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“Renal Arterial Disease and Hypertension”

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Renovascular hypertension has been recognized for more than 80 years, when seminal experimental studies demonstrated that progressive occlusion of the renal vessels produces a rise in systemic arterial pressure. These data established a central role of the kidney in blood pressure regulation and provided one of the most widely studied models of “angiotensin-dependent” hypertension¹. This can occur at levels of renal pressure above those that impair kidney function, although progressive reduction in renal blood flow ultimately leads to additional disturbances, including impaired volume control, circulatory congestion and ultimately irreversible kidney injury. Hence, occlusive renovascular disease (RVD) comprises a spectrum of disorders ranging from incidental, minor disease to incipient occlusion with tissue ischemia as illustrated in **FIGURE 1**.

Epidemiology

The dominant cause (at least 85%) of RVD in western countries is atherosclerotic renal artery stenosis (ARAS). This often develops as part of systemic atherosclerotic disease affecting multiple vascular beds, including coronary, cerebral and peripheral vessels. Community based studies suggest that up to 6.8% of individuals older than 65 have ARAS more than 60% occlusion². Screening studies indicate rising prevalence of detectable ARAS in hypertensive subjects from 3% (ages 50-59) to 25% (above age 70) with older ages³. Clinically significant atherosclerotic RVD often is manifest by worsening or accelerating blood pressure elevations in older individuals with pre-existing hypertension.

Any flow-limiting vascular lesion within the renal circulation can produce RVH. This can arise from a variety of fibromuscular dysplasias (FMD), such as medial fibroplasia that typically presents an appearance of “string-of-beads” or focal narrowing in the midportion of the renal artery⁴(**FIGURE 2**). Some form of FMD may be detected incidentally in up to 3% of normotensive men or women presenting as potential kidney donors⁵. Those that progress

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to develop renovascular hypertension are predominantly females, some of which are smokers. This gender predominance suggests that hormonal factors modulate the progression of this disorder and its clinical phenotype. Other disorders that produce RVH include renal trauma, arterial occlusion from dissection or thrombosis, and embolic occlusion of the renal artery (**Box 1**). Particularly in Asia, inflammatory vascular disorders such as Takayasu's arteritis commonly affect the renal circulation. An emerging iatrogenic form of RVD includes occlusion of the renal arteries from endovascular aortic stent grafts, for which landing zones may migrate or be deliberately placed across the origins of the renal arteries ⁶.

Pathophysiology

RVH is triggered initially by activation of the renin-angiotensin-aldosterone system. Studies over several decades have identified multiple actions of angiotensin II (Ang II), including its role as a direct vasoconstrictor, stimulation of adrenal release of aldosterone, and induction of sodium retention. Ang II recruits additional pressor mechanisms, such as sympathetic adrenergic pathways, vascular remodeling and modification of prostaglandin dependent vasodilation ⁷. Blockade of the renin-angiotensin system or genetic knockout of AT-1 receptors prevent the development of experimental RVH ⁸. After some time, secondary vasoconstrictor pathways can become dominant with the result that pharmacologic RAAS blockade and/or renal revascularization may no longer completely reverse RVH.

Two major models of RVH have been proposed, depending upon the functional role of the remaining kidney (the non-stenotic or “contralateral” kidney) ⁹. When the contralateral kidney is normal, it responds to rising systemic pressure with suppression of its own renin release and enhanced “pressure natriuresis”. This “2-kidney-1clip” condition is characterized by unilateral release of renin into the renal veins, elevated levels of plasma renin activity and arterial pressure demonstrably dependent upon the pressor effects of Ang II. The second model has been designated “1-kidney-1 clip” RVD in which either a functional contralateral kidney is not present or is not capable of ongoing pressure natriuresis. As a result, the rise in systemic pressure no longer is offset by increased sodium excretion, leading to volume expansion and secondary reduction in renin release from the stenotic kidney. These events lead to lower values for circulating plasma renin activity, loss of renal vein renin lateralization and loss of detectable angiotensin dependence of systemic hypertension, unless or until diuresis and volume contraction is accomplished. In reality, the contralateral kidney in 2-kidney-1-clip renovascular hypertension is rarely normal, possibly as a result of tissue injury from direct effects of angiotensin II and/or other pathways. As a result, impaired contralateral kidney function impairs sodium excretion in many patients with longstanding RVH. Hence, clinical laboratory manifestations in human subjects vary widely between the extremes predicted by 1-kidney and 2-kidney experimental models.

