effect on antithrombin III or protein C, direct binding to activated coagulation factors that prevents their inactivation by natural anticoagulants), interaction with plasminogen and its activators that leads to an impairment of fibrinolysis, and activation of several cells leading to endothelial dysfunction, platelet aggregation and release of tissue factor from circulating monocytes [25]. Similarly, the nephrotic syndrome can be viewed as an acquired thrombophilic condition and the pathogenesis of thromboembolic events is multifactorial involving an imbalance between the prothrombic and antithrombotic clotting and fibrinolytic factors, inflammation associated with certain glomerular disorders, medication and a genetic background [26].

In terms of the pathophysiology of renal artery occlusion in the setting of blunt trauma, several mechanisms have been proposed: rapid deceleration with stretching and subsequent tear of the renal artery intima, dissection and thrombosis, renal artery contusion against the vertebral column or extrinsic compression of renal artery by a retroperitoneal hematoma [1, 16].

Clinical Features

There are no specific clinical symptoms and/or signs for the diagnosis of renal artery occlusion. Given that the clinical features may mimic an acute renal colic, acute pyelonephritis or other intraabdominal processes, renal artery thrombosis is frequently misdiagnosed or diagnosed late, which often results in irreversible loss of renal parenchyma.

The clinical presentation of renal artery occlusion is variable being influenced by the size of infarction. The most common clinical features are abdominal and/or flank pain, followed by nausea, vomiting (up to 50% of cases) and fever (up to 30% of cases) [2, 6]. The severity of pain is related to the size of the occluded vessel and corresponding infarction size of the renal parenchyma. While in a series of 94 patients with acute renal infarction pain was present in 96.8% of cases, in another series that reported iatrogenic renal artery occlusion following endovascular abdominal aortic aneurysm repair all patients were asymptomatic and the renal infarcts were discovered by serial CT monitoring [6, 12]. Anuria or oliguria generally occur in patients with bilateral kidney involvement or unilateral occlusion in those with solitary kidneys [27]. However, a concomitant reflex arteriolar vasospasm of the contralateral kidney or other causes of acute kidney injury (e.g., contrast-induced nephropathy) have also been incriminated in this setting [27]. Macroscopic hematuria is relatively rare (less than 20% of cases) [6]. In addition, worsening of preexisting arterial hypertension or new-onset arterial hypertension in a patient with abdominal/flank pain should raise the suspicion of concomitant renal artery thrombosis [28].

Laboratory features are non-specific and have a limited value for the diagnosis of renal artery occlusion. The most common findings are leukocytosis, increased serum enzymes [lactate dehydrogenase (LDH), aspartate aminotransferase, alkaline phosphatase] and increased inflammatory markers (C-reactive protein, fibrinogen) [1]. Leukocyte count gradually normalizes after 15 days, while LDH concentrations remain elevated for more than 2–3 weeks [6]. Urinalysis usually identifies microscopic hematuria, leukocyturia and mild proteinuria [2]. Acute kidney injury (AKI) occurs with variable frequency in renal artery occlusion and is related to the severity of occlusion and the coexistence of collateral circulation. Bae et al reported a frequency of AKI of 30% in patients with acute renal infarction, the occurrence of AKI being related to older age, increased size of renal infarct and preexisting chronic kidney disease [8].

Despite that the clinical presentation of renal artery occlusion is non-specific, identification of comorbidities or coexisting precipitating factors may further raise the suspicion of renal artery occlusion (e.g. trauma, systemic atherosclerosis, preexisting cardiac disorders, arrythmias, signs of systemic inflammatory or autoimmune disorders, etc.).

Diagnosis

Given that there are no pathognomonic clinical or laboratory features for renal artery thrombosis, imaging remains the gold standard for diagnosis.

Although Doppler ultrasound may represent a first-line approach because of its wide availability, it is of limited value in the diagnosis of renal artery occlusion because is operator-dependent and yields a high risk of false-negative results, especially with occlusion of more distal or segmental branches of the renal artery [3].

However, Doppler ultrasound may be useful in cases of renal artery thrombosis post-kidney transplantation [29].

Thus, in cases with high clinical suspicion, a contrast-enhanced CT scan is the imaging modality of choice to identify areas of renal parenchyma that are not perfused [1]. CT findings in renal artery occlusion include: focal wedge-shaped areas of non-enhancement, global or multifocal infarcts, typical "cortical rim sign" or a mass effect (Figs. 1 and 2) [30]. The "cortical rim sign" reflects a cortical area with preserved perfusion by perforating branches of renal capsular arteries. In a retrospective review of 41 renal infarcts from 37 patients, 9 patients had global infarcts, 23 patients had wedge shaped infarcts and 5 patients had multifocal infarcts, while the "cortical rim sing" was identified in 18.9% of cases with a predilection in those with global infarcts [30]. In a study that included patients with renal traumatic injuries, contrast-enhanced CT scan had an excellent sensitivity and specificity for the

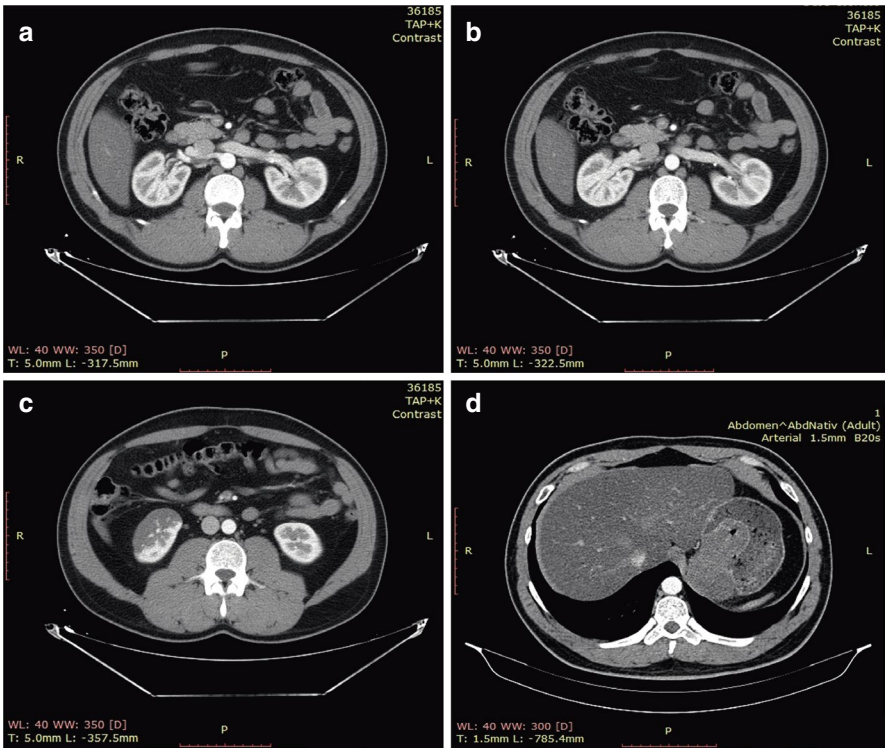

Fig. 1 Acute right renal artery thrombosis and renal infarction. A 35-year old male admitted for severe right lumbar pain, with a subsequent diagnosis of right renal artery thrombosis and renal infarction. Etiological work-up pointed toward a hypercoagulable state due to an inherited thrombophilia (hyperhomocysteinemia) and a gastrointestinal stromal tumor. **Contrast-enhanced CT scan**. (**a** and **b**) Acute right renal artery thrombosis; (**c**) Right renal infarction; (**d**) Gastrointestinal stromal tumor (*From the collection of the Nephrology Department of Fundeni Clinical Institute, with the permission of Prof. Dr. Gener Ismail*)

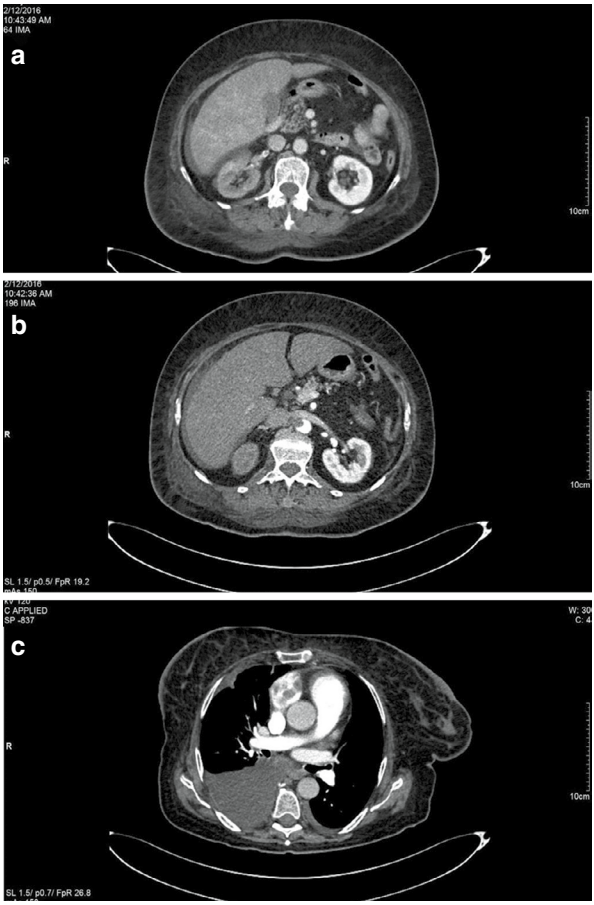

Fig. 2 Right renal artery occlusion [27]. A 65-year old woman, with a past medical history of breast malignancy, evaluated in the Nephrology Department for right flank pain, macroscopic hematuria and acute kidney injury. **Contrast-enhanced CT scan**. (**a**) Absent uptake of contrast in the right kidney; (**b**) Endoluminal aortic thrombus at the emergence of the right renal artery with complete absence of nephrogram of the right kidney suggestive of renal infarction; (**c**) Multiple thrombi in the left atrium. (*From the collection of the Nephrology Department of Fundeni Clinical Institute, with the permission of Prof. Dr. Gener Ismail*)

diagnosis of renal infarction, while dynamic CT scan had an even better diagnostic performance [31].

Magnetic resonance angiography is an alternative diagnostic modality for renal artery occlusion, but its use is limited by the lower availability and the increased examination time. Renal arteriography remains the gold-standard diagnostic method and offers the additional benefit for an immediate endovascular intervention [32].

In addition, after the diagnosis of renal artery occlusion is confirmed, the further work-up should be guided towards identification of the underlying mechanism in order to select the adequate treatment approach. The etiologic work-up varies significantly among centers. However, one study outlined the need for an extensive investigation of other arterial sites in addition to the occluded renal artery (e.g., contralateral renal artery, aortoiliac and digestive axis, carotid and Willis polygon) [5]. Following this approach, the majority of previously labeled idiopathic cases have been successfully reclassified as occurring in the context of renal artery lesions. After exclusion of arterial lesions, the additional investigations should include

echocardiography (transthoracic and transesophageal), Holter-EKG monitoring or thrombophilia evaluation.

Treatment

Given the rarity of renal artery occlusion, the lack of a consensus and adequate guidelines, the treatment approach relies on the experience driven from case series or individual case reports [33].

Initial approach to treatment should rely on whether the renal artery occlusion is embolic or thrombotic. In addition, the response to therapy is related to the warm ischemia time, location and severity of occlusion (partial or total) and the presence of collateral circulation. It is generally accepted that renal parenchyma resists to complete ischemia for 60–90 min, beyond this point irreversible kidney damage occurs [27]. Animal models of unilateral renal artery occlusion have shown a graded irreversible renal parenchyma loss ranging from 40% to 100% after persistent renal artery occlusion for at least 1 h and up to 3 h [2]. However, cases of favorable outcomes with recovery of renal function have been described after late revascularization, with delays of up to several days [34, 35]. In such cases, the presence of collateral circulation may be responsible for the renal recovery after late revascularization.

Therapeutic options for renal artery occlusion include anticoagulation with or without intraarterial thrombolysis, endovascular or surgical thrombectomy and, in rare cases, nephrectomy [1]. The choice between these treatment options relies primarily on the warm ischemia time and delay in confirming the diagnosis, etiology and mechanism of occlusion, extent of the occlusion, comorbidities and the general status of the patient [27].

The majority of cases of thromboembolic renal artery occlusion are management by a combination of anticoagulation and thrombolysis, with percutaneous or surgical thrombectomy being reserved for patients with a significant risk of renal function loss (e.g. bilateral renal artery occlusion or unilateral occlusion of a solitary kidney, those that fail medical management, vascular complications in the setting or renal transplantation) [2]. Nonetheless, a surgical approach in those with unilateral renal infarction and normal contralateral kidney remains controversial [1].

Intraarterial thrombolysis may be suitable in cases of acute thromboembolic events, although with mixed results in terms of the ability to restore renal function [3]. In a historical case series of 33 patients with renal artery embolism, of whom 12 patients were treated by surgical embolectomy, 12 patients by intravenous anticoagulation alone and 9 patients by intraarterial thrombolysis, thrombolysis yielded the best results in terms of renal function recovery and overall mortality [36]. The rates of renal function recovery were 20%, 30% and 100%, while rates of mortality were 25%, 0% and 0% for surgical embolectomy, anticoagulation alone and thrombolysis, respectively [36]. Nonetheless, while normal renal arterial blood flow was seen in several patients after thrombolysis, none had a completely normal renal

function on long-term follow-up. In addition, there was no correlation between the ischemia time and the success of revascularization, as patients with prolonged ischemia duration (over 25 h) showed at least a partial renal function recovery [36]. Contrary, in another case series of 14 patients with acute embolic renal artery occlusion, 13 had a restoration of renal perfusion but the renal function did not improve on the side of complete renal artery occlusion [37]. Given that these patients had a delay between the onset of symptoms and treatment of at least 12 h, a "critical ischemia time" of 3 h was proposed beyond which there is a high likelihood of irreversible renal parenchyma loss [37].

Anticoagulation therapy in patients with embolic or thromboembolic renal artery occlusion is generally started with unfractionated heparin or low-molecular weight heparin followed by oral agents [1]. Given that there are no dedicated guidelines, the approach to anticoagulation therapy should rely on the risk of future embolic or thrombotic events and the patient's comorbidities [2]. The current clinical guidelines outline that, in patients with atrial fibrillation, the primary prevention of thromboembolism relies on the assessment of both thromboembolic and hemorrhagic risk [38]. As the experience with non-vitamin K antagonist oral anticoagulants is scarce in renal artery occlusion, a vitamin K antagonist should be used with a target INR (international normalized ratio) of 2–3 and a time in therapeutic range over 70% [38]. In patients with prosthetic valves the target INR varies between 2.5 and 4, depending on prosthesis thrombogenicity and patient-related risk factors [39]. Another clinical scenario for which dedicated guidelines for thromboprophylaxis have been developed is antiphospholipid syndrome. Accordingly, a primary thromboprophylaxis in asymptomatic patients with a high-risk antiphospholipid antibody profile is recommended with low-dose aspirin (75–100 mg/daily) [40]. Additionally, in patients with definitive antiphospholipid syndrome and a first arterial thrombosis, treatment with a vitamin K antagonist with a target INR of 2–3 or 3–4 is recommended, depending on the individual risk of bleeding and recurrent thrombosis [40]. A vitamin K antagonist with a target INR of 2–3 with the addition of low-dose aspirin may also be considered, while in those with recurrent arterial events an increase of INR to 3–4 or switching to low-molecular weight heparin should be considered [40].

Endovascular or surgical thrombectomy have yielded conflicting results across different case series. Several case reports have outlined that an endovascular approach is a valuable treatment option for renal artery occlusion, even in cases with a significant prolonged ischemia time [41, 42]. However, the presence of distal thrombi has been shown to limit the efficacy of revascularization of the main renal artery [43]. Surgical thrombectomy should be limited to those at high risk for renal function loss (as previously mentioned). In a retrospective case series of 35 patients treated for renal artery occlusion, a surgical approach was ineffective in restoring of renal function in those with embolic and traumatic occlusions [44].

In the setting of traumatic renal artery occlusion, the choice between a conservative approach and an endovascular/surgical revascularization is dictated by the extent of injury (e.g., unilateral occlusion versus bilateral occlusion or unilateral occlusion of a solitary kidney), the ischemia time, the hemodynamic status and

presence of additional intra-abdominal injuries that need to be addressed [18]. In a literature review of 128 cases of renal artery trauma (120 patients with renal artery thrombosis and 8 patients with renal artery avulsions), a successful revascularization occurred in 80%, 57% and 0% of cases if performed within 12 h, 12–18 h and over 19 h after the injury [45]. Endovascular treatment can be attempted in hemodynamically stable trauma patients and several case reports have reported successful outcomes even with late revascularization if no distal thrombi are present [32, 41].

Prognosis

In the study by Bae et al, among the patients that developed AKI, none required renal replacement therapy in the acute setting, with the majority of patients recovering (76.7%) and only 23.3% developing persistent renal function impairment on long-term follow-up [8]. In another series of 438 patients with renal infarction, during a median follow-up period of 20 months, 2.8% of patients had recurrent infarction, 20.1% of patients developed AKI, 10.9% of patients developed chronic-kidney disease and 2.1% of patients progressed to ESRD [7]. As previously mentioned, the long-term renal outcomes and success of revascularization depend on the warm ischemia time, severity of occlusion and presence of collateral circulation. Thus, although the incidence of AKI observed in various cohorts is low, other reports have outlined that a successful restoration of renal blood flow did not translate into a complete recovery of renal function.

The mortality rate has been reported to be increased, but this is likely determined by the coexisting comorbidities and not to renal artery occlusion by itself. Accordingly, a literature review has reported a mortality of 14.3% within 1 year from diagnosis, the majority of cases being attributed to cardiovascular disease (embolic disease-50%, myocardial infarction-25%), followed by sepsis (25%) [46].

Renal Vein Thrombosis

Introduction and Epidemiology

Renal vein thrombosis (RVT) is a rare disorder with variable clinical presentation. Although it can be associated with a variety of conditions such as trauma, malignancy, inherited thrombophilia, extrinsic compression of the renal vein, RVT most commonly occurs as a complication of nephrotic syndrome [47, 48]. Therefore, the frequency of RVT in other conditions is largely unknown and difficult to estimate, while in patients with nephrotic syndrome varies widely, with a reported prevalence between 5% and 60% [26]. Accordingly, during the past decades, significant

attention has been directed towards the thromboembolic risk in patients with nephrotic syndrome.

This large variability of RVT prevalence is likely due to the underlying nature of different studies (retrospective versus prospective) and the diagnostic approach [49]. Thus, studies conducted in the 1980s–1990s focused mainly on the detection of RVT and used renal venography as a screening method that led to identification of many asymptomatic events [49]. Accordingly, Llach et al identified, in a prospective study of 151 patients with nephrotic syndrome, 33 cases of renal vein thrombosis (21.9%), of which 4 had acute and 29 chronic presentation [50]. While all patients with acute RVT had suggestive symptoms, none of those with a chronic presentation of RVT had flank pain and only two patients had gross hematuria [50]. Similarly, 51.9% of the 27 patients with membranous nephropathy from another study had RVT identified by renal venography [51].

Contrary to past reports, more recent studies focused on identifying symptomatic events. As an example, in a large study of 298 patients with nephrotic syndrome, the annual incidence of venous thromboembolic events was 1.02% (95%CI, 0.68–1.46%) with RVT occurring in combination with pulmonary embolism in 10% of cases, while 3% of patients had isolated RVT [52]. In our experience, the cumulative incidence of venous thromboembolic events in a prospective cohort of 256 patients with primary nephrotic syndrome was 11%. Among these, 14% had isolated RVT and 3% had combined RVT and pulmonary embolism. Notably, the median time to a venous thromboembolic event was 4 months, with 62% and 98% of the events occurring within 6 months and 1 year after presentation, respectively [53].

Etiology

Similar to the renal artery occlusion, the etiology of RVT can be classified according to the main underlying pathophysiological mechanism as originally defined by Rudolf Virchow: endothelial injury, venous stasis and hypercoagulability (Table 3) [47].

In a study that enrolled all patients diagnosed with RVT during a two-decade period (n = 218), the most common underlying cause was active malignancy (66.2%), the majority of patients having a renal cell carcinoma (77.6%) [55]. By contrary, nephrotic syndrome was present in 43 patients, with the majority having membranous nephropathy (87%) [55]. Notably, among patients with active malignancy the occurrence of RVT is likely determined by local factors and not necessarily due to a malignancy-induced hypercoagulability state as a tumor thrombus was histologically confirmed in 62 patients [55]. These findings may have therapeutic implications as tumor thrombi may be less responsive to conventional anticoagulation therapy and may need a surgical excision along with the primary tumor (Fig. 3).

Apart from the previous study, RVT in adults is most frequently reported as a complication of nephrotic syndrome. Nonetheless, although traditionally linked to the degree of proteinuria and hypoalbuminemia, the risk of venous thromboembolic

Table 3 Causes of renal vein thrombosis [47, 54]

Endothelial injury	Venous stasis	Hypercoagulability
Tumor infiltration	Blood volume depletion	Nephrotic syndrome
Systemic vasculitis	• Dehydration in neonates	Antiphospholipid syndrome
• Polyarteritis nodosum	• Intensive diuretic therapy	Systemic lupus erythematosus
• Behcet disease	Extrinsic RV compression	ANCA-associated vasculitis
• ANCA-associated vasculitis	• Retroperitoneal tumors	Inherited thrombophilia
• Systemic lupus erythematosus	• Lymphoma	• Factor V Leiden
Trauma	• Nutcracker syndrome	• Prothrombin gene mutations
• Blunt trauma	• Pregnancy	• Antithrombin deficiency
• Penetrating injury		• Protein C and S deficiency
Iatrogenic		• Hyperhomocysteinemia
• Post-renal transplantation		Malignancy
• Post-venography		Medication
		• Oral contraceptives
		• Corticosteroids
		• Heparin
		• Chemotherapy
		Sepsis
		Pregnancy

events has also been associated with the underlying histological diagnosis [56]. In an analysis of the Toronto Glomerulonephritis Registry that included 1313 patients with idiopathic glomerulonephritis (370 patients with focal segmental glomerulosclerosis, 548 patients with IgA nephropathy and 395 patients with membranous nephropathy), the prevalence of venous thromboembolic events was 3.4% (with 19 renal vein thrombosis events), significantly higher in membranous nephropathy compared to the other glomerulonephritis [57]. The risk of venous thromboembolic events in membranous nephropathy was approximately 11-fold higher than IgA nephropathy, even after adjusting for the traditional risk factors such as severity of proteinuria, degree of hypoalbuminemia and malignancy history. Despite the strong association, the reason for the higher prevalence of RVT in membranous nephropathy is not fully understood.

Isolated RVT has been described in patients with inherited thrombophilia [58]. In addition, a genetic predisposition for thromboembolic events has been identified in patients with nephrotic syndrome, additionally increasing the risk for RVT in such clinical scenarios [49, 59]. We have reported, in a study of 36 patients with nephrotic syndrome (of whom 28% developed venous thromboembolic events), a prevalence of factor V Leiden, prothrombin gene mutation (G20210A) and MTHFR gene mutation of 14%, 5.6% and 27.8%, respectively [49].

Renal vein thrombosis has been reported in patients with systemic lupus erythematosus and/or antiphospholipid syndrome, although the prevalence of this complication appears to be lower than that of pulmonary embolism, deep vein thrombosis or cerebrovascular events (e.g., stroke, transient ischemic attack) [19, 20, 25, 60]. In

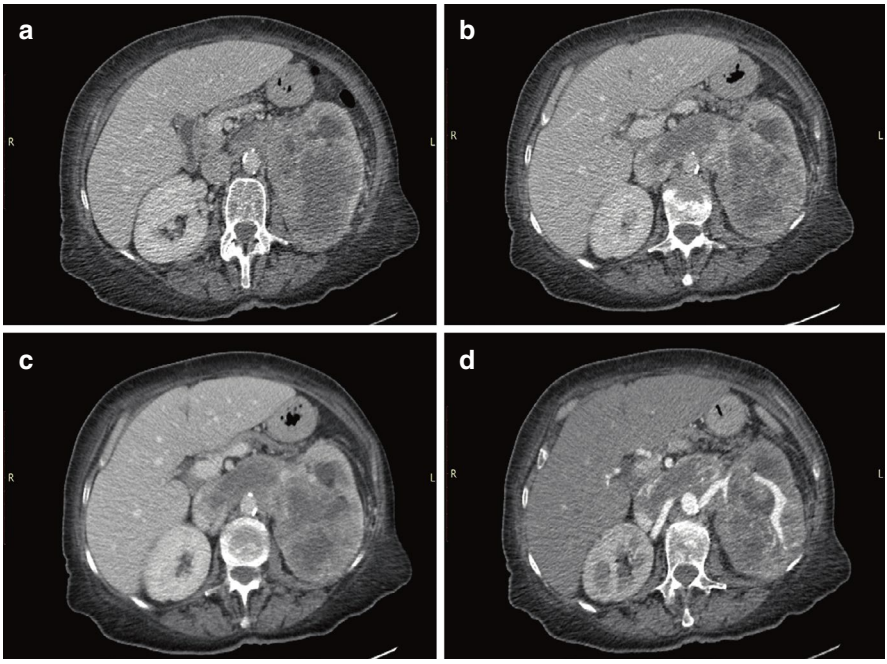

Fig. 3 Left renal vein thrombosis. A 72-year old female admitted for gross hematuria. Etiological work-up identified a large left renal tumor with complete occlusion of the left renal vein due to a tumor thrombus, with extension into the inferior vena cava. **Contrast-enhanced CT scan**. (**a**) Voluminous left renal tumor; (**b**–**d**) Complete left renal vein thrombosis with extensions into the inferior vena cava. (*From the collection of the Nephrology Department of Fundeni Clinical Institute, with the permission of Prof. Dr. Gener Ismail*)

a Chinese population of 625 patients with systemic lupus erythematosus diagnosed over a 14-year period, only six patients had an angiographically confirmed RVT [61]. Notably, four of these six patients had positive antiphospholipid antibodies and all had lupus nephritis with active nephrotic syndrome [61]. The presence of antiphospholipid syndrome is also relevant to renal transplant outcomes. Accordingly, in a study of 96 patients with systemic lupus erythematosus who underwent kidney transplantation, 25 patients had positive antiphospholipid antibodies, with 60% of these having clinically meaningful vascular events, including four with graft loss due to renal vein or artery thrombosis [62]. Despite that an increased frequency of venous thromboembolic events has been also described in systemic vasculitis, such as ANCA-associated vasculitis, RVT remains a rare occurrence being limited to isolated case reports [63]. Nonetheless, a higher prevalence of anti-plasminogen antibodies has been identified in patients with ANCA-associated vasculitis that may account for this increased thrombotic risk [64, 65].

Isolated RVT occurs rarely after blunt abdominal trauma, being usually associated with renal artery or parenchymal injury [66]. Similarly, RVT occurs rarely after

renal transplantation with a prevalence of 0.1% being reported in a study of 1200 consecutive living-donor renal transplant recipients [15].

Pathophysiology

The pathogenesis of thromboembolic events involves an interplay of the Virchow's triad factors (endothelial injury, stasis and hypercoagulability). Although in isolated cases a single precipitating factor may trigger venous thrombosis, more frequently it is of multifactorial origin [47].

Accordingly, the pathogenesis of RVT in nephrotic syndrome is multifactorial and, despite being extensively studied, is still not completely understood [23, 26]. Nephrotic syndrome should be viewed as an acquired thrombophilia due to a shift of the hemostatic balance towards a prothrombotic environment (Table 4). Nonetheless, although several studies have documented changes in serum levels of proteins involved in the coagulation and fibrinolytic pathway, the definitive proof of the pathogenicity of these abnormalities is lacking as these studies did not include venous thromboembolism as outcome events [26].

Many studies over the past decades have outlined that an albumin level below 2–2.5 g/dL is a significant risk factor for venous thromboembolic events, but other failed to confirm this association [49, 67]. In our experience, patients with nephrotic

Table 4 Abnormalities contributing to RVT in nephrotic syndrome (Adapted after [23, 26])

System	Abnormality
Coagulation pathway	↑ level of fibrinogen, factor V, factor VIII ↓ level of antithrombin III, protein S Immune complex activation of the coagulation pathway
Fibrinolytic pathway	↑ level of α_2-macroglobulin, lipoprotein (a) ↓ level of plasminogen, tissue-type plasminogen activator (t-PA)
Platelets	↑ platelet count Increased platelet aggregability
Intravascular volume depletion or hemoconcentration	Hypoalbuminemia, diuretic therapy, hyperfibrinogenemia
Other factors	
• Genetic abnormalities	Factor V Leiden, prothrombin gene mutations, hyperhomocysteinemia
• Medication-related	Corticosteroids
• Intravascular devices	Central venous catheters
• Primary renal disorder	Anti-enolase antibodies in membranous nephropathy
• Clot structure	More resistant to fibrinolysis
• Hyperlipidemia	Increases platelet aggregability
• Immobilization	
• Inflammation	

syndrome that developed thromboembolic events had a significantly lower albumin level compared to those without events, with a serum albumin cutoff of 1.5 g/dL having a positive and negative predictive value of 69% and 93%, respectively [53]. By contrary, in the study by Llach et al, patients without RVT, with acute RVT and with chronic RVT had similar baseline albumin levels (mean, 2.4 vs. 2.1 vs. 2.2 g/dL, respectively) [50]. Thus, hypoalbuminemia may be a surrogate marker of increased risk, but is not prerequisite for the development of venous thromboembolic events [49].

Nonetheless, as the degree of hypoalbuminemia or proteinuria do not fully account for the risk of venous thrombotic events, other factors are implicated in its pathogenesis [23, 26]. The hemostatic derangements associated with nephrotic syndrome involve activation of the coagulation system, a decrease of endogenous anticoagulants, impaired fibrinolytic activity and increased platelet aggregability [23]. Urinary losses of antithrombin III (molecular weight, 65 kDa) and protein S (molecular weight, 62 kDa) are among the most studies abnormalities, although inconsistently associated with thrombotic events [23, 26]. We have identified that antithrombin III activity, but not protein S, was independently associated with venous thromboembolic events [53]. Contrary, several procoagulant proteins (fibrinogen, factor V and VII) with higher molecular weight (over 300 kDa) show markedly elevated levels in nephrotic syndrome, presumably due to increased hepatic synthesis determined by hypoalbuminemia [23]. The impairment of fibrinolytic system has been also implicated in the pathogenesis of thromboembolic events in nephrotic syndrome. Accordingly, several studies have identified a decrease of the plasminogen levels and its activator (t-PA) in addition to an increased concentration of several fibrinolysis inhibitors [α_2-macroglobulin and lipoprotein (a)] [23].

