CHAPTER

42 Renal Artery Stenosis, Renovascular Hypertension, and Ischemic Nephropathy

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The identification and management of renovascular disease presents a clinical challenge that is directly relevant to nephrologists, and also one that relates to many other medical specialties, including cardiovascular specialists, internal medicine physicians, vascular surgeons, and interventional clinicians. How best to manage renovascular disease remains controversial, in part because of the near simultaneous development of far more effective diagnostic tools, medical therapy, and revascularization techniques over the past decade that has ever been available before. It behooves clinicians caring for patients with renal disease to have a solid understanding of these concepts as part of their clinical responsibility to prevent an irreversible loss of kidney function and adverse effects of arterial hypertension.

Few conditions are more rewarding to treat than new onset severe hypertension and/or progressive renal insufficiency that reverses after the successful restoration of renal blood flow. Occlusive lesions of the main renal arteries can now be detected readily with any of a variety of imaging tools. Determining when to pursue renovascular lesions in clinical hypertension, renal insufficiency, or circulatory congestion; establishing their pathophysiologic role; and whether the hazards associated with revascularization are warranted are pressing concerns regularly faced by nephrologists. Although recent trial data fail to provide compelling evidence in favor of endovascular stenting for all patients with atherosclerotic disease, the validity of prospective clinical trials in this disorder has been fiercely challenged.[1,2] Experienced clinicians understand that renal revascularization in these disorders sometimes should be undertaken both to improve hypertension and to salvage renal function.

Recognition that reduced renal perfusion activates pressor systems that raise systemic blood pressure remains one of the seminal observations and most widely studied mechanisms in cardiovascular physiology. Reversal of renovascular hypertension can provide major benefits to patients with accelerating hypertension (e.g., allowing effective blood pressure control and reduction of long-term drug therapy). Selecting patients and determining optimal timing for vascular intervention at a reasonable risk is rarely simple, however.

These issues are complicated further by the rapid expansion of endovascular procedures over the past two decades. Although restoring lumen patency in partially occluded vessels intuitively may seem beneficial, recent trials indicate that revascularization procedures carry both substantial costs and some risks, whereas the clinical benefits remain ambiguous.[3,4] This is a remarkable turn of events, insofar as renovascular hypertension traditionally has been considered a prototype for "curable" secondary hypertension. Most diseases of the renal arteries are progressive, and the clinical manifestations develop gradually over time, either because the vascular compromise worsens or because adaptive mechanisms to offset hemodynamic effects become overwhelmed. Because advances in medical therapy have allowed more effective antihypertensive drug treatment than ever before, more patients are appearing clinically at later stages in their disorder with a manifest loss of kidney function and/or circulatory disorders.[5] It may be argued that such patients face more severe consequences of renovascular compromise and may have less of a likelihood of benefit from restoring the renal circulation. Hence, it behooves nephrologists to recognize the importance of a close follow-up of vascular disease in the kidney, as with many other vascular conditions. Before moving forward with renal revascularization, both affected patients and physicians should consider carefully the potential benefits and risks. Understanding the pathophysiologic basis for the clinical syndromes associated with renal artery stenosis is an important first step in this process. This chapter will review the background and basis for much of the clinical information related to these disorders.

The basic clinical syndromes to be discussed are outlined in Figure 42.1. Many renal artery stenoses produce little hemodynamic effect and represent "incidental" disease. Such lesions sometimes may be found in asymptomatic, normotensive individuals. Because many renal arterial lesions are detected in patients with preexisting hypertension, the role of renovascular disease itself may be obscured. Renovascular hypertension denotes the syndrome of rising arterial pressures specifically caused by impaired renal perfusion that leads to the activation of pressure pathways. When the severity and duration of reduced blood flow threatens the viability of kidney tissue, many authors

