Chapter 4
Syndromes of Renovascular Hypertension

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Introduction

The central role of the kidney in the regulation of blood pressure was first established by the seminal studies of Loesch and Goldblatt in 1933 and 1934, respectively. They described the rise in arterial pressure that followed clamping of renal arteries in dogs [1, 2]. The mechanisms underlying this form of hypertension were elucidated following the pivotal discovery of the renal pressor system by Page and Braun-Menendez [3–5]. These findings led to the first surgical nephrectomy to cure hypertension in the late 1930s [6]. The concept of surgical treatment for renovascular hypertension (RVH) was appealing, since antihypertensive medications were not available until later. However, not all patients remained normotensive 1 year post surgery [7]. Therefore, there was great interest in defining this disease process, as well as those patients who would benefit from either nephrectomy or, eventually, renal revascularization. Over the last few decades, marked by the aging of the population and advances in imaging technology and therapy, there has been a paradigm shift in occlusive renovascular disease (RVD). Despite compelling evidence in recent clinical trials favoring medical therapy, experienced clinicians still recognize the need for renal artery revascularization in high-risk patients, such as those presenting with flash pulmonary edema, accelerated hypertension, and a rapid decline in renal function [8–11]. Therefore, it is important to understand the mechanisms and implications of renal artery stenosis, as well as the risks and benefits of renal artery revascularization in addition to medical therapy.

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Epidemiology and Causes of Renovascular Disease

Renovascular disease is a major cause of secondary hypertension. It accounts for 1–5 % of hypertension cases in the general population, and reaches a prevalence of 20–40 % in highly selected referral populations [12, 13]. The vast majority of renal artery lesions (90 %) are caused by atherosclerosis, followed by variants of fibromuscular disease (FMD). Far less common causes include vasculitis, dissection, radiation, and extrinsic compression by tumors [14, 15] (see Fig. 4.1).

Atherosclerotic renovascular disease (ARVD) is typically seen in patients older than 65 years of age, often in conjunction with a number of comorbidities and progressive loss of renal function. Fibromuscular dysplasia, on the other hand, is commonly seen in women 15–50 years of age, not related to atherosclerosis and/or inflammation and involving only a few additional vascular territories, mainly the carotid arteries [16, 17]. Multiple subtypes of FMD have been described, depending upon the portion of the vessel wall that is primarily involved. Medial fibroplasia, which is characterized by its classic "string of beads" appearance, represents the most common dysplastic lesion. This is followed by perimedial fibroplasia, characterized by a homogeneous collar of elastic tissue at the junction of the media and the adventitia. This subtype may also produce a "beaded" renal artery appearance, but luminal dimensions are typically much smaller than normally seen. Intimal and adventitial hyperplasia account for less than 10 % and 1 % of the other cases of FMD, respectively [17]. The natural history of FMD tends to be more predictable than that of ARVD. Usually, FMD responds well to angioplasty and does not culminate in renal failure unless complicated by dissection or occasionally thrombosis [14]. The other miscellaneous causes of renal artery stenosis are fairly less common and include acute occlusion by an embolus or dissection of the aorta or renal artery, as illustrated in Table 4.1.

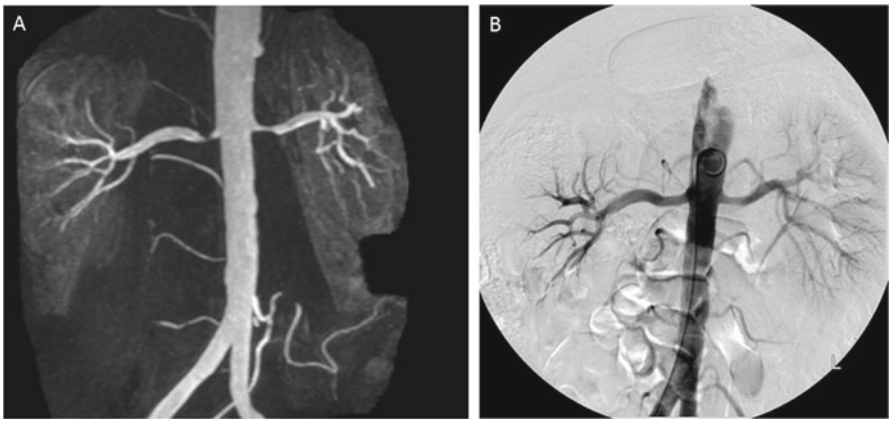

Fig. 4.1 High-grade renal artery stenosis after radiation therapy with accelerated hypertension (**a**) resolved after revascularization (**b**). The magnetic resonance angiogram (MRA) and post-stent pictures are from a patient with accelerated hypertension presenting more than 20 years after radiation for testicular cancer that resolved after revascularization

Table 4.1 Causes of renovascular disease

Unilateral renal artery disease
Unilateral atherosclerotic renal artery stenosis
Unilateral fibromuscular dysplasias
Renal artery aneurism
Arterial embolus
Arteriovenous fistula (e.g., congenital, traumatic)
Segmental arterial occlusion (e.g., posttraumatic, radiation, thrombi)
Extrinsic compression of renal artery (e.g., tumor)
Bilateral renal artery disease or solitary functional kidney
Renal artery stenosis to a solitary kidney
Bilateral renal artery stenosis
Aortic coarctation
Systemic vasculitis (e.g., polyarteritis nodosa, Takayasu's arteritis)
Vascular occlusion due to endovascular stent graft
Atheroembolic disease

Physiopathology of Renovascular Hypertension

Evidence from experimental renovascular models demonstrate that the renin–angiotensin–aldosterone system (RAAS) and sodium retention play a major role in RVH. The precise role of each depends in part on whether a contralateral, nonstenotic kidney is present. Seminal studies in animals performed by Mueller et al. [18] have shown that partial ligation of one renal artery reduces perfusion and glomerular filtration rate (GFR); this culminates in reduced excretion of salt and water. If the normal nonstenotic contralateral kidney is now removed, the stenotic kidney still promptly excretes the same amount of salt and water as both kidneys combined. Furthermore, there is little increase in GFR. Howard and colleagues [19] found similar results in patients, showing that reduced renal blood flow and consequently reduced perfusion pressure to the stenotic kidney was associated with a reduced water and sodium excretion as compared to the nonstenotic contralateral kidney. These studies underscored both the effect of the stenotic kidney in excretory function and the importance of the contralateral kidney in restoring homeostasis. As the renal perfusion pressure decreases and the fraction of salt and water absorbed in the proximal tubule increases, therefore, the kidney supplied by a narrowed artery excretes a lesser quantity of urine and sodium [20].