Remarkably, studies using blood oxygen level dependent (BOLD) MR indicate that reductions in blood flow (up to 35-40%) can occur without demonstrable tissue hypoxia or evident long-term kidney fibrosis ¹⁰. This is due partly to the overperfusion of the kidney cortex as part of its filtration function, consistent with the observation that less than 10% of oxygen is required for the fulfilling the energy requirements of the kidney ¹¹. The medulla,

by contrast, normally is supplied by post-glomerular arterioles with lower blood flow and has greater oxygen extraction due to energy-dependent active solute transport¹². Thus, the kidney normally has a large cortical-medullary oxygen gradient with areas of markedly reduced oxygen tension in deep medullary areas. Moderate reductions in blood flow therefore exert only minor effects on oxygen delivery to the cortex and the reductions in glomerular filtration that result also reduce the net solute transport and thereby reduce oxygen requirements in medullary regions. An important corollary of these observations is that medical therapy of renovascular hypertension —albeit commonly reducing blood flow to the post-stenotic kidney —can be tolerated, sometimes for many years, without inducing parenchymal kidney damage.

Renal tolerance to reduced blood flow has limits, of course. More severe and prolonged reductions in blood flow eventually threaten both tissue oxygenation and viability of the post-stenotic kidney¹³. Studies of both experimental and human RVD indicate that cortical hypoxia eventually is associated with activation of inflammatory pathways¹⁴ as depicted schematically in **FIGURE 3**. These are characterized by abundant renal vein levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α , MCP-1), biomarkers of injury (e.g. neutrophil gelatinase-associated lipocalin (NGAL) in addition to the appearance of t-lymphocytes and macrophages within the tissue parenchyma^{15,16}. Inflammatory changes associated with severe ischemia lead to obliteration of tubules with failure to regenerate intact epithelial surfaces with resulting atubular glomeruli¹⁷. At some point, these processes become refractory to restoring vessel patency with revascularization, despite restoring renal blood flow and reversal of tissue hypoxia¹⁸. This transition from simply a hemodynamic reduction in blood flow triggering RVH to an inflammatory, pro-fibrotic state complicates the clinical decisions regarding optimal timing for renal revascularization.

DIAGNOSIS: Clinical Manifestations

RVH and ischemic nephropathy are diagnosed primarily by recognition of a clinical syndrome defined by progressive or severe hypertension with/without unexplained CKD. Occlusive RVD produces a range of manifestations generally related to the severity of vascular occlusion, as illustrated in **FIGURE 1**. Many incidental lesions are now identified during imaging procedures for other indications, including CT and/or MR angiography. It should be emphasized that hemodynamic effects of lumen occlusion such as changes in either translesional pressure or flow are barely detectable until lumen occlusion reaches a “critical level” in the vicinity of 70-80% lumen occlusion¹⁹. Studies in humans subjected to stepwise partial balloon obstruction of the renal artery indicate that gradients of at least 10-20% reductions in post-obstruction pressures are required to detect measurable renin release²⁰. An important corollary is that failure to identify a pressure gradient across such a vascular lesion makes it unlikely that renal revascularization will have clinical benefit.

Clinical characteristics of atherosclerotic RVH include rapid changes in arterial pressure, often in subjects with pre-existing hypertension (**Box 2**). The average age of recent interventional reports for RVH is above 70 years. Arterial pressure rises with age in Western societies, so the majority of these individuals will have pre-existing hypertension already

treated with antihypertensive drugs. Recognizing progression and rising antihypertensive drug requirements should raise the question of a superimposed secondary process such as atherosclerotic RVH. As compared with essential hypertension, patients with RVH have more evident activation of the renin-angiotensin system and increased sympathetic nerve activation, sometimes associated with wide pressure fluctuations and variability. Target organ manifestations including vascular injury, left ventricular hypertrophy and renal dysfunction are more common with RVH as compared with age-matched subjects with essential hypertension of similar levels ²¹.