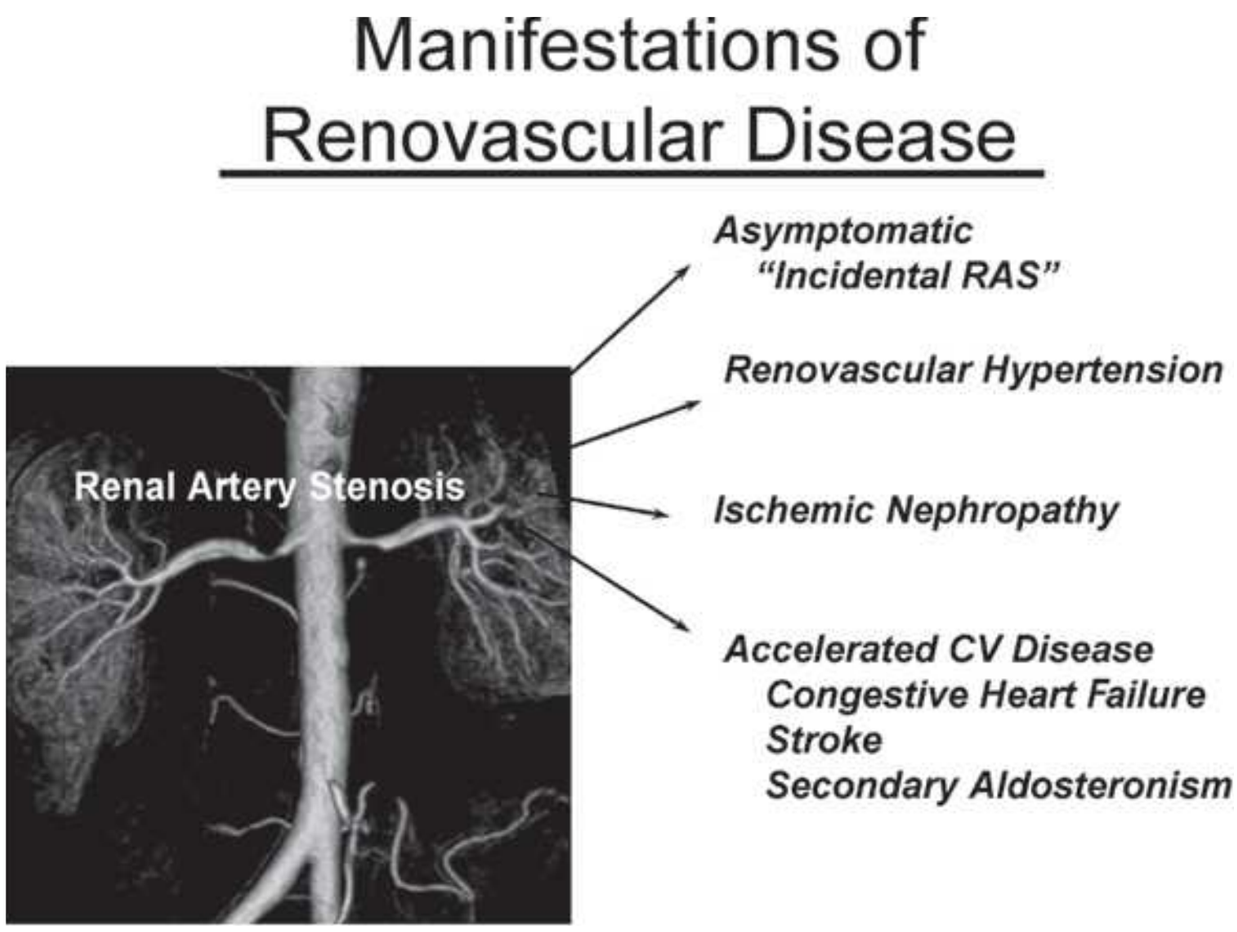


FIGURE 42.1 Clinical manifestations of renal artery stenosis range across a broad spectrum. Many, perhaps most, represent incidental lesions with minimal hemodynamic effects. Some reach levels wherein the activation of pressor mechanisms produces a rise in blood pressure, identified as renovascular hypertension, and at some point, threaten kidney function sufficiently to warrant the term ischemic nephropathy (see text). Particularly when the entire renal mass is affected, impaired kidney function and solute excretion from renovascular disease can accelerate cardiovascular morbidity, sometimes identified as one of the cardiorenal syndromes, with worsening congestive heart failure. The task facing the clinician is to identify where along this spectrum an individual patient lies. *CV,* cardiovascular; *RAS,* renal artery stenosis.

have designated this condition as ischemic nephropathy, which some believe is a major cause for some patients reaching end-stage renal disease (ESRD).[6,7] More recently, attention has been focused on the role of renovascular disease in impairing cardiac function, both by reducing the systemic excretion of sodium and volume and by producing abrupt rises in arterial afterload that magnify cardiac dysfunction. The primary task of the clinician is to elucidate the role of renal arterial stenosis in a given patient and to direct therapy accordingly.

HISTORICAL PERSPECTIVE

Observations in the 1800s regarding blood pressure measurements revealed important connections between fluid volume, arterial pressure, and vascular resistance. How these observations ultimately led to the elucidation of the renin-angiotensin-aldosterone system has been reviewed.[8] In 1898, Tigerstedt and Bergman established that extracts of the kidney had pressor effects in the whole animal, and these authors are credited with the identification of renin. The identification of each component of the renin-angiotensin system represents a remarkable series of research ventures spanning a half century and several investigators in many countries. Goldblatt and others provided seminal experiments with the development of an animal model in which reduced renal perfusion produced hypertension, published between 1932 and 1934. Numerous investigators thereafter identified the peptide nature of angiotensin, the role of renin substrate or angiotensinogen, the role of nephrectomy in sensitizing the animal to the pressor effects of angiotensin, and the sequential phases of renovascular hypertension. Hence, the renin-angiotensin system owes its initial discovery and nomenclature primarily to early studies related to the regulation of blood pressure by the kidney. Only recently have the multiple additional effects of angiotensin become evident regarding vascular remodeling, the modulation of inflammatory pathways, and interactions with fibrogenic mechanisms. Understanding that reduced renal blood flow produces sustained elevations in arterial pressure led to a broad study of the mechanisms underlying many forms of hypertension. Experimental models of two-kidney and one-kidney renal clips (two-kidney and one-kidney Goldblatt hypertension) represent some of the most extensively studies models of blood pressure and cardiovascular regulation.