Unilateral Renovascular Disease

Unilateral renovascular hypertension in humans corresponds to the animal model of two-kidney one-clip (2K1C) Goldblatt hypertension, in which a normal, contralateral kidney is present (see Fig. 4.2a). The clipped kidney secretes renin, an enzyme localized in the juxtaglomerular cells of the kidney, which acts on its substrate angiotensinogen and leads to increased angiotensin I production. Angiotensin-converting enzyme located in the pulmonary capillary bed acts on angiotensin I to cleave off two amino acids to generate the eight amino-acid peptide angiotensin II. Angiotensin II acts as a potent vasoconstrictor, which leads to elevation in blood pressure [21]. Angiotensin II also acts indirectly through the central nervous system [22] and stimulates secretion of aldosterone by the adrenal cortex [23]. The rise in blood pressure stimulates pressure natriuresis by the intact contralateral kidney, which restores volume. Accordingly, the presence of the intact kidney prevents significant sodium retention. Thus, hypertension in unilateral disease is not primarily volume dependent, but is "angiotensin-dependent," and tests of both renin release and function demonstrate the effects of reduced perfusion to the stenotic kidney. Lateralization of renal vein renin secretion to the hypoperfused kidney as compared to the contralateral kidney (renin ratio levels >1.5) and asymmetric radionucleotide renography showing delayed uptake magnified in the presence of captopril have been utilized to predict the response to revascularization. This model is most closely related to the early phase (see below) of rapidly developing renovascular hypertension, such as that associated with renal artery dissection.

Based on pathophysiology and reversibility of hypertension, hypertension in the 2K1C model can be better understood by considering three phases: acute, intermediate, and chronic. Phase I, also called the acute phase, occurs between 2 and 4 weeks after clipping and is characterized by elevated plasma renin activity and angiotensin II. Phase II, the intermediate phase occurs between 5 and 9 weeks after clipping, wherein renin levels start to decline, but blood pressure remains elevated; removal of the clip or angiotensin II blockade still produces decline in blood pressure. Phase III, or chronic phase, eventually develops beyond 9 weeks after clipping of renal artery. This phase is associated with reduced renin activity and angiotensin levels, but sustained hypertension. Removal of the clip in this phase no longer lowers the blood pressure [21]. It may be surprising that removal of the instigating lesion is no longer capable of restoring normotension in the chronic phase. Mechanisms that have been proposed for maintenance of hypertension include increased oxidative stress, inflammation, and structural vascular changes [24, 25].

RVD rarely affects both kidneys to an equal degree. Hence, the kidney with more significant stenosis can lose viable function, as the contralateral unaffected kidney is capable of adaptive changes, developing hypertrophy, and undergoing a compensatory rise in single-kidney GFR, albeit to varying degrees. As a result, overall GFR may not change [26]. Unilateral ARVD is often accompanied by a progressive increase in oxidative stress and inflammation, especially in an atherosclerotic milieu. These effects are reflected by increased circulating and renal venous inflammatory biomarkers, evident not only from the stenotic kidney, but also from