Occlusive RVD and RVH can accelerate manifestations of other vascular disease. Impaired volume control related to RVD worsens circulatory congestion associated with left-ventricular dysfunction. When RVD triggers additional rises in arterial pressure, the resulting left-ventricular outflow resistance can precipitate congestive heart failure, sometimes named “flash” pulmonary edema ^{22,23}. This is a recognizable clinical syndrome and is often associated with rapid worsening of renal function as arterial pressure is lowered and/or diuresis is achieved. Observational series report higher rates of mortality and re-hospitalization for patients with combined congestive heart failure and RVD ^{24,25}.

Ultimately, progressive atherosclerotic RVD leads to loss of kidney function in the affected kidney(s). Prospective trials including ASTRAL and CORAL indicate that 15-22% of subjects with RVD progress to a renal “end-point” over a follow-up period between three and four years ²⁶. As a practical matter, establishing whether progressive CKD reflects underlying vascular disease should be a central concern for the clinician.

Diagnosis

Current diagnostic studies and interpretation for renovascular disease have been reviewed ²⁷. General values for hematologic and electrolyte levels are normal or consistent with the degree of GFR reduction (level of CKD). Unexplained elevations of serum creatinine merit further evaluation with at least ultrasound duplex imaging. Urinalyses are typically “bland” with few cellular elements or proteinuria. The presence of significant albuminuria (or elevation of urinary albumin/creatinine ratio) should raise concerns about other parenchymal renal disorders, including diabetic nephropathy.

Measurement of circulating plasma renin activity can be helpful, but limited. As noted above, elevated levels are consistent with RVH, although sodium retention, drug effects, and transitions to alternative pressor pathways sometimes leave these levels normal or low. Examination of the aldosterone/renin ratio typically is consistent with secondary aldosterone excess, and may account for hypokalemia observed either spontaneously or during diuretic therapy. Both hormonal and electrolyte levels are affected by many other factors, making their diagnostic value limited.

Measurement of renal vein renin levels was commonly performed during planning for surgical renal artery procedures when this was the primary therapy for RVH. Identification of overt lateralization to the post-stenotic kidney along with suppression of renin release from the contralateral kidney has been associated with pressure reduction in more than 90% of subjects ²⁷. Once again, the utility of this procedure is limited by variable conditions

under which the measurements are made, which are often associated with external sodium chloride administration. Hence, failure to identify lateralization was associated with improved blood pressure in at least 50% of cases, rendering it of limited sensitivity and specificity. Repeat measurement after sodium depletion has been demonstrated to “unmask” renal vein lateralization and identify RVH²⁸. As a clinical measure, identifying a specific kidney as a “pressor kidney” with unilateral renin release is most useful when contemplating therapeutic nephrectomy for blood pressure control.

Imaging Studies

Establishing the diagnosis of occlusive RVD intrinsically requires demonstrating renal arterial obstruction. Hence, imaging studies are a “sine-qua-non” for this diagnosis. A detailed discussion of the relative benefits and characteristics of specific renovascular imaging methods is beyond the scope of this discussion. Before undertaking imaging procedures, some of which are expensive and potentially hazardous, clinicians would do well to establish exactly what goals of the imaging study should be. Is the purpose simply to identify if one or both arteries have evident occlusive disease? Is it to establish the viability and functional characteristics of the post-stenotic kidney? Is it to identify the specific location and severity of RVD for revascularization? Is it to identify translesional gradient information and/or response to revascularization? Perhaps most importantly, to what degree do the clinical conditions of the specific patient warrant consideration of acting on the imaging data, specifically regarding either renal revascularization or nephrectomy? Hence, the choice and pace of diagnostic imaging depend partly on the response to medical therapy and the clinical status of the specific patient. Duplex ultrasound is often the first and least expensive study.