Enhanced platelet aggregability has been hypothesized to increase the thromboembolic risk in patients with nephrotic syndrome [23]. Platelet hyperaggregability *in vitro* was demonstrated in 72% of patients with nephrotic syndrome after exposure to agonists such as ADP or collagen [68]. In addition, the level of circulating platelets that express on their surface activation dependent-antigens (P-selectin and lysosomal GP53) was higher in patients with nephrotic syndrome compared to controls [68]. Moreover, the hyperlipidemia and intravascular volume depletion associated with nephrotic syndrome may further enhance the platelet hyperaggregability [23].

Genetic predisposition linked to mutations or single nucleotide polymorphisms of genes associated with inherited thrombophilia may also increase the likelihood of venous thromboembolic events in patients with nephrotic syndrome [26]. We have shown that the prevalence of polymorphisms for Factor V gene (G1691A), PAI gene (plasminogen activator inhibitor—4G/5G) and methylene tetrahydrofolate reductase (MTHFR) gene (C677T) was higher in patients with nephrotic syndrome and thrombotic events, while the association of two genetic abnormalities increased the risk for such events by almost 9-fold [49].

The predilection of RVT development in patients with nephrotic syndrome remains incompletely understood, but a local generation of thrombin within efferent vasculature subsequent to glomerular injury has been proposed [26, 69]. In addition,

the reason underlying a higher thromboembolic risk in membranous nephropathy remains largely speculative at this point. It was suggested that anti-enolase antibodies, identified in patients with membranous nephropathy, may inhibit the fibrinolytic pathway [3].

Perturbances of the hemostatic milieu have also been described in conditions other than nephrotic syndrome (e.g., antiphospholipid syndrome, systemic lupus erythematosus, ANCA-associated vasculitis). As previously outlined, antiphospholipid antibodies directly interfere with regulatory proteins of the clotting pathway, inhibit fibrinolysis, and activate of several cells leading to endothelial dysfunction, platelet aggregation and release of tissue factor from circulating monocytes [25]. In addition, anti-plasminogen and anti-tissue plasminogen activator antibodies were identified in 25% and 18% of patients with ANCA-associated vasculitis, respectively, and were shown to inhibit fibrinolysis *in vitro* [65].

Clinical Features

Similar to renal artery occlusion, there are no specific clinical symptoms and/or signs for the diagnosis of RVT [47]. Moreover, the clinical presentation depends on the rapidity of occlusion and development of collateral circulation (Fig. 4) [3].

In the largest study of patients with RVT (n = 218) the most common symptoms were abdominal and/or flank pain (73%) and macroscopic hematuria (36%), while

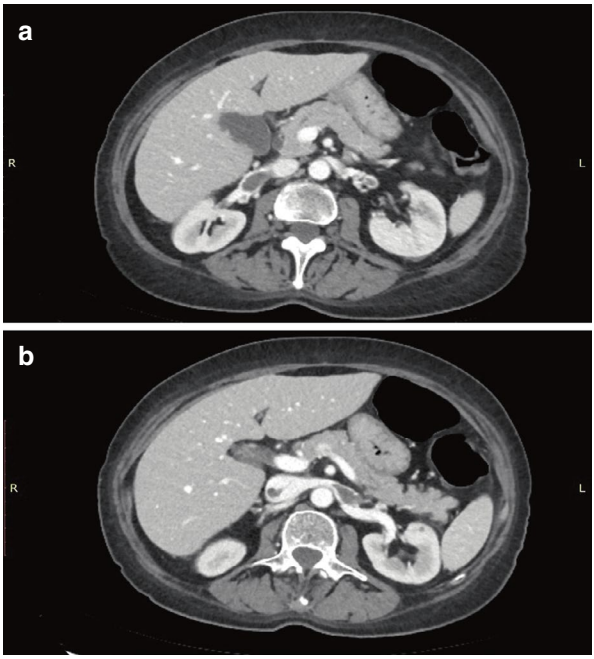

Fig. 4 Bilateral renal vein thrombosis. A 67-year old female with a histological diagnosis of primary membranous nephropathy underwent a CT scan as part of the work-up for potential secondary causes of nephrotic syndrome. (**a**, **b**) The contrast-enhanced CT scan identified a covert, bilateral, partial renal vein thrombosis with development of collateral circulation in the renal hilum. In addition, the imaging study excluded a coexisting malignancy. (*From the collection of the Nephrology Department of Fundeni Clinical Institute, with the permission of Prof. Dr. Gener Ismail*)

non-specific symptoms (such as nausea, fever, anorexia, vomiting) were present in approximately 40% of cases [55]. On clinical examination, asterixis was present in half of patients, 9% had lower limb edema, 9% had a palpable flank mass and 6% ascites. Additionally, 9 patients (4%) presented with peritoneal signs suggestive of an acute abdomen [55]. Thus, similar to acute renal artery occlusion, flank pain and gross hematuria might be mistaken for renal colic or acute pyelonephritis that may lead to a delay in the diagnosis of RVT.

In studies that included only patients with nephrotic syndrome, the clinical presentation varies significantly according to the intensity of screening employed [49]. Thus, studies performed in the 1980s and 1990s focused on the detection of RVT by renal venography, thereby identifying many asymptomatic events [49]. In the prospective study conducted by Llach et al, most of the 29 patients with chronic RVT had clinical features suggestive of nephrotic syndrome (69% with lower limb edema), but only two had gross hematuria and none flank pain compared to a frequency of 100% of flank pain/gross hematuria in those with acute RVT. In addition, patients with chronic RVT were older (mean age, 38 versus 20 years) and had a longer evolution of the nephrotic syndrome (mean, 8.7 versus 6 months) compared to those with acute RVT [50]. Given the non-specific clinical findings, a high index of suspicion should be maintained in such patients especially in the first 6–12 months after the nephrotic syndrome onset, when the majority of venous thromboembolic events occur [53]. Occasionally, the diagnosis of RVT is frequently overlooked until the occurrence of other thromboembolic complications such as pulmonary embolism [47].

While there are no specific laboratory tests, initial work-up might unveil the underlying disorder associated with RVT (e.g., hypoalbuminemia and proteinuria in nephrotic syndrome, positive serology for autoimmune disorders, etc.). In addition, patients at high-risk for RVT could be screened for earlier identification of asymptomatic events by periodic measurement of D-dimer levels [49].

Regarding the renal function, in the largest study of patients with RVT, approximately half of patients had renal impairment at the time of diagnosis, while 5.5% of cases required renal replacement therapy [55]. A serum creatinine level over 2 mg/dL was identified in 9.8% of patients at baseline, this percentage increasing to 19% after a mean follow-up period of 42 months. Bilateral RVT or unilateral RVT of a solitary kidney may present with oliguria/anuria and acute kidney injury [47].

Diagnosis

Given the lack of specific clinical manifestations and diagnostic laboratory tests, imaging is the cornerstone of diagnosis of RVT.

Doppler ultrasound may represent a first-line approach to the diagnosis of RVT because of its wide availability [47]. Ultrasound findings include enlarged and hyper-echogenic kidney in the acute phase, direct visualization of thrombi in the renal vein, dilation of renal vein proximal to the occlusion point, increased blood

velocity, turbulence or even complete cessation of blood flow if the occlusion is complete [2, 3]. Nonetheless, ultrasound is highly operator dependent and has an overall diagnostic performance lower than renal venography, with a low specificity (56%) despite having a high sensitivity (85%). In addition, Doppler ultrasound may have a limited value in the evaluation of segmental or distal thromboses, but may be useful in cases of RVT post-kidney transplantation [70].

Although inferior venacavography with selective catheterization of the renal vein is the gold standard for the diagnosis of RVT, it is an invasive procedure that has been progressively replaced by contrast-enhanced CT and MRI [47]. Currently, in cases with high clinical suspicion, a contrast-enhanced CT scan is the imaging modality of choice because is non-invasive, widely available, less expensive than MRI and has a high diagnostic accuracy with almost 100% sensitivity and specificity [1]. CT findings include enlarged kidney, decreased opacification of the collecting duct, persistent nephrogram due to poor venous washout and persistent corticomedullary differentiation [47]. In addition, a CT scan can identify underlying pathologies such as malignancy or other causes of extrinsic renal vein compression [47]. Nonetheless, one study identified a limited capacity of CT scan to detect isolated thrombi within intrarenal veins [71]. Magnetic resonance angiography is an alternative diagnostic modality for RVT, but its use is limited by lower availability and the increased examination time [72].

Treatment

Despite there are no dedicated guidelines, the management of RVT is similar to any other thrombotic or embolic event. Thus, the treatment of RVT currently relies on sequential anticoagulation with initial full-dose high or low molecular weight heparin followed by oral coumarin agents (vitamin K antagonists or warfarin) [47]. The use of direct oral anticoagulant agents (DOACs) has been limited to case reports and cannot be currently recommended due to a lack of dedicated trials evaluating their safety and efficacy in RVT associated or not with nephrotic syndrome [47, 73, 74]. In addition to anticoagulation, a treatment of the underlying cause of RVT should be employed.

Anticoagulation treatment should be continued for at least 6 months and the total duration is likely dependent on the risk on recurrences and/or subsequent pulmonary embolism [1]. Accordingly, for patients with nephrotic syndrome, the KDIGO 2021 guideline (Kidney Disease Improving Global Outcomes) suggests that full dose anticoagulation for thromboembolic events is required for 6–12 months and/or for the duration of nephrotic syndrome [73]. A previous study has shown a lower rate of recurrent thrombotic events in those with RVT compared to those with deep vein thrombosis (1 event/100 patient-year) [55]. Among the eight patients with RVT and recurrent thrombotic events, five had active malignancy and one had nephrotic syndrome. Recurrent thrombotic events included mainly deep vein thrombosis, while no RVT recurrences were noted. Another potential issue complicating the

approach to anticoagulation in nephrotic syndrome is whether we need to better distinguish between a prophylactic scenario and a treatment scenario in patients that may have an underlying chronic, asymptomatic RVT and therefore be at a higher risk for a further pulmonary embolism [75]. A previous study has identified 7 episodes of pulmonary embolism in 6 of the 29 patients with nephrotic syndrome and chronic RVT (20.6%) compared to 11 episodes in 8 of the 118 patients with nephrotic syndrome and no RVT (6.8%) [50]. At this moment, a routine screening for RVT in patients with nephrotic syndrome cannot be recommended in clinical practice. Moreover, while an initial imaging study confirming a covert chronic RVT will mandate secondary prophylactic anticoagulation for a pulmonary embolism, a negative imaging study does preclude any future RVT [75].

Currently there is insufficient evidence to routinely recommend prophylactic anticoagulation in patients with nephrotic syndrome due to the lack of dedicated randomized, controlled trials [75]. As the degree of hypoalbuminemia and proteinuria correlates with the risk of thromboembolic events in nephrotic syndrome, the current KDIGO guideline suggests that prophylactic anticoagulation may be considered in those with a serum albumin below 2–2.5 g/dL and additional risk factors (e.g., proteinuria>10 g/day, body mass index over 35 kg/m^2, coexistence of inherited thrombophilia, class III or IV heart failure, recent orthopedic or abdominal surgery, prolonged immobilization), if the thrombotic risk exceeds the hemorrhagic risk [73]. Given the lack of controlled trials, the decision to initiate prophylactic anticoagulation in nephrotic syndrome relies on several studies that employed hypothetical assumptions based on Markov modeling and decision analysis [75]. Sarasin and Schifferli evaluated by this approach the consequences of recurrent embolism and bleeding events of two strategies, prophylactic anticoagulation versus anticoagulation after the first thromboembolic event [76]. They have estimated from the literature a monthly incidence of 0.5% and 1% for RVT and deep vein thrombosis, with a probability of pulmonary embolism of 30% and 50% following RVT and deep vein thrombosis, respectively. Similarly, the estimated monthly incidence of anticoagulation-related major bleeding events was 0.25%. The probability of death from pulmonary embolism was 30%, while from major bleeding was 12%. Thus, using this analysis they concluded that the number of fatal emboli prevented by prophylactic anticoagulation exceeds the fatal bleeding episodes. Hypothetically, in a 50-year-old patient with persistent nephrotic syndrome for 2 years, prophylactic anticoagulation would result in additional 2.5 months of quality-adjusted life expectancy gained [76]. A similar decision analysis was undertaken by Bellomo and Atkins [77]. They estimated an incidence of hemorrhagic complications associated with anticoagulation of 17 events per 1000 patient-months at an INR of approximately 2, while the risk for thromboembolic events was assumed at about 40%. In their analysis, a prophylactic anticoagulation was associated with a 32% lower rate of morbid events [77].

Another approach to the prevention of thromboembolic events was evaluated in a retrospective study with 143 patients with nephrotic syndrome [78]. Thus, patients were stratified according to baseline albumin level. Those with serum albumin below 2 g/dL received low-molecular weight heparin (enoxaparin 20 mg or

equivalent formulation) and, if the hypoalbuminemia persisted for more than 3 months, were switched to warfarin for a target INR of 1.5–2.5. Patients with a baseline serum albumin of 2–3 g/dL received aspirin (75 mg/day), while those with serum level over 3 g/dL did not receive thromboprophylaxis. This approach was deemed effective for thromboembolic prophylaxis in nephrotic syndrome, but the results should be interpreted with caution as the number of both thrombotic and hemorrhagic events was very low (1.39% and 0.69%, respectively) [78]. Lastly, the optimal duration of prophylactic anticoagulation remains unknown but should be maintained for at least until the remission of the nephrotic syndrome [75].

As outlined in the renal artery thrombosis section, dedicated guidelines for primary and secondary thromboprophylaxis have been developed for patients with antiphospholipid antibody syndrome [40]. Thus, a primary prevention of thrombotic events in asymptomatic patients with a high-risk antiphospholipid antibody profile with low-dose aspirin (75–100 mg/daily) is recommended [40]. Additionally, in patients with definitive antiphospholipid syndrome and a first venous thrombosis, treatment with a vitamin K antagonist with a target INR of 2–3 is recommended and should be continued long-term [40]. There is a suggestion that rivaroxaban should not be used in patients with triple antibody positivity due to a high risk of recurrences.

Thrombolysis and thrombectomy are viable options in severe cases with acute kidney injury due to bilateral RVT or unilateral RVT on a solitary kidney, renal transplantation, extension into inferior vena cava or development of pulmonary embolism, treatment failure of anticoagulation or severe flank pain [1, 47, 79, 80].

Prognosis

The prognosis of patients with RVT should be evaluated in terms of recurrences, occurrence of complications (pulmonary embolism), renal survival and mortality.

In a study that included all patients with RVT diagnosed at a tertiary clinic between 1980 and 2000 (n = 218), there were eight recurrent venous thrombotic events during a mean follow-up period of 42 ± 57 months (1 event/100 patient-years), with the majority being deep vein thrombosis and no recurrent RVT events [55]. In addition, the risk of pulmonary embolism following RVT may be as high as 30%, especially with covert, asymptomatic forms [50, 76]. A mortality rate of approximately 10% per year was identified in patients with membranous nephropathy as a result of thromboembolism [76]. Nonetheless, while the survival of patients with RVT was lower (18 deaths per 100 patient-years) compared to those with deep vein thrombosis, the increased mortality was not driven by the presence of nephrotic syndrome, but due to active malignancy [55].

In terms of renal outcomes, in the previous study, approximately half of patients had renal impairment at the time of diagnosis, while 5.5% of cases required renal replacement therapy. The prevalence of patients with renal impairment doubled with long-term follow-up [55]. Among the most important prognostic factors for renal outcome in RVT are the baseline renal function and the risk of progression of

the underlying disease, the extent of thrombosis (unilateral versus bilateral), rapidity of onset and development of collateral circulation [47].

References

1. Woo JR, Yun EJ, Kane CJ. Renal artery embolism and renal vein thrombosis. In: Wessells H, editor. Urological emergencies. Current clinical urology. Totowa: Humana Press; 2013.
2. Coffman TM, Falk RJ, Molitoris BA, Neilson EG, Schrier RW. Chapter 56: Renal artery thrombosis, thromboembolism, aneurysms, Atheroemboli, and renal vein thrombosis. In: Schrier's diseases of the kidney. 9th ed. Philadelphia: Lippincott, Williams and Wilkins; 2013. p. 1605–26.
3. Skorecki K, Chertow GM, Marsden PA, Taal MW, Yu ASL. Chapter 35: Microvascular and macrovascular diseases of the kidney. In: Brenner & Rector's the kidney. 10th ed. Philadelphia: Elsevier; 2016. p. 1175–208.
4. Huang CC, Lo HC, Huang HH, Kao WF, Yen DH, Wang LM, Huang CI, Lee CH. ED presentations of acute renal infarction. Am J Emerg Med. 2007;25(2):164–9.
5. Faucon AL, Bobrie G, Jannot AS, Azarine A, Plouin PF, Azizi M, Amar L. Cause of renal infarction: a retrospective analysis of 186 consecutive cases. J Hypertens. 2018;36(3):634–40.
6. Bourgault M, Grimbert P, Verret C, Pourrat J, Herody M, Halimi JM, et al. Acute renal infarction: a case series. Clin J Am Soc Nephrol. 2013;8(3):392–8.
7. Oh YK, Yang CW, Kim YL, Kang SW, Park CW, Kim YS, Lee EY, Han BG, Lee SH, Kim SH, Lee H, Lim CS. Clinical characteristics and outcomes of renal infarction. Am J Kidney Dis. 2016;67(2):243–50.
8. Bae EJ, Hwang K, Jang HN, Kim MJ, Jeon DH, Kim HJ, et al. A retrospective study of short- and long-term effects on renal function after acute renal infarction. Ren Fail. 2014;36(9):1385–9.
9. Hazanov N, Somin M, Attali M, Beilinson N, Thaler M, Mouallem M, Maor Y, Zaks N, Malnick S, Acute renal embolism. Forty-four cases of renal infarction in patients with atrial fibrillation. Medicine (Baltimore). 2004;83(5):292–9.
10. Antopolsky M, Simanovsky N, Stalnikowicz R, Salameh S, Hiller N. Renal infarction in the ED: 10-year experience and review of the literature. Am J Emerg Med. 2012;30(7):1055–60.
11. Frost L, Engholm G, Johnsen S, Møller H, Henneberg EW, Husted S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. Arch Intern Med. 2001;161(2):272–6.
12. Krämer SC, Seifarth H, Pamler R, Fleiter T, Bühring J, Sunder-Plassmann L, Brambs HJ, Görich J. Renal infarction following endovascular aortic aneurysm repair: incidence and clinical consequences. J Endovasc Ther. 2002;9(1):98–102.
13. Böckler D, Krauss M, Mansmann U, Halawa M, Lange R, Probst T, Raithel D. Incidence of renal infarctions after endovascular AAA repair: relationship to infrarenal versus suprarenal fixation. J Endovasc Ther. 2003;10(6):1054–60.
14. Holden A, Hill A. Renal angioplasty and stenting with distal protection of the main renal artery in ischemic nephropathy: early experience. J Vasc Surg. 2003;38(5):962–8.
15. Osman Y, Shokeir A, Ali-el-Dein B, Tantawy M, Wafa EW, el-Dein AB, Ghoneim MA. Vascular complications after live donor renal transplantation: study of risk factors and effects on graft and patient survival. J Urol. 2003;169(3):859–62.
16. van der Wal MA, Wisselink W, Rauwerda JA. Traumatic bilateral renal artery thrombosis: case report and review of the literature. Cardiovasc Surg. 2003;11(6):527–9.
17. Jawas A, Abu-Zidan FM. Management algorithm for complete blunt renal artery occlusion in multiple trauma patients: case series. Int J Surg. 2008;6(4):317–22.

18. Singh O, Gupta SS, Sharma D, Lahoti BK, Mathur RK. Isolated renal artery thrombosis because of blunt trauma abdomen: report of a case with review of the literature. Urol Int. 2011;86(2):233–8.
19. Tektonidou MG. Antiphospholipid syndrome nephropathy: from pathogenesis to treatment. Front Immunol. 2018;9:1181.
20. Sciascia S, Cuadrado MJ, Khamashta M, Roccatello D. Renal involvement in antiphospholipid syndrome. Nat Rev Nephrol. 2014;10(5):279–89.
21. Tsugawa K, Tanaka H, Kudo M, Nakahata T, Ito E. Renal artery thrombosis in a pediatric case of systemic lupus erythematosus without antiphospholipid antibodies. Pediatr Nephrol. 2005;20(11):1648–50.
22. Kaushik S, Federle MP, Schur PH, Krishnan M, Silverman SG, Ros PR. Abdominal thrombotic and ischemic manifestations of the antiphospholipid antibody syndrome: CT findings in 42 patients. Radiology. 2001;218(3):768–71.
23. Singhal R, Brimble KS. Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. Thromb Res. 2006;118(3):397–407.
24. Sullivan MJ 3rd, Hough DR, Agodoa LC. Peripheral arterial thrombosis due to the nephrotic syndrome: the clinical spectrum. South Med J. 1983;76(8):1011–6.
25. Bienaimé F, Legendre C, Terzi F, Canaud G. Antiphospholipid syndrome and kidney disease. Kidney Int. 2017;91(1):34–44.
26. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. Clin J Am Soc Nephrol. 2012;7(3):513–20.
27. Jurubita R, Obrisca B, Ismail G. A rare cause of acute kidney injury in a female patient with breast cancer presenting as renal colic. Case Rep Nephrol. 2016;2016:9565873.
28. Paris B, Bobrie G, Rossignol P, Le Coz S, Chedid A, Plouin PF. Blood pressure and renal outcomes in patients with kidney infarction and hypertension. J Hypertens. 2006;24(8):1649–54.
29. Cai S, Ouyang YS, Li JC, Dai Q, Tan L, Xia Y, Xu ZH, Li HJ, Jiang YX. Evaluation of acute renal artery thrombosis or embolism with color Doppler sonography. Clin Imaging. 2008;32(5):367–71.
30. Suzer O, Shirkhoda A, Jafri SZ, Madrazo BL, Bis KG, Mastromatteo JF. CT features of renal infarction. Eur J Radiol. 2002;44(1):59–64.
31. Lang EK, Sullivan J, Frentz G. Renal trauma: radiological studies. Comparison of urography, computed tomography, angiography, and radionuclide studies. Radiology. 1985;154(1):1–6.
32. Lang EK. Arteriography in the assessment of renal trauma. The impact of arteriographic diagnosis on preservation of renal function and parenchyma. J Trauma. 1975;15(7):553–66.
33. Lengelé JP, Christophe JL, Persu A. Renal infarction management: towards an etiological approach? J Hypertens. 2018;36(3):490–2.
34. Dardik A, Ballermann BJ, Williams GM. Successful delayed bilateral renal revascularization during active phase of Takayasu's arteritis. J Vasc Surg. 1998;27(3):552–4.
35. Yavuzgil O, Gürgün C, Zoghi M, Tekin F. Bilateral renal arterial embolisation in a patient with mitral stenosis and atrial fibrillation: an uncommon reason of flank pain. Anadolu Kardiyol Derg. 2003;3(1):73–5.
36. Gasparini M, Hofmann R, Stoller M. Renal artery embolism: clinical features and therapeutic options. J Urol. 1992;147(3):567–72.
37. Blum U, Billmann P, Krause T, Gabelmann A, Keller E, Moser E, Langer M. Effect of local low-dose thrombolysis on clinical outcome in acute embolic renal artery occlusion. Radiology. 1993;189(2):549–54.
38. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, GYH L, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL, ESC Scientific Document Group. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with

the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42(5):373–498.
39. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W, ESC/EACTS Scientific Document Group. 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2022;43(7):561–632.
40. Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, Cuadrado MJ, Dörner T, Ferrer-Oliveras R, Hambly K, Khamashta MA, King J, Marchiori F, Meroni PL, Mosca M, Pengo V, Raio L, Ruiz-Irastorza G, Shoenfeld Y, Stojanovich L, Svenungsson E, Wahl D, Tincani A, Ward MM. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019;78(10):1296–304.
41. Vidal E, Marrone G, Gasparini D, Pecile P. Radiological treatment of renal artery occlusion after blunt abdominal trauma in a pediatric patient: is it never too late? Urology. 2011;77(5):1220–2.
42. Chabrot P, Cassagnes L, Alfidja A, Mballa JC, Nasser S, Guy L, Diop AN, Ravel A, Boyer L. Revascularization of traumatic renal artery dissection by endoluminal stenting: three cases. Acta Radiol. 2010;51(1):21–6.
43. Kushimoto S, Shiraishi S, Miyauchi M, Tanabe S, Fukuda R, Tsujii A, Masuno T, Kim S, Kawai M, Yokota H, Tajima H. Traumatic renal artery occlusion treated with an endovascular stent—the limitations of surgical revascularization: report of a case. Surg Today. 2011;41(7):1020–3.
44. Ouriel K, Andrus CH, Ricotta JJ, DeWeese JA, Green RM. Acute renal artery occlusion: when is revascularization justified? J Vasc Surg. 1987;5(2):348–55.
45. Maggio AJ Jr, Brosman S. Renal artery trauma. Urology. 1978;11(2):125–30.
46. Kansal S, Feldman M, Cooksey S, Patel S. Renal artery embolism: a case report and review. J Gen Intern Med. 2008;23(5):644–7.
47. Asghar M, Ahmed K, Shah SS, Siddique MK, Dasgupta P, Khan MS. Renal vein thrombosis. Eur J Vasc Endovasc Surg. 2007;34(2):217–23.
48. Berbecar VT, Jurubita R, Paraschiv M, Obrisca B, Sorohan B, Ismail G. Inferior vena cava and renal vein thrombosis associated with thymic carcinoma. Case Rep Med. 2017;2017:1793952.
49. Ismail G, Obrișcă B, Jurubiță R, Andronesi A, Sorohan B, Hârza M. Inherited risk factors of thromboembolic events in patients with primary nephrotic syndrome. Medicina (Kaunas). 2020;56(5):242.
50. Llach F, Papper S, Massry SG. The clinical spectrum of renal vein thrombosis: acute and chronic. Am J Med. 1980;69(6):819–27.
51. Wagoner RD, Stanson AW, Holley KE, Winter CS. Renal vein thrombosis in idiopathic membranous glomerulopathy and nephrotic syndrome: incidence and significance. Kidney Int. 1983;23(2):368–74.
52. Mahmoodi BK, ten Kate MK, Waanders F, Veeger NJ, Brouwer JL, Vogt L, Navis G, van der Meer J. High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. Circulation. 2008;117(2):224–30.
53. Ismail G, Mircescu G, Ditoiu AV, Tacu BD, Jurubita R, Harza M. Risk factors for predicting venous thromboembolism in patients with nephrotic syndrome: focus on haemostasis-related parameters. Int Urol Nephrol. 2014;46(4):787–92.
54. Adams RL, Bird RJ. Review article: coagulation cascade and therapeutics update: relevance to nephrology. Part 1: overview of coagulation, thrombophilias and history of anticoagulants. Nephrology (Carlton). 2009;14(5):462–70.
55. Wysokinski WE, Gosk-Bierska I, Greene EL, Grill D, Wiste H, McBane RD 2nd. Clinical characteristics and long-term follow-up of patients with renal vein thrombosis. Am J Kidney Dis. 2008;51(2):224–32.
56. Hârza M, Ismail G, Mitroi G, Gherghiceanu M, Preda A, Mircescu G, Sinescu I. Histological diagnosis and risk of renal vein thrombosis, and other thrombotic complications in primitive nephrotic syndrome. Romanian J Morphol Embryol. 2013;54(3):555–60.

57. Barbour SJ, Greenwald A, Djurdjev O, Levin A, Hladunewich MA, Nachman PH, Hogan SL, Cattran DC, Reich HN. Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. Kidney Int. 2012;81(2):190–5.
58. Wolak T, Rogachev B, Tovbin D, Hertzanu Y, Zlotnik M, Lugassy G. Renal vein thrombosis as a presenting symptom of multiple genetic pro-coagulant defects. Nephrol Dial Transplant. 2005;20(4):827–9.
59. Irish AB. The factor V Leiden mutation and risk of renal vein thrombosis in patients with nephrotic syndrome. Nephrol Dial Transplant. 1997;12(8):1680–3.
60. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, Mejía JC, Aydintug AO, Chwalinska-Sadowska H, de Ramón E, Fernández-Nebro A, Galeazzi M, Valen M, Mathieu A, Houssiau F, Caro N, Alba P, Ramos-Casals M, Ingelmo M, Hughes GR, Party EW, on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore). 2003;82(5):299–308.
61. Lai NS, Lan JL. Renal vein thrombosis in Chinese patients with systemic lupus erythematosus. Ann Rheum Dis. 1997;56(9):562–4.
62. Stone JH, Amend WJ, Criswell LA. Antiphospholipid antibody syndrome in renal transplantation: occurrence of clinical events in 96 consecutive patients with systemic lupus erythematosus. Am J Kidney Dis. 1999;34(6):1040–7.
63. Wlodek C, Robson MG. Anti-neutrophil cytoplasmic antibody vasculitis presenting with bilateral renal vein thrombosis. Clin Kidney J. 2012;5(3):229–31.
64. Bautz DJ, Preston GA, Lionaki S, Hewins P, Wolberg AS, Yang JJ, Hogan SL, Chin H, Moll S, Jennette JC, Falk RJ. Antibodies with dual reactivity to plasminogen and complementary PR3 in PR3-ANCA vasculitis. J Am Soc Nephrol. 2008;19(12):2421–9.
65. Berden AE, Nolan SL, Morris HL, Bertina RM, Erasmus DD, Hagen EC, Hayes DP, van Tilburg NH, Bruijn JA, Savage CO, Bajema IM, Hewins P. Anti-plasminogen antibodies compromise fibrinolysis and associate with renal histology in ANCA-associated vasculitis. J Am Soc Nephrol. 2010;21(12):2169–79.
66. Parmar K, Thakur A, Sharma A, Kumar S. Isolated renal vein and inferior vena cava thrombus following blunt trauma abdomen. A rare case scenario. Trauma Case Rep. 2020;25:100282.
67. Kumar S, Chapagain A, Nitsch D, Yaqoob MM. Proteinuria and hypoalbuminemia are risk factors for thromboembolic events in patients with idiopathic membranous nephropathy: an observational study. BMC Nephrol. 2012;13:107.
68. Sirolli V, Ballone E, Garofalo D, Merciaro G, Settefrati N, Di Mascio R, Di Gregorio P, Bonomini M. Platelet activation markers in patients with nephrotic syndrome. A comparative study of different platelet function tests. Nephron. 2002;91(3):424–30.
69. Llach F. Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome. Kidney Int. 1985;28(3):429–39.
70. Avasthi PS, Greene ER, Scholler C, Fowler CR. Noninvasive diagnosis of renal vein thrombosis by ultrasonic echo-Doppler flowmetry. Kidney Int. 1983;23(6):882–7.
71. Wei LQ, Rong ZK, Gui L, Shan RD. CT diagnosis of renal vein thrombosis in nephrotic syndrome. J Comput Assist Tomogr. 1991;15(3):454–7.
72. Kanagasundaram NS, Bandyopadhyay D, Brownjohn AM, Meaney JF. The diagnosis of renal vein thrombosis by magnetic resonance angiography. Nephrol Dial Transplant. 1998;13(1):200–2.
73. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4):S1–276.
74. Shimada Y, Nagaba Y, Nagaba H, Kamata M, Murano J, Kamata F, Okina C, Nonoguchi H, Shimada H, Takeuchi Y. Edoxaban was effective for treating renal vein thrombosis in a patient with nephrotic syndrome. Intern Med. 2017;56(17):2307–10.
75. Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. J Am Soc Nephrol. 2007;18(8):2221–5.