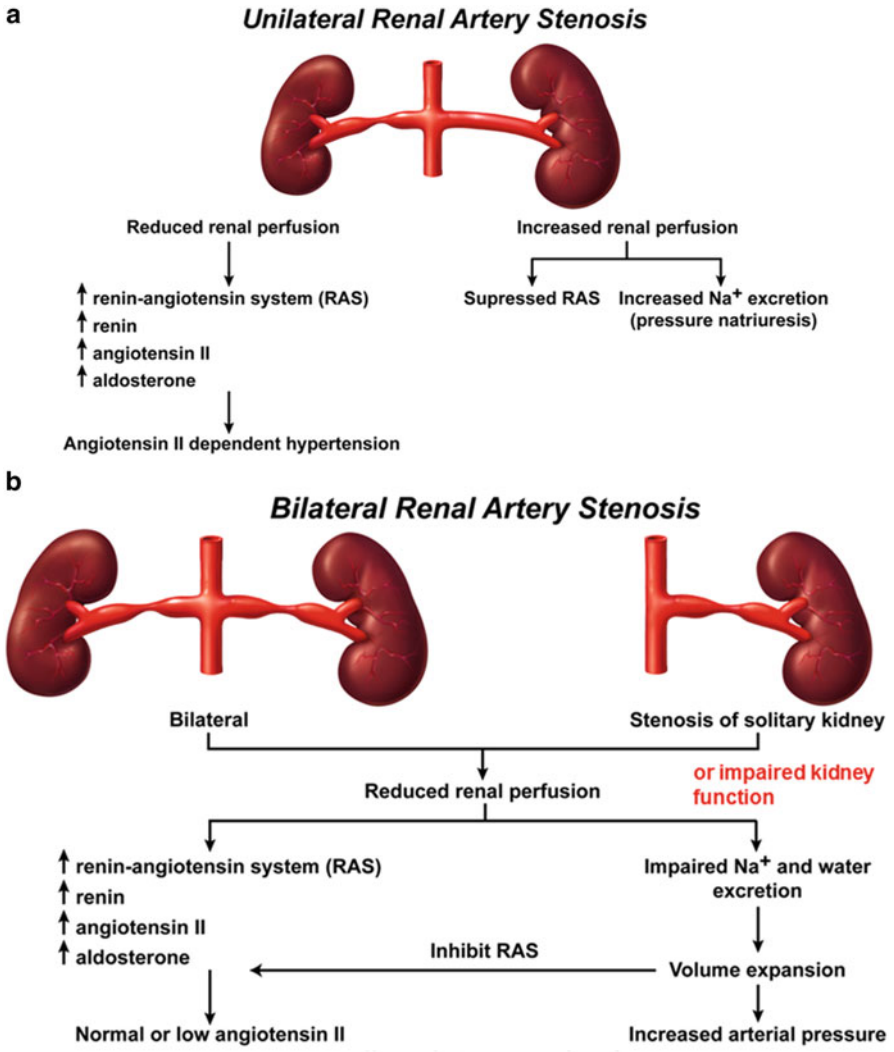

Fig. 4.2 Schematic view of two-kidney one-clip (**a**) and one-kidney one-clip (**b**) renovascular hypertension. The presence of a contralateral kidney exposed to elevated perfusion pressures in two-kidney one-clip hypertension tend to allow pressure natriuresis to ensue while ongoing stimulation of renin release from the stenotic kidney. The one-kidney model (or bilateral renal vascular disease) eventually produces sodium retention and a fall in renin level with minimal evidence of angiotensin dependence, unless sodium depletion occurs

the contralateral kidney [24, 27]. The long-term pro-inflammatory effects of elevated blood pressure and resultant renal damage—affecting both the stenotic and the contralateral kidney—likely are the result of complex interactions, including changes in renal hemodynamics, hormonal and sympathetic nervous activity in conjunction with increased oxidative stress, and inflammation leading to structural changes and fibrosis [28].

Bilateral Renovascular Disease or Stenosis to a Solitary Functioning Kidney

The one-kidney one-clip (1K1C) model corresponds to bilateral renovascular disease or stenosis to a solitary functioning kidney in humans (see Fig. 4.2b). Circumstantial evidence suggests that both renin and volume factors are involved. In this model, the contralateral kidney is removed. Decreased renal perfusion triggers initial RAAS activation and sodium retention. Without a contralateral kidney, pressure natriuresis can no longer occur, and sodium retention becomes the primary mechanism supporting hypertension. The volume expansion associated with sodium retention inhibits renin secretion such that renin activity level is normal or low in this model [29]. Following clipping of the renal artery, glomerular filtration pressure is maintained distal to the stenosis by angiotensin II-mediated vasoconstriction preferentially on the efferent glomerular arterioles, which helps to maintain GFR despite reduced perfusion [30]. Therefore, administration of antihypertensive medications such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with bilateral stenosis or solitary stenotic kidney potentially causes worsening of renal function due to disruption of this mechanism.

Undoubtedly, the RAAS is a primary driver for the development of renovascular hypertension in both models. Animal models that lack angiotensin receptors (AT1 receptor knockout animals), for example, fail to develop hypertension despite renal artery clipping [31]. However, other mechanisms play a substantial role in at least some of these patients (see Fig. 4.3).

Renovascular Syndromes

Reduced renal perfusion provokes chronic stimulation of the RAAS and renal adrenergic nerves, and downstream adverse effects besides hypertension [32]. For example, angiotensin II has been implicated, in animal studies, in the development of renal damage by enhancing the effects of inflammatory chemokines and factors promoting fibrosis [33]. Combined with severely decreased perfusion and evolving hypoxia, ischemic nephropathy develops, ultimately with irreversible kidney damage [32]. Furthermore, chronic RAAS activity is implicated in the development of abnormal left ventricular remodeling, which leads to cardiac dysfunction [34]. Cardiac output is frequently elevated in patients with RVD, and demonstrates exaggerated responses to hypertension and to drugs that suppress sympathetic adrenergic function [20]. Heart failure and flash pulmonary edema are two of the clinical syndromes associated with RVD (see Table 4.2).

The clinical manifestations of RVD are protean. New onset of hypertension in a young female patient should raise suspicion for secondary causes of hypertension, including renovascular hypertension. As such, sudden development of accelerated

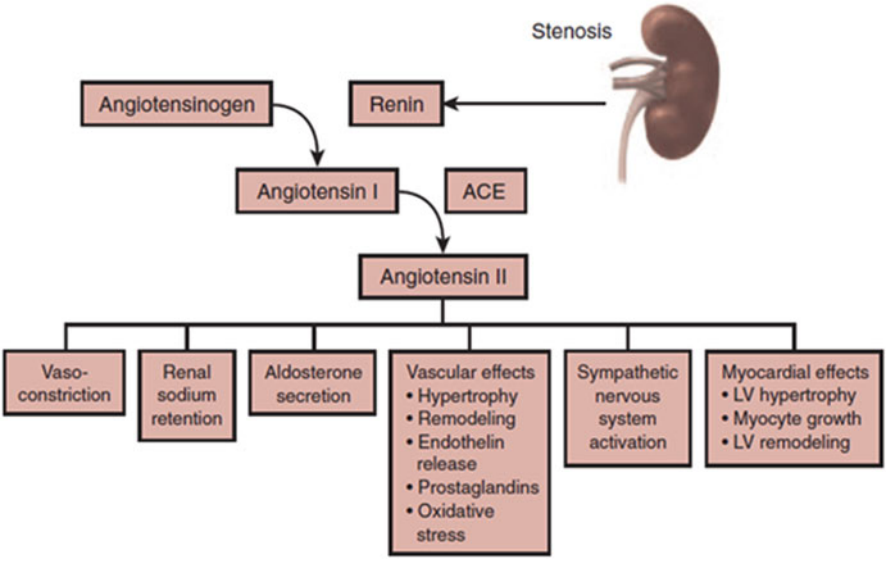

Fig. 4.3 Schematic view of activation of the renin–angiotensin system in occlusive vascular disease. Decreased renal perfusion to the kidney provokes renin release by juxtaglomerular cells in the kidney, which leads to increased circulating and local angiotensin II; a downstream effect follows, which includes arteriolar vasoconstriction, sodium retention, and elevated systemic vascular resistance. Studies implicate angiotensin II in many other pathways of vascular and cardiac smooth muscle remodeling, activation of inflammatory and fibrogenic cytokines, and induction of other vasoactive systems. *ACE* indicates angiotensin-converting enzyme, *LV* left ventricular. Adapted from: Garovic VD, Textor SC. Circulation. 2005;112:1362–1374