Differential diagnosis

RVH remains one of the most common contributors to “resistant hypertension”. The differential diagnosis for resistant hypertension includes other secondary causes, including obstructive sleep apnea, primary renal diseases, inappropriate aldosterone production/activity and others²⁹. Most commonly, the question arises as to whether renal dysfunction represents parenchymal renal injury from hypertension itself (hypertensive nephrosclerosis). The latter is largely a diagnosis of exclusion, and it has been questioned whether non-malignant forms of hypertension actually lead to renal failure³⁰. Recent studies indicate that other factors, including specific genetic predisposition in African-Americans, may determine the risk for renal dysfunction in such individuals. Some individuals have small vessel disease with or without thrombotic phenomena that mimics large vessel RVD, for which little can be done at present. In general, exclusion of RVD is an important step in the evaluation of otherwise unexplained renal dysfunction with or without hypertension.

Management of Renovascular Hypertension

Few conditions have undergone more radical paradigm shifts than the management of RVH. While it remains a prototype for “reversible” causes of secondary hypertension, current practice has migrated to favor primary medical management as the mainstay of therapy. No doubt restoring vessel patency and perfusion pressures sometimes can lower blood pressure to normal. This is particularly applicable to younger individuals, such as women with

renovascular hypertension from fibromuscular disease, whose hypertension sometimes regresses completely with technically successful renal artery angioplasty³¹. By contrast, older individuals with widespread atherosclerotic vascular disease and pre-existing hypertension likely will require ongoing medical antihypertensive therapy regardless of the success of revascularization.

Since the introduction of blockers of the renin-angiotensin system, medical therapy has achieved goal blood pressures more than 80% of the time, although multiple agents may be required³² **FIGURE 4**. In such patients, pursuing expensive and invasive intervention is difficult to justify. Patients with RVH treated with ACE/ARB therapy appear to have a long-term mortality benefit as compared to those without such treatment^{33,34}. Importantly, results from recent prospective, randomized trials fail to demonstrate substantial additional benefit from renal revascularization procedures for many patients that can be controlled with effective antihypertensive drug therapy.

Accordingly, management of RVH begins with optimizing medical therapy, which necessarily includes withholding tobacco use, introduction of statins, glucose control, and effective antihypertensive drug treatment, most often including either an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)³⁴. If this approach achieves excellent blood pressure levels with stable renal function, no further action may be required, other than surveillance for disease progression.

Atherosclerosis is intrinsically progressive, however, albeit at variable rates between individuals. Post-stenotic perfusion pressures are lower than those in the aorta or pre-stenosis levels, thereby subjecting the kidney to reduced renal perfusion. As noted above, the kidney can tolerate moderate reductions in pressure without developing tissue hypoxia (as shown in **FIGURE 3**) or structural renal injury³⁵, sometimes for many years. At some point, however, overt tissue hypoxia does develop, along with inflammatory injury. Glomerular filtration at reduced renal perfusion pressure eventually depends upon the post-glomerular efferent arteriolar effects of angiotensin II. Hence blockade of the RAAS is particularly capable of reducing filtration pressure at critical levels of kidney perfusion. Progressive loss of GFR in such patients can sometimes recover substantially by withholding these ACE inhibitors and/or ARB's, as some authors have advocated routinely³⁶. Such a critical dependence signals near critical levels of occlusive disease that may benefit from renal revascularization.

Revascularization for renal arterial disease—Restoration of blood flow to the kidney beyond a stenotic lesion remains an obvious approach to improving renovascular hypertension and halting progressive vascular occlusive injury. A major shift from surgical reconstruction ensued in the 1990s in favor of endovascular stent procedures. While some patients benefit enormously, revascularization procedures have both benefits and risks. With older patients having preexisting hypertension, the likelihood of a cure for hypertension is small. Although complications are not common, they can be catastrophic, including atheroembolic disease and aortic dissection. Knowing when the benefits of revascularization outweigh the risks is central to the challenges of managing renovascular disease.

Angioplasty for fibromuscular disease—Most lesions of medial fibroplasia are located away from the renal artery ostium. Many of these have multiple webs within the vessel, which can be successfully traversed and opened by balloon angioplasty. Experience in the 1980s indicated more than 94% technical success rates. Some of these lesions (approximately 10-15%) develop restenosis for which repeat procedures have been used. Clinical benefit regarding blood pressure control has been reported in observational outcome studies in 65% to 75% of patients, although the rates of cure are less secure³⁷. Cure of hypertension, defined as sustained blood pressure levels less than 140/90 mm Hg with no antihypertensive medications, may be obtained in 35% to 50% of patients. Predictors of cure (normal arterial pressures without medication beyond 6 months after angioplasty) include lower systolic blood pressures, younger age, and shorter duration of hypertension. A majority of patients with RVH and FMD are female and generally have less aortic disease and are at lower risk for major complications of angioplasty. Most clinicians favor early intervention for hypertensive patients with FMD with the hope of reduced antihypertensive medication requirements after successful angioplasty.