76. Sarasin FP, Schifferli JA. Prophylactic oral anticoagulation in nephrotic patients with idiopathic membranous nephropathy. Kidney Int. 1994;45(2):578–85.
77. Bellomo R, Atkins RC. Membranous nephropathy and thromboembolism: is prophylactic anticoagulation warranted? Nephron. 1993;63(3):249–54.
78. Medjeral-Thomas N, Ziaj S, Condon M, Galliford J, Levy J, Cairns T, Griffith M. Retrospective analysis of a novel regimen for the prevention of venous thromboembolism in nephrotic syndrome. Clin J Am Soc Nephrol. 2014;9(3):478–83.
79. Markowitz GS, Brignol F, Burns ER, Koenigsberg M, Folkert VW. Renal vein thrombosis treated with thrombolytic therapy: case report and brief review. Am J Kidney Dis. 1995;25(5):801–6.
80. Kim HS, Fine DM, Atta MG. Catheter-directed thrombectomy and thrombolysis for acute renal vein thrombosis. J Vasc Interv Radiol. 2006;17(5):815–22.

Renovascular Disease: Updated Management Protocols

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Abstract Renovascular disease (RVD), including atherosclerotic renovascular disease (ARVD) and fibromuscular disease (FMD), significantly contributes to renal artery stenosis (RAS). ARVD, the predominant cause in Western populations, and FMD, more common in younger women, require distinct management approaches. Recent shifts in ARVD management focus on medical therapy rather than routine revascularization, driven by neutral outcomes from large randomized controlled trials (RCTs) like ASTRAL and CORAL. These studies highlight the limited benefit of revascularization for unselected patients, though high-risk individuals with severe hypertension or heart failure may still benefit. FMD management often includes revascularization, particularly effective for hypertension control. Current protocols emphasize comprehensive medical management for ARVD, utilizing antihypertensives, statins, and antiplatelet agents to mitigate cardiovascular risks. Identifying patients who benefit most from revascularization remains a priority, requiring a personalized, multidisciplinary approach. Future research aims to explore therapies targeting inflammation and fibrosis to enhance renal outcomes. Understanding patient-specific characteristics and employing targeted strategies are crucial for optimizing clinical outcomes in RVD management.

Keywords Renovascular disease · Atherosclerotic renovascular disease · Fibromuscular disease · Renal artery stenosis · Revascularization

Introduction

Renovascular disease (RVD) is a common condition that can cause, or be associated with, serious clinical abnormalities. Atherosclerotic renovascular disease (ARVD) accounts for >90% of renal artery stenosis (RAS) in Western populations, the rest resulting from fibromuscular disease (FMD). In the Indian subcontinent and Far

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East, vasculitis may be responsible for a significant proportion of cases of RAS. The epidemiology and outcomes of FMD and ARVD differ markedly and will be considered separately. With respect to treatment, the focus for ARVD has shifted significantly from renal revascularization for all those with RAS and hypertension or renal impairment to targeted medical management. This has altered the progression and the clinical outcomes of those with RVD including both ARVD and FMD. The results of large RCTs of revascularization in ARVD have to date been essentially neutral but there has been significant bias in terms of patient selection with high-risk patients or those with FMD largely excluded; the degree of stenosis has also varied. However, there is evidence of benefit of revascularization in those with FMD or those ARVD patients presenting with a high-risk clinical syndrome. The challenges of identifying these individuals still exist. The future management should involve identifying the patients most likely to benefit from revascularization and, as well as restoring renal blood flow in ARVD, attention should be focused on preventing the activation of or ameliorating inflammatory pathways that ultimately lead to fibrosis and chronic kidney disease or other cardiovascular complications.

Fibromuscular Disease (FMD)

Epidemiology, Clinical Presentation and Prognosis

FMD is nine times more common in women than men and can affect any vascular bed, but most commonly involves the renal arteries followed by the cranial arteries. Hence, if renal FMD is detected imaging to identify disease elsewhere is important, especially CT or MR brain imaging to look for intracranial aneurysms. Some patients present with sudden coronary artery dissection (SCAD). Renal FMD prevalence is as high as 3–4% in the general population as determined by live kidney donor data. In patients with renovascular hypertension, data from the CORAL trial showed an FMD prevalence of 6% [1]. Renal FMD most commonly manifests symptomatically as hypertension, with significant renal impairment being unusual.

Treatment of Renal Fibromuscular Disease (FMD)

Being a less common condition, FMD has been less extensively studied in comparison to ARVD and many questions remain in terms of its aetiology and management. In comparison to atherosclerotic RAS, revascularization appears to be effective at lowering blood pressure in patients with focal FMD of the renal arteries. However, randomised control trials of revascularization for FMD are lacking and observational studies can be biased. A large meta-analysis of 47 angioplasty studies (1616 patients) and 23 surgical studies (1014 patients) showed that hypertension was cured (defined as normalised blood pressure and no requirement of anti-hypertensive

medication) by balloon angioplasty in 40–52% of cases and by surgery in 53–62% of the cases. The risks of periprocedural complications was 12% after angioplasty and 17% after surgery. The blood pressure outcome was strongly influenced by age. Younger patients and those diagnosed early in the disease likely have better blood pressure outcomes [2]. Even in those in FMD in whom 'cure' of hypertension was not achieved with angioplasty, improvements in blood pressure, renal function (with average increase in eGFR of 6–7 ml/min), and in the number of antihypertensive agents required are seen [3].

This significant difference in benefit of revascularization compared to ARVD patients is likely explained by preservation of the microvascular function in kidneys affected by FMD, whereas in ARVD years of microvascular damage due to hypertension, dyslipidaemia and ischaemia may well have preceded the clinical RAS presentation. The international consensus is that angioplasty alone is the treatment of choice for those with RAS >50% due to FMD and hypertension, with stenting reserved for complications in those with a haemodynamically significant lesion and poorly controlled hypertension or in those with a renal aneurysm >2 cm diameter. These suggestions are based on limited data and ongoing registries will contribute to better understanding of the disease and the potential benefit of revascularization.

Atherosclerotic Renovascular Disease (ARVD)

Epidemiology, Clinical Presentation and Prognosis

Patients with ARVD present in many ways, the most common being hypertension refractory to multiple blood pressure–lowering agents. Patients with severe hypertension have a high likelihood of ARVD with prevalence 10–40% depending on the CKD or vascular enrichment of the population [4]. Decline in eGFR after initiation of RAAS inhibitor therapy is a hallmark presentation, as is 'flash' pulmonary oedema. In a single centre study of almost 500 ARVD patients, approximately half presented with a high risk clinical phenotype defined as acute pulmonary oedema, refractory hypertension and rapidly declining renal function [5].

Data from Medicare show that in the general population aged ≥67 years the incidence of ARVD is around 0.4 cases per 100 patient years [6]. However, in CKD cohorts the prevalence of ARVD can be up to 20% and about 10% of patients initiating dialysis will have ARVD [7]. In a large cohort of CKD patients with >550 having ARVD, this diagnosis was associated with a greater risk of death (HR 1.5 (1.2–1.8), $P < 0.001$) but not renal replacement therapy compared to other causes of CKD. In fact the likelihood of death in ARVD is almost three times that of RRT (44% versus 16% over 4 years), and patients commencing RRT with ARVD have a 50% mortality at 16 months [7].

Echocardiography is abnormal in 95% of ARVD patients especially with greater prevalence of left ventricular hypertrophy compared to eGFR matched controls

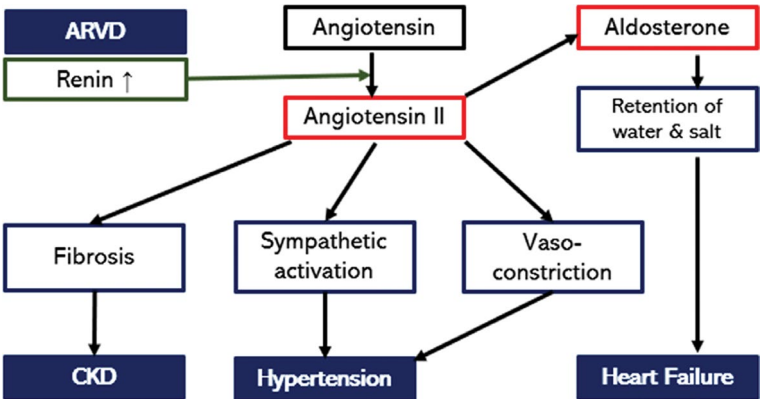

Fig. 1 The role of overactivation of the renin-angiotensin pathway in the development of cardiovascular complications in renal artery stenosis

(78.5% versus 46.0%, $p < 0.001$) [8]. Patients have a marked burden of cardiovascular complications due to hypertension and also extra-renal vascular disease. A third of patients had a cardiovascular event in a 4 year follow up study after ARVD diagnosis, and incidence of coronary, peripheral vascular disease, stroke and heart failure events are all 3–5 times greater than in the age matched general population [6]. This association with other cardiovascular disease explains why ARVD is commonly diagnosed in patients with heart failure (prevalence of ARVD may be >50%) [9] and 14–30% of patients undergoing coronary angiography will have evidence of ARVD [10]. A schematic representation of the pathway to development of cardiovascular complications and CKD is found in Fig. 1.

The History of Atherosclerotic Renovascular Disease (ARVD) Treatment Over the Last 50 Years

The treatment of ARVD has evolved substantially over the course of the last 50 years, guided latterly by controlled trial and high quality clinical data and an evidence based approach, and it is helpful to articulate these phases:

1970–1980 No statins and no angioplasty; the main stay of treatment was surgical with attention directed mainly to treatment of very severe hypertension and progressive renal failure. A lot of procedures for RAS had the aim of preventing later renal artery occlusion (RAO) as the risk of this was around 10% per year for severe RAS. Nephrectomy was undertaken for the atrophic kidney supplied by severe RAS as contemporary anti-hypertensive therapy was sub-optimal and prone to marked side effects, with endarterectomy or arterial by-pass procedures (e.g. spleno-renal) undertaken when renal preservation was desired.

1980–1990 The advent of percutaneous arterial procedures; percutaneous angioplasty (PCTA) was increasingly used in preference to surgery and although no RCT were performed, some clinicians maintained quality databases. Outcome data generally focused on blood pressure control. However, there was recognition that severe RAS could present with 'flash pulmonary oedema' which essentially was heart failure due to severe hypertension.

1990–2000 The arrival of statins focused clinicians' attention to the value of medical therapy in slowing progressive narrowing of RAS lesions. PCTA was ever increasingly used but concerns were emerging of the risk of re-stenosis, especially of ostial lesions. A small study of just 85 patients by Van de Ven, published in 1998, had a huge impact by showing that the re-stenosis rate was far less with use of renal arterial stents and renal artery stenting became the standard revascularization technique for most atherosclerotic RAS lesions, and so it is to this day [11]. In the latter part of this decade small RCT were being developed and three were published. Two of these concentrated on blood pressure control in patients with fairly well-preserved kidney function; the largest study included just 106 patients. The results were largely neutral although a meta-analysis of all three found that PCTA improved systolic blood pressure control in patients with bilateral RAS [12].

2000–2010 In the next decade percutaneous renal artery procedures reached their peak, with the health insurance provider Medicare alone recording >30,000 stent procedures being undertaken annually in the United States. Indications for this treatment were unregulated until guidelines were developed by JACC in 2005, emphasising the importance of taking note of the severity of stenosis, the presence of bilateral disease and the associated clinical syndrome. With this proliferation of revascularization activity that was wholly non evidence-based, with RAS treated 'just because it was there', there was a call for larger RCT, and the ASTRAL (806 patients) [13] and CORAL (947 patients) [1] trials were undertaken. ASTRAL was published in 2009 and CORAL in 2013.

2010–2020 ASTRAL showed that in unselected patients with RAS stenting in addition to medical therapy did not improve kidney function over time (the primary outcome), or blood pressure control, cardiovascular events or survival (secondary end-points), when compared with medical therapy alone. CORAL had more stringent selection criteria based on the need for demonstration of radiological confirmation of severity of RAS and had a real-world applicable composite primary outcome that included MACE, renal functional decline and death, but it again showed no value of renal revascularization and medical therapy over the latter alone. These two RCT changed the global face of ARVD management with a significant decline in stenting procedures and emphasis upon medical therapy with statins, anti-platelets and optimal blood pressure control based upon renin angiotensin aldosterone system inhibition (RAASi). However, the results of these RCT were necessarily presented as large group comparisons, and many patients who were believed to have 'established indications' for revascularization were not included. Acknowledgment

of the latter led to the call for a more personalised approach to treating atherosclerotic RAS with the growing recognition that sub-groups of patients with severe RAS exist who had a beneficial response to stenting.

Present Day Although many centres have stopped investigating for atherosclerotic RAS and no longer undertake renal revascularization procedures, others are now taking a more focused personalised approach with multi-disciplinary evaluation of the suitability of RAS lesions for revascularization, and attention to the clinical presentation of the patient, with certain clinical scenarios being more worthy of stenting. An example or RAS revascularization is found in Fig. 2.

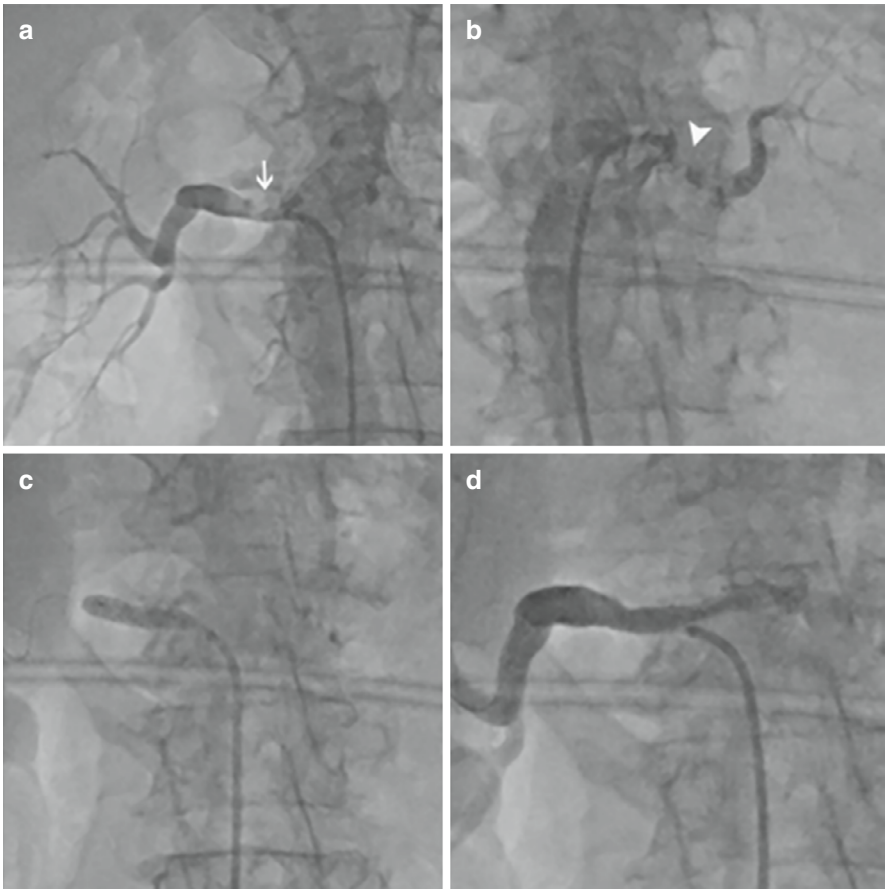

Fig. 2 Case example of successful revascularisatoin with symptomatic benefit. Bilateral renal artery stenosis in a patient with flash pulmonary edema and rapidly declining renal function. The tight stenosis on the right renal artery (**panel a**) was stented (**panel c**) with a good final result (**panel d**). The subocluded left renal artery (**panel b**) subtended a small kidney (presumably, non-viable). Serum creatinine normalized 72 h after the procedure, there were no recurrences of pulmonary edema at 2 years of follow-up and hypertension was controlled with a single drug. (Taken from Homorodean et al. [34])

Evidence Base Underpinning the Current Management of ARVD

As evidence emerged regarding the lack of benefit of renal revascularisation there was also significant progress in relation to optimal medical management. Patients with ARVD are now largely treated with lipid lowering agents, mainly statins, anti-platelet and RAASi rather than renal revascularisation procedures. An Italian study followed 54 patients with ARVD treated medically and 136 patients treated with angioplasty for an average of 54.4 months [14]. Statins were only prescribed for those with documented hypercholesterolaemia and a third of patients were receiving ACE-I. ACE-I was associated with improved survival in both groups. Again, revascularization did not confer an advantage over medical therapy in terms of mortality or renal outcomes. A retrospective non-randomised study by Silva et al involved 104 ARVD patients followed up over an 11 year period; of the 68 patients treated with statins lesser progression of renal insufficiency was noted with 7.4% statin-treated patients reaching renal end points such as doubling of baseline creatinine or ESKD requiring renal replacement versus 38.9% of those not receiving a statin. There was also a considerably lower mortality in the statin group (5.9% versus 36.1% with $p < 0.001$) despite patients having virtually identical lipid profiles [15].

It is generally accepted that anti-platelet agents should be part of the medical therapy for ARVD patients due to their widespread extra-renal burden of atheromatous disease. Cholesterol embolization is a rare but devastating complication of renal revascularization and one study has illustrated a significant reduction in the rate of cholesterol embolization when clopidogrel is added to standard care with aspirin prior to renal revascularization. In these patients it also important not to overlook the importance of lifestyle modifications such as smoking cessation, moderate alcohol intake, physical activity, weight loss and low fat diet to reduce their atherosclerotic risk.

As summarised above, large trial data has largely reduced the interest in renal revascularization in the setting of ARVD, with dramatic reduction in the number of procedures being performed; a Cochrane meta-analysis from 2015 concluded that there was insufficient evidence to support renal revascularization over medical treatment for those with atherosclerotic RAS, despite the minor signal for improvement in diastolic blood pressure and slightly reduced anti-hypertensive tablet load [16]. An earlier meta-analysis from 2011 came to the same conclusion with smaller numbers—6 trials with 1208 patients. The authors concluded that revascularization did not confer any benefit in addition to medical treatment in terms of renal or clinical outcomes but that it might result in reduction in number of anti-hypertensive agents [17]. A comparative effectiveness analysis in 2016 concluded there was low strength of evidence for the benefits and harms of revascularisation in comparison to medical therapy in patients with ARVD. This was an analysis of 83 studies including randomised controlled trials, nonrandomised studies, small group studies and case studies that reported renal and cardiovascular outcomes [18].

However, it is important to note that there were some flaws in the RCT including, in ASTRAL, the severity of the RAS (only 60% of the patients had a >70% lesion in either or both kidney), the inclusion and exclusion criteria and inconsistent definitions of "cure". They also varied in terms of follow up times; follow up ranged from 1 month to 5 years in the 8 RCT included in the 2015 meta-analysis whereas the mean follow-up in the meta-analysis from 2011 was 29 months which is unlikely to adequately address issues such as recurrent admissions for heart failure syndromes or progression to ESKD over a significant period.

Although the RCT data would suggest and recommend that the treatment of symptomatic renal artery disease should be guideline directed medical treatment both the ACC/AHA guidelines and the Society for Cardiovascular Angiography and Intervention (SCAI) [19] introduced criteria highlighting that those most likely to benefit from revascularization will have a haemodynamically significant RAS lesion and severe hypertension failing to respond to maximum tolerated medical therapy. Better blood pressure control and better clinical outcomes can be achieved if patients are appropriately selected based on their clinical phenotype and the severity of their lesion. In experienced centres, renal stenting should now be a safe procedure with a major complication risk of 2% and it can be an effective treatment in appropriately selected patients.

Many of the patients shown in single centre studies and case reports to benefit from revascularization have the phenotypes that were excluded from revascularization RCT. A report from our centre that spanned management of ARVD patients between 1986 and 2014 focused on patients with a high-risk clinical presentation [5]. High risk was defined as RAS > 70% along with a typical clinical phenotype such as a decompensated heart failure syndrome, severe hypertension (BP > 160/100 despite 3 anti-hypertensive agents including diuretic) or rapidly deteriorating renal function. The median follow up in this retrospective study was 58.4 months and revascularization was associated with reduced risk of progression to ESKD, CVE and all combined events in those with rapidly progressive CKD (HR 0.47, 0.51 and 0.57, respectively). Those with significant bilateral lesions and proteinuria of <1 g/day also had significantly improved renal and cardiovascular outcomes. Although this was a single centre study it certainly supports the concept that revascularization should be offered to those with a significant RAS lesion and high-risk clinical phenotype. The Cardiac Benefits of Renal Artery Stenting (CARMEL) study also showed marked improvement in left ventricular filling pressures in those with RAS and heart failure after renal artery stenting [20].

Patients unlikely to benefit from revascularization include those who are asymptomatic with RAS found on routine imaging, those without an associated clinical syndrome, those with uncontrolled blood pressure but not receiving maximum tolerated doses of three anti-hypertensive agents, those with a RAS lesion supplying a kidney sized <7 cm or those patients having been receiving dialysis for more than 3 months. However, as well as renal atrophy, another important marker of the condition of the underlying renal parenchyma is proteinuria. Several non-randomised

studies, such as that from this centre over two decades ago [21], have shown the adverse prognostic value of significant proteinuria, with proteinuria of >0.5 gm/day seemingly being a cut-off above which positive outcomes are less likely. A post hoc analysis of the CORAL study that involved 826 of the original 947 patients has also emphasised the importance of proteinuria. When baseline urine albumin: creatinine ratio was less than or equal to the median value (a cut off of only 2.2 mg/mmol), renal artery revascularization was associated with significantly better event-free survival from the primary composite end point (73% versus 59% at 5 years; $P = 0.02$), cardiovascular disease—related death (93% versus 85%; $P \leq 0.01$), progressive renal impairment (91% versus 77%; $P = 0.03$), and overall survival (89% versus 76%; $P \leq 0.01$), but these benefits were not observed when baseline urine albumin: creatinine ratio was greater than the median [22].

Hence renal revascularization remains an effective treatment of ARVD if patients are carefully selected. Other factors predictive of a successful revascularization procedure include low renal resistive index as detected by doppler ultrasound, and eGFR decline in the previous 6 months with normal size of kidneys. Imaging parameters such as renal parenchymal volume and cortical thickness as assessed by MRI, when considered in relation to the degree of function of an individual kidney, might also identify patients with RAS that would benefit from renal revascularization [23].

Summary of Current Management Protocols for ARVD

Medical Therapy

As detailed above, ARVD typically represents one component of a complex burden of multisystem cardiovascular disease. Therefore, the primary focus of treatment in ARVD is to reduce the overall cardiovascular risk with standard secondary prevention medicines. There are no clinical trials that have specifically demonstrated a survival benefit adopting this approach in ARVD and recommendations are extrapolated from observational data or from the results of trials in other cardiovascular conditions. In many cases, therapies will be indicated for other reasons but are likely to confer benefit to the ARVD. Target BP in ARVD is 130/80 mmHg, as recommended by the European Society of Cardiology and the American Heart Association/American College of Cardiology. However, it must be noted that in critical RAS, any antihypertensive that reduces the pressure gradient across a critical stenosis has the potential to cause a decrease in renal function. Other important therapeutic approaches are anti-platelet therapy, beta-blockers and lipid-lowering drugs. Intervention to improve glycaemic control in ARVD associated with diabetes has been shown to improve outcome, as does smoking cessation. A summary of medical therapies to address ARVD is found in Fig. 3.

- RAASi is first line anti-hypertensive therapy.
- RAASi may also provide benefit for heart failure and proteinuria.
- RAASi are tolerated in >90% of patients.
- Intolerance to RAASi may indicate critical stenosis and warrant further investigation.
- If blood pressure remains >130/80mmHg on RAASi, introduce other antihypertensives.
- Standard cardiovascular secondary preventative therapies should be offered:
  - Antiplatelet therapy
  - Lipid-lowering therapy
  - Beta-blockade
- Smoking cessation support should be offered where needed.
- Improved glycaemic control improves ARVD outcome in diabetes.

Fig. 3 Recommended medical therapy for atherosclerotic renovascular disease

Revascularization

Globally, percutaneous techniques now account for >98% of renal revascularization procedures. At least six RCT have been undertaken to provide the current evidence base for whether revascularization is beneficial for patient outcome. The largest of these, ASTRAL (806 patients) [13] and CORAL (947 patients) [1], concluded that revascularization for atherosclerotic RAS did not improve renal or cardiac outcomes. However, the phenotypes of the patients enrolled in these trials were generally of lower risk than patients who in that era continued to be treated with stenting outside of the trials, such as those with rapidly declining kidney function, very tight RAS or decompensated heart failure syndromes. Outside of RCTs, there have been many reports of cases benefitting from renal revascularization, but ARVD patients are a heterogeneous group with varying renovascular anatomy, renal parenchymal and cardiovascular damage and consequent clinical presentations. ARVD registries and cohort studies suggest that patients with 'higher-risk' presentations that include the characteristics listed above, and who were a minority in the RCTs, are patients more likely to clinically benefit from renal stenting [24]. Our local practice is to evaluate ARVD cases via multidisciplinary team (MDT) review, with interventional radiology and nephrology input; however, other MDTs might justifiably include cardiologists, depending upon the design of the local service. This approach can increase the chances of successful outcomes after revascularization [25, 26]. Individualised patient selection is necessary and this should be based on three important aspects: the presence of a high-grade RAS lesion (>75% or with

Table 1 KDIGO consensus on renal artery revascularization in atherosclerotic renovascular disease: indications and non-indications

Definite indications
• Acute pulmonary edema, or decompensations of heart failure with high-grade RAS
• Rapid CKD progression in high-grade (>75%) RAS (bilateral or solitary kidney)
• Acute kidney injury due to acute renal artery occlusion or high-grade RAS
• ACEi or ARB intolerance in high-grade RAS where these are necessary drugs
• Kidney transplant with RAS (including asymptomatic)
Possible indications
• Chronic heart failure with high-grade RAS
• CKD progression combined with uncontrolled hypertension
• Asymptomatic high-grade RAS (either bilateral or supplying solitary kidney) with viable renal parenchyma (to prevent atrophy)
• New (<3 months) dialysis patient with nonfunctioning but possibly viable kidney
Nonindications
• Hypertension alone
• Asymptomatic unilateral or bilateral (<75%) RAS

radiological evidence suggesting compromised blood flow), the clinical presentation of the patient and a reasonably sized kidney with likely viable parenchymal tissue.

There remains a place for further RCTs in selected patients with high-risk phenotypes, especially those with severe RAS and rapidly declining kidney function or hypertensive chronic heart failure. However, it is difficult to justify RCTs in other clinical presentations such as acute kidney injury or acute decompensated heart failure, as the likely detrimental outcomes in any control arm could be catastrophic. Carefully curated real-world outcome data should be collected in these latter scenarios. A recent KDIGO Controversies Conference on central and peripheral arterial diseases in CKD included an ARVD working group. The consensus of the group for definite, possible and non-indications for revascularization in ARVD are shown in Table 1 [27]. A further group of experts have also provided a scientific statement on behalf of the American Heart Association that includes similar recommendations [28]. An example of a local organisational pathway underpinned by the evidence discussed is found in figure 1 of [29].

Potential Future Therapeutic Interventions in ARVD

There are several scientific avenues currently under exploration for adjunctive novel therapies in ARVD. One target is to reduce the inflammation and fibrosis stimulated by reduced renal blood flow, and as RAS kidneys exhibit increased expression of monocyte chemoattractant protein (MCP-1), animal models with the MCP-1 inhibitor, Bindarit, have shown improved renal outcomes due to decrease of inflammation and oxidative stress [29]. Vascular endothelial growth factor (VEGF) is important in

the preservation of microvasculature as it promotes vascular proliferation and endothelial repair. In animal models of RAS, VEGF therapy has been shown to preserve renal function and to decrease renal fibrosis [30].

Mesenchymal stem cells have been shown to be effective in several animal models of renal disease, with evidence of enhanced repair and reduced renal injury in CKD [31]. In RAS models adding mesenchymal stem cells at the time of renal angioplasty reduces inflammation and fibrosis and improves vascular remodelling [32]. Encouragingly, a phase-2 human study involved intra-arterial mesenchymal stem cell therapy in a small number of patients with RAS and the infusion induced an increase in cortical perfusion, renal blood flow and tissue oxygenation. The stem cell therapy was well tolerated [33].