Table 4.2 Clinical syndromes associated with renovascular disease

Onset of hypertension before age 30 or after age 50
Accelerated, resistant, malignant hypertension
Deterioration of renal function in response to renin–angiotensin blockade
Flash pulmonary edema
Progressive renal failure
Refractory congestive heart failure

hypertension (sometimes associated with hyponatremic-hypertensive syndrome in a patient not known to be hypertensive, or with previously well-controlled hypertension) can be seen in RVD, especially in patients with acute unilateral renal artery occlusion [35, 36].

By far, the most common presentation of RVD is progressive worsening of preexistent hypertension. This may be accompanied by a small increase in serum creatinine concentration. RVD is especially common in patients with resistant hypertension. A review of patients older than 50 years of age referred to a hypertension center were found to have secondary causes in 12.5 %, the most common of which was RVD (35 %) [37]. Another usual clinical feature of RVD is worsening

kidney function after initiation of renin–angiotensin blockade therapy, which decreases systemic blood pressure and magnifies the already reduced renal perfusion provoked by the critical artery lesion. This usually is functional and reversible after discontinuation of the of renin–angiotensin blockade therapy [38]. Intolerance of these agents due to renal dysfunction can be particularly significant in bilateral or solitary kidney RVD and renal artery revascularization should be considered in order to facilitate their re-introduction [39]. Bilateral RVD should also be considered in patients with a history of "flash" or episodic pulmonary edema, especially in patients with heart failure with a preserved ejection fraction (HFpEF) [40]. In one study, congestive heart failure was present in one-third of patients with ARVD and renal dysfunction. Referral of these patients for renal artery revascularization resulted in improvement of congestive heart failure (CHF) control and reduced number of hospitalizations [41]. Progressive renal dysfunction presenting with advanced renal failure is also another clinical presentation of RVD. Hypertension is usually present in these cases. Using data from the United States Renal Data System (USRDS), Guo et al. [42] discovered the presence of ARVD in 11.2 % of patients aged 67 years or older at dialysis inception between 1996 and 2001. However, renal failure was attributed to ARVD in less than half of these patients. Anecdotal cases and observational series indicate that some patients may have some stabilization or improvement of kidney function after revascularization, although this is uncommon [43, 44]. Prospective randomized trials have failed to show compelling benefits of revascularization compared with current medical therapy. The only caveat with these studies is that a subgroup of high-risk patients, including those with episodes of flash pulmonary edema and rapidly deteriorating GFR and accelerated hypertension, were not included in prospective trials and may have experienced reduced mortality rates with effective renal revascularization [11].

Diagnostic Approach in Renovascular Hypertension

Many patients are diagnosed with hypertension and treated with first-line therapy for hypertension without screening for RVD. Indeed, such screening is not indicated unless the patient presents with clinical symptoms suggestive of RVD, as illustrated in Table 4.2. The tools for screening allow for greater diagnostic sensitivity and accuracy than ever before, due to advances in noninvasive imaging techniques. In the past, most lesions were detected with the goal of identifying lesions suitable for revascularization. Results of recent randomized clinical trials have modified this practice, favoring medical therapy as the initial mode of therapy [8–10].

It is worth emphasizing that the presence of a renovascular lesion does not translate necessarily into functional importance. Studies in humans using progressive balloon occlusion show that renin release does not occur until the pressure distal to the lesion falls at least 10–20 % below the pressure proximal to the lesion [45]. Some degree of renal artery stenosis is incidentally identified in patients who are undergoing vascular imaging for different reasons [46, 47]. The great majority of

these stenotic lesions is minor, and does not produce a degree of obstruction hemodynamically significant enough to cause RVH. Actually, many patients have moderate ARVD that remains clinically silent for several years. However, occlusive vascular disease progresses in a subset of patients with ARVD, which can cause progressive tissue injury and accelerating hypertension, in which case a benefit from revascularization can be noted. Identification of patients who would benefit from further evaluation, however, remains challenging. Selecting patients for further studies depends on the commitment to act upon the results of those tests. Clinicians need to ascertain when medical therapy alone is insufficient and further tests are to be pursued with the intention of restoring renal blood flow to a kidney that remains viable [48]. Several clinical features should be considered in this context, particularly for the subset of patients with high-risk presentations [11, 49].

Imaging procedures are important for diagnosis, the choice of diagnostic imaging technique for RVD depends on patient characteristics, local availability, and expertise and is discussed further below.