Angioplasty and stenting for atherosclerotic renal artery stenosis—Angioplasty alone commonly fails to maintain patency for proximal or ostial atherosclerotic lesions, in part because of extensive recoil of the plaque extending into the main portion of the aorta. These lesions develop restenosis rapidly even after early success. Introduction of endovascular stents provide an indisputable advantage. An example of successful renal artery stenting is shown in **Figure 5**. As technical success continues to improve, many reports suggest nearly 100% technical success in early vessel patency, although rates of restenosis continue to reach 14% to 25%³⁸.

Several observational studies suggest that progression of renal failure attributed to ischemic nephropathy may be reduced by endovascular procedures. Harden and associates presented reciprocal creatinine plots in 23 (of 32) patients suggesting that the slope of loss of GFR could be favorably changed after renal artery stenting.³⁹ It should be emphasized that 69% of patients “improved or stabilized,” indicating that 31% worsened, consistent with results from other series. Perhaps the most convincing group data in this regard derives from serial renal functional measurement in 33 patients with high-grade (>70%) stenosis to the entire affected renal mass (bilateral disease or stenosis to a solitary functioning kidney) with creatinine levels between 1.5 and 4.0 mg/dL. Follow-up over a mean of 20 months indicates that the slope of GFR loss converted from negative (−0.0079 dL/mg per month) to positive (0.0043 dL/mg per month)⁴⁰. These studies agree with other observations that long-term survival is reduced in bilateral disease and that the potential for renal dysfunction and accelerated cardiovascular disease risk is highest in such patients^{25,41}.

Treatment trials: Over the past two decades, several prospective RCT's have attempted to quantify the role for renal revascularization when added to medical therapy. Three early trials in renovascular hypertension from the 1990s addressed the added value of endovascular repair using PTRAs without stenting as compared to medical therapy for atherosclerotic RVH. Crossover rates for failure of medical therapy ranged from 22-44%, suggesting a role for PTRAs in refractory hypertension, although the overall “intention-to-

treat” analyses were negative ⁴². There was greater blood pressure benefit after PTR in those with bilateral renal artery stenosis.

Recent prospective trials include STAR, ASTRAL and CORAL as summarized in **TABLE 1**. In some cases, revascularization achieved slightly improved blood pressure levels and/or reduced drug requirements, but the differences have been minor. No definitive benefits regarding recovery of renal function, blood pressure control, or reduction of serious comorbid vascular events have been identified in any of these trials lasting 3-5 years ^{43,44}. These negative results have dampened the argument for early intervention in atherosclerotic RVD.

The limitations of these trials have been substantial, however, particularly as many severe cases of rapidly progressive renal insufficiency, intractable hypertension, and/or episodic pulmonary edema have not been enrolled ^{26,45}. Hence, these trials suffer from underrepresentation of high-risk disease, as has been emphasized from registry ^{25,41} and observational reports ⁴⁶. These series identify “high-risk” subsets of patients with rapidly advancing disease and/or clinical problems related to fluid retention (pulmonary edema), acute kidney injury (AKI) during initiation of ACE/ARB therapy, or rapidly developing renal failure that benefit enormously from revascularization. An important role for the clinician remains to identify and intervene for such individuals.