Conclusion

In recent decades there have been major changes in the understanding and treatment of ARVD with a move away from an 'intervention for most' to adopting a more conservative optimal medical treatment approach. When broadly utilised in all patients with ARVD renal revascularisation does not confer an additional benefit to medical treatment. The current approach should instead involve maximum vascular protective therapy with revascularisation reserved for those with a high-risk clinical presentation, or in the case of FMD, those with severe hypertension.

Specifically in ARVD, clinical trials that target the inflammatory process and oxidative stress induced by reduced by renal ischaemia are also required, likely with VEGF and anti-MCP-1; the encouraging outcomes after mesenchymal stem cell therapy in RAS need to be evaluated in larger populations. It maybe that in the future our standard treatment for severe atherosclerotic RAS will be a combination of restoration of blood flow and targeted anti-inflammatory/anti-fibrotic treatment to maintain the microvascular architecture and improve the renal function.

References

1. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med. 2014;370(1):13–22.
2. Airoldi F, Palatresi S, Marana I, Bencini C, Benti R, Lovaria A, et al. Angioplasty of atherosclerotic and fibromuscular renal artery stenosis: time course and predicting factors of the effects on renal function. Am J Hypertens. 2000;13(11):1210–7.
3. Smit JV, Wierema TKA, Kroon AA, de Leeuw PW. Blood pressure and renal function before and after percutaneous transluminal renal angioplasty in fibromuscular dysplasia. J Hypertens. 2013 Jun;31(6):1183–8.
4. Dworkin LD, Cooper CJ. Clinical practice. Renal-artery stenosis. N Engl J Med. 2009;361:1972–8.

5. Ritchie J, Green D, Chrysochou C, Chalmers N, Foley RN, Kalra PA. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. Am J Kidney Dis. 2014;63(2):186–97.
6. Kalra PA, Guo H, Kausz AT, Gilbertson D, Liu J, Chen SC, Ishani A, Collins AJ, Foley RN. Atherosclerotic renovascular disease in US medicare recipients aged 67 years or more: risk factors, revascularization and prognosis. Kidney Int. 2005;68(1):293–301.
7. Ritchie J, Green D, Alderson HV, et al. Risks for mortality and renal replacement therapy in atherosclerotic renovascular disease compared with other causes of chronic kidney disease. Nephrology (Carlton). 2015;20:688–96.
8. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. J Am Soc Nephrol. 2005;16(9):2746–53. https://doi.org/10.1681/ASN.2005010043. Epub 2005 Jul 27. PMID: 16049071.
9. de Silva R, Loh H, Rigby AS, Nikitin NP, Witte KK, Goode K, et al. Epidemiology, associated factors, and prognostic outcomes of renal artery stenosis in chronic heart failure assessed by magnetic resonance angiography. Am J Cardiol. 2007;100:273–9.
10. Burlacu A, Siriopol D, Voroneanu L, Nistor I, Hogas S, Nicolae A, Nedelciuc I, Tinica G, Covic A. Atherosclerotic renal artery stenosis prevalence and correlations in acute myocardial infarction patients undergoing primary percutaneous coronary interventions: data from nonrandomized single-center study (REN-ACS)—a single center, prospective, observational study. J Am Heart Assoc. 2015;4(10):e002379.
11. Van De Ven PJG, Kaatee R, Beutler JJ, Beek FJA, Woittiez AJJ, Buskens E, et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. Lancet. 1999;353(9149):282–6.
12. Ives NJ, Wheatley K, Stowe RL, Krijnen P, Plouin PF, van Jaarsveld BC, Gray R. Continuing uncertainty about the value of percutaneous revascularization in athero-sclerotic renovascular disease: a meta-analysis of randomized trials. Nephrol Dial Transplant. 2003 Feb;18(2):298–304. https://doi.org/10.1093/ndt/18.2.298.
13. Investigators ASTRAL, Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, Baigent C, Carr S, Chalmers N, Eadington D, Hamilton G, Lipkin G, Nicholson A, Scoble J. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med. 2009;361:1953–62.
14. Losito A, Errico R, Santirosi P, Lupattelli T, Scalera GB, Lupattelli L. Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition. Nephrol Dial Transplant. 2005;20(8):1604–9.
15. Silva VS, Martin LC, Franco RJS, Carvalho FC, Bregagnollo EA, Castro JH, et al. Pleiotropic effects of statins may improve outcomes in atherosclerotic renovascular disease. Am J Hypertens. 2008;21(10):1163–8.
16. Jenks S, Yeoh SE, Conway BR. Balloon angioplasty, with and without stenting, versus medical therapy for hypertensive patients with renal artery stenosis. Cochrane Database of Systematic Reviews. Wiley; 2014.
17. Kumbhani DJ, Bavry AA, Harvey JE, De Souza R, Scarpioni R, Bhatt DL, et al. Clinical outcomes after percutaneous revascularization versus medical management in patients with significant renal artery stenosis: a meta-analysis of randomized controlled trials. Am Heart J. 2011;161(3):622–630.e1.
18. Raman G, Adam GP, Halladay CW, Langberg VN, Azodo IA, Balk EM. Comparative effectiveness of management strategies for renal artery stenosis: an updated systematic review. Ann Intern Med. 2016;165:635–49.
19. Klein AJ, Jaff MR, Gray BH, Aronow HD, Bersin RM, Diaz-Sandoval LJ, et al. SCAI appropriate use criteria for peripheral arterial interventions: an update. Catheter Cardiovasc Interv. 2017;90(4):E90–110.
20. Kawarada O, Yokoi Y, Morioka N, Shiotani S, Higashimori A. Cardiac benefits of renal artery stenting. EuroIntervention [Internet]. 2010;6(4):485–91. [cited 2023 May 28]. Available from: https://europepmc.org/article/med/20884436

21. Wright JR, Shurrab AE, Cheung C, Waldek S, O'Donoghue DJ, Foley RN, Mamtora H, Kalra PA. A prospective study of the determinants of renal functional outcome and mortality in atherosclerotic renovascular disease. Am J Kidney Dis. 2002;39(6):1153–61.
22. Murphy TP, Cooper CJ, Pencina KM, D'Agostino R, Massaro J, Cutlip DE, et al. Relationship of albuminuria and renal artery stent outcomes: results from the CORAL randomized clinical trial (cardiovascular outcomes with renal artery lesions). Hypertension. 2016;68(5):1145–52.
23. Chrysochou C, Mendichovszky IA, Buckley DL, Cheung CM, Jackson A, Kalra PA. BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. Nephrol Dial Transplant [Internet]. 2012;27(3):1013–9. [cited 2023 Jan 8].
24. de Bhailis Á, Al-Chalabi S, Hagemann R, Ibrahim S, Hudson A, Lake E, Chysochou C, Green D, Kalra PA. Managing acute presentations of atheromatous renal artery stenosis. BMC Nephrol. 2022;23(1):210.
25. Sens F, Normand G, Fournier T, Della-Schiava N, Luong S, Pelletier C, et al. Blood pressure decreases after revascularization in atherosclerotic renal artery disease: a cohort study based on a multidisciplinary meeting. PLoS One. 2019;14(6):e0218788.
26. de Bhailis ÁM, Lake E, Chrysochou C, Green D, Chinnadurai R, Kalra PA. Improving outcomes in atherosclerotic renovascular disease: importance of clinical presentation and multidisciplinary review. J Nephrol. 2024; https://doi.org/10.1007/s40620-024-01902-1.
27. Hicks CW, Clark TW, Cooper CJ, de Bhailís ÁM, De Carlo M, Green D, et al. Atherosclerotic renovascular disease: a KDIGO (kidney disease: improving global outcomes) controversies conference. Am J Kidney Dis. 2022;79(2):289–301.
28. Bhalla V, Textor SC, Beckman JA, Casanegra AI, Cooper CJ, Kim ESH, Luther JM, Misra S, Oderich GS. Revascularization for renovascular disease: a scientific statement from the American Heart Association. American Heart Association Council on the Kidney in Cardiovascular Disease; Council on Hypertension; Council on Peripheral Vascular Disease; and Council on Cardiovascular Radiology and Intervention. Hypertension. 2022;79(8):e128–43. https://doi.org/10.1161/HYP.0000000000000217.
29. Patel SM, Li J, Parikh SA. Renal artery stenosis: optimal therapy and indications for revascularization. Curr Cardiol Rep. 2015;17:76. https://doi.org/10.1007/s11886-015-0623-7.
30. Eirin A, Gloviczki ML, Tang H, Gössl M, Jordan KL, Woollard JR, et al. Inflammatory and injury signals released from the post-stenotic human kidney. Eur Heart J. 2013;34(7):540–8.
31. Iliescu R, Fernandez SR, Kelsen S, Maric C, Chade AR. Role of renal microcirculation in experimental renovascular disease. Nephrol Dial Transplant. 2010;25(4):1079–87.
32. Ebrahimi B, Eirin A, Li Z, Zhu XY, Zhang X, Lerman A, et al. Mesenchymal stem cells improve medullary inflammation and fibrosis after revascularization of swine atherosclerotic renal artery stenosis. Sen U, editor. PLoS ONE. 2013;8(7):e67474.
33. Saad A, Dietz AB, Herrmann SMS, Hickson LJ, Glockner JF, McKusick MA, et al. Autologous mesenchymal stem cells increase cortical perfusion in renovascular disease. J Am Soc Nephrol. 2017;28(9):2777–85.
34. Homorodean C, Ober MC, Spinu M, et al. Outcomes after stenting of renal artery stenosis in patients with high-risk clinical features. Egypt Heart J. 2024;76:4. https://doi.org/10.1186/s43044-024-00435-z.

Arterial Hypertension and Renal Vessels

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Abstract Arterial hypertension, a highly prevalent disease in the modern world, is characterized by a complex pathophysiology, closely related to the kidney and its vessels. Nephrosclerosis remains a diagnosis of exclusion and usually appears when the intrinsic renal autoregulatory mechanisms are exceeded. Delving into the complex interplay between renal vessels and arterial hypertension seems to be essential in better understanding and managing patients with hypertension. The renin-angiotensin-aldosterone system remains the main therapeutic target for patients with hypertensive chronic kidney disease. Sodium-glucose cotransporter two inhibitors, glucagon-like peptide analogues, aldosterone synthase inhibitors, and endothelin receptor antagonists are promising drug classes for both blood pressure control and chronic kidney disease progression. Future therapeutic options are currently being studied, especially regarding device therapy.

Keywords Arterial hypertension · Renal vessels · Nephrosclerosis

Introduction

Arterial hypertension is a major risk factor of cardiovascular morbidity and mortality in the general population, despite major therapeutic advances made in the last decades. Characterized by a high prevalence in the general population, which doubled between 1990 and 2019 [1], it implies a high burden on the public health service. The most recent worldwide report published by the World Health Organization in 2023 states that one in three adults suffers from hypertension, half of them are

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unaware of the diagnosis and four out of five hypertensive people are not adequately treated, remaining subject to possible complications [1].

Hypertension is defined by the European Society of Hypertension as an office-measured systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg [2]. The American Heart Association defines a lower threshold of 130–80 mmHg, respectively [3]. Essential or primary hypertension is the most prevalent cause of hypertension and it is characterized by the heterogeneity of the pathophysiological factors [4]. Activation of neurohormonal systems such as the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) play an important role in the pathogenesis of arterial hypertension [5]. As a consequence, it determines the appearance of renal alterations which can either cause or sustain hypertension. Ultimately, a vicious circle results, suggesting the importance of prevention and early interventions as a therapeutic target in the clinical practice. While secondary hypertension accounts for a smaller fraction of cases, two of the most prevalent causes involve the kidney—renal parenchymal hypertension and renovascular hypertension [6]. The latter is predominantly determined by renal ischemia due to obstructive atherosclerosis and mostly affects the elderly population and people with known atherosclerotic diseases, such as coronary artery disease, carotid artery disease, or peripheral artery disease [6, 7].

The heart and the kidney are two interconnected organs and hypertension is one of the connecting lines. From one perspective, hypertension determines renal structural and functional alterations. As an adaptive mechanism to increased pressure, there is a thickening of the vessel walls, determining arterial lumen narrowing and, consecutively, a reduction in kidney perfusion [8]. This triggers the activation of compensatory mechanisms, such as the RAAS, further contributing to hypertension. Moreover, increased pressure at the glomerular capillary level results in structural damage defined as glomerulosclerosis, profoundly altering kidney function [9].

On the other hand, a variety of pathophysiological mechanisms play a role in blood pressure regulation, part of which are related to the kidney. Renal vessels play a role in blood pressure regulation by modulating renal blood flow and glomerular filtration pressure [10]. The autonomic nervous system and secretion of local acting factors such as nitric oxide or prostaglandins modulate renal artery blood flow to maintain adequate perfusion pressure. Increasing the glomerular blood flow and, subsequently, the glomerular filtration rate by dilation of the afferent arterioles, determines excess fluid excretion and lowers the blood pressure. In contrast, constriction of the afferent arterioles maintains a normal fluid volume and blood pressure. Additionally, renal vessels influence the activity of the RAAS, which will be detailed in the next subchapter.

Pathophysiology of the Connection

Hypertension is a complex disease determined by an interplay of genetic, environmental, anatomical, hemodynamic, adaptive, humoral, endocrine, and neural factors, which is known in the medical field as the mosaic theory of hypertension [11]. As new research data is discovered, a new Mosaic diagram could be created to include novel factors, such as oxidative stress, inflammation, and the microbiome [12]. Blood pressure homeostasis is the result of a complex equilibrium between multiple systems, with the kidney and its vessels playing one of the central roles.

The vascular supply of the kidneys is made by the renal arteries, emergent branches of the abdominal aorta. A significant renal artery atherosclerotic lesion decreases the renal blood flow, hence activating the baroreceptor mechanism and subsequently determining renin release and activation of the RAAS system [4]. However, the implication of renal vessels in blood pressure homeostasis goes beyond the presence of atherosclerotic lesions. More often than previously thought in the general population, accessory arteries supply blood to the kidneys and they are not only implicated in the pathophysiology of renal hypertension by sympathetic activity but also have treatment implications, as their presence can complicate a renal denervation procedure [13].

The regulation of arterial blood flow at the kidney level as a result of complex mechanisms has the crucial role of maintaining normal systemic blood pressure and renal function. Three main processes, involving renal autoregulation function, the renin-angiotensin-aldosterone pathway, and the SNS play a direct role in arterial blood pressure control.

The kidneys possess an important autoregulation function to maintain a stable glomerular filtration rate despite arterial pressure fluctuations. This is mainly based on two important mechanisms, the myogenic response and the tubuloglomerular feedback [14]. The myogenic response, a fast-acting feedback requiring less than 10 s, refers to the ability of the vascular smooth muscle to contract in response to a rise in arterial pressure, thus increasing vascular resistance and allowing for autoregulation of the flow [14]. The tubuloglomerular feedback takes 30–60 s and, as a response to an increase or decrease in sodium chloride concentration in the early distal tubule, determines afferent arteriole constriction or dilatation, respectively [14]. These changes happen as a consequence of locally acting substances released by the macula densa cells with either vasoconstrictor properties, such as adenosine triphosphate and adenose, or vasodilator properties, such as nitric oxide.

A decrease in renal arterial pressure or in sodium chloride delivery to the macula densa, as well as activation of sympathetic nerves that innervate the juxtaglomerular cells are the three main factors that trigger renin release by the juxtaglomerular cells of the afferent arteriole [4]. Angiotensinogen, produced by the liver, is cleaved under the influence of renin into angiotensin I, which then converts to angiotensin II, a substance with a potent arterial vasoconstrictive effect [4]. The conversion of angiotensin I to angiotensin II is made by the angiotensin-converting enzyme, which represents a key therapeutic target of the blockade of RAAS [4]. Angiotensin II

determines vasoconstriction of renal arterioles, reducing the glomerular filtration rate [4]. In addition, angiotensin II stimulates aldosterone release by the adrenal cortex, further augmenting the blood pressure by sodium and water retention [4].

Renal sympathetic nerve activity also plays an important role in blood pressure regulation. The majority of renal nerves are efferents, delivering sympathetic information to the kidney, while a smaller part is afferent nerves, capable of sending signals to the brain. Modulation of afferent sympathetic nerve activity is achieved by efferent renal nerve activity via the release of norepinephrine and is influenced by dietary sodium intake [15, 16]. Stimulation of efferent sympathetic nerve fibers either by hypoxia, ischemia, or oxidative stress, increases sodium absorption in renal tubules, while decreasing renal blood flow, thus contributing to fluid retention [17]. Renal blood flow is modulated by vasoconstriction of the afferent and efferent arterioles in response to the activation of alfa-adrenoreceptors found in the renal vascular smooth muscle cells [18]. Norepinephrine also increases renin secretion by stimulating beta-adrenergic receptors of juxtaglomerular cells, further sustaining hypertension via RAAS [17].

Interaction Between Arterial Hypertension and Renal Vessels

Hypertension leads to both the development of chronic kidney disease (CKD) as well as its progression to advanced stages [19].

The kidney possesses an inherent capability to safeguard itself against rises in systemic blood pressure by employing autoregulatory vasoconstriction within the preglomerular vasculature. This mechanism helps to sustain the stability of renal blood flow and glomerular hydrostatic pressures [20]. When preglomerular arterioles are impacted, it affects not only the glomerulus but also other compartments of the kidney. Arteriolar vasoconstriction resulting from persistent hypertension leads to glomerular ischemia, ultimately causing the retraction of the glomerular tuft and a reduction in glomerular filtration over time. Renal ischemia triggers the production of angiotensin II, endothelin-1, and TGF-beta, ultimately resulting in interstitial fibrosis [21].

Uncomplicated essential hypertension seldom results in renal impairment. Renal damage induced by hypertension can present in two forms: benign nephrosclerosis and malignant nephrosclerosis. In benign nephrosclerosis, renal function remains relatively intact, and proteinuria is typically insignificant. Conversely, malignant nephrosclerosis entails vascular and glomerular injury, along with fibrinoid necrosis and thrombosis. Without targeted treatment, renal failure becomes inevitable in this scenario [22]. In response to chronic hypertension, the renal vessels undergo intimal thickening and luminal narrowing, affecting both renal arteries and glomerular arterioles. These changes are attributed to medial hypertrophy, fibroblastic intimal thickening, and the deposition of hyaline-like material within the arteriolar walls [23]. Over time, the glomeruli undergo either global sclerosis in response to ischemic injury or focal segmental sclerosis as a compensatory reaction to nephron loss.

Both vascular and glomerular changes are associated with interstitial fibrosis and atrophy. In a cohort of young patients who underwent renal biopsy after their initial episode of malignant hypertension, approximately half of them received a clinical diagnosis of severe nephrosclerosis. Fibrosis emerged as an independent risk factor for progression to end-stage renal disease. Interestingly, the presence of any thrombotic microangiopathy lesion on renal biopsy unexpectedly served as a protective factor [24].

The relationship between blood pressure variability and CKD is bidirectional. On one hand, experimental studies have linked variability in blood pressure with the development of focal sclerotic lesions and interstitial fibrosis in the renal cortex. Over time, this could potentially result in arteriosclerotic changes and gradual narrowing of the luminal diameter [25]. Several clinical studies support these mechanisms, showing a significant association between a nondipper pattern, proteinuria, and reduced estimated glomerular filtration rate [26, 27]. On the other hand, CKD is associated with increased blood pressure variability through sodium and fluid retention, the activation of the SNS and RAAS, and baroreceptor dysfunction [28].

In hypertensive CKD, there are both structural and functional alterations in the vasculature. Structural changes generally involve an increase in vascular resistance, while functional changes are associated with deficiencies in acetylcholine relaxation and the overexpression of the intracellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) [29].

Endothelial dysfunction is an essential step for both the development of CKD and its progression. Several endothelium-derived relaxing and constricting factors have been proposed as contributors to hypertensive CKD. Microalbuminuria is by itself a manifestation of endothelial dysfunction. Through the production of TGF-β and bone morphogenetic proteins, endothelial cells also lead to vascular hypertrophy. The decreased availability of nitric oxide is a significant contributor to endothelial dysfunction associated with CKD. Concurrently, CKD serves as a stimulus for inflammatory responses, which can impact the bioavailability of nitric oxide [29]. Endothelin is recognized as a promoter of vasoconstriction of the efferent arterioles, resulting in hyperfiltration, podocyte damage, proteinuria, and ultimately, the progression of CKD. Furthermore, endothelin-1 induces podocyte injury, proliferation of mesangial cells, accumulation of mesangial matrix, as well as inflammation and fibrosis [30].

Clinical Manifestations and Diagnosis

Nephrosclerosis typically occurs in individuals with a prolonged history of hypertension, accompanied by mild renal dysfunction and proteinuria. Elevated uric acid levels serve as an early marker for benign nephrosclerosis [23]. Traditionally, focal nephrosclerosis is linked with mild proteinuria (less than 1 g/day), while severe proteinuria is more commonly observed in patients with malignant hypertension or a history of renovascular disease [31].

Diagnosing hypertensive nephrosclerosis typically involves a process of exclusion. Patients commonly present with left ventricular hypertrophy, normal urine sediment, small kidneys, and a gradual decline in kidney function. In contrast to renal stenosis, in hypertensive CKD the kidneys are small but equal in size. Hypertension is typically diagnosed before kidney impairment becomes evident. Moreover, renal failure and progressive proteinuria appear later in evolution. In microscopy, there is arteriosclerosis of the afferent arteriole together with arterial hyalinosis [32, 33]. Differential diagnosis is usually made with other forms of vascular nephropathies and should ideally include a genetic testing panel to exclude familial kidney disease. A conclusive diagnosis of hypertensive nephrosclerosis relies on kidney biopsy, which is indicated when there is a suspicion of angiosclerosis and there is a need to exclude other primary kidney diseases. Data derived from studies performed on patients who underwent renal biopsy show that a significant number of patients have in reality another primary nephropathy. A high percentage of glomerulosclerosis and interstitial fibrosis together with tubular atrophy are predictors of progression towards end-stage renal disease [34]. Patients with overt proteinuria have a lower glomerular density [35]. A sub-analysis of the AASK study shows that African-American patients are at higher risk of developing nephroangiosclerosis when compared to Caucasian patients, even at older age. This fact is explained by polymorphisms in the MYH9 gene and apolipoprotein gene 1 (APOL1) risk variants. While identifying patients with gene alterations helps stratify the patient's risk of developing hypertension and kidney disease, the extent to which these will influence the clinicians' therapeutic approach remains to be discovered [36].

Treatment Approaches

In hypertensive patients with CKD the blood pressure target is influenced by the association of both diseases, the European Society of Hypertension guidelines, as well as the American Heart Association suggesting a threshold of <130/80 mmHg [2, 3]. A clinically important entity has been described, namely resistant hypertension, defined by blood control values above the established target, in the presence of maximally tolerated doses of at least three antihypertensive drug classes, including a diuretic [2].

Although there is currently no conclusive research on nephroangiosclerosis treatment, current guidelines suggest that angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers are the primary treatment options for proteinuric CKD. These medications also demonstrate beneficial effects for patients with benign nephrosclerosis, as demonstrated in the AASK trial. Treatment with ramipril notably resulted in a slower progression of CKD in individuals exhibiting proteinuria [37]. Mineralocorticoid receptor antagonists are recognized as effective treatments for both hypertension and CKD. Recently, finerenone has shown clinical

benefits in CKD patients with type 2 diabetes by exerting direct anti-fibrotic effects [38].

Recent epidemiological data confirming poor worldwide control of hypertension suggest a need for better blood pressure control [1]. As such, medical research is focusing on novel medications targeting specific pathways involved in hypertension, as well as cutting-edge technology. A phase 2 trial has shown promising results of baxdrostat, a selective aldosterone synthase inhibitor, regarding blood pressure control in patients with resistant hypertension [50]. This novel drug targets the RAAS pathway by reducing aldosterone production and is currently undergoing multiple phase 3 trials addressing patients with resistant hypertension and chronic kidney disease and also patients with primary aldosteronism, being a promising drug for both resistant hypertension and CKD progression (NCT05137002, NCT05432167, NCT04605549, NCT06168409) progression [39]. Endothelin receptor antagonists represent a small interfering RNA targeting angiotensinogen that might represent a potential breakthrough in hypertension medical management [51], a phase I study being currently under development (NCT03934307).

Sodium-glucose-cotransporter 2 inhibitors (SGLT2i) exert a renoprotective effect by mitigating hyperfiltration and restoring the tubuloglomerular feedback [40]. The nephroprotective effects of SGLT2i are partly attributed to their association with inflammation, hypoxia, and metabolism. Additionally, SGLT2i treatment is linked to a decrease in dysfunctional nephrons, as well as reductions in proteinuria and blood pressure [41]. Animal studies have demonstrated its inhibitory effect on TGF-β1 and its induced expression of key mediators of interstitial fibrosis in human proximal tubular cells, including thrombospondin-1 (THBS1), tenascin-C (TNC), and platelet-derived growth factor-β (PDGF-B) [42].

The combination of dapagliflozin with sacubitril/valsartan was observed to preserve residual renal function and reduce proteinuria and blood pressure in animals with hypertensive kidney disease. Furthermore, the combination therapy also demonstrated beneficial effects on renal tubular cells [43].

Additionally, GLP-1 receptor agonists have been shown to decrease angiotensin II levels and inhibit their activation. They also exhibit natriuretic, anti-inflammatory, and antifibrotic effects [44].

The therapeutic approach to renovascular hypertension may include in specific cases interventional therapy. Percutaneous angioplasty seems to be the primary choice for significant atherosclerotic lesions in renovascular hypertension. However, the lack of consistent clinical evidence regarding the benefits of renal artery revascularization has placed this therapy under the umbrella of uncertainty.

A significant atherosclerotic lesion is defined as a >75% stenosis in The Kidney Disease: Improving Global Outcomes (KDIGO) Consensus, while the threshold is placed at >70% by the European Society of Hypertension guidelines [2, 45]. Irrespective of the anatomical severity of the stenosis, its hemodynamic consequence is of importance when opting for an interventional approach. The purpose of renal artery angioplasty is not only to control arterial hypertension but also to ameliorate the renal prognosis by preventing further renal function deterioration. As such, identifying the patients who are more likely to benefit from this procedure is

of great importance. In their most recently published guidelines, the European Society of Hypertension recommends a revascularization approach in patients with significant artery stenosis and renovascular hypertension or high-risk clinical profiles, defined as flash pulmonary edema, rapid loss of kidney function, or refractory hypertension [2]. The KDIGO Consensus has divided the indication into two categories, definite and possible. As expected, clinical scenarios like acute pulmonary edema or acute decompensated heart failure, progressive CKD, kidney transplant, or acute kidney injury in the context of a high-grade renal artery stenosis are definite indications for revascularization therapy [45]. Progressive CKD in patients with significant bilateral stenosis or on a solitary kidney is a definite indication, while accompanied by uncontrolled hypertension represents a possible indication. Patients with chronic heart failure or those in the first 3 months of renal replacement therapy with a viable kidney could possibly benefit from revascularization [45].

In the most recently published guideline, in contrast to the one from 2018, the European Society of Hypertension changed its perspective on renal denervation, recommending it as an additional therapy to patients with resistant hypertension and a glomerular filtration rate over 40 ml/min/1.73 m^2, or as an alternative to patients intolerant to pharmacotherapy (II B recommendation) [2]. It is an endovascular method that uses neuromodulation to combat the overactivity of the SNS in hypertension. Despite recent advances, the mechanism involved in blood pressure regulation through renal denervation is not yet fully understood. A recent meta-analysis included 11 studies comprising over 400 patients undergoing renal denervation for resistant or uncontrolled hypertension. It concluded that the intervention has a significant and consistent (over a 6-month follow-up period) blood pressure reduction, as well as muscle sympathetic nerve activity reduction, though the two changes were not related, implying the involvement of other mechanisms in the BP lowering effect of denervation procedure [46].

By disrupting the brain-kidney neurohormonal communication, renal denervation reduces the central sympathetic drive to multiple organs, including the vascular system. It is a promising therapeutic option, showing favorable results across the spectrum of CKD, including patients with resistant hypertension and end-stage renal disease [47–49]. This exerts important prognostic implications, as these patients are characterized by a higher cardiovascular morbidity and mortality than other hypertensive populations. Further investigation is needed to support the nephroprotective effect of renal denervation and establish standard indications in patients with CKD. Current ongoing trials are designed to better understand the efficiency and indications of renal denervation using different devices (NCT03503773, NCT02439775, NCT02910414).

Novel device-based therapies targeting the autonomic nervous system as a means to treat hypertension are currently being investigated. There are randomized controlled studies currently investigating the possibility of endovascular carotid baroreceptor stimulation as a means of long-term blood pressure regulation (NCT02827032, NCT03179800). A recent case report displaying the beneficial antihypertensive effect of transcutaneous electrical nerve stimulation has been published [52], a method that is currently being investigated in a clinical trial (NCT02365974).

Another future therapeutic perspective refers to cardiac neuromodulation therapy, which aims to inhibit the activation of the SNS via compensatory baroreflex mechanisms with the help of a dedicated pacemaker and a new pacing algorithm. Short-term efficacity and safety of this procedure have been reported [53, 54], though long-term outcome data is lacking. Whether pacemaker devices could be used solely for blood pressure regulation is still a significant journey ahead, as previously mentioned results were obtained in patients with an indication of a dual-chamber pacemaker. While these device therapies do not directly implicate the renal vessels, they do represent possible therapeutic options involving autonomic modulation that may further develop shortly, allowing for early optimal blood pressure control and prevention of vascular damage, especially in patients with resistant hypertension. In addition, further development of wearable devices and telemedicine will further improve patient adherence to medical recommendations, thus increasing the chances of better blood pressure management.

Conclusion

Hypertension exerts a great impact on renal vessels, precipitating structural and vascular alterations which further impair the kidney function and ultimately translate to nephrosclerosis. Understanding the complex interplay between arterial hypertension and renal vessels is crucial for the accurate management of both conditions. A detrimental cycle is established between high blood pressure and renal medullary lesions, which may be interrupted by implementing therapeutic approaches targeting medullary fibrosis. As our understanding of pathophysiological mechanisms deepens and medical research advances, novel therapies will emerge for blood pressure control, improving health outcomes and the quality of life of these patients.