Imaging

Duplex Doppler Ultrasonography

Ultrasonography is widely accepted as the first-line diagnostic imaging test because of its availability and cost. Duplex Doppler renal ultrasonography combines grey-scale imaging from traditional ultrasound with a Doppler technique to assess renal blood flow velocities, evaluating renal morphology and the presence of significant stenosis. With experienced operators, it is an excellent initial imaging study, with up to 95 % sensitivity and 90 % specificity in dedicated laboratories, providing both structural and functional assessment of the kidneys [50, 51]. In a patient with normal cardiac function, peak systolic velocities (PSV) in the main renal artery range between 60 and 100 cm/s. In a region of focal vascular disease, the reduced cross-sectional area of the stenotic segment causes increased blood velocity to maintain flow. Although relationships between PSV and the degree of vessel occlusion are approximate, PSV levels above 180–200 cm/s translate into more than 60 % lumen occlusion and are considered "hemodynamically significant." [52] (See Fig. 4.4a.) The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial required PSV values above 300 cm/s for entry by ultrasound criteria [10]. A more accurate method may be to calculate the ratio of the renal artery to aorta velocities (RA:aorta). A threshold of >3.5:1 ratio suggests relatively high-grade RVD. However, overlying bowel gas and complex anatomy may make assessment of the entire renal arterial tree technically difficult. Alternatively, evaluating the renal segmental arteriolar bed distal to the stenotic lesion, where the peak velocity is decreased, allows identification of the loss of the normal sharp upstroke of velocity in systole causing parvus tardus waveform indicative of upstream vascular obstruction [53] (see Fig. 4.4b).

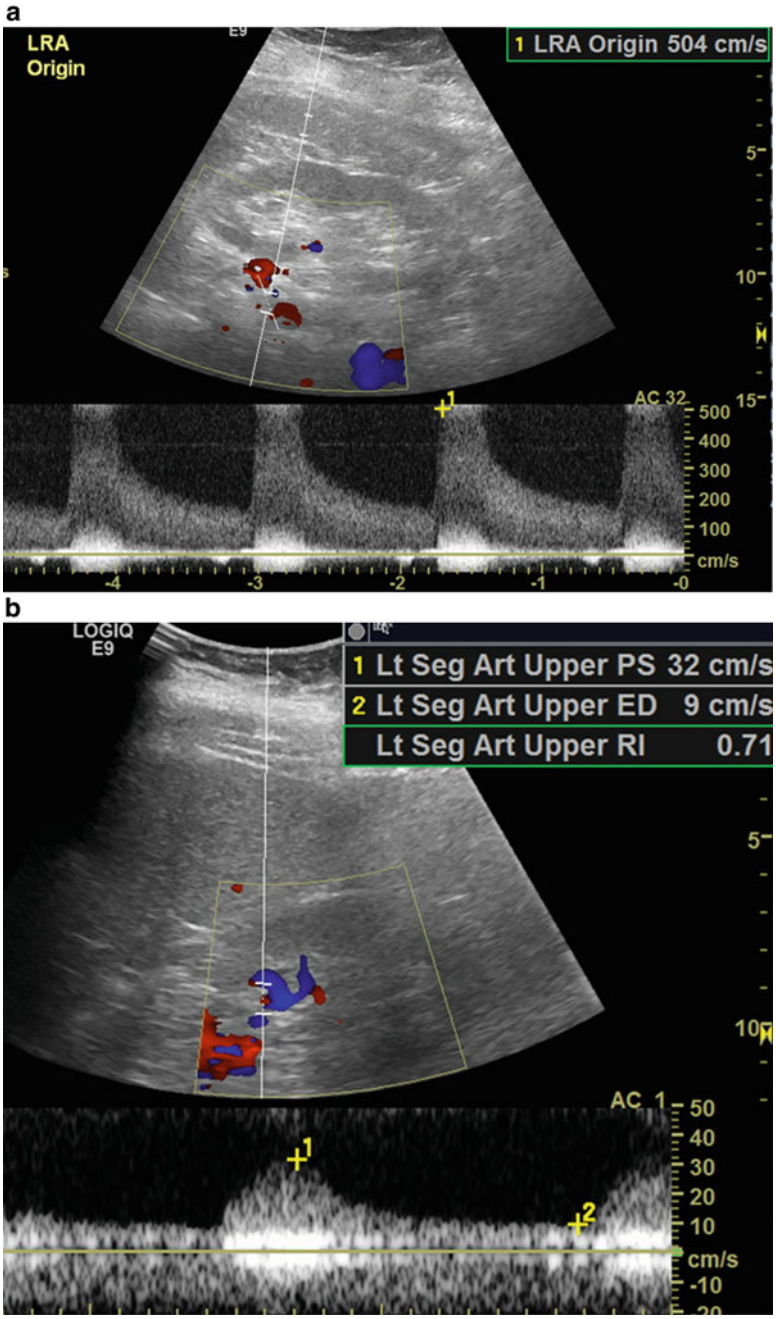

Fig. 4.4 Duplex ultrasound showing renal artery peak systolic velocity (**a**) and parvus tardus in left segmental artery (**b**): **a** shows elevated peak systolic velocity of more than 500 cm/s of the left renal artery (LRA). PSV levels above 180–200 cm/s translate into more than 60 % lumen occlusion and are considered "hemodynamically significant." **b** demonstrates parvus tardus (*arrow*), note the slope of the systolic upstroke and absence of early systolic peak associated with diminished amplitude of the waveform

Another parameter obtained with Doppler ultrasound is the evaluation of resistive index (RI). The RI is defined as height of the PSV minus height of the end-diastolic velocity (EDV) divided by the PSV [RI = (PSV − EDV)/PSV] and reflects the status of the flow characteristics in the renal microcirculation beyond the main renal arteries. RI < 0.8, in conjunction with clinical findings, has been promoted as a useful parameter to predict benefit after revascularization [54, 55]. However, similar outcomes have been reported independent of renal parenchymal values for RI greater than or less than 0.8 [56]. In our experience, lower RI likely is associated with better preserved renal flow characteristics and likely better kidney functional outcomes, but this alone is rarely decisive as to whether or not to proceed with renal artery revascularization. Situations that one may consider revascularization despite RI > 0.8 include patients with RVD without atrophic kidney presenting with recurrent flash pulmonary edema, rapidly declining kidney function, and/or refractory hypertension.