Management Strategies for Renovascular Disease

A clinical algorithm for managing RVH and ischemic nephropathy is presented in **FIGURE 6**. In most cases, RVH surfaces as progressive (or de-novo) hypertension with some decrement in kidney function. Reduction of cardiovascular risk is paramount and includes antihypertensive drug therapy to goal levels, along with removal of tobacco use, likely initiation of statins and aspirin, particularly with atherosclerotic disease. Duplex imaging will evaluate basic kidney structure, size, and whether occlusive disease is present, unilateral or bilateral. In most cases, drug therapy will be sufficient to achieve BP goals. If kidney function and BP are stable on therapy, results of prospective, randomized trials suggest that little further is to be gained from revascularization, at least in follow-up intervals between 3-5 years. However, rates of progression and stability vary widely between individual patients. Important considerations include whether kidney function deteriorates in the presence of RAAS blockade and/or if a high-risk syndrome develops, including circulatory congestion (pulmonary edema) and/or progressive renal insufficiency with failure to achieve BP targets. In such cases, clinicians must carefully weigh the potential benefits and risks of restoring vessel patency and blood flow to the affected kidney at a point when renal function can be salvaged.

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Box 1 Renal Arterial Lesions that produce the Syndrome of Renovascular Hypertension

Unilateral disease (analogous to 1-clip-2-kidney hypertension)

Unilateral atherosclerotic renal artery stenosis

Unilateral fibromuscular dysplasia (FMD)

Medial fibroplasia

Perimedial fibroplasia

Intimal fibroplasia

Medial hyperplasia

Renal artery aneurysm

Arterial embolus

Arteriovenous fistula (congenital / traumatic)

Segmental arterial occlusion (post-traumatic)

Extrinsic compression of renal artery, e.g. pheochromocytoma

Renal compression, e.g. metastatic tumor

Bilateral Disease or Solitary Functioning Kidney (analogous to 1-clip-1-Kidney model)

Stenosis to a solitary functioning kidney

Bilateral renal arterial stenosis

Aortic coarctation

Systemic vasculitis (e.g. Takayasu's, Polyarteritis)

Atheroembolic disease

Vascular occlusion due to endovascular aortic stent graft

**Box 2: Clinical Features of Patients with Renovascular hypertension
Syndromes associated with Renovascular Hypertension**

1. Early or Late Onset Hypertension (<30 years > 50 Years)
2. Acceleration of treated essential hypertension
3. Deterioration of renal function in treated essential hypertension
4. Acute renal failure during treatment of hypertension
5. “Flash” Pulmonary Edema
6. Progressive renal failure
7. Refractory congestive cardiac failure

The above “syndromes” should alert the clinician to the possible contribution of renovascular disease in a given patient. The bottom three are most common in patients with bilateral disease, many of whom are treated as “essential hypertension” until these characteristics appear (see text)

Key Points

1. Renal artery disease produces a spectrum of progressive clinical manifestations ranging from minor degrees of hypertension to circulatory congestion and kidney failure
2. Moderate reductions in renal blood flow do not induce tissue hypoxia or damage, making medical therapy of renovascular hypertension feasible for many.
3. Several prospective trials indicate that optimized medical therapy utilizing agents that block the renin-angiotensin system should be the initial management.
4. Evidence of progressive disease and/or treatment failure should allow recognition of high-risk subsets that benefit from renal revascularization
5. Severe reductions in kidney blood flow ultimately activate inflammatory pathways that do not reverse with restoring blood flow alone

Manifestations of Renovascular Disease

Figure 1.

Schematic view of progressively more severe clinical manifestations associated with occlusive renovascular disease (RVD). Minor degrees of lumen obstruction are manifest as “incidental” lesions of minimal hemodynamic importance. As obstruction leads to reduced pressures and flow beyond the lesion, renovascular hypertension and acceleration of cardiovascular events ensue, particularly when associated with impaired sodium excretion. Ultimately, severe and longstanding RVD activates injury pathways within the kidney parenchyma that may no longer depend primarily upon hemodynamic effects of stenosis and respond only partially to restoring vessel patency.

Figure 2.

Examples of fibromuscular renovascular disease. **Left panel** depicts an angiogram with a typical “string-of-beads” appearance typical of medial fibroplasia. Indentation of the vessel wall represents a series of internal webs that reduce distal perfusion and trigger RVH. Such lesions can respond to intra-arterial balloon angioplasty (PTA). **Right panel** depicts an angiogram with a focal stenosis causing severe hypertension. Recent classification schemes distinguish mainly between “multifocal” disease (left) and “focal” disease (right).