References

1. World Health Organization. Global report on hypertension: the race against a silent killer [Internet]. Geneva; 2023. Available from: https://www.who.int/publications-detail-redirect/9789240081062.
2. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874–2071.
3. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. J Am Coll Cardiol. 2018;71(19):e127–248.

4. Harrison-Bernard LM. The renal renin-angiotensin system. Adv Physiol Educ. 2009;33(4):270–4.
5. Takahashi H, Yoshika M, Komiyama Y, Nishimura M. The central mechanism underlying hypertension: a review of the roles of sodium ions, epithelial sodium channels, the renin–angiotensin–aldosterone system, oxidative stress and endogenous digitalis in the brain. Hypertens Res. 2011;34(11):1147–60.
6. Rimoldi SF, Scherrer U, Messerli FH. Secondary arterial hypertension: when, who, and how to screen? Eur Heart J. 2014;35(19):1245–54.
7. Leertouwer TC, Pattynama PMT, Berg-Huysmans AVD. Incidental renal artery stenosis in peripheral vascular disease: a case for treatment? Kidney Int. 2001;59(4):1480–3.
8. Renna NF, de las Heras N, Miatello RM. Pathophysiology of vascular remodeling in hypertension. Int J Hypertens. 2013;2013:808353.
9. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis. 2004;43(2):368–82.
10. Samuel SA, Francis AO, Anthony OO. Role of the kidneys in the regulation of intra-and extra-renal blood pressure. Ann Clin Hypert. 2018;2(1):048–58.
11. Lip S, Padmanabhan S. Genomics of blood pressure and hypertension: extending the mosaic theory toward stratification. Can J Cardiol. 2020;36(5):694–705.
12. Harrison DG, Coffman TM, Wilcox CS. Pathophysiology of hypertension. Circ Res. 2021;128(7):847–63.
13. Sato Y, Kawakami R, Jinnouchi H, Sakamoto A, Cornelissen A, Mori M, et al. Comprehensive assessment of human accessory renal artery periarterial renal sympathetic nerve distribution. J Am Coll Cardiol Intv. 2021;14(3):304–15.
14. Just A. Mechanisms of renal blood flow autoregulation: dynamics and contributions. Am J Physiol Regul Integr Comp Physiol. 2007;292:R1–R17.
15. Kopp UC, Cicha MZ, Smith LA, Mulder J, Hökfelt T. Renal sympathetic nerve activity modulates afferent renal nerve activity by PGE2-dependent activation of alpha1- and alpha2-adrenoceptors on renal sensory nerve fibers. Am J Physiol Regul Integr Comp Physiol. 2007;293(4):R1561–72.
16. Kopp UC, Cicha MZ, Smith LA, Ruohonen S, Scheinin M, Fritz N, et al. Dietary sodium modulates the interaction between efferent and afferent renal nerve activity by altering activation of α2-adrenoceptors on renal sensory nerves. Am J Physiol Regul Integr Comp Physiol. 2011;300(2):R298–310.
17. Kannan A, Medina RI, Nagajothi N, Balamuthusamy S. Renal sympathetic nervous system and the effects of denervation on renal arteries. World J Cardiol. 2014;6(8):814–23.
18. Pettinger WA, Jackson EK. α 2-adrenoceptors: challenges and opportunities—enlightenment from the kidney. Cardiovasc Ther. 2020;2020:2478781–9.
19. Hanratty R, Chonchol M, Havranek EP, Powers JD, Dickinson LM, Ho PM, et al. Relationship between blood pressure and incident chronic kidney disease in hypertensive patients. Clin J Am Soc Nephrol [Internet]. 2011;6(11). Available from: https://journals.lww.com/cjasn/fulltext/2011/11000/relationship_between_blood_pressure_and_incident.10.aspx.
20. Bidani AK, Griffin KA. Long-term renal consequences of hypertension for normal and diseased kidneys. Curr Opin Nephrol Hypert [Internet]. 2002;11(1). Available from: https://journals.lww.com/co-nephrolhypertens/fulltext/2002/01000/long_term_renal_consequences_of_hypertension_for.11.aspx.
21. Heras BM. Nephroangiosclerosis: an update. Hipertensión y Riesgo Vascular. 2023;40(2):98–103.
22. Bidani AK, Griffin KA. Pathophysiology of hypertensive renal damage. Hypertension. 2004;44(5):595–601.
23. Harvey JM, Beevers DG, Howie AJ, Lee SJ, Newbold KM, Adu D, et al. Renal biopsy findings in hypertensive patients with proteinuria. Lancet. 1992;340(8833):1435–6.
24. Bureau C, Jamme M, Schurder J, Bobot M, Robert T, Couturier A, et al. Nephrosclerosis in young patients with malignant hypertension. Nephrol Dial Transplant. 2023;38(8):1848–56.

25. Aoki Y, Kai H, Kajimoto H, Kudo H, Takayama N, Yasuoka S, et al. Large blood pressure variability aggravates arteriolosclerosis and cortical sclerotic changes in the kidney in hypertensive rats. Circ J. 2014;78(9):2284–91.
26. Pogue V, Rahman M, Lipkowitz M, Toto R, Miller E, Faulkner M, et al. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. Hypertension. 2009;53(1):20–7.
27. Fava C, Montagnana M, Burri P, Almgren P, Minuz P, Hulthén UL, et al. Determinants of kidney function in Swedish families: role of heritable factors. J Hypert [Internet]. 2008;26(9) Available from: https://journals.lww.com/jhypertension/fulltext/2008/09000/determinants_of_kidney_function_in_swedish.10.aspx.
28. Borrelli S, Garofalo C, Gabbai FB, Chiodini P, Signoriello S, Paoletti E, et al. Dipping status, ambulatory blood pressure control, cardiovascular disease, and kidney disease progression: a multicenter cohort study of CKD. Am J Kidney Dis. 2023;81(1):15–24.e1.
29. Ameer OZ. Hypertension in chronic kidney disease: what lies behind the scene. Front Pharmacol [Internet]. 2022;13. Available from: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2022.949260.
30. Leoncini G, Russo E, Bussalino E, Barnini C, Viazzi F, Pontremoli R. SGLT2is and renal protection: from biological mechanisms to real-world clinical benefits. Int J Mol Sci. 2021;22(9)
31. Thadhani R, Pascual M, Tolkoff-Rubin N, Nickeleit V, Colvin R. Preliminary description of focal segmental glomerulosclerosis in patients with renovascular disease. Lancet. 1996;347(8996):231–3.
32. Zarif L, Covic A, Iyengar S, Sehgal AR, Sedor JR, Schelling JR. Inaccuracy of clinical phenotyping parameters for hypertensive nephrosclerosis. Nephrol Dial Transplant. 2000;15(11):1801–7.
33. Meyrier A. Nephrosclerosis: update on a centenarian. Nephrol Dial Transplant. 2015;30(11):1833–41.
34. Liang S, Le W, Liang D, Chen H, Xu F, Chen H, et al. Clinico-pathological characteristics and outcomes of patients with biopsy-proven hypertensive nephrosclerosis: a retrospective cohort study. BMC Nephrol. 2016;17(1):42.
35. Haruhara K, Tsuboi N, Kanzaki G, Koike K, Suyama M, Shimizu A, et al. Glomerular density in biopsy-proven hypertensive nephrosclerosis. Am J Hypertens. 2015;28(9):1164–71.
36. Marcantoni C, Ma LJ, Federspiel C, Fogo AB. Hypertensive nephrosclerosis in African Americans versus Caucasians. Kidney Int. 2002;62(1):172–80.
37. Wright J, Jackson T, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease results from the AASK trial. JAMA. 2002;288(19):2421–31.
38. Droebner K, Pavkovic M, Grundmann M, Hartmann E, Goea L, Nordlohne J, et al. Direct blood pressure-independent anti-fibrotic effects by the selective nonsteroidal mineralocorticoid receptor antagonist finerenone in progressive models of kidney fibrosis. Am J Nephrol. 2021;52(7):588–601.
39. Weldon SM, Brown NF. Chapter nine—inhibitors of aldosterone synthase. In: Litwack G, editor. Vitamins and hormones [Internet]. Academic; 2019. p. 211–39. Available from: https://www.sciencedirect.com/science/article/pii/S0083672918300748.
40. Palmer BF, Clegg DJ. Kidney-protective effects of SGLT2 inhibitors. Clin J Am Soc Nephrol [Internet]. 2023;18(2) Available from: https://journals.lww.com/cjasn/fulltext/2023/02000/kidney_protective_effects_of_sglt2_inhibitors.20.aspx.
41. Clemmer JS, Yen TE, Obi Y. Modeling the renoprotective mechanisms of SGLT2 inhibition in hypertensive chronic kidney disease. Physiol Rep. 2023;(11, 21):e15836.
42. Pirklbauer M, Schupart R, Fuchs L, Staudinger P, Corazza U, Sallaberger S, et al. Unraveling reno-protective effects of SGLT2 inhibition in human proximal tubular cells. Am J Physiol-Renal Physiol. 2019;316(3):F449–62.
43. Ko SF, Yang CC, Sung PH, Cheng BC, Shao PL, Chen YL, et al. Dapagliflozin-entresto protected kidney from renal hypertension via downregulating cell-stress signaling and upregulat-

ing SIRT1/PGC-1α/Mfn2-medicated mitochondrial homeostasis. Exp Biol Med (Maywood). 2023;248(23):2421–39.
44. Winiarska A, Knysak M, Nabrdalik K, Gumprecht J, Stompór T. Inflammation and oxidative stress in diabetic kidney disease: the targets for SGLT2 inhibitors and GLP-1 receptor agonists. Int J Mol Sci. 2021;22(19)
45. Hicks CW, Clark TWI, Cooper CJ, de Bhailís ÁM, De Carlo M, Green D, et al. Atherosclerotic renovascular disease: a KDIGO (Kidney Disease: Improving Global Outcomes) controversies conference. Am J Kidney Dis. 2022;79(2):289–301.
46. Biffi A, Dell'Oro R, Quarti-Trevano F, Cuspidi C, Corrao G, Mancia G, et al. Effects of renal denervation on sympathetic nerve traffic and correlates in drug-resistant and uncontrolled hypertension: a systematic review and meta-analysis. Hypertension. 2023;80(3):659–67.
47. Scalise F, Quarti-Trevano F, Toscano E, Sorropago A, Vanoli J, Grassi G. Renal denervation in end-stage renal disease: current evidence and perspectives. High Blood Press Cardiovasc Prev. 2024;31(1):7–13.
48. Schlaich MP, Bart B, Hering D, Walton A, Marusic P, Mahfoud F, et al. Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease. Int J Cardiol. 2013;168(3):2214–20.
49. Xia M, Liu T, Chen D, Huang Y. Efficacy and safety of renal denervation for hypertension in patients with chronic kidney disease: a meta-analysis. Int J Hyperth. 2021;38(1):732–42.
50. Freeman MW, Yuan-Di H, William M, Mackenzie P, Jon I, Catherine P, et al. Phase 2 trial of Baxdrostat for treatment-resistant hypertension. N Engl J Med. 2023;388(5):395–405.
51. Huang S, Taubel J, Fiore G, Dewland P, Bakris G, Desai A, et al. Abstract 14387: dose-related reductions in blood pressure with a RNA interference (RNAi) therapeutic targeting angiotensinogen in hypertensive patients: interim results from a first-in-human phase 1 study of ALN-AGT01. Circulation. 2020;142
52. Giollo-Junior LT, Cosenso-Martin LN, Lopes V d S, Landim MP, LAB F, Oliveira KA d, et al. The effect of transcutaneous electrical nerve stimulation in peripheral and central hemodynamic parameters on resistant hypertension: a case report. VHRM. 2023;19:317–23.
53. Neuzil P, Merkely B, Erglis A, Marinskis G, de Groot JR, Schmidinger H, et al. Pacemaker-mediated programmable hypertension control therapy. J Am Heart Assoc. 2017;6(12):e006974.
54. Kalarus Z, Merkely B, Neužil P, Grabowski M, Mitkowski P, Marinskis G, et al. Pacemaker-based cardiac neuromodulation therapy in patients with hypertension: a pilot study. J Am Heart Assoc. 2021;10(16):e020492.

Renal Artery Denervation: Evidence, Guidelines, and Major Trials

Paula Cristina Morariu, Alexandru Florinel Oancea, and Mariana Floria

Abstract Renal artery denervation (RDN) has emerged as a promising treatment for resistant hypertension, characterized by high blood pressure (BP) unresponsive to three or more antihypertensive medications. This chapter reviews current evidence, guidelines, and major trials related to RDN. RDN targets the sympathetic nervous system in the renal arteries to reduce BP through radiofrequency ablation of sympathetic nerves. Key mechanisms include sympathetic nerve ablation, modulation of the renin-angiotensin system (RAS), and enhancement of baroreflex sensitivity. Clinical trials such as SYMPLICITY HTN-1 and HTN-2 demonstrated significant BP reductions, sustained for up to 36 months. However, SYMPLICITY HTN-3 found no significant difference between RDN and sham procedures, highlighting issues like incomplete nerve ablation. Subsequent SPYRAL HTN and RADIANCE-HTN trials addressed these limitations, showing consistent BP reductions and supporting RDN's efficacy as both a standalone and adjunctive therapy. Guidelines from the European Society of Hypertension (ESH) 2023 recommend RDN for select patients with resistant hypertension, emphasizing optimal pharmacological treatment and lifestyle adherence. The American Heart Association (AHA) suggests RDN cautiously for patients failing multiple medications. In conclusion, RDN offers a novel approach to BP management in resistant hypertension. Continued research is essential to refine patient selection, procedural techniques, and long-term outcomes, enhancing the therapeutic potential of RDN in clinical practice.

Keywords Renal artery denervation · Resistant hypertension · Sympathetic nervous system · Blood pressure · Clinical trials · Antihypertensive therapy

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Introduction

Hypertension, a common cardiovascular disorder affecting millions worldwide, poses a significant health risk when left uncontrolled. While lifestyle modifications and pharmacological therapies are effective in many cases, a subset of patients with resistant hypertension struggle to achieve adequate blood pressure (BP) control. In recent years, renal artery denervation has emerged as a promising therapeutic option for managing resistant hypertension. This chapter explores the evidence, guidelines and major trials of renal artery denervation in the treatment of resistant hypertension.

The incidence of hypertension is staggering, with millions of people affected globally. According to the World Health Organization (WHO), hypertension affects approximately 1.13 billion individuals worldwide, and this number is expected to rise significantly in the coming years. In many cases, hypertension is asymptomatic, earning its notorious reputation as the "silent killer." This lack of symptoms often leads to delayed diagnosis and treatment, further exacerbating the risks associated with uncontrolled hypertension [1].

Uncontrolled hypertension poses a myriad of serious health risks. It is a major risk factor for various cardiovascular diseases, including heart attacks, strokes, and heart failure. Controlling BP in hypertensive patients is essential to reduce the risk of complications and improve overall health outcomes. There are a lot of studies, which have consistently shown that controlling BP in hypertensive patients can significantly reduce the risk of many cardiovascular events and can prevent the development of atherosclerosis and other cardiovascular complications. By controlling BP, hypertensive patients can protect the target organs (heart, kidneys and brain) and not at least they may improve their quality of life by avoiding headaches, dizziness, and fatigue, which can significantly impact a patient's quality of life. The SPRINT found that lowering systolic BP to less than 120 mm Hg significantly reduced the risk of cardiovascular events compared to standard BP targets. The United Kingdom Prospective Diabetes Study (UKPDS), which investigated the effects of BP control on cardiovascular outcomes in patients with type 2 diabetes, showed that tight BP control in hypertensive diabetic patients reduced the risk of complications such as stroke and heart failure [2, 3].

Resistant hypertension is a condition characterized by high BP that remains uncontrolled despite the use of three or more antihypertensive medications, including a diuretic.

Despite the availability of various antihypertensive medications and lifestyle modifications, approximately 5–30% remains with resistant hypertension. This failure to control hypertension effectively underscores the need for alternative treatment strategies to improve patient outcomes and reduce the burden of cardiovascular disease [4].

Renal artery denervation (RDN) has emerged as a novel and promising therapeutic approach for the management of resistant hypertension. By targeting the sympathetic nervous system activity in the renal arteries, RDN aims to reduce BP levels in patients who have not achieved adequate control with standard antihypertensive medications.

Clinical studies evaluating the efficacy of RDN in resistant hypertension have shown promising results. Reductions in both systolic and diastolic BP levels have been observed following the procedure, with some patients achieving significant and sustained improvements in BP control. Additionally, RDN has been associated with improvements in cardiovascular function, including reduced left ventricular hypertrophy and arterial stiffness. For example, the landmark SYMPLICITY HTN-1 and 2 trials, which investigated the efficacy of RDN in patients with resistant hypertension, demonstrated a significant reduction in systolic BP in the RDN group compared to the sham procedure group, highlighting the efficacy of RDN in lowering BP levels. Similar results were obtained during The SPYRAL HTN-OFF MED trial, which evaluated the blood pressure-lowering effects of renal denervation in hypertensive patients not taking antihypertensive medications and which showed a significant reduction in BP in patients who underwent RDN compared to the control group, supporting the efficacy of RDN as a standalone treatment [5, 6].

Renal artery denervation offers a unique approach to BP management by targeting the sympathetic nerves in the renal arteries. By disrupting sympathetic activity, RDN helps lower BP levels and improve overall hypertension control in patients with resistant hypertension. In addition, patients undergoing RDN may experience a reduction in the number of antihypertensive medications needed to control BP and an improved quality of life.

Evidence

Renal artery denervation is a minimally invasive procedure which targets the sympathetic nervous system activity in the renal arteries, leading to a reduction in BP levels. The sympathetic nervous system plays a pivotal role in the regulation of BP through its effects on vascular tone, heart rate, and renal function. In hypertensive patients, increased sympathetic nervous system activity is often observed, contributing to elevated BP levels and cardiovascular complications. The kidneys are key targets of sympathetic innervation, with the renal nerves located in the adventitia of the renal arteries.

Physiopathological Mechanisms of Renal Artery Denervation

Sympathetic Nerve Ablation

The sympathetic nerves in the renal arteries are primarily located in the adventitia, the outermost layer of the arterial wall. These nerves play a crucial role in regulating renal blood flow, renin release, and sodium excretion through their effects on vascular tone and kidney function. By delivering radiofrequency energy RDN interrupts the neural pathways responsible for sympathetic nerve signaling. This leads to a

decrease in sympathetic activity, resulting in vasodilation of the renal vasculature and reduced renal vascular resistance. Patient selection is crucial for the success of renal artery denervation. Candidates typically include individuals with resistant hypertension who have failed to achieve adequate BP control with medications alone. Careful assessment of patient characteristics, including renal anatomy and comorbidities, is essential to ensure the safety and efficacy of the procedure. Clinical trials and studies have demonstrated the efficacy and safety of RDN in lowering BP and improving cardiovascular outcomes in selected patient populations. While the procedure is generally well-tolerated, ongoing research is needed to further elucidate its long-term effects, optimal patient selection criteria, and procedural techniques [7, 8].

Renin-Angiotensin System

The renin-angiotensin system (RAS) plays a crucial role in regulating BP and fluid balance in the body. Renin is an enzyme produced and released by the kidneys in response to various signals, such as low BP or low blood volume. Renin acts on angiotensinogen, which is produced in the liver, to convert it into angiotensin I, which will be then converted into angiotensin II by the angiotensin-converting enzyme (ACE), primarily in the lungs. Angiotensin II is a potent vasoconstrictor, which causes blood vessels to constrict, leading to an increase in BP. It also stimulates the release of aldosterone from the adrenal glands, which will act on the distal convuleted tube of the nephron to increase the reabsorption of sodium and water, leading to an increase in blood volume and BP (Fig. 1). In hypertension, there can be an overactivation of the renin-angiotensin system, leading to chronically elevated

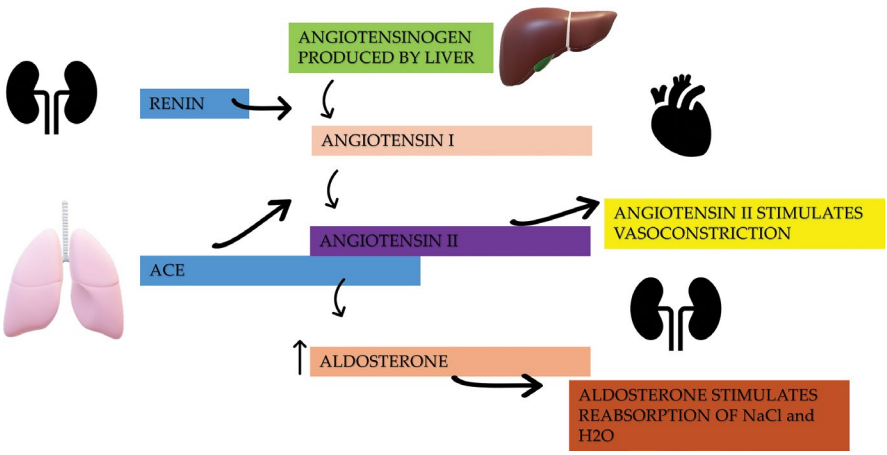

Fig. 1 Renin-angiotensin-aldosterone system

levels of angiotensin II. This can result in sustained vasoconstriction, increased blood volume, and ultimately contribute to the development and progression of cardiovascular diseases [9].

RDN exerts multifaceted effects on the RAS. By reducing renal sympathetic activity, RDN can lead to decreased renin release from the juxtaglomerular cells of the kidney, thereby lowering the production of angiotensin II, the key regulator of aldosterone secretion. Jiayi Lu et al. showed that RDN using saline-irrigated radiofrequency ablation catheter, caused a significant and uniform reduction in plasma level of renin, angiotensin II, and endothelin-1 (ET-1), leading in this way a progressive and substantial BP reduction. Mahfoud et al. showed also that plasma renin activity and aldosterone levels for RDN patients were significantly reduced at 3 months when compared with baseline as well as when compared with sham control. Additionally, RDN may also influence the expression of angiotensin receptors and other components of the RAS, contributing to a rebalancing of the system towards a less vasoconstrictive and pro-inflammatory state [10, 11].

Baroreflex Sensitivity

The baroreflex is a vital regulatory mechanism that helps maintain BP stability by adjusting heart rate and vascular tone in response to changes in BP. Baroreflex sensitivity refers to the speed and magnitude of these compensatory responses. RDN may also influence baroreflex sensitivity by disrupting the aberrant sympathetic signaling in the renal arteries, which may contribute to its long-term efficacy in controlling hypertension. There are studies, which have shown that RDN may lead to alterations in baroreflex sensitivity and moreover, it may enhance baroreflex sensitivity in certain individuals with hypertension by reducing sympathetic activity and improving autonomic balance. Ormezzano et al. showed in a study of 50 patients, that the antihypertensive effect of RDN was greater in patients with impaired cardiac baroreflex sensitivity, and that this effect was associated with restoration of cardiac baroreflex sensitivity after the procedure. These positive results were obtained with cardiac baroreflex sensitivity measured in two ways, namely, the classical sequence method (BRSseq) and the bivariate phase rectified signal averaging method (BRSprsa). Kopp et al. showed in a study using rats fed high-sodium diet, that the arterial baroreflex control of efferent renal sympathetic nerve activity is impaired in afferent renal denervated by dorsal rhizotomy. These rats also showed that increased efferent renal sympathetic nerve activity responses to environmental and somatic stimulation, these data suggesting that in conditions of high-sodium dietary intake, activation of the afferent renal nerves contributes to the arterial baroreceptor-mediated suppression of efferent renal sympathetic nerve activity in the overall goal of preventing sodium retention and maintaining water and sodium homeostasis [12, 13].

Major Clinical Trials

Initial studies demonstrated BP reductions in treatment-resistant hypertension patients using various energy modalities. Subsequent randomized trials yielded mixed results, with early sham-controlled trials highlighting methodological flaws and incomplete RDN. To address these issues, a Clinical Consensus Conference recommended standardized evaluation of endovascular therapies, leading to improved study quality. Recent studies, guided by these recommendations, showed consistent effectiveness of both radiofrequency (Spyral catheter) and ultrasound (Paradise system) RDN approaches. Unlike earlier trials, minimal changes in BP were observed in sham groups, contrasting with findings from the SIMPLICITY HTN-3 trial [14].

SYMPLICITY-HTN Trials

Numerous device-oriented treatments have been developed to address hypertension that is resistant to standard therapies. Among these, renal denervation (RDN) stands out as the most extensively studied method. The investigation of the clinical feasibility, efficacy, and safety of RDN used for treating resistant hypertension has been supported by the encouraging outcomes of the SIMPLICITY HTN-1 and HTN2 randomized controlled clinical trials.

The SYMPLICITY HTN-1 study was an open-label cohort study aimed at evaluating the effectiveness and safety of RDN in patients with treatment-resistant hypertension. The study enrolled 153 patients across 19 centers in Australia, Europe, and the USA, who had systolic BP (SBP) of 160 mmHg or higher despite being on at least three antihypertensive drugs or having confirmed intolerance to medications. Renovascular abnormalities were excluded [15].

Patients underwent percutaneous RDN using the Symplicity renal denervation catheter, with multiple radiofrequency ablations applied to disrupt the sympathetic plexus surrounding the renal artery. SBP, diastolic BP (DBP), adverse events, renal function, and vital signs were monitored during follow-up visits. Results showed significant reductions in both SBP (−32.0 mmHg, 95% CI −35.7 to −28.2) and DBP (−14.4 mmHg, CI −16.9 to −11.9) persisting up to 36 months post-RDN. Moreover, over 93% of patients at the 36-month mark experienced a reduction in SBP greater than 10 mmHg [15].

Regarding safety, no major clinical complications were associated with RDN. Complications were rare and manageable [15]. Changes in BP did not significantly differ across age groups, renal function, or diabetes status. However, there were transient decreases in eGFR observed in some patients, which mostly resolved spontaneously or with subsequent follow-up.

The study concluded that RDN appeared to be effective and safe in reducing BP in patients with treatment-resistant hypertension, with sustained effects observed up

to 36 months [15]. Nevertheless, patients continued their prescribed antihypertensive medication throughout the study. The mean number of antihypertensive medications at baseline before renal denervation was 5.1, and it slightly increased to 5.2 for the patients evaluated at the 36-month mark [15]. The protocol allowed for adjustments to antihypertensive medication during extended follow-up, this could have led to a more effective treatment regimen and subsequent reduction in BP [16]. In conjunction with the lack of a control group, this situation rendered it impossible to dismiss the potential impact of the Hawthorne effect [15, 16] Additionally, only a small proportion (5%) of the study population represented individuals of non-white ethnic origin, limiting the generalizability of the results to other ethnicities [15, 16].

The SIMPLICITY HTN-2 trial was a multicentre, international randomized study aimed at assessing the safety and efficacy of RDN in patients between 18 and 85 years with SBP of 160 mm Hg or more (≥150 mm Hg for patients with type 2 diabetes) despite adherence to three or more antihypertensive drugs. Patients were randomly assigned to either the intervention group, undergoing RDN, or the control group [17]. This study also showed a significant reduction in office-based BP in the RDN group compared to controls. Six months after randomization, the RDN group exhibited a reduction in office-based BP measurements by 32/12 mm Hg (SD 23/11, $p < 0.0001$), whereas the control group showed no significant change. Similar reductions were observed in home-based (20/12 mm Hg, SD 17/11, $p < 0.0001$) and 24-h ambulatory BP (11/7 mm Hg, SD 15/11, $p < 0.006$) measurements. Additionally, 84% of patients who underwent RDN experienced a decrease in SBP of ≥10 mmHg [17]. No serious complications related to the device or procedure were reported. Minor periprocedural events were managed without significant sequelae. Renal function remained stable, and adverse events were comparable between the two groups, with no notable differences in cardiovascular events [17].

However, the multiple limitations of the study must be emphasized. The secondary etiologies of hypertension were not conclusively excluded [17]. A difference in the extent of BP decrease was observed between office-based and ambulatory testing, hinting at potential white-coat hypertension involvement [16–18]. The reduction in BP was compared to previous office visit readings rather than to a control group, raising the prospect of the reductions being influenced by regression to the mean, representing natural BP fluctuations [16–18]. Moreover, the absence of sham controls and lack of blinding for patients and assessors introduces the possibility of misattributing a placebo effect as a treatment outcome [16–18].

Although promising, initial studies have been limited by the abovementioned factors. Therefore, the SYMPLICITY HTN-3 trial was meticulously elaborated to address these methodological limitations [19]. The trial enrolled 535 patients with severe resistant hypertension, excluding those with secondary causes and specific anatomical criteria. Renal angiography was performed before randomization, and patients in the control group were allowed to crossover after 6 months. RDN was performed using radiofrequency energy, with patients unaware of their group assignment. Blinding was maintained throughout, and changes in antihypertensive medications during follow-up were limited [19]. The primary efficacy endpoint was

the change in office SBP at 6 months compared to baseline, with a superiority margin of 5 mm Hg. Secondary efficacy endpoints included changes in ambulatory BP at 6 months. Analyses were performed on an intention-to-treat basis, revealing no significant difference between the denervation and sham-procedure groups in office or ambulatory BP changes at 6 months [6] Office BP decreased by 14.13 ± 23.93 mm Hg in the denervation group and by −11.74 ± 25.94 mm Hg in the sham-procedure group at the 6-month mark, resulting in a non-significant difference of −2.39 mm Hg, failing to meet the predefined superiority margin. Similarly, the change in ambulatory BP after 6 months was −6.75 ± 15.11 mm Hg in the denervation group and −4.79 ± 17.25 mm Hg in the sham-procedure group, with a non-significant difference of −1.96 mmHg compared to the predefined superiority margin [18, 19].

These findings are the result of various reasons. In this trial, RDN demonstrated efficacy in patients with systolic-diastolic hypertension but not in those with isolated systolic hypertension, potentially due to increased arterial stiffness. The study lacked standardization of baseline antihypertensive treatment, which remained constant throughout the study, and adherence to medication was not assessed. More than that, a considerable number of interventionalists had limited experience in RDN, with 34% performing only one procedure. Additionally, most patients (only 19) did not undergo circumferential renal nerve ablation, the recommended procedure [16, 19, 20]. Therefore, even if contradictory results to the first studies were found in this trial, they do not contraindicate the use of RDN.