Computed Tomography and Magnetic Resonance Angiography

Although catheter angiography remains the gold standard for imaging of the renal vascular system, it is costly, invasive, and adds the risks that come with intra-arterial instrumentation. It is commonly reserved for endovascular procedures, such as balloon angioplasty and stenting. Advances in computed tomography angiography (CTA) and magnetic resonance angiography (MRA) have allowed for more precise evaluation of RVD and may be undertaken to define vascular anatomy, functional characteristics, and abnormalities within the kidneys.

CTA is noninvasive and provides excellent spatial and temporal resolution for imaging of the renal arteries and surrounding tissues, making it sensitive for diagnosis of other secondary causes of hypertension, such as adrenal disease and other atherosclerotic disease [57]. Recent studies indicate that the risk of contrast-induced changes in renal function from intravenous dosing is extremely low using standard volume expansion, possibly no different from a non-contrast CT, even among those with impaired kidney function [58–60]. Although gadolinium contrast-enhanced MRA provides excellent functional and structural vascular imagingmagnetic resonance angiography (MRA) of the kidney, the use of gadolinium for patients with any reduction in estimated glomerular filtration rate (eGFR) has virtually disappeared out of concern for the potential toxicity related to nephrogenic systemic fibrosis (an eGFR of 40 mL/min/m^2 was defined by the American College of Radiology on MR safety as the cutoff below which no gadolinium should be given). CTA and MRA are of comparable accuracy, reaching sensitivity and specificity >90 % in a number of single-center studies compared with catheter angiography [61, 62].

Intra-Arterial Angiography

Intra-arterial angiography is considered the gold standard for the diagnosis of renal artery stenosis, but it is invasive and likely not indicated as the primary and initial diagnostic methodology. It should be reserved to confirm the occlusive vascular lesion and to perform renal artery revascularization. Besides the concern of interobserver variability in estimating stenosis severity, angiography per se does not provide reliable functional or hemodynamic information. However, measuring the pressure gradient during angiography overcomes these limitations and allows for functional evaluation of the hemodynamic significance prior to revascularization [63]. Gradients above 22 mmHg are usually in agreement of estimating stenosis of 50 %, and there is a curvilinear relationship between the systolic resting gradient and systolic blood pressure [64]. The level of translesional pressure gradient helps to determine the hemodynamic significance of an apparent occlusive lesion. Due to the invasive nature of intra-arterial angiography and its associated possible risks, such as vascular injury and bleeding, it should not be used as a screening method [65].

Radionucleotide Renography

After the injection of radioisotopes, the kidney can be visualized and the contribution of each kidney to the glomerular filtration can be estimated. The two most common radiolabelled pharmaceutical agents used are Tc99m-MAG3 (mercaptoacetyltriglycine) and Tc99m-DTPA (diethylenetriamine pentaacetic acid), with the former being more reliable in renal insufficiency (MAG3 is secreted effectively by the proximal tubule, whereas DTPA is excreted by glomerular filtration). Any prescribed ACE inhibitor or ARB therapy must be discontinued 2–5 days previously. The criteria for RVD include (a) a decrease in the percentage of uptake of the isotope by the affected kidney to <40 % of the total; (b) delayed time to peak uptake of the isotope to >10–11 min, well above the normal value of 6 min; and (c) delayed excretion of the isotope with retention at 25 min or >20 % [48]. The addition of captopril and comparison with a baseline (non-captopril) renogram allows estimation of the functional role of angiotensin in maintaining glomerular filtration and exaggerates hemodynamic differences between a kidney with stenosis and one without [66]. This test provides no information about the cause of the stenosis, nor does it reliably distinguish unilateral from bilateral RVD, since asymmetry can be presented if one side is more affected than the other [67, 68]. The sensitivity of renal renography ranges from 58 to 95 % and its specificity ranges from 17 to 100 %, even when studies were performed in selected patients who had an intervention based on positive results on angiography [62]. Moreover, renogram sensitivity decreases with the decline of renal function, especially when creatinine reaches levels >2 mg/dL or CKD stage 4 or 5 [69]. The role of renography in the current era is best used to determine split renal function prior to proceeding with therapeutic nephrectomy for RVD, however, captopril

renogram is not recommended by current American College of Cardiology-American Heart Association guidelines for the management of patients suspected of having RVD [49].

Selection of Therapy

Medical Therapy for Renovascular Disease

Our understanding of therapy for ARVD has changed substantially over the last 15–20 years, and its management for specific patients is more controversial than ever before. In the past, the lack of effective antihypertensive drug therapy led to more widespread efforts to identify and reverse RVH by means of either surgical or endovascular renal revascularization. Several prospective, randomized controlled trials in the last decade, however, indicate that many patients with ARVD can achieve satisfactory blood pressure control for years with current medical therapy alone [8–10]. Management of systemic atherosclerotic disease should be achieved with widespread administration of statins, aspirin, and smoking cessation. The development of specific clinical features over time, including progressive vascular occlusion, worsening of kidney function while taking ACE/ARB therapy, accelerated hypertension, and recurrent pulmonary edema, warrant consideration for revascularization and suggest that the atherosclerotic process has advanced [11, 70].

It is important to reiterate that ARVD is part of the continuum of atherosclerotic cardiovascular disease (ASCVD). Patients with significant ARVD, as outlined in the CORAL trial, are far more likely to die from cardiovascular causes than to develop renal failure. The main goal of therapy is the prevention of events such as stroke and acute myocardial infarction, which can have a direct impact on survival [10]. Glucose control is also important. Hypertensive patients with ARVD of any extent, compared with hypertensive patients without ARVD, carry a substantially increased risk for future cardiovascular events, which indicates that systemic hypertension is both a manifestation of ARVD and a risk factor for the progression and downstream consequences of ARVD. Therefore, even in patients with low-grade ARVD, aggressive pharmacological treatment strategies should be adopted as a preventive measure [71].