Tissue oxygenation (BOLD MR) and inflammatory injury in occlusive Renovascular Disease

Figure 3.

Tissue oxygenation as measured by Blood Oxygen Level Dependent (BOLD) MR remains stable during moderate reductions in renal blood flow in atherosclerotic renovascular disease. At some level, severe and prolonged blood flow reductions lead to overt tissue hypoxia associated with rarefaction of small vessels, activation of inflammatory pathways and interstitial fibrosis. Eventually, restoration of large vessel patency no longer reverses this process.

**Medications: Lisinopril 40 mg
Amlodipine 5 mg
indapamide 1.25 mg**

**BP: 136 / 82 mm Hg
Creatinine 1.1 mg/dL
eGFR: 47 ml/min/1.73m2**

Figure 4.

CT angiogram from a patient with unilateral atherosclerotic RVD manifest by high Doppler velocities and recently progressive hypertension. This was treated with drug therapy including ACE inhibition with satisfactory BP levels and GFR (serum creatinine 1.1 mg/dL). Results of prospective, randomized trials indicate that little additional benefit is to be gained by further intervention, e.g. renal revascularization, so long as this remains stable (see text).

Figure 5.

(A, left) Angiographic image of high-grade stenosis manifest by new-onset accelerated hypertension more than 20 years after mantle radiation for malignancy. Drug therapy was associated with declining kidney function. (B, right) Endovascular stent placement in the proximal right renal artery achieved excellent recovery of lumen patency. This maneuver was followed with normalization of blood pressure and withdrawal of medications over two months.

Duplex Ultrasonography of the Renal Vessels

Figure 6.

Schematic illustration of steps in the management of RVH and ischemic nephropathy. The foremost goals are to reduce morbidity associated with hypertension by reaching goal BP and to preserve kidney function. Should that not be achievable by medical therapy or should vascular disease progress, renal revascularization should be considered, either by endovascular or surgical intervention (see text).

Table 1

Randomized Clinical Trials: PTRAs with Stenting versus Medical Therapy alone for renal function and/or cardiovascular outcomes with ARVD

Trials	N	Population	Inclusion Criteria	Exclusion Criteria	Outcomes
STAR (2009) 10 centers f/up 2 years	Med Tx:76 PTRAs: 64	Patients with impaired renal function, ostial ARVD detected by various imaging studies and stable blood pressure on statin and aspirin	ARVD >50% Creatinine clearance <80 ml/min/1.73 m ² Controlled blood pressure one month before inclusion	Kidney < 8 cm and, renal artery diameter < 4 mm, eCrCl< 15 mL/min per 1.73 m ² , DM with proteinuria (>3 g/d), malignant hypertension	No difference in GFR decline (primary endpoint 20% change in clearance), but many did not undergo PTRAs due to ARVD <50% on angiography Serious complication in the PTRAs group Study was underpowered
ASTRAL (2009) 57 centers f/up 5 years	Med Tx:403 PTRAs:403	Patients with uncontrolled or refractory hypertension or unexplained renal dysfunction with unilateral or bilateral ARVD on statin and aspirin	ARVD substantial disease suitable for endovascular and patient's doctor uncertainty of clinical benefit from revascularization	High likelihood of PTRAs in <6 months Without ARVD, previous ARVD PTRAs FMD	No difference in BP, renal function, mortality, CV events (primary endpoint: 20% reduction of in the mean slope of the reciprocal of the serum creatinine level) Substantial risk in the PTRAs group
CORAL (2013) 109 centers f/up 5 years	Med Tx:480 PTRAs:467	Hypertension 2 or more anti-hypertensives or CKD stage 3 with ARVD with unilateral or bilateral disease on statin	SBP>155 mmHg, at least two drugs ARVD >60% Subsequent changes included that the SBP> 155 mm Hg for defining systolic hypertension was no longer specified as long patient had CKD stage 3	FMD Creatinine >4.0 mg/dL kidney length < 7 cm and use of >1 stent	No difference of death from CV or renal causes. Modest improvement of SBP in the stented group Total 26 complications (5.5%)

SBP indicates, systolic blood pressure; Tx, therapy; N, number of patients; CV, cardiovascular; FMD, fibromuscular dysplasia