Following the release of the findings from the third clinical trial, the utilization of RDN became more restricted, prompting the development of additional studies aimed at emphasizing the efficacy of this therapy. Simultaneously, various collaborations have been launched to enhance the standardization of testing methodologies, as well as the devices and protocols employed in upcoming clinical trials [20].

SPYRAL HTN-OFF MED and ON MED Trials

The SPYRAL HTN Clinical Trial Program is a comprehensive series of trials aimed at assessing the effectiveness of RDN therapy for hypertension patients. It comprises two initial phases conducted simultaneously, focusing on renal denervation versus sham procedures. These trials, SPYRAL HTN-OFF MED, and SPYRAL HTN-ON MED, aim to enroll up to 120 and 100 patients, respectively, to inform the design of subsequent phases [21–23].

The “off medication” study assesses the basic hypothesis of BP reduction without antihypertensive medications, while the “on medication” trial evaluates renal denervation alongside standard drug therapy. These trials utilized the multielectrode SPYRAL radiofrequency catheter to conduct renal denervation (RDN) [21–23].

The OFF MED trial indicated a significant reduction of 3.9 mm Hg in 24-h SBP within the RDN group compared to the sham control (95% CI, −6.2 to −1.6). Moreover, a noteworthy difference of 6.5 mmHg (95% CI, −9.6 to −3.5) between the two groups was observed in terms of office SBP at the 3-month mark [16, 21–23].

The primary objective of the ON MED trial was to assess the disparity in 24-h ambulatory SBP between the sham and RDN groups 6 months after ablation. Secondary measures included office systolic/diastolic BP, as well as SBP measured in the morning, daytime, and nighttime. The results showed that after 36 months, there was a decrease in ambulatory BP of 18.7 mm Hg in the RDN group and 8.6 mm Hg in the sham-controlled group. Comparing the two groups, RDN continued to demonstrate a significant reduction in ambulatory BP, with a decrease of 10.0 mm Hg (95% CI, −16.6–−3.3; p = 0.0039). This finding holds significance beyond evaluating the efficacy of RDN, as a consistent reduction in BP, especially during both daytime and nighttime, is linked to a lower risk of cardiovascular events [18, 21, 23].

The positive outcomes of these two studies were encouraging, affirming the notion that through innovative technologies and stringent protocols, RDN therapy can effectively lower BN in individuals with arterial hypertension [24].

RADIANCE-HTN Trials

Ultrasound-based therapies utilizing frictional thermal energy emitted from a piezoelectric crystal have shown effectiveness in reducing BP. Among these, the most researched system is the PARADISE system, employing a 6 French balloon catheter with a cylindrical transducer. This system emits ultrasonic energy to a depth of 1–6 mm, resulting in circumferential nerve injury. The ultrasound balloon is positioned at the center of the renal artery by inflating a water-cooled balloon, which also safeguards the endothelial wall from frictional heat [24].

The RADIANCE-HTN trials were structured to assess two distinct patient cohorts: the RADIANCE-HTN SOLO study, encompassing individuals with mild-to-moderate hypertension following a 4-week cessation of antihypertensive medications, and the RADIANCE-HTN TRIO study, involving patients with resistant hypertension despite being on three antihypertensive medications [24–26].

Compared to previously published studies, RADIANCE-HTN SOLO trial focused on the procedural technique (Paradise endovascular ultrasound RDN) and included patients with less severe hypertension, meaning mild to moderate hypertension, following a 4-week antihypertensive washout period. The trial demonstrated that RDN using ultrasound significantly lowered daytime ambulatory SBP compared to a sham procedure. The study involved 146 patients and showed a mean reduction of 6.3 mmHg in the RDN group compared to the sham group. Importantly, the reduction was consistent across various subgroups, except for patients with abdominal obesity who exhibited a greater treatment effect. The procedure was well-tolerated, with no major adverse events reported [18, 25]. This research indicates that employing endovascular RDN with ultrasound could hold promise as a therapy for hypertension. Its strengths lie in the design featuring a sham-control, rigurous protocol implementation, and blinding. However, the study's limitation arises from the selection of patients with low cardiovascular risk, posing a challenge

to the generalizability of the findings. Moreover, the absence of medication monitoring could potentially affect the outcomes of RDN, either underestimating or overestimating its effectiveness [18, 25].

The RADIANCE-HTN TRIO study, a multi-center, single-blind, sham-controlled trial, involved 136 patients with resistant hypertension (defined as office BP >140/90 mmHg despite taking three or more antihypertensive medications, including a diuretic). Participants were randomized 1:1 to undergo ultrasound RDN using the PARADISE system or to sham-control. To streamline medication management and enhance adherence, patients were transitioned from their existing medication regimens to a fixed-dose combination pill containing amlodipine 10 mg (or 5 mg for those with leg edema), valsartan 160 mg (or olmesartan 40 mg if available), and hydrochlorothiazide 25 mg if BP remained elevated, for a period of 4 weeks before randomization. Medication adherence was assessed through urine samples, revealing similar adherence rates between the two groups at the 2-month mark (82% in both the RDN and sham arms). Notably, ultrasound-mediated RDN led to a significant reduction in daytime ambulatory SBP compared to sham at 2 months [8 mmHg (95% CI −16.4 to 0] vs. −3.0 mmHg (95% CI −10.3 to −1.8 mmHg); median between-group difference −4.5 mmHg [95% CI −8.5 to 0.3], p = 0.022] [24, 26].

Despite efforts to address limitations observed in previous studies, several significant constraints persist and warrant acknowledgment. Regardless of implementing a sham procedure in the control group to maintain blinding, achieving complete blinding in a surgical context can be difficult. Moreover, the primary endpoint, a change in SBP at 2 months post-procedure, offers limited insight into treatment durability over the long term. Although 989 patients were initially enrolled, only a subset of 136 met the inclusion criteria, potentially compromising the statistical power and ability to detect rare adverse events. Furthermore, ensuring consistent performance of the RDN procedure across multiple centers presents a challenge and could introduce variability that impacts the study results [18, 26].

The RADIANCE II trial was another clinical study that aimed to assess the efficacy of ultrasound RDN in treating resistant hypertension, free from the influence of antihypertensive medications. Patients were randomly assigned to either receive RDN or a sham procedure, following a 4-week period without antihypertensive drugs. Renal nerve ablation was performed using the Paradise endovascular ultrasound denervation system. The primary endpoint was the change in daytime ambulatory SBP after 2 months. Results showed a significant reduction of −7.9 mm Hg in the RDN group compared to −1.8 mm Hg in the sham group (difference of −6.3 mm Hg, $p < 0.0001$). Secondary endpoints also favored the RDN group, except for office diastolic BP, which demonstrated no significant reduction between the two groups. However, the trial's short follow-up duration of 2 months limits long-term assessment, though extended follow-up is planned. Furthermore, the enrollment criteria included low cardiovascular risk and specific health conditions, limiting the generalizability of results. Variability in the RDN procedure may also affect outcomes [27].

Guidelines

Early trials of RDN did not consistently demonstrate a reduction in BP. However, recent trials have learned from these early experiences, implementing more robust methodologies and including a more representative study population [14, 16]. Multiple systematic reviews have concluded that these recent studies show a modest yet clinically significant BP reduction.

On one hand, **the European Society of Hypertension (ESH) guidelines** on the management of arterial hypertension in 2023 stated that RDN may be considered (with an indication of IIB) in select patients with resistant hypertension who meet specific criteria, including:

1. Confirmation of resistant hypertension despite optimal pharmacological treatment.
2. Adherence to lifestyle modifications and antihypertensive medications.
3. Exclusion of secondary causes of hypertension.
4. Informed consent after discussion of risks and benefits.
5. Only in patients with eGFR > 40 ml/min/1.73 m^2.

The ESH guidelines also recommends that RDN should be performed only in experienced and specialized centers that have established a multidisciplinary team with a structured pathway for evaluating hypertensive patients and moreover, to consider the patients' perspective and expectation [28].

On the other hand, **the American Heart Association (AHA) guidelines** does not strongly recommend renal denervation as a routine treatment for hypertension. The AHA guidelines generally emphasized lifestyle modifications and pharmacological treatments as the primary approaches for managing hypertension. However, the AHA recognized that renal denervation could be considered for a specific subset of patients with resistant hypertension who have failed to achieve adequate blood pressure control with lifestyle modifications and multiple medications [29].

The AHA guidelines typically recommended that renal denervation should be performed in specialized centers with expertise in the procedure, and it should be reserved for carefully selected patients after a multidisciplinary evaluation [29].

Finally, a standardized shared decision-making process is recommended to incorporate patients' preferences and individualize treatment strategies. However, this paper has also highlighted variability in BP reduction among trials, prompting the need for additional research, as outlined in the ESH position paper. This includes identifying predictors of significant response to RDN, factors enhancing procedural efficacy, RDN efficacy in the presence of comorbidities, and direct comparisons of different RDN techniques [14].

References

1. Judd E, Calhoun DA. Apparent and true resistant hypertension: definition, prevalence and outcomes. J Hum Hypertens. 2014;28:463–8. https://doi.org/10.1038/jhh.2013.140.
2. The SPRINT Research Group a randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373:2103–16. https://doi.org/10.1056/NEJMoa1511939.
3. King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. Brit J Clin Pharm. 1999;48:643–8. https://doi.org/10.1046/j.1365-2125.1999.00092.x.
4. Lamirault G, Artifoni M, Daniel M, Barber-Chamoux N. Nantes University Hospital Working Group on hypertension resistant hypertension: novel insights. CHYR. 2020;16:61–72. https://doi.org/10.2174/1573402115666191011111402.
5. Bhatt DL, Vaduganathan M, Kandzari DE, Leon MB, Rocha-Singh K, Townsend RR, Katzen BT, Oparil S, Brar S, DeBruin V, et al. Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 trial. Lancet. 2022;400:1405–16. https://doi.org/10.1016/S0140-6736(22)01787-1.
6. Böhm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE, Tsioufis K, Pocock S, Konstantinidis D, Choi JW, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED pivotal): a multicentre, randomised, sham-controlled trial. Lancet. 2020;395:1444–51. https://doi.org/10.1016/S0140-6736(20)30554-7.
7. Krum H, Schlaich M, Sobotka P. Renal sympathetic nerve ablation for treatment-resistant hypertension. Brit J Clin Pharm. 2013;76:495–503. https://doi.org/10.1111/bcp.12171.
8. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. N Engl J Med. 2009;361:932–4. https://doi.org/10.1056/NEJMc0904179.
9. Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. Vet Intern Med. 2019;33:363–82. https://doi.org/10.1111/jvim.15454.
10. Lu J, Ling Z, Chen W, Du H, Xu Y, Fan J, Long Y, Chen S, Xiao P, Liu Z, et al. Effects of renal sympathetic denervation using saline-irrigated radiofrequency ablation catheter on the activity of the renin-angiotensin system and endothelin-1. J Renin-Angiotensin-Aldosterone Syst. 2014;15:532–9. https://doi.org/10.1177/1470320313506480.
11. Mahfoud F, Townsend RR, Kandzari DE, Kario K, Schmieder RE, Tsioufis K, Pocock S, David S, Patel K, Rao A, et al. Changes in plasma renin activity after renal artery sympathetic denervation. J Am Coll Cardiol. 2021;77:2909–19. https://doi.org/10.1016/j.jacc.2021.04.044.
12. Ormezzano O, Baguet J-P. Baroreflex sensitivity and renal sympathetic denervation. J Am Coll Cardiol. 2014;63:2433–4. https://doi.org/10.1016/j.jacc.2013.12.048.
13. Kopp UC, Jones SY, DiBona GF. Afferent renal denervation impairs Baroreflex control of efferent renal sympathetic nerve activity. Am J Phys Regul Integr Comp Phys. 2008;295:R1882–90. https://doi.org/10.1152/ajpregu.90529.2008.
14. Schmieder RE, Mahfoud F, Mancia G, Azizi M, Böhm M, Dimitriadis K, Kario K, Kroon AA, Lobo MD, Ott C, et al. European Society of Hypertension Position Paper on renal denervation 2021. J Hypertens. 2021;39:1733–41. https://doi.org/10.1097/HJH.0000000000002933.
15. Krum H, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K, Katholi R, Esler MD. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet. 2014;383:622–9. https://doi.org/10.1016/S0140-6736(13)62192-3.
16. Shah RT, Wang BX. Effectiveness of renal denervation in the treatment of hypertension: a literature review. Clin Hyperten. 2022;28:11. https://doi.org/10.1186/s40885-022-00194-6.
17. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. Lancet. 2010;376:1903–9. https://doi.org/10.1016/S0140-6736(10)62039-9.

18. Salehin S, Karnkowska B, Hamza I, Malik H, Syeda D, Hasan SM, Rangasetty U, Gilani S, Jneid H, Raja M. Renal denervation in the management of resistant hypertension: a comprehensive review of literature. Curr Probl Cardiol. 2024;49:102137. https://doi.org/10.1016/j.cpcardiol.2023.102137.
19. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370:1393–401. https://doi.org/10.1056/NEJMoa1402670.
20. Bruno RM, Taddei S, Borghi C, Colivicchi F, Desideri G, Grassi G, Mazza A, Muiesan ML, Parati G, Pontremoli R, et al. Italian Society of Arterial Hypertension (SIIA) position paper on the role of renal denervation in the management of the difficult-to-treat hypertensive patient. High Blood Press Cardiovasc Prev. 2020;27:109–17. https://doi.org/10.1007/s40292-020-00367-0.
21. Kandzari DE, Kario K, Mahfoud F, Cohen SA, Pilcher G, Pocock S, Townsend R, Weber MA, Böhm M. The SPYRAL HTN global clinical trial program: rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications. Am Heart J. 2016;171:82–91. https://doi.org/10.1016/j.ahj.2015.08.021.
22. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, Ewen S, Tsioufis K, Tousoulis D, Sharp ASP, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet. 2017;390:2160–70. https://doi.org/10.1016/S0140-6736(17)32281-X.
23. Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, Tsioufis K, Tousoulis D, Choi JW, East C, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet. 2018;391:2346–55. https://doi.org/10.1016/S0140-6736(18)30951-6.
24. Guber K, Kirtane AJ. Renal sympathetic denervation for hypertension. Kidney Int Rep. 2022;7:2129–40. https://doi.org/10.1016/j.ekir.2022.06.019.
25. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, Basile J, Kirtane AJ, Wang Y, Lobo MD, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet. 2018;391:2335–45. https://doi.org/10.1016/S0140-6736(18)31082-1.
26. Azizi, M.; Sanghvi, K.; Saxena, M.; Gosse, P.; Reilly, J.P.; Levy, T.; Rump, L.C.; Persu, A.; Basile, J.; Bloch, M.J.; et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial, Lancet 2021, 397, 2476–2486, doi:https://doi.org/10.1016/S0140-6736(21)00788-1.
27. Azizi M, Saxena M, Wang Y, Jenkins JS, Devireddy C, Rader F, Fisher NDL, Schmieder RE, Mahfoud F, Lindsey J, et al. Endovascular ultrasound renal denervation to treat hypertension. JAMA. 2023;329:651. https://doi.org/10.1001/jama.2023.0713.
28. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, Muiesan ML, Tsioufis K, Agabiti-Rosei E, Algharably EAE, Azizi M, Benetos A, Borghi C, Hitij JB, Cifkova R, Coca A, Cornelissen V, Cruickshank JK, Cunha PG, Danser AHJ, et al. 2023 ESH guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874–2071. https://doi.org/10.1097/HJH.0000000000003480.
29. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens. 2020;38(6):982–1004. https://doi.org/10.1097/HJH.0000000000002453.

Beyond Blood Pressure: Expanding the Use of Renal Denervation in Diverse Pathologies

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Abstract Renal denervation (RDN), initially developed for resistant hypertension, has demonstrated promising therapeutic potential beyond high blood pressure. RDN holds promise in reducing atrial fibrillation recurrence rates, particularly when combined with catheter ablation. RDN has also shown potential benefits in improving heart failure (HF) symptoms, functional capacity, and left ventricular function. Studies have documented a significant reduction in HF hospitalization rates following RDN, suggesting its role in enhancing overall patient outcomes. RDN emerged as a viable treatment option for resistant hypertension and chronic kidney disease (CKD). Studies have demonstrated its ability to effectively lower blood pressure and reduce proteinuria. Moreover, RDN is associated with improvements in renal function and overall cardiovascular outcomes in CKD patients. RDN has shown potential in improving glycemic control in metabolic syndrome patients. Some studies have documented improvements in insulin sensitivity, fasting glucose levels, and overall metabolic parameters following RDN. Additionally, RDN has been shown to significantly reduce ventricular arrhythmias in post-myocardial infarction patients. RDN can also lead to a significant improvement in sleep quality in patients with obstructive sleep apnea. While promising, further studies are needed to fully evaluate the long-term efficacy, safety, and optimal patient selection criteria for RDN in these specific clinical settings.

Keywords Renal denervation · Atrial fibrillation · Heart failure · Cardiac remodeling · CKD · Ventricular arrhythmias · Obstructive sleep apnea

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Introduction

While renal artery denervation (RDN) is generally indicated for patients with arterial hypertension, its potential applications extend to several other clinical settings, including atrial fibrillation (AF), heart failure, chronic kidney disease (CKD), and ventricular arrhythmias. The broader utility of RDN, beyond arterial hypertension, is commonly acknowledged in guidelines as an existing research gap or a prospective area for future investigation [1–4]. Therefore, a critical assessment and up-to-date evaluation of the efficacy and safety of RDN in these specific conditions are warranted to facilitate its integration into clinical practice and upcoming guidelines (Fig. 1).

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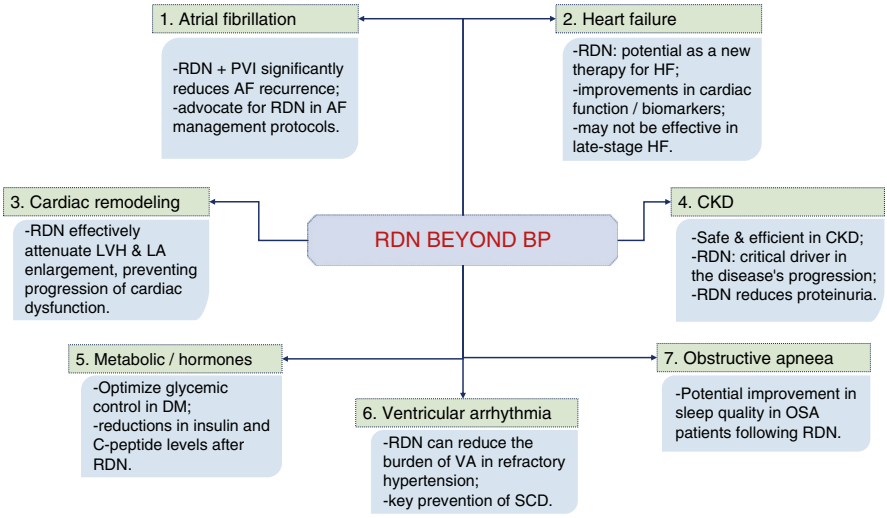

Fig. 1 Extended use of renal denervation in other pathologies. *AF* atrial fibrillation, *BP* blood pressure, *CKD* chronic kidney disease, *DM* diabetes mellitus, *HF* heart failure, *LA* left atrium, *LVH* left ventricular hypertrophy, *OSA* obstructive sleep apnea, *PVI* pulmonary vein isolation, *RDN* renal denervation, *SCD* sudden cardiac death, *VA* ventricular arrhythmias

The Potential of Renal Denervation in Atrial Fibrillation Management

The European Society of Cardiology (ESC), the American College of Cardiology, and the American Heart Association (ACC/AHA) guidelines acknowledged a potential lower risk of recurrent AF following pulmonary vein isolation (PVI) combined with RDN [1, 2]. However, this approach has not yet received formal guideline endorsement due to a paucity of large randomized controlled trials (RCT). Nonetheless, accumulating data support the efficacy and safety of RDN in AF, warranting further consideration for its integration into clinical practice and subsequent guideline updates [5, 6]. A summary of the analyzed studies is presented in Table 1.

A landmark RCT that evaluated the role of RDN in AF was The Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation (ERADICATE-AF) trial [5]. This study enrolled patients with paroxysmal AF and hypertension, excluding those with persistent AF (>7 days). In the final analysis, 302 patients were randomized into two groups: PVI-only therapy and PVI combined with RDN. The primary efficacy outcome was freedom from AF, atrial flutter, and atrial tachycardia at 12-month follow-up, assessed by Holter monitorization (without antiarrhythmic drug therapy). Substantially higher proportions of patients were free from these arrhythmias in the RDN-combined with PVI group compared to the PVI-only group (respectively, 72.1% vs 56.5%) [5]. Notably, combined therapy with RDN was linked to a 45% lower risk of AF compared to patients from the PVI-only group (HR 0.55, 95% CI, 0.37–0.83, $p = 0.004$). Furthermore, systolic blood pressure demonstrated a significant reduction only in patients who underwent RDN ($p < 0.001$). Additionally, a substantially larger proportion of patients in the RDN group (47.4%) experienced a reduction in left atrial size by at least 2 mm compared to the PVI-only group (6.0%) ($p = 0.001$). These findings underscore the effectiveness of RDN as an adjunct therapy to PVI in hypertensive patients with paroxysmal AF, warranting its consideration for these patients to mitigate arrhythmia recurrence. However, the applicability of RDN to patients with persistent AF remains inconclusive due to the exclusion of these patients from the final analysis [5]. Also, the study lacked a sham control; thus it is unclear whether the observed improvements were solely attributable to RDN or could have been influenced by factors unrelated to the intervention [5].

Another RCT involved 69 hypertensive patients with paroxysmal AF (<7 days) [7]. Participants were randomly assigned to two treatment groups: PVI combined with spironolactone and PVI combined with RDN. Notably, all patients had dual-chamber pacemakers, allowing for precise assessment of AF recurrence and burden throughout the study [7]. Compared to spironolactone + PVI, RDN significantly reduced AF recurrence over 12 months, with 61% of RDN patients remaining AF-free compared to 36% in the spironolactone group ($p = 0.0242$). Interestingly, the two treatment arms exhibited contrasting effects on renal function. In the PVI + spironolactone group, eGFR showed a trend toward a modest decrease from baseline to 12 months (from 66.7 ± 7.7 mL/min/1.73 m^2 to 64.8 ± 9.9 mL/

Table 1 Studies investigating RDN as a complementary therapy for AF

Author, year	Design	Patients, No	Clinical context	Interventions	Follow-up	Outcomes
Steinberg, 2020	RCT	302	Hypertensive patients with paroxysmal AF (≤7 days)	PVI + RDN vs PVI-only therapy	12 months	*Free from AF, atrial flutter, and atrial tachycardia*: 72.1% in PVI + RDN vs. 56.5% in PVI-only (HR 0.57, 95% CI, 0.38–0.85, p = 0.006)
Kiuchi, 2018	RCT	69	Hypertensive patients with paroxysmal AF (<7 days) and dual-chamber pacemaker	PVI + spironolactone vs PVI + RDN	12 months	*Free from AF*: 36% patients from PVI + spironolactone group vs 61% patients in PVI + RDN group (p = 0.0242)
Kiuchi, 2016	RCT	45	Patients with paroxysmal AF (<7 days) or persistent AF (>7 days) and dual-chamber pacemaker	PVI + RDN vs PVI-only therapy	12 months	*Free from AF*: 76% patients in PVI + RDN group vs 25% patients in PVI-only group (p = 0.0007)
Romanov, 2017	RCT	76	Patients with paroxysmal or persistent AF, resistant hypertension, and implantable cardiac monitor	PVI + RDN vs PVI-only therapy	12 months	*AF recurrence*: PVI + RDN (HR 0.40, 95% CI, 0.21–0.80)
Kiuchi, 2017	Obs	236	Patients with controlled hypertension and paroxysmal AF	PVI + RDN vs PVI-only therapy	22.4 ± 12.1 months	*AF recurrence*: PVI alone (HR 1.86, 95% CI, 1.14–3.03, p = 0.0251)
Pokushalov, 2012	RCT	27	Patients with resistant hypertension and paroxysmal or persistent AF	PVI + RDN vs PVI-only therapy	12 months	*Free from AF*: 69% of patients in the PVI + RDN group vs 29% of patients in the PVI-only group

Kirstein, 2023	RCT	61	Patients with uncontrolled hypertension and paroxysmal or persistent AF	AF ablation-only vs. AF ablation + RDN	24 months	AF recurrence: similar rate of recurrence at 12 and 24 months (respectively, p = 0.622 and p = 0.927)
Turagam, 2021 (HFIB-1)	RCT	30	Patients with paroxysmal or persistent AF and drug-resistant hypertension	AF ablation-only vs. AF ablation + RDN	24 months	*AF, atrial flutter, or atrial tachycardia recurrence rate:* 53% in AF ablation-only vs 38% in RDN group (p = 0.43)
Turagam, 2021 (HFIB-2)	RCT	50	Patients with paroxysmal or persistent AF and drug-resistant hypertension	AF ablation-only vs. AF ablation + RDN	24 months	*AF, atrial flutter, or atrial tachycardia recurrence rate:* 27% in AF ablation-only vs. 25% in RDN group (p = 0.8)

AF atrial fibrillation, *Obs* observational, *PVI* pulmonary vein isolation, *RCT* randomized controlled trial, *RDN* renal artery denervation

min/1.73 m^2). Conversely, the RDN group demonstrated a significant increase in eGFR, from 69.2 ± 6.7 mL/min/1.73 m^2 at baseline to 81.8 ± 6.8 mL/min/1.73 m^2 at 12 months ($p < 0.0001$) [7]. These findings support the effectiveness of RDN in both reducing AF recurrence after PVI and improving (or at least preserving) renal function [7].

RDN could be a viable therapeutic option in patients with persistent AF [6]. In a double-blinded RCT, 27 patients with paroxysmal AF (<7 days) and 18 patients with persistent AF (>7 days) were enrolled [6]. The participants were randomized to PVI-only therapy and PVI combined with RDN. Compared to PVI-only therapy, RDN was associated with an increased proportion of patients free from AF at 12 months (76% vs 25%, $p = 0.0007$) [6]. Interestingly, 24% of patients who experienced AF recurrence during follow-up from the RDN group all had stage 3 CKD, suggesting a potential influence of renal function on outcomes. Moreover, patients who underwent RDN complementary to PVI had an improved renal function at 12 months, compared to baseline (baseline eGFR 59.3 ± 13.3 mL/min/1.73 m^2 vs 65.7 ± 14.0 mL/min/1.73 m^2 at 12 months, $p < 0.001$). Thus, RDN appeared to be an effective procedure even in patients with persistent AF [6].

Another study involving 76 patients with paroxysmal or persistent AF confirmed these findings, reporting a significantly lower 12-month AF recurrence rate (HR 0.40, 95% CI 0.21–0.80) in patients who underwent PVI combined with RDN compared to PVI alone [8]. Despite improved outcomes after RDN in patients with persistent AF, the presence of persistent AF itself remained a significant independent predictor of AF recurrence (HR 2.76, 95% CI, 1.29–5.91). Furthermore, a significant decrease in AF burden was observed alongside a reduction in mean blood pressure, suggesting an additive beneficial effect of RDN in this subgroup of patients [8]. Similar beneficial results of RDN combined with PVI in patients with paroxysmal or persistent AF were documented in other observational studies and RCTs [9, 10].

Discrepant data were reported in a recent RCT (the RDN + AF study) that enrolled patients with uncontrolled hypertension and paroxysmal or persistent AF [11]. Patients were divided into two treatment groups: AF ablation-only therapy and AF ablation + RDN. Freedom from AF rate was similar among both treatment arms at 12 months (61% in RDN + AF ablation and 53% in AF ablation-only group, $p = 0.622$) and at 24 months (39% in RDN + AF ablation and 47% in AF ablation-only group, $p = 0.927$) [11]. However, in the RDN + AF study, patients had severe multidrug-resistant hypertension with a high prevalence of comorbidities, including diabetes mellitus and coronary artery disease [11].

Conflicting results were also reported in RCTs, respectively, the HFIB-1 (Adjunctive Renal Denervation to Modify Hypertension and Sympathetic tone as Upstream Therapy in the Treatment of Atrial Fibrillation) and HFIB-2 studies [12]. In both studies, patients underwent AF ablation alone or combined with RDN. AF recurrence rate at 24 months in the HFIB-1 trial was similar in both treatment groups (53% in the AF ablation group and 38% in the AF ablation + RDN group, $p = 0.43$). However, the results should be interpreted cautiously due to the premature discontinuation of the trial related to renal complications, including renal artery stenosis

and dissection. Likewise, in the HFIB-2 trial, the AF recurrence rate was similar in AF ablation-only and AF ablation + RDN groups (respectively, 27% and 25%, $p = 0.8$) [12]. Nevertheless, the recurrence of AF included atrial flutter and atrial tachycardia, raising concerns about the generalizability of these findings to AF exclusively [12]. Moreover, these findings might also be influenced by the type of catheters used for AF ablation and RDN [12].

One recent meta-analysis on RDN for AF included seven trials with 711 patients, comparing outcomes in groups receiving RDN plus PVI against PVI alone [13]. It found significantly lower rates of AF recurrence in the RDN + PVI group (31.3%) compared to PVI alone (52.9%), $p < 0.00001$. Additionally, the study observed significant reductions in systolic blood pressure in the RDN + PVI group, although diastolic blood pressure differences were not significant [13]. The analysis underscores the potential benefits of RDN in conjunction with PVI for patients with AF, highlighting its role in reducing AF recurrence and improving blood pressure control. This finding marks a pivotal step in enhancing AF treatment strategies, potentially reshaping clinical practices to integrate RDN as a standard adjunct to PVI in suitable cases [13].

Based on these findings, RDN emerges as a promising add-on therapy for patients undergoing AF ablation, both with paroxysmal and persistent forms, to reduce arrhythmic recurrence. However, considering the inclusion of patients with controlled and resistant hypertension in previous clinical trials, further large-scale randomized studies are crucial to solidify RDN efficacy across the entire spectrum of arterial hypertension, particularly in case of severe, multidrug-resistant forms. Moreover, prospective research should focus on identifying the optimal patient profile within the AF population in whom RDN would be most effective in terms of preventing AF recurrence.