With the current availability of broad-spectrum antihypertensives, the ability to control blood pressure in patients with ARVD has been greatly improved. Failure to achieve goal blood pressure in early trials was associated with treatment crossover rates to the interventional arm up to 40 %, whereas the crossovers in recent trials (ASTRAL and CORAL) were below 10 % [72, 73]. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are considered as first-line drugs. If goal blood pressure is not reached, one may add a thiazide diuretic, calcium channel blocker, β[beta] blocker, or aldosterone antagonist [49, 72]. The use of a protocol-driven approach produced excellent overall blood pressure control in the CORAL

trial [10]. A caveat to recognize is the possible decline in renal function with ACE/ARB therapy, especially with bilateral ARVD or solitary kidney.

On the other hand, reduction in renal perfusion pressure distal to the stenosis, especially if encountered on a chronic basis, can lead to cortical hypoxia, microvascular rarefaction, and development of interstitial inflammation, tubular atrophy, and irreversible fibrosis [74–76]. Decline in GFR by 20 % or doubling of serum creatinine, also known as a "renal event" in clinic trials, can be noted in 1 in 5 patients over 2–4 years [8, 9]. Progression is more likely in patients with bilateral renal artery stenosis or stenosis of a solitary functioning kidney [77]. Also, the rate of progression of ARVD is much greater in these patients (60 %) than the usual rate of 35 % at 3 years, and more than 50 % at 5 years [78, 79] (see Fig. 4.5).

The rate of occlusion is 2 % at 1 year, 5 % at 2 years, and may be as high as 15 % at 5 years [80]. Thus, without physical intervention, patients with ARVD are at risk of progression of stenosis to the point of complete occlusion, ischemic nephropathy to the point of end-stage renal disease, and acute kidney failure with antihypertensive therapy, especially with renin–angiotensin inhibition. The only question remaining to the clinicians is: Which patients should be referred for revascularization and at which time?

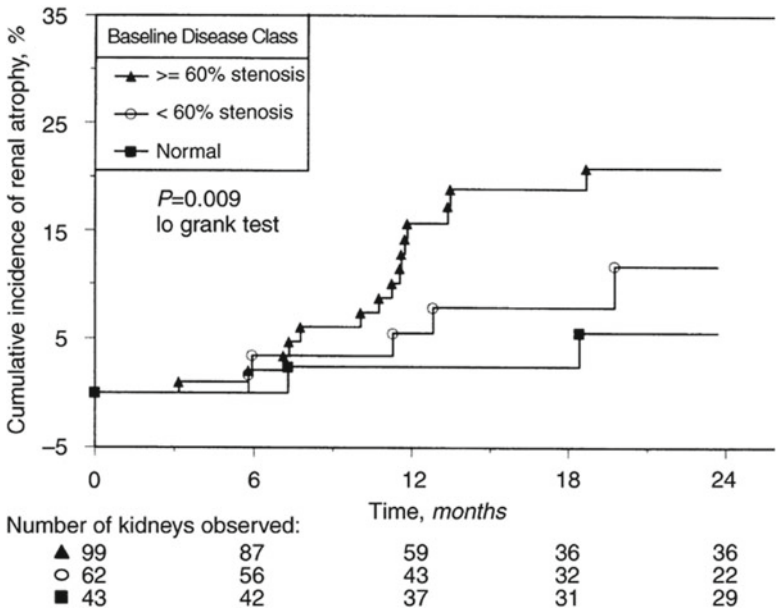

Fig. 4.5 Cumulative incidence of renal atrophy in atherosclerotic renovascular disease, as measured by renal artery Doppler ultrasonography. Standard error is 10 % through 24 months for all plots. (*Filled triangle*) indicates ≥60 % stenosis; (*open circle*), <60 % stenosis; (*filled square*), no stenosis. $P = 0.009$, log rank test. Reprinted with permission from Caps MT, Zierler E, Polissar NL, et al. Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. Kidney Int. 1998;53(3):735–42

Revascularization Therapies for Renovascular Disease

Various surgical interventions to control RVH have been pursued in the past, but largely were replaced by the introduction of catheter-based intervention, also known as percutaneous transluminal renal angioplasty (PTRA), by Andreas Gruentzig in 1978 [81]. Although not widely accepted initially, PTRA with stenting has now become the main mode of revascularization for patients with ARVD. Stenting yields higher procedural success and long-term patency rates, especially for ostial lesions, and is more effective in terms of improving blood pressure and stabilizing or improving renal function over time [65, 82–87]. In general, the maximum antihypertensive response is observed within 2 days, and the final durable outcome within 2–4 weeks. The blood pressure-reducing effects in more recent trials ranged between 8 and 16 mmHg, but not necessarily reduction of the number of antihypertensive medications [8, 9].

The ideal candidate for PTRA is the patient who has ARVD with either drug intolerance or has refractory hypertension, recurrent flash pulmonary edema, refractory heart failure, or rapid decline of renal function [11].

Similarly, patients with renal artery FMD undergoing PTRA have beneficial long-term effects, however the longer the duration of the hypertension or higher the patients' age the less the benefit of PTRA and more adverse the prognosis of renovascular hypertension in this population [88].

The main risks of the procedure include bleeding at the access site, retroperitoneal hematoma, and renal artery dissection. Other, more serious complications of the procedure include renal artery perforation, requiring surgery, and renal artery thrombosis contributing to acute kidney injury, otherwise seen with atheroembolization or as a contrast reaction. Depending on the extent of structural damage, acute kidney injury in this setting can be reversible or irreversible.

With the introduction of drug-eluting stents, acute restenosis rates have declined from 9–76 % to 0–4 %, and late restenosis from 25–45 % to 3–39 % compared to angioplasty alone [86]. In-stent restenosis, nevertheless, should be suspected clinically with a rise in blood pressure and the need for intensive antihypertensive therapy. These patients should undergo duplex ultrasonography, and decisions on repeat intervention should follow the general considerations, also taking into account that restenosis rates may be higher with bare-metal stents [89, 90].