Improving Outcomes in Heart Failure: The Evolving Role of Renal Denervation

While RDN was originally developed for the treatment of hypertension, recent studies have revealed its potential benefits for HF patients [14, 15]. These studies have demonstrated that RDN can modulate the sympathetic nervous system by suppressing components such as angiotensin-converting enzyme (ACE), angiotensin II, and angiotensin II type-1 receptor while simultaneously enhancing the protective factors (ACE2) [14, 15]. These findings suggest that RDN could be a promising new therapeutic approach for HF, potentially providing cardiac protection, improving cardiac function, and reducing fluid retention [14, 15]. Key findings from analyzed studies regarding RDN in HF patients are presented in Table 2.

A proof-of-concept study enrolled seven patients with severe chronic HF, New York Heart Association (NYHA) class III or IV, despite the optimal medical therapy (OMT) [16]. The study investigated primarily the safety profile of RDN in patients with HF. None of the patients experienced rehospitalization due to HF

Table 2 Studies investigating the efficacy of RDN in patients with HF

Author, year	Design	Patients, No	Clinical context	Interventions	Follow-up	Outcomes
Davies, 2013 [16]	Obs	7	Patients with chronic HF and NYHA class III or IV despite OMT	RDN	6 months	*Six-minute walk test:* significantly increased after RDN (249 ± 34 m, from 221 ± 33 m, p = 0.03)
Chen, 2016 [17]	RCT	60	HF patients with NYHA class II-IV and LVEF ≤ 40% despite OMT	RDN + OMT vs OMT alone	6 months	(*a*) *LVEF*: patients from RDN group had an improved LVEF (41.9 ± 7.9% vs 31.1 ± 5.7% at baseline, p < 0.001); (*b*) *SMWT*: improved only in the RDN group (374.9 ± 91.9 m at 6 months vs 285.5 ± 84.3 m at baseline)
Gao, 2019 [18]	RCT	60	HF patients with NYHA class II or III and LVEF ≤ 40%	RDN vs drug therapy alone	6 months	(*a*) *NT-proBNP*: significantly lower levels in the RDN group than in the drug-therapy group (440.1 ± 226.5 pg/mL vs 790.8 ± 287.0 pg/mL, p < 0.001); (*b*) *SMWT:* improved distance in RDN patients (301.2 ± 139.5 m vs 227.2 ± 65.0 m, p = 0.01) (*c*) *LVEF:* improved values in RDN group (39.1 ± 7.3% vs 35.6 ± 3.3%, p = 0.017)
Hopper, 2017 [19]	Obs	39	HF patients with NYHA class II or III and LVEF < 40%	RDN (single-arm)	12 months	(*a*) *SMWT:* no significant improvement (p = 0.584) (*b*) *LVEF:* no significant improvement (p = 0.536) (*c*) *NT-proBNP:* significant decrease from baseline (1466 ± 1782 ng/L vs 1899 ± 1818 ng/L, p = 0.006)

(continued)

Table 2 (continued)

Author, year	Design	Patients, No	Clinical context	Interventions	Follow-up	Outcomes
Feyz, 2022 [20]	RCT	50	HF patients with NYHA class II-IV and LVEF ≤ 35%	RDN + OMT vs OMT alone	6 months	*Composite of cardiovascular death, rehospitalization for HF and AKI:* 8.3% in RDN patients and 8.0% in OMT alone group (p = 0.97)
Pietila-Effati, 2022 [21]	Obs	11	HF patients with NYHA class III or IV and CRT	CRT	24 months	(*a*) *SMWT:* at baseline 305 m (187 –398 m) and at 24 months 232 m (129 m–340 m), p = 0.01; (*b*) *LVEF:* at baseline 29% (22–38%) and at 24 months 27% (20–39%), p = 0.21

AKI acute kidney injury, *CRT* cardiac resynchronization therapy, *HF* heart failure, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *Obs* observational, *OMT* optimal medical therapy, *RCT* randomized controlled trial, *RDN* renal denervation, *SMWT* six-minute walk test

symptoms or complications related to RDN during 6 months of follow-up. Notably, all patients had significant improvements in their symptoms following RDN, with a marked increase in the six-minute walk test (from 221 ± 33 m to 249 ± 34 m, p = 0.03) [16]. Also, blood pressure, heart rate, and creatinine levels were similar after RDN as compared to baseline values. This study provided preliminary evidence supporting the use of RDN as a viable therapeutic approach for improving symptoms in HF patients, establishing a background for larger-scale clinical trials [16].

An RCT of 60 HF patients with moderate to severe symptoms (NYHA class II-IV) and reduced left ventricular ejection fraction (LVEF ≤ 40%) found that RDN combined with OMT provided significant benefits [17]. At 6 months follow-up, LVEF was significantly increased compared to baseline values only in patients who underwent RDN (41.9 ± 7.9% at 6 months vs 31.1 ± 5.7% at baseline, p < 0.001) [17]. Also, the six-minute walk test was improved exclusively in patients from the RDN group (374.9 ± 91.9 m at 6 months vs 285.5 ± 84.3 m at baseline). Moreover, N-terminal pro-b-type natriuretic peptide (NT-proBNP) decreased significantly in patients from the RDN group (422.7 ± 257.0 pg/mL from 1519.9 ± 599.3 pg/mL) as compared to those from OMT alone group (p < 0.001) [17]. Therefore, RDN could be used in symptomatic HF patients on top of OMT to improve symptoms, left ventricular systolic function, and biomarkers of HF [17].

In another RCT, 60 chronic HF patients with NYHA class II or III and LVEF < 40% were divided into two groups (RDN or drug therapy alone) [18]. After 6 months, patients who underwent RDN showed significantly lower levels of NT-proBNP compared to the drug therapy group (respectively, 440.1 ± 226.5 pg/

mL vs 790.8 ± 287.0 pg/mL, $p < 0.001$) [18]. Additionally, RDN led to improvements in both six-minute walk test distance (301.2 ± 139.5 m vs 227.2 ± 65.0 m, $p = 0.01$) and LVEF (39.1 ± 7.3% vs 35.6 ± 3.3%, $p = 0.017$). Moreover, RDN induced left ventricular reverse remodeling, with a significantly reduced left ventricular end-systolic diameter (LVESD) at 6 months ($p < 0.001$) [18].

Contradictory results were reported in the Symplicity feasible study in HF patients [19]. Both the six-minute walk test distance and LVEF values were similar at 12 months compared to baseline (respectively, 391 ± 97 m vs 384 ± 96 m, $p = 0.584$ and 29 ± 11% vs 28 ± 9%, $p = 0.536$). Nevertheless, NT-proBNP values were significantly decreased after 12 months (1466 ± 1782 ng/L vs 1899 ± 1818 ng/L, $p = 0.006$) [19]. However, the lack of randomization and small sample size of the study limit the generalizability of these findings [19].

Furthermore, one RCT reported a similar composite rate of cardiovascular death, rehospitalization for HF, and acute kidney injury in RDN patients as compared to those receiving OMT alone (respectively, 8.3% vs 8.0%, $p = 0.97$) [20]. However, due to the small sample size and short follow-up (6 months), large RCTs are warranted to investigate the impact of RDN on long-term adverse cardiovascular events, including mortality [20].

RDN therapy showed limited benefit in a study of advanced HF patients who did not respond to cardiac resynchronization therapy (CRT) [21]. While left ventricular function and biomarker levels remained unchanged, functional capacity, as measured by six-minute walk test distance, declined significantly at 24 months (232 m vs 305 m, $p = 0.01$) [21]. Similar results were reported in another clinical trial involving HF patients with CRT [22]. These findings suggest that RDN may not be a viable option for late-stage HF management when left ventricular remodeling is not reversible. Further research is crucial to investigate the potential of RDN in earlier stages of the disease, where intervention might have a greater impact on preventing clinical deterioration [21, 22].

In a meta-analysis comprising 11 studies involving HF patients, RDN was associated with an improved LVEF ($p = 0.0004$) and a six-minute walk test ($p < 0.00001$) [23]. Also, other echocardiographic parameters, such as left ventricular end-diastolic diameter (LVEDD), LVESD, and left atrial diameter decreased significantly after RDN (respectively, $p < 0.0001$, $p < 0.0001$, and $p = 0.007$). Moreover, NT-proBNP levels also showed a substantial decline following RDN ($p < 0.00001$) [23]. Nevertheless, the results should be interpreted cautiously due to the high heterogeneity across studies [23].

Therefore, RDN should be considered in patients with HF and reduced LVEF to enhance functional capacity, improve ejection fraction, and decrease HF biomarkers in moderate-to-severe patients (NYHA class II-IV) [17]. Based on existing literature, RDN should be avoided in advanced HF stages, who did not respond to CRT [21]. Further large RCTs are required to solidify the long-term safety and efficacy of RDN, especially in earlier HF stages. These studies should also focus on identifying the optimal patient selection criteria to maximize RDN benefits and personalize treatment strategies.

Cardiac Remodeling and Renal Denervation: Efficacy and Future Perspectives

The primary drivers of cardiac remodeling are the chronic activation of neurohormonal systems, particularly the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system [24, 25]. As a result, studies have explored the therapeutic potential of RDN to address cardiac remodeling by disrupting these maladaptive pathways [26]. Studies have demonstrated that RDN can effectively attenuate left ventricular hypertrophy (LVH) and left atrial enlargement, thereby preventing the progression of cardiac dysfunction [27].

In one study RDN was associated with a significant reduction in cardiac parameters assessed by cardiac magnetic resonance (CMR) at 12 months of follow-up [28]. Patients who underwent RDN exhibited a substantial decrease in left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), and left ventricular mass ($p < 0.0001$ for all). Furthermore, an improvement in LVEF was reported in patients following RDN compared to baseline values ($p = 0.001$) [28]. Also, some studies on HF patients have reported a significant reduction in left ventricular dimensions and an improvement in systolic function [18, 23].

RDN has been shown to significantly reduce LVH, improve myocardial function, and reduce LAE in patients with resistant hypertension [29]. RDN reduced left ventricular mass indexed to body surface area (LVMI) by 7.1% ($p < 0.001$), improved LVEF (50% after RDN vs 43% at baseline, $p < 0.001$), and left ventricular circumferential strain by 21% ($p = 0.001$ [29]). Additionally, RDN was associated with a reduction in left atrial size ($p = 0.026$). While the findings of the study are encouraging, longer-term follow-up studies are needed to assess the durability of RDN's effects and to evaluate its impact on cardiovascular outcomes such as heart failure and stroke [29].

One meta-analysis evaluated nine studies on the impact of RDN on cardiac remodeling, encompassing 300 patients [27]. The analysis focused on CMR-derived cardiac indices, comparing parameters before and after RDN. Results indicate a significant reduction in LVMI following RDN, with a mean difference of -4.15 g/m^2 ($p = 0.002$) [27]. Additionally, LVEDVI and LVESVI both exhibited significant reductions of -3.47 ml/m^2 ($p = 0.01$) and -3.04 ml/m^2 ($p < 0.001$), respectively. Notably, LVEF demonstrated a statistically significant increase, with a mean difference of 3.49% ($p = 0.01$). Further analyses of office and 24-h blood pressure measurements revealed significant reductions in both systolic and diastolic blood pressure following RDN. This meta-analysis underscores the potential beneficial role of RDN in cardiac remodeling and its impact on CMR-derived indices, advocating for further research to solidify the position of RDN in clinical practice [27].

Therefore, RDN is a promising new therapeutic approach to induce reverse cardiac remodeling, especially in patients with resistant hypertension. As documented in clinical studies, RDN could significantly reduce LVH, improve systolic function,

and decrease left atrial enlargement. Nevertheless, further large RCTs are required to confirm these results, including the long-term safety and efficacy of RDN.

Renal Denervation and Chronic Kidney Disease: A Promising Area of Research

Renal denervation is a novel and promising approach to the management of CKD. This technique, which involves disrupting the renal sympathetic nerves, has garnered significant attention in the medical community, particularly due to its potential to address one of the key factors in CKD progression: hypertension. RDN's role in patients with CKD is of significant interest due to the potential for sympathetic nervous system modulation [30].

Recent studies have provided insights into the efficacy and safety of RDN in this patient population, emphasizing the potential benefits and considerations in the management of hypertension associated with CKD. A systematic review and meta-analysis exploring the effects of RDN on kidney function in patients with CKD demonstrated the procedure's safety and potential for blood pressure reduction. This analysis, which included multiple studies with diverse patient populations, indicated that RDN could be effective in lowering office blood pressure in CKD patients without significant declines in kidney function over a follow-up period [30].

Further, a study focusing on the blood pressure-lowering effects and safety of RDN in patients with and without CKD found similar reductions in both office and 24-h ambulatory blood pressure across these groups. This suggests that RDN can be an effective and safe treatment option for hypertension in patients with CKD, comparable to its effects in those without CKD [31]. Recent developments in both clinical and preclinical research on RDN have provided a deeper understanding of its broader impacts, including potential risks and the identification of biomarkers that could predict success in denervation procedures [32].

These findings align with the broader perspective on the role of RDN in patients with CKD, as outlined in a review that discusses the current evidence and future directions. The review emphasizes the importance of further research to establish definitive conclusions regarding the benefits of RDN in CKD patients, particularly in terms of long-term outcomes and specific CKD stages [33].

Schmieder's research highlights that hypertension is not only a common comorbidity in CKD patients but also a critical driver of the disease's progression [33]. By effectively lowering blood pressure, RDN directly impacts one of the primary pathways through which CKD worsens. Beyond its impact on hypertension, RDN offers several other potential benefits in CKD management. Schmieder's paper points out that the sympathetic nervous system plays a multifaceted role in kidney function. It influences renal hemodynamics, sodium retention, and the renin-angiotensin-aldosterone system—all of which are crucial in the pathophysiology of CKD. By modulating the activity of the sympathetic nervous system, RDN can potentially alleviate the adverse effects these factors have on kidney health [33].

Another crucial aspect discussed by Schmieder is the role of RDN in reducing proteinuria, a significant marker of kidney damage [33]. Proteinuria not only indicates ongoing kidney damage but also contributes to the progression of CKD. RDN's ability to reduce proteinuria presents a direct therapeutic benefit in slowing down the disease's progression. Furthermore, Schmieder elaborates on the potential of RDN to improve overall cardiovascular health in CKD patients. Given that cardiovascular complications are the leading cause of death in CKD, any intervention that improves cardiovascular outcomes can significantly impact patient prognosis. RDN, by reducing blood pressure and possibly improving other cardiovascular risk factors, can play a vital role in enhancing the overall health and lifespan of CKD patients [33].

In conclusion, the intersection of RDN and CKD presents a promising area of research and clinical application. The existing evidence suggests that RDN is a viable option for managing hypertension in CKD patients, with similar efficacy and safety profiles to those observed in the general hypertensive population. RDN not only addresses hypertension—a key contributor to CKD progression—but also impacts various other aspects like proteinuria and cardiovascular health. Future studies are necessary to fully understand the long-term implications of RDN in this specific patient group and to optimize patient selection for this intervention.

Challenges and Limitations of Renal Denervation for Metabolic Management

Despite the availability of multiple pharmacological interventions, achieving adequate glycemic control remains a challenge for a significant portion of diabetic patients [34]. RDN has emerged as a possible therapeutic option to optimize glycemic control in patients with diabetes mellitus, as heightened sympathetic activity was observed in patients with metabolic syndrome components. The bidirectional relationship between sympathetic overactivity and insulin resistance forms a vicious cycle, suggesting a potential connection between sympathetic activity and glucose metabolism [35]. The rationale for RDN in diabetic patients stems from the role of the sympathetic nervous system in exacerbating insulin resistance and impairing glucose metabolism [36].

One study investigated the impact of RDN on glucose homeostasis in hypertensive patients [37]. RDN not only significantly lowered systolic and diastolic blood pressure after 3 months ($P < 0.001$) but also demonstrated marked improvements in glucose metabolism [37]. Fasting glucose levels decreased significantly (108 ± 3.8 mg/dL from 118 ± 3.4 mg/dL, $p = 0.039$), accompanied by reductions in insulin and C-peptide levels after RDN therapy. Furthermore, insulin sensitivity significantly improved following RDN ($p = 0.001$). The study suggests that RDN may represent a dual therapeutic approach, not only effectively addressing resistant hypertension but also exerting a substantial impact on glucose metabolism. These findings emphasize the potential of RDN as a novel, non-pharmaceutical strategy

for simultaneously treating insulin resistance and drug-resistant hypertension, opening new possibilities for further exploration and clinical application [37].

In another study, RDN did not lead to a significant impact on insulin sensitivity indexes despite a reduction in ambulatory blood pressure values [38]. The study results contradicted previous findings that suggested an improvement in insulin sensitivity following RDN therapy. Additionally, the study reported no significant changes in sympathetic nervous system activity, measured through muscle sympathetic nerve activity and heart rate variability [38]. The study acknowledged limitations, such as a small sample size and the absence of a control group. However, the findings emphasize the need for further exploration of the role of RDN in metabolic parameters, especially in RCT with larger populations. The observed disconnect between the effects on blood pressure and insulin sensitivity raises questions about the specific patient populations and denervation techniques that may yield optimal results. Also, the study underscores the importance of ongoing research to refine RDN interventions and explore potential periprocedural markers to assess the efficacy of targeting renal sympathetic nerves accurately [38].

One meta-analysis aimed to consolidate existing data on RDN's influence on glucose and lipid metabolism [39]. The study encompassed 19 trials involving 2245 patients. Key findings indicated that RDN had no significant impact on fasting glucose, C-peptide, glycated hemoglobin levels, and neural response to glucose loading, suggesting no beneficial effect on glucose metabolism [39]. However, slight improvements in HDL-cholesterol and triglyceride levels were observed, though deemed clinically negligible. The findings, while suggestive, were not entirely conclusive due to limitations like observational cohort study dominance and potential biases. The study underscores the need for further research using contemporary catheter techniques and rigorous designs to definitively establish the effects of RDN on glucose and lipid metabolism. Determining optimal indications and biomarkers for predicting metabolic responses to RDN remains a priority [39].

The Benefits of Renal Denervation on Ventricular Arrhythmias

Renal denervation has emerged as a significant therapeutic intervention, not just for hypertension and chronic kidney disease, but also for its potential role in the management of ventricular arrhythmias. This novel approach, focusing on the disruption of renal sympathetic nerves, shows promise in addressing the complex interplay between the sympathetic nervous system and cardiac arrhythmias, particularly ventricular arrhythmias [40].

The sympathetic nervous system (SNS) plays a pivotal role in the pathogenesis of ventricular arrhythmias. Increased sympathetic activity can lead to arrhythmogenic substrates, primarily due to its effects on cardiac electrophysiology [41]. These changes can predispose individuals to life-threatening ventricular

arrhythmias. By modulating the activity of the SNS, RDN offers a unique mechanism to mitigate this risk [41].

Clinical evidence, as explored in studies [42], indicates that RDN can reduce the burden of ventricular arrhythmias in patients with refractory hypertension. This reduction is primarily attributed to the decrease in sympathetic nerve activity, which is known to be a contributing factor in the genesis of these arrhythmias. By attenuating the sympathetic drive, RDN can stabilize the cardiac electrical environment, thereby reducing the propensity for the development of ventricular arrhythmias [42].

Moreover, RDN's impact extends beyond direct modulation of cardiac electrophysiology. It also offers potential benefits in improving overall cardiovascular health [10, 43]. This improvement is crucial as structural heart diseases, often exacerbated by conditions like hypertension, are a significant risk factor for ventricular arrhythmias. By addressing the underlying cardiovascular issues, RDN indirectly contributes to lowering the risk of these arrhythmias [28, 43].

Additionally, RDN may play a role in reducing the incidence of sudden cardiac death (SCD), which is often precipitated by ventricular arrhythmias. This aspect is particularly important for patients with heart failure, left ventricular hypertrophy, or after acute MI, who are at a higher risk for SCD [44]. RDN, through its multifaceted impact on the cardiovascular system and sympathetic nervous activity, could emerge as a key player in the prevention of SCD.

Finally, the relationship between RDN and ventricular arrhythmias highlights a promising area of therapeutic intervention. By modulating the sympathetic nervous system, RDN not only addresses the direct mechanisms contributing to ventricular arrhythmias but also improves overall cardiovascular health, thereby reducing the arrhythmic risk [44]. This dual benefit positions RDN as a potentially vital tool in the management of ventricular arrhythmias, especially in patients with concurrent cardiovascular conditions.

Renal Denervation in the Treatment of Obstructive Sleep Apnea: Benefits and Limitations

The advent of RDN as a therapeutic intervention offers a novel approach to the treatment of obstructive sleep apnea (OSA), a condition traditionally managed through modalities focusing on airway management and lifestyle changes. The intersection of RDN's efficacy in modulating the sympathetic nervous system and its implications for OSA patients presents an intriguing avenue for exploration [45].

One of the primary mechanisms through which RDN confers its therapeutic benefits in the context of OSA is the modulation of the sympathetic nervous system. OSA is characterized by increased sympathetic activity, which contributes to a range of cardiovascular complications. By mitigating this overactivity, RDN may offer a reduction in OSA-associated cardiovascular risks. Furthermore, the interplay between OSA and hypertension is well-documented, and the efficacy of RDN in

blood pressure reduction may indirectly benefit OSA patients, as observed in the SYMPLICITY-HTN3 [46]. Additionally, preliminary studies have suggested a potential improvement in sleep quality in OSA patients following RDN. This improvement is hypothesized to result from the reduction of nighttime blood pressure surges and sympathetic overactivity. Such an effect on sleep quality not only addresses a direct symptom of OSA but may also contribute to the overall cardiovascular health of the patient [46].

However, the application of RDN in OSA is not without limitations. A significant challenge is the lack of extensive research specifically targeting the OSA patient population. The majority of RDN studies have concentrated on hypertension, providing only indirect insights into its benefits for OSA. Moreover, the variability in individual responses to RDN poses another challenge. While some patients may experience substantial improvements, others may see only minimal changes in their OSA symptoms, as noted in a study where the severity of sleep apnea worsened in some cases after RDN [47].

Furthermore, the long-term effects of RDN on OSA are not well-characterized, necessitating further longitudinal studies to fully understand the durability of its benefits and any long-term risks. In summary, renal denervation presents a promising yet cautiously optimistic option in the treatment landscape of obstructive sleep apnea. Its potential to ameliorate sympathetic overactivity and improve cardiovascular outcomes in OSA patients is counterbalanced by the current limitations in research specificity and understanding of long-term effects. Future studies, specifically targeting OSA populations and investigating long-term outcomes, are essential to fully elucidate the role of RDN in this context [47].

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42(5):373–498.
2. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149(1):e1–e156.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726.
4. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895–e1032.
5. Steinberg JS, Shabanov V, Ponomarev D, Losik D, Ivanickiy E, Kropotkin E, et al. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence

among patients with paroxysmal atrial fibrillation and hypertension: the ERADICATE-AF randomized clinical trial. JAMA. 2020;323(3):248–55.
6. Kiuchi MG, Chen S, Gr ES, Paz LM, Kiuchi T, de Paula Filho AG, et al. Pulmonary vein isolation alone and combined with renal sympathetic denervation in chronic kidney disease patients with refractory atrial fibrillation. Kidney Res Clin Pract. 2016;35(4):237–44.
7. Kiuchi MG, Chen S, Hoye NA, Pürerfellner H. Pulmonary vein isolation combined with spironolactone or renal sympathetic denervation in patients with chronic kidney disease, uncontrolled hypertension, paroxysmal atrial fibrillation, and a pacemaker. J Interv Card Electrophysiol: Int J Arrhythmia Pac. 2018;51(1):51–9.
8. Romanov A, Pokushalov E, Ponomarev D, Strelnikov A, Shabanov V, Losik D, et al. Pulmonary vein isolation with concomitant renal artery denervation is associated with reduction in both arterial blood pressure and atrial fibrillation burden: data from implantable cardiac monitor. Cardiovasc Ther. 2017;35(4)
9. Kiuchi MG, Chen S, Gr ES, Rodrigues Paz LM, Kiuchi T, de Paula Filho AG, et al. The addition of renal sympathetic denervation to pulmonary vein isolation reduces recurrence of paroxysmal atrial fibrillation in chronic kidney disease patients. J Interv Card Electrophysiol: Int J Arrhythmia Pac. 2017;48(2):215–22.
10. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol. 2012;60(13):1163–70.
11. Kirstein B, Tomala J, Mayer J, Ulbrich S, Wagner M, Pu L, et al. Effect of concomitant Renal DeNervation and cardiac ablation on atrial fibrillation recurrence—RDN+AF study. J Cardiovasc Electrophysiol. 2023;34(1):44–53.
12. Turagam MK, Whang W, Miller MA, Neuzil P, Aryana A, Romanov A, et al. Renal sympathetic denervation as upstream therapy during atrial fibrillation ablation: pilot HFIB studies and meta-analysis. JACC Clin Electrophysiol. 2021;7(1):109–23.
13. Nawar K, Mohammad A, Johns EJ, Abdulla MH. Renal denervation for atrial fibrillation: a comprehensive updated systematic review and meta-analysis. J Hum Hypertens. 2023;37(1):89–90.
14. Katsurada K, Kario K. Intrarenal neurohormonal modulation by renal denervation: benefits for chronic kidney disease and heart failure. Hypertens Res. 2023;46(2):518–20.
15. Lai Y, Zhou H, Chen W, Liu H, Liu G, Xu Y, et al. The intrarenal blood pressure modulation system is differentially altered after renal denervation guided by different intensities of blood pressure responses. Hypertens Res. 2023;46(2):456–67.
16. Davies JE, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, et al. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. Int J Cardiol. 2013;162(3):189–92.
17. Chen W, Ling Z, Xu Y, Liu Z, Su L, Du H, et al. Preliminary effects of renal denervation with saline irrigated catheter on cardiac systolic function in patients with heart failure: a prospective, randomized, controlled, pilot study. Catheter Cardiovasc Interv. 2017;89(4):E153–E61.
18. Gao J-Q, Yang W, Liu Z-J. Percutaneous renal artery denervation in patients with chronic systolic heart failure: a randomized controlled trial. Cardiol J. 2019;26(5):503–10.
19. Hopper I, Gronda E, Hoppe UC, Rundqvist B, Marwick TH, Shetty S, et al. Sympathetic response and outcomes following renal denervation in patients with chronic heart failure: 12-month outcomes from the Symplicity HF feasibility study. J Card Fail. 2017;23(9):702–7.
20. Feyz L, Nannan Panday R, Henneman M, Verzijlbergen F, Constantinescu AA, van Dalen BM, et al. Endovascular renal sympathetic denervation to improve heart failure with reduced ejection fraction: the IMPROVE-HF-I study. Neth Hear J. 2022;30(3):149–59.
21. Pietilä-Effati P, Höglund M, Käräjämäki A, Höglund F, Nabb A-M, Matila E, et al. Renal denervation in patients who do not respond to cardiac resynchronization therapy. Scand Cardiovasc J. 2022;56(1):103–6.

22. Drożdż T, Jastrzębski M, Moskal P, Kusiak A, Bednarek A, Styczkiewicz K, et al. Renal denervation in patients with symptomatic chronic heart failure despite resynchronization therapy—a pilot study. Adv Interven Cardiol/Postępy w Kardiologii Interwencyjnej. 2019;15(2):240–6.
23. Li M, Ma W, Fan F, Yi T, Qiu L, Wang Z, et al. Renal denervation in management of heart failure with reduced ejection fraction: a systematic review and meta-analysis. J Cardiol. 2023;81(6):513–21.
24. Wang Y, Jiang W, Chen H, Zhou H, Liu Z, Liu Z, et al. Sympathetic nervous system mediates cardiac remodeling after myocardial infarction in a circadian disruption model. Front Cardiovas Med. 2021;8:668387.
25. Roncalli J, Tronchère H, Lax A, Kunduzova O. Editorial: myocardial remodeling: mechanisms and translational implications. Front Pharmacol. 2022;13:930387.
26. Qin F, Li J, Dai YF, Zhong XG, Pan YJ. Renal denervation inhibits the renin-angiotensin-aldosterone system in spontaneously hypertensive rats. Clin Exp Hypert (New York, NY: 1993). 2022;44(1):83–92.
27. Bazoukis G, Thomopoulos C, Tse G, Vassiliou VS, Liu T, Dimitriadis K, et al. Impact of renal sympathetic denervation on cardiac magnetic resonance-derived cardiac indices in hypertensive patients—a meta-analysis. J Cardiol. 2021;78(4):314–21.
28. Kiuchi MG, Gr ES, Paz LM, Chen S, Souto GL. Proof of concept study: renal sympathetic denervation for treatment of polymorphic premature ventricular complexes. J Interven Card Electrophysiol: Int J Arrhythmia Pac. 2016;47(2):221–9.
29. Mahfoud F, Urban D, Teller D, Linz D, Stawowy P, Hassel J-H, et al. Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multicentre cardiovascular magnetic resonance imaging trial. Eur Heart J. 2014;35(33):2224–31.
30. Mohammad AA, Nawar K, Binks O, Abdulla MH. Effects of renal denervation on kidney function in patients with chronic kidney disease: a systematic review and meta-analysis. J Hum Hypertens. 2023;
31. Günes-Altan M, Schmid A, Ott C, Bosch A, Pietschner R, Schiffer M, et al. Blood pressure reduction after renal denervation in patients with or without chronic kidney disease. Clin Kidney J. 2023;17(1)
32. Drawz P, Baumann D, Dayton A. Renal denervation: recent developments in clinical and preclinical research. Curr Opin Nephrol Hypertens. 2023;32(5)
33. Schmieder RE. Renal denervation: where do we stand and what is the relevance to the nephrologist? Nephrol Dial Transplant. 2020;37(4):638–44.
34. Thrasher J. Pharmacologic management of type 2 diabetes mellitus: available therapies. Am J Med. 2017;130(6, Supplement):S4–S17.
35. Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension. Circulation. 2011;123(18):1940–6.
36. Moreira MC, Pinto IS, Mourão AA, Fajemiroye JO, Colombari E, Reis ÂA, et al. Does the sympathetic nervous system contribute to the pathophysiology of metabolic syndrome? Front Physiol. 2015;6:234.
37. Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation. 2011;123(18):1940–6.
38. Verloop WL, Spiering W, Vink EE, Beeftink MM, Blankestijn PJ, Doevendans PA, et al. Denervation of the renal arteries in metabolic syndrome: the DREAMS-study. Hypertension (Dallas, Tex: 1979). 2015;65(4):751–7.
39. Zhang Z, Liu K, Xiao S, Chen X. Effects of catheter-based renal denervation on glycemic control and lipid levels: a systematic review and meta-analysis. Acta Diabetol. 2021;58(5):603–14.
40. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. N Engl J Med. 2009;361(9):932–4.

41. Hawson J, Harmer JA, Cowan M, Virk S, Campbell T, Bennett RG, et al. Renal denervation for the management of refractory ventricular arrhythmias: a systematic review. JACC: Clin Electrophysiol. 2021;7(1):100–8.
42. Prado GM, Mahfoud F, Lopes RD, Moreira DAR, Staico R, Damiani LP, et al. Renal denervation for the treatment of ventricular arrhythmias: a systematic review and meta-analysis. J Cardiovasc Electrophysiol. 2021;32(5):1430–9.
43. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet (London, England). 2009;373(9671):1275–81.
44. Zhang WH, Zhou QN, Lu YM, Li YD, Zhang L, Zhang JH, et al. Renal denervation reduced ventricular arrhythmia after myocardial infarction by inhibiting sympathetic activity and remodeling. J Am Heart Assoc. 2018;7(20):e009938.
45. Goyal A, Jain H, Verma A, Jain J, Shamim U, Kanagala SG, et al. The role of renal denervation in cardiology and beyond: an updated comprehensive review and future directives. Curr Probl Cardiol. 2024;49(2):102196.
46. Kario K, Bhatt DL, Kandzari DE, Brar S, Flack JM, Gilbert C, et al. Impact of renal denervation on patients with obstructive sleep apnea and resistant hypertension—insights from the SYMPLICITY HTN-3 trial. Circ J. 2016;80(6):1404–12.
47. Korostovtseva LS, Ionov MV, Shcherbakova EA, Bochkarev MV, Emelyanov IV, Yudina YS, et al. Progression of obstructive sleep apnoea after renal denervation is not associated with hypertension exaggeration. BMC Pulm Med. 2023;23(1):467.

Kidney Transplantation and Renal Vascular Issues

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Abstract Kidney transplantation offers superior survival and quality of life for patients with end-stage kidney disease (ESKD) compared to dialysis. However, vascular complications remain a significant concern, impacting graft survival and transplant success. This chapter explores perioperative vascular considerations, focusing on complications such as transplant renal artery stenosis (TRAS), renal artery thrombosis, renal vein thrombosis, and other vascular injuries. Vascular complications, including stenosis and thrombosis, occur in 3–23% of kidney transplant patients. The left donor kidney is typically preferred due to anatomical advantages, though using the right kidney can increase thrombotic risks. Hemorrhagic complications from antithrombotic agents or induction therapies can range from minor hematomas to severe hemorrhagic shock, potentially leading to antibody-mediated rejection. Renal vein thrombosis, occurring in 0.5–4% of cases, often results from mechanical issues or extraluminal compression, requiring emergent Doppler ultrasound for diagnosis. Renal artery thrombosis, occurring in 0.5–3.5% of cases, typically presents within the first month post-transplant, necessitating surgical revascularization or thrombolytic therapy. TRAS, with an incidence of 1–23%, significantly impacts graft survival and patient outcomes. Treatment options include medical therapy, endovascular approaches, and surgical revascularization, with percutaneous transluminal angioplasty often preferred. Maintaining vascular health could enhance graft survival in kidney transplant recipients, requiring a comprehensive, multimodal treatment approach.

Keywords Graft failure · Renal artery · Stenosis · Ischemia · Thrombosis · Vascular calcifications

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Introduction

Kidney transplantation is commonly considered as the treatment of choice for eligible patients with kidney failure, offering numerous noteworthy advantages compared with dialysis. Transplantation decreases the risk of death and offers a longer life expectancy and a better quality of life for patients with end-stage kidney disease (ESKD) [1, 2].

Vascular complications in renal transplantation are relatively common and may frequently lead to allograft damage; transplant renal artery stenosis, transplant renal artery thrombosis, transplant renal vein thrombosis, biopsy-induced vascular injuries, pseudoaneurysm formation, and hematomas are the most frequent [3]. Vascular complications following kidney transplantation appears in 3–23% of patients. However, the incidence has decreased significantly over decades; in a monocentric series of 3129 consecutive kidney transplantation made over 3 decades, vascular complication occurred in 13.5% of the recipients with a mean 3-year decrease in kidney graft function [4]; in contrast, Srivastava et al. reported a significantly lower frequency of vascular complications (1.29%), including a cohort of 1945 kidney transplant recipients [5].

Perioperative Vascular Considerations

During kidney transplantation, certain issues deserve special consideration. The left donor kidney is frequently preferred due to the anatomical advantages of a longer renal vein and a shorter artery. Using the right kidney, an augmented risk of delayed graft function, thrombotic complications, and early graft loss was reported in a recent meta-analysis [6]. Still, a noteworthy effect on long-term survival has not been confirmed. Additionally, an increased risk of hemorrhagic complications was associated with the use of antithrombotic agents, induction treatment with thymoglobulin or use of plasma exchange as part of a desensitization protocol. These hemorrhagic complications can vary from asymptomatic small hematomas to hemorrhagic shock due to cortical rupture or anastomotic disruption. A significant bleeding may require imperative red blood cell transfusion, unfortunately associated with development of de novo donor specific antibodies and higher rates of antibody-mediated rejection and graft loss [7].

Renal Artery and Vein Thrombosis in Kidney Transplant

Thrombosis remains a significant complication after renal transplantation; Clarke et al. reported a first case of allograft renal vein thrombosis requiring thrombectomy in early 70s; these complications are responsible for about 2–7% early graft losses

in adults, usually in the early postoperative period or require surgical intervention [8]. In a large retrospective study of 2381 patients, early graft failure inside 30 days after transplantation appeared in 4.6% of cases; 44% of these were due to allograft thrombosis [9]. The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) noticed that graft thrombosis represented the chief cause of graft failure in the first year [10].

In the pathogenesis of graft thrombosis several important factors may be involved. Technical errors, vascular clamp injury or perfusion cannulation injury were described. The vascular abnormalities in the donor kidney may be also accountable—multiple renal arteries or the presence of atheroma. The cadaver donors <5 years of age had a knowingly higher thrombosis rate, due to the discrepancy in the size between the vessels of the donor and the recipient. Also, an elderly donor can amplify this risk, probably because donor hypotension combined with ischemia-reperfusion injury can activate a procoagulant surface. The administration of the monoclonal antibody OKT3 can also induce procoagulant activity and amplify this risk, mainly in patients pretreated with high-dose intravenous methylprednisolone. Genetic coagulation abnormalities can predispose to early vein thrombosis and graft loss; also, may be cause by kinking of the renal vein or stenosis of the venous anastomosis [11].

Thrombotic renal vein occlusion occurs mainly in the early post-transplant period; has a prevalence of 0.5%4% and it is thus typically attributable to a mechanical issue [12]. Later, transplant renal vein thrombosis is often the result of extraluminal compression by other masses or collection or may be produced by direct extension of deep vein thrombosis. The features of the recipient are also significant. A past history of renal or extrarenal venous thrombosis, diabetic nephropathy, poor hemodynamic status is notably related with an amplified risk of graft thrombosis [13].

Sudden onset of abdominal pain, progressive loss of diuresis, hematic drainage, macroscopic hematuria or altered renal kidney function in the early posttransplant period can suggest the diagnosis. Emergent Doppler ultrasound may be of particularly valuable in sustaining the diagnosis [14]. Magnetic resonance venography will deliver superior details, but it is infrequently done due to time limitations [15].

This critical complication is associated with a very high risk of graft loss but may also results in a high mortality rate due to graft rupture and serious hemorrhage or embolic complication [16]. It demands almost generally surgical management. Efficacious revascularization with thrombolytic therapy, thrombus-aspiration, or direct surgical thrombectomy have been reported. Evidence of necrosis at the time of reintervention requires urgent transplantectomy. However, if viable tissue is present, the approach may include repairing the anastomosis or performing an explantation with flushing and immediate reimplantation [17]. No therapy with benefits for dropping the rate of early graft thrombosis has been proven. Moreover, unfractioned heparin may amplify the risk of major bleeding [18].

Renal artery thrombosis is also a rare event, involving 0.5–3.5%. Is one of the most important vascular complications and is a main reason of graft loss in the early post-transplant period [15]. It classically occurs within the first month after

transplantation, and more than 90% of cases occur in the first year [19]. There are five main independent risk factors for renal artery thrombosis, involving the use of the donor's right kidney, a history of venous thrombosis in the recipient, surgical technique (such as a kink or torsion of the vascular pedicle or a missed intimal flap or end-to-end anastomosis of the donor artery to the recipient artery when there is a size discrepancy), diabetic nephropathy, and the perioperative hemodynamic status of the recipient [20].

The central symptoms of the main renal artery thrombosis are: an abrupt drop in urine output and acute worsening of renal function. When several donor arteries are anastomosed, thrombosis of one of these branches can lead to segmental infarctions, which may be completely asymptomatic or evident as increasing creatinine levels or new-onset hypertension. Thrombosis disturbing a lower polar branch is particularly remarkable because it can conduct to ureteric ischemia and subsequent urine leaks [3]. Gradually progressive thrombosis has been described related with vasculitis, thrombophilic conditions, and hemolytic uremic syndrome.

Doppler ultrasound is the primary option of imaging. It will indicate absent flow in the main renal artery and in the intrarenal segmental branches. A totally infarcted kidney will appear as a hypoechoic mass. Magnetic resonance angiography or digital subtraction angiography will deliver superior details, but it is infrequently done due to time limitations [15].

The prognosis is guided significantly by the extent of thrombosis and infarction. Longer warm ischemia periods are related with inferior prognoses due to increased tissue damage. Surgical revascularization or intra-arterial thrombolytic therapy is the most common treatment. Pressing reexploration should be performed to assess graft viability. If the graft seems salvageable, thrombectomy and correction of the cause for the thrombosis should be done. This will usually require a reanastomosis.

Transplant Renal Artery Stenosis (TRAS)

Extensive differences in the incidence of TRAS has been reported, primarily due to differences in diagnostic modalities. The incidence varies between 1% and 23% [21]. Frequently Doppler evaluation immediately post-transplantation reported a 10% diagnosis rate of TRAS. When performing arteriography in kidney transplant patients with hypertension and/or kidney function impairment, TRAS had a prevalence of 3.1%. Using the United States Renal Data System (USRDS) registry, Hurst et al. found a cumulative incidence of TRAS—2% at 3 years and an overall incidence rate—8.3 cases per 1000 patient-years [22]. In children, the prevalence of TRAS appears to be lower, likely due to a minor extent of vascular changes in younger donors; a retrospective study reported a prevalence of 4.6% among pediatric patients who underwent kidney transplantation between 2001 and 2011 [23].

TRAS is a major source of graft loss and premature death in transplant recipients; it explains 1–5% cases of post-transplant hypertension and ∼75% of post-transplant vascular complications [24]. However, non-significant stenosis (defined

as a luminal obstruction <50%) was not linked with long-term unfavorable allograft outcomes [25]. Stenotic lesions of a solitary renal artery, will determine a maladaptive activation of the renin-angiotensin-aldosterone system. Consequently, patients experience resistant or worsening arterial hypertension, fluid overload often connected with renal dysfunction [26]. Finally, TRAS may lead recurrent episodes of "flash pulmonary edema" [27]. The interaction among avid sodium retention, altered natriuresis, progressive worsening of renal function, increased pulmonary vascular permeability, hypertension and a stiff left ventricle with impaired filling represents the source for the brusque alveolar congestion and pulmonary edema [28].

TRAS may be *multifactorial a*nd may be restricted (pre-anastomotic, post-anastomotic) or diffuse, the last one revealing immunological injury to the endothelium. The most important risk factors associated with TRAS are: atheroma in the donor renal artery or in the recipient iliac artery, mechanical issues (suture techniques, vessel trauma during surgery or arterial kinking), extraluminal compression (enlarged polycystic kidney, pseudoaneurysm, abdominal masses) or immunological and endothelial damage [26].

TRAS diagnosis requires the use of noninvasive and invasive tests. Color Doppler ultrasonography is a non-invasive imaging test, frequently used as a preliminary tool since it can be executed safely regardless of renal function. It has proved high specificity and sensitivity when used by experienced operators [29]. Intrarenal resistive index <0.5, intrarenal acceleration time ≥0.1 s, peak systolic velocity >300 cm/s, a ratio of peak systolic velocity in the transplant renal artery to external iliac artery >1.8, the presence or absence of spectral broadening in the transplant renal artery are used to diagnosticate TRAS [30]. Contrast enhanced ultrasound (CEUS) remains a non-invasive and non-nephrotoxic tool and has the potential to effectively evaluate vascular patency (may facilitate direct visualization of stenotic arterial segments and suggests stenosis when there is a longer flow of the contrast agent [31]. CEUS has a better prediction potential for TRAS compared to Doppler ultrasound, with an area under the curve of 0.92 [32].

Computed tomography angiography (CTA) is an extensively accessible and used tool for accurate and non-invasive diagnosis of TRAS. Three-dimensional reconstruction permits to determine and even quantify stenotic or thrombotic lesions, calcifications, aneurysms or dissections. It involves administration of a potentially nephrotoxic agent [33]. In contrast, gadolinium-enhanced magnetic resonance angiography provides the same predictive power while avoiding administration of iodinated contrast or exposure to radiation. Advantages: high sensitivity (67–100%), high specificity (75–100%), no radiation, no iodinated contrast [34]. However, artifacts from adjacent surgical clips, claustrophobia, high cost, patient hardware compatibility, use of gadolinium and limited availability are the main disadvantages [35]. Both methods proved a similar capability to assess and quantify TRAS [36].

Differential diagnosis—with other cause of hypertension after kidney transplantation (native kidney disease in the recipients, donor age, cold ischemia time, delayed graft function, allograft rejection and use of immunotherapy such as corticosteroid and calcineurin inhibitors) [37].

The optimal treatment of the stenotic lesions—medical therapy alone, or a more invasive option represented either by endovascular approach (angioplasty only or stent placement) or by surgical intervention for revascularization, each with medical therapy. If renal function is stable and there is no hemodynamically significant stenosis on imaging, conservative treatment with antihypertensive medications can be used to control blood pressure [38, 39]. The latest ACC/AHA guidelines (2022) stated that the kidney transplant patients with confirmed TRAS with or without calcineurin inhibitors are part of a population that benefit from renal revascularization. Also, for patients with a hemodynamically significant arterial stenosis in a solitary kidney with progressive chronic kidney disease there is a class IIa recommendation for revascularization [40]. Renal revascularization leads to an improvement of allograft perfusion and mitigates the pathogenic maladaptive hormonal activation of the renin-angiotensin-aldosterone axis [41]. The favorite approach is the percutaneous transluminal angioplasty. The success rate of renal revascularization varies widely in the literature, ranging from 65.5% to 94% [42]. One significant reason is the differences between included patients in reported analyses [24]Also, there is no homogeneity in reported outcomes and success may be defined differently: graft function improvement, blood pressure reduction or technical success. Furthermore, endovascular treatment remains an invasive procedure and may lead to important periprocedural complications in about 9% of interventions (arterial dissection, hemorrhagic events, thrombosis, pseudoaneurysms) [43]. Even after an initial success, restenosis may occur [44]. Theoretically, prevention of restenosis relies on stent placement at the moment of intervention [45].

The interventional approach led to better renal function and improved blood pressure. One systematic review found that percutaneous intervention (with transluminal angioplasty or stent placement) leads to favorable outcomes measured as technical and clinical success and long-term patency. Also, authors obtained from pooled analyses a potential benefit for stent placement compared with angioplasty alone in term of patency rate, need for re-intervention and overall technical success [42]. A more recent meta-analysis that included 1522 patients showed a significant benefit of stenting in lowering the creatinine level (mean difference of 0.68 mg/dl with 95% confidence interval of 0.17–1.19) with lower rates of restenosis [46]. When comparing different types of stents, one analyses showed a higher rate of patency when employing drug-eluting stents in comparison with bare-metal stent when correcting post-anastomotic TRAS [47].

Because high rates of success obtained with percutaneous interventions for TRAS, surgical revascularization represents a salvage therapy reserved for cases of failed endovascular treatment or severe anatomical difficulties that make the angioplasty unsuitable [48]. The techniques required for surgical repair are laborious and may expose the patient to complications. In a retrospective study of ten patients treated by surgical revascularization, there was universally recovery of kidney allograft with good results on the long-term for patency and graft survival [49]. Historical cohorts describe a higher success rate and lower morbidity with surgical repair when compared to percutaneous angioplasty. However, it is difficult to interpret these results in modern times given the privilege for less-invasive methods [50].

Transplant Renal Vein Stenosis

Is a considerably infrequent phenomenon, with limited literature; the main risk factors are: external compression from perigraft fluid collections, injury to the renal vein during organ gaining, infection, rejection or simultaneous intrarenal arteriovenous fistulae [51].

The presentation classically involves worsening renal function. Diagnosis is established after eliminating more common causes of graft dysfunction such as rejection, TRAS and hydronephrosis. The diagnosis requires a Doppler ultrasonography; it may describe the presence of a stenosis in the renal vein, with raised flow velocities at the site of narrowing and turbulent flow just distal to this point. Resistance to intrarenal blood flow will be obvious with the decreased diastolic flow in the renal artery and high resistance indexes in the intrarenal branch arteries. For confirmation, computed tomography angiography, magnetic resonance venography, and conventional venography can be used [3].

The release of external pressure on the renal vein (if the external compression is the provoking factor) or balloon angioplasty with or without stenting when there is a fibrotic stricture in the vein wall are the main therapeutic options [52].

Summary of Findings

Preserving vascular health is vital in order to improve graft survival. Vascular complications have a main impact on allograft function and integrity. The extensive spectrum of pathogenic pathways that can potentially alter the vessel wall and a complex multimodal treatment strategy is required to address the vascular issues in kidney transplant patients.

References

1. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341(23):1725–30.
2. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Transplant. 2011;11(10):2093–109.
3. Gunawardena T. Update on vascular complications after renal transplantation. Exp Clin Transplant. 2022;20(4):333–41. https://doi.org/10.6002/ect.2021.0303. Epub 2021 Nov 10. PMID: 34775937.
4. Bessede T, Droupy S, Hammoudi Y, Bedretdinova D, Durrbach A, Charpentier B, Benoit G. Surgical prevention and management of vascular complications of kidney transplantation. Transpl Int. 2012;25(9):994–1001. https://doi.org/10.1111/j.1432-2277.2012.01533.x. Epub 2012 Jul 21. PMID: 22816523.

5. Srivastava A, Kumar J, Sharma S, Abhishek, Ansari MS, Kapoor R. Vascular complication in live related renal transplant: an experience of 1945 cases. Indian J Urol. 2013;29(1):42–7. https://doi.org/10.4103/0970-1591.109983.
6. Carolan C, Tingle SJ, Thompson ER, Sen G, Wilson CH. Comparing outcomes in right versus left kidney transplantation: a systematic review and meta-analysis. Clin Transplant. 2021;35(11):e14475.
7. Kang ZY, Ma S, Liu W, Liu C. Effect of blood transfusion post kidney transplantation on de novo human leukocytes antigen donor-specific antibody development and clinical outcomes in kidney transplant recipients: a systematic review and meta-analysis. Transpl Immunol. 2023;78:101801.
8. Zilinska Z, Chrastina M, Trebaticky B, et al. Vascular complications after renal transplantation. Bratisl Lek Listy. 2010;111:586–9.
9. Phelan PJ, O'Kelly P, Tarazi M, Tarazi N, Salehmohamed MR, Little DM, Magee C, Conlon PJ. Renal allograft loss in the first post-operative month: causes and consequences. Clin Transplant. 2012;26(4):544–9. https://doi.org/10.1111/j.1399-0012.2011.01581.x. PMID: 23050275.
10. Balachandra S, Tejani A. Recurrent vascular thrombosis in an adolescent transplant recipient. J Am Soc Nephrol. 1997;8:1477–81.
11. Ponticelli C, Moia M, Montagnino G. Renal allograft thrombosis. Nephrol Dial Transplant. 2009;24(5):1388–93. https://doi.org/10.1093/ndt/gfp003.
12. Dimitroulis D, Bokos J, Zavos G, et al. Vascular complications in renal transplantation: a single-center experience in 1367 renal transplantations and review of the literature. Transplant Proc. 2009;41(5):1609–14. https://doi.org/10.1016/j.transproceed.2009.02.077.
13. Bakir N, Sluiter WJ, Ploeg RJ, van Son WJ, Tegzess AM. Primary renal graft thrombosis. Nephrol Dial Transplant. 1996;11(1):140–7. PMID: 8649623.
14. Sadej P, Feld RI, Frank A. Transplant renal vein thrombosis: role of preoperative and intraoperative Doppler sonography. Am J Kidney Dis. 2009;54(6):1167–70.
15. Tavakkoli M, Zafarghandi RM, Taghavi R, Ghoreifi A, Zafarghandi MM. Immediate vascular complications after kidney transplant: experience from 2100 recipients. Exp Clin Transplant. 2017;15(5):504–8. https://doi.org/10.6002/ect.2016.0057.
16. Giustacchini P, Pisanti F, Citterio F, De Gaetano AM, Castagneto M, Nanni G. Renal vein thrombosis after renal transplantation: an important cause of graft loss. Transplant Proc. 2002;34(6):2126–7.
17. Cambou L, Millet C, Terrier N, Malvezzi P, Timsit MO, Anglicheau D, et al. Management and outcome after early renal transplant vein thrombosis: a French multicentre observational study of real-life practice over 24 years. Transpl Int. 2023;36:10556.
18. Surianarayanan V, Hoather TJ, Tingle SJ, Thompson ER, Hanley J, Wilson CH. Interventions for preventing thrombosis in solid organ transplant recipients. Cochrane Database Syst Rev. 2021;3(3):CD011557.
19. Kobayashi K, Censullo ML, Rossman LL, et al. Interventional radiologic management of renal transplant dysfunction: indications, limitations, and technical considerations. Radiographics. 2007;27:1109–30.
20. Bakir N, Sluiter WJ, Ploeg RJ, van Son WJ, Tegzess AM. Primary renal graft thrombosis. Nephrol Dial Transplant. 1996;11:140–7.
21. Mayrdorfer M, Liefeldt L, Osmanodja B, Naik MG, Schmidt D, Duettmann W, et al. A single centre in-depth analysis of death with a functioning kidney graft and reasons for overall graft failure. Nephrol Dial Transplant. 2023;38(8):1857–66.
22. Hurst FP, Abbott KC, Neff RT, et al. Incidence, predictors and outcomes of transplant renal artery stenosis after kidney transplantation: analysis of USRDS. Am J Nephrol. 2009;30:459–67.
23. Ghirardo G, De Franceschi M, Vidal E, et al. Transplant renal artery stenosis in children: risk factors and outcome after endovascular treatment. Pediatr Nephrol. 2014;29:461–7.

24. Hurst FP, Abbott KC, Neff RT, Elster EA, Falta EM, Lentine KL, et al. Incidence, predictors and outcomes of transplant renal artery stenosis after kidney transplantation: analysis of USRDS. Am J Nephrol. 2009;30(5):459–67.
25. Barteczko MLM, Orellana HC, Santos GRF, Galhardo A, Kanhouche G, Faccinetto ACB, et al. Long-term clinical outcomes of patients with nonsignificant transplanted renal artery stenosis. BMC Nephrol. 2022;23(1):61.
26. Chen W, Kayler LK, Zand MS, Muttana R, Chernyak V, DeBoccardo GO. Transplant renal artery stenosis: clinical manifestations, diagnosis and therapy. Clin Kidney J. 2015;8(1):71–8.
27. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. JACC Heart Fail. 2017;5(8):543–51.
28. Sanga V, Bertoli E, Crimi F, Barbiero G, Battistel M, Seccia TM, Rossi GP. Pickering syndrome: an overlooked renovascular cause of recurrent heart failure. J Am Heart Assoc. 2023;12(19):e030474.
29. Rengel M, Gomes-Da-Silva G, Inchaustegui L, Lampreave JL, Robledo R, Echenagusia A, et al. Renal artery stenosis after kidney transplantation: diagnostic and therapeutic approach. Kidney Int Suppl. 1998;68:S99–106.
30. Fananapazir G, McGahan JP, Corwin MT, Stewart SL, Vu CT, Wright L, Troppmann C. Screening for transplant renal artery stenosis: ultrasound-based stenosis probability stratification. AJR Am J Roentgenol. 2017;209(5):1064–73.
31. Grzelak P, Kurnatowska I, Nowicki M, Muras K, Podgorski M, Strzelczyk J, Stefanczyk L. Detection of transplant renal artery stenosis in the early postoperative period with analysis of parenchymal perfusion with ultrasound contrast agent. Ann Transplant. 2013;18:187–94.
32. Pan FS, Liu M, Luo J, Tian WS, Liang JY, Xu M, et al. Transplant renal artery stenosis: evaluation with contrast-enhanced ultrasound. Eur J Radiol. 2017;90:42–9.
33. Sun IO, Hong YA, Kim HG, Park HS, Choi SR, Chung BH, et al. Clinical usefulness of 3-dimensional computerized tomographic renal angiography to detect transplant renal artery stenosis. Transplant Proc. 2012;44(3):691–3.
34. Huang Y, Zhang B, Zheng J, Ma X, Zhang S, Chen Q. Diagnostic performance of magnetic resonance angiography for artery stenosis after kidney transplant: a systematic review and meta-analysis. Acad Radiol. 2023;30(9):2021–30.
35. Gaddikeri S, Mitsumori L, Vaidya S, Hippe DS, Bhargava P, Dighe MK. Comparing the diagnostic accuracy of contrast-enhanced computed tomographic angiography and gadolinium-enhanced magnetic resonance angiography for the assessment of hemodynamically significant transplant renal artery stenosis. Curr Probl Diagn Radiol. 2014;43(4):162–8.
36. Pan L, Shen L, Fan M, Xing Z, Ding J, Du Y, et al. Assessment of transplant renal artery stenosis with non-contrast-enhanced magnetic resonance angiography: comparison with digital subtraction angiography. Acad Radiol. 2023;
37. Mangray M, Vella JP. Hypertension after kidney transplant. Am J Kidney Dis. 2011;57:331–41.
38. Bruno S, Remuzzi G, Ruggenenti P. Transplant renal artery stenosis. J Am Soc Nephrol. 2004;15:134–41.
39. Zhang X, Wang H, Liu S, Yan J, Liu X, Xu D, Tian C. Three-dimensional computed tomography reconstruction in transplant renal artery stenosis. Exp Clin Transplant. 2017;15(6):615–9.
40. Spinosa DJ, Isaacs RB, Matsumoto AH, Angle JF, Hagspiel KD, Leung DA. Angiographic evaluation and treatment of transplant renal artery stenosis. Curr Opin Urol. 2001;11(2):197–205.
41. Li X, Wang W, Cheng D, Yu Y, Wu Q, Ni X, et al. Perfusion and oxygenation in allografts with transplant renal artery stenosis: evaluation with functional magnetic resonance imaging. Clin Transplant. 2022;36(11):e14806.
42. Ngo AT, Markar SR, De Lijster MS, Duncan N, Taube D, Hamady MS. A systematic review of outcomes following percutaneous transluminal angioplasty and stenting in the treatment of transplant renal artery stenosis. Cardiovasc Intervent Radiol. 2015;38(6):1573–88.
43. Pini A, Faggioli G, Pini R, Mauro R, Gallitto E, Mascoli C, et al. Assessment and management of transplant renal artery stenosis. A literature review. Ann Vasc Surg. 2022;82:13–29.

44. Peregrin JH, Stribrna J, Lacha J, Skibova J. Long-term follow-up of renal transplant patients with renal artery stenosis treated by percutaneous angioplasty. Eur J Radiol. 2008;66(3):512–8.
45. Bruno S, Remuzzi G, Ruggenenti P. Transplant renal artery stenosis. J Am Soc Nephrol. 2004;15(1):134–41.
46. Hinojosa-Gonzalez DE, Salgado-Garza G, Torres-Martinez M, Villegas-De Leon SU, Bueno-Gutierrez LC, Herrera-Carrillo FE, et al. Endovascular treatment of transplant renal artery stenosis: a systematic review and meta-analysis. J Endovasc Ther. 2022;29(2):294–306.
47. Biederman DM, Fischman AM, Titano JJ, Kim E, Patel RS, Nowakowski FS, et al. Tailoring the endovascular management of transplant renal artery stenosis. Am J Transplant. 2015;15(4):1039–49.
48. Seratnahaei A, Shah A, Bodiwala K, Mukherjee D. Management of transplant renal artery stenosis. Angiology. 2011;62(3):219–24.
49. Rouer M, Godier S, Monnot A, Etienne I, Bertrand D, Guerrot D, Plissonnier D. Long-term outcomes after transplant renal artery stenosis surgery. Ann Vasc Surg. 2019;54:261–8.
50. Benoit G, Moukarzel M, Hiesse C, Verdelli G, Charpentier B, Fries D. Transplant renal artery stenosis: experience and comparative results between surgery and angioplasty. Transpl Int. 1990;3(3):137–40.
51. Olliff S, Negus R, Deane C, Walters H. Renal transplant vein stenosis: demonstration and percutaneous venoplasty of a new vascular complication in the transplant kidney. Clin Radiol. 1991;43(1):42–6. https://doi.org/10.1016/s0009-9260(05)80353-8.
52. Obed A, Uihlein DC, Zorger N, et al. Severe renal vein stenosis of a kidney transplant with beneficial clinical course after successful percutaneous stenting. Am J Transplant. 2008;8(10):2173–6. https://doi.org/10.1111/j.1600-6143.2008.02356.x.