Retreatment with angioplasty with or without repeat stenting (preferably drug-eluting stents) can be attempted, but the restenosis rate after repeat intervention is higher.

In the current era, surgical renal revascularization surgery is preferred only for selected patients with complex anatomic lesions [91, 92], including multiple small renal arteries, early primary branching of the main renal artery, requirement for aortic reconstruction near the renal arteries for other indications (such as aneurysm repair or severe aortoiliac occlusive disease), or to avoid manipulation of a highly diseased aorta or failed endovascular stents, including repeated in-stent restenosis [49, 93]. For unilateral ARVD nephrectomy can be performed in cases with nearly

complete renal artery occlusion and a small atrophic kidney, or otherwise single bypass grafting (either aorto-renal or, in case of a diseased aorta, hepato-renal or spleno-renal bypass) or unilateral repair with contralateral nephrectomy of a non-functioning, atrophic kidney [94]. Surgical intervention leads to improvement in hypertension in up to 95 % of patients [95]. It can even grant a "cure" in those without concomitant essential (primary) hypertension or intrarenal vascular disease (nephrosclerosis) of the contralateral kidney due to chronic (usually >5 years) exposure to hypertension [96]. Compared with PTRA, surgery used to have a higher primary success rate (approaching 100 %) and a fivefold lower restenosis rate (4 %) at 2 years. However, with improvement in techniques and the possibilities of repeat intervention, the outcomes have become quite similar.

In distinction from PTRA, surgery has a tangible mortality risk that varies from less than 2.5–10 % depending on age, comorbidities (especially the severity of the extrarenal ASCVD), and surgical extent and experience [16, 73, 94, 95, 97, 98]. Independent risk factors for in-hospital mortality are age, history of chronic kidney disease, heart failure, or chronic lung disease, each increasing the risk twofold. As such, the ideal candidate is the younger individual (<65 years) without symptomatic coronary or cerebrovascular disease and who requires renal artery surgery only.

In more recent randomized controlled trials, it has been shown that patients with ARVD will escape early detection as a result of diminished enthusiasm for vascular intervention. This will certainly be appropriated for most of the patients with patients with ARVD, as suggested by CORAL and the other cohorts [8–10]. However, progressive occlusive vascular disease associated with clinical manifestations, including progression of chronic renal disease and recurrent pulmonary edema out of proportion to the degree of cardiac disease, will continue to develop. The role of nephrologists is to recognize this subgroup of patients at risk of developing ischemic nephropathy and other high-risk manifestations of ARVD at a time when they still may benefit from revascularization with or without adjunctive maneuvers.

Summary

Renal vascular disease is a common cause of hypertension, particularly ARVD, in the elderly population. It can manifest from asymptomatic disease, be found incidentally by imaging studies, or be identified clinically by presenting with renovascular syndromes such as accelerated hypertension, flash pulmonary edema, and/or progressive renal dysfunction. It is of paramount importance that the clinician evaluate the significance of the RVD in the individual bases and weight the risk and benefits of renal artery revascularization versus medical therapy alone. Management of ASCVD and hypertension is the main goal of medical therapy. However, patients with a high risk of progression, such as patients with significant renal artery stenosis with bilateral disease or solitary kidney are likely to benefit from revascularization of the kidney by decreasing the risk of developing circulatory congestion and/or

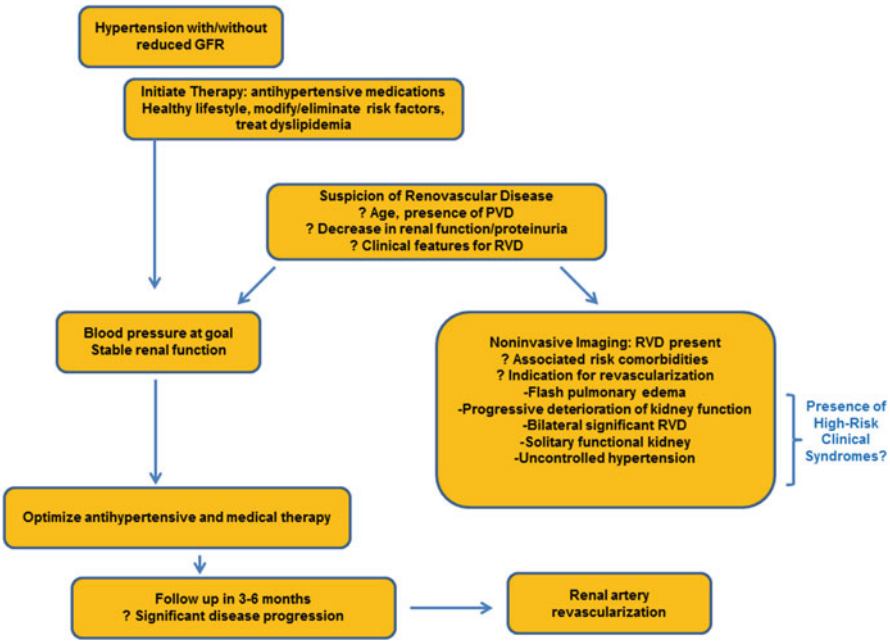

Fig. 4.6 Management of renovascular hypertension and ischemic nephropathy. Algorithm summarizing the management scheme for patients with renovascular hypertension and/or ischemic nephropathy. *GFR* indicates glomerular filtration rate, *PVD* peripheral vascular disease, *RVD* renovascular disease

progression of renal dysfunction. Follow-up is necessary, even after revascularization, due to potential restenosis or disease recurrence. An algorithm for the management of ARVD is provided for guidance (see Fig. 4.6).

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