Extension of these studies into clinical medicine followed soon thereafter. A time line highlighting these developments is illustrated in Figure 42.2.[9] Some patients presented with malignant forms of hypertension during the late 1930s and 1940s, so designated due to remarkably poor survival if the patient's blood pressure could not be lowered successfully. Few antihypertensive agents were known until the 1950s, and intervention consisted mainly of extremely low sodium intake diets and/or lumbar sympathectomy.

Recognition that some forms of severe hypertension were secondary to occlusive renovascular disease led surgeons to undertake unilateral nephrectomies for small kidneys in 1937.[10] The fact that some of these were indeed pressor kidneys and blood pressure fell to normal levels provided proof of concept and led to more widespread use of nephrectomies. Unfortunately, achieving a cure of hypertension after the nephrectomy was rare, and Homer Smith reviewed the poor results overall in a 1956 paper discouraging this practice.[10]

The 1960s marked the introduction of methods of vascular surgery to restore renal blood flow. These procedures carried substantial morbidity associated with aortic surgery, but offered an opportunity to improve the renal circulation and to potentially reverse renovascular hypertension. One result of this development was a series of studies aiming to characterize the functional role of each vascular lesion in producing hypertension, thereby allowing a prediction of the outcomes of vascular surgery.[10] A large, cooperative study of renovascular hypertension[81] included major vascular centers and reported on the results of more than 500 surgical procedures. These results provided limited support for vascular repair,

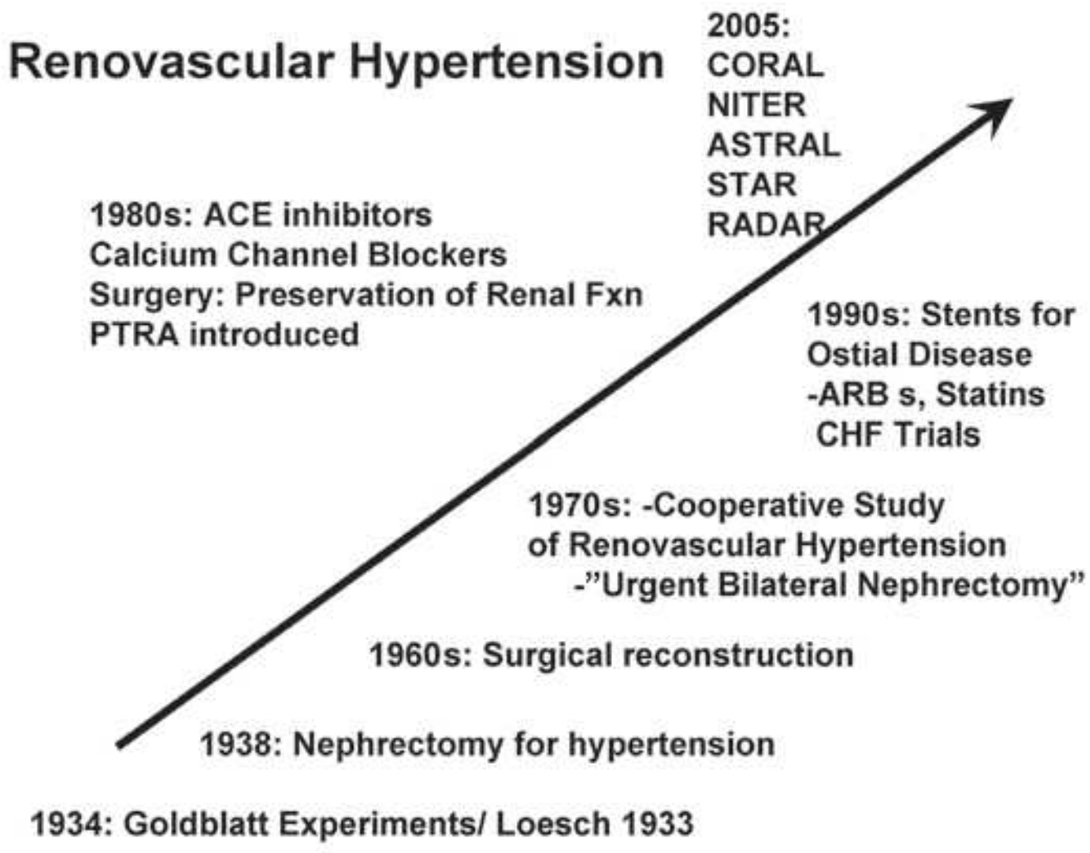


FIGURE 42.2 A time line with major events in the understanding of renovascular hypertension. Goldblatt and Loesch are identified as the original investigators in the 1930s who linked reduced kidney perfusion to the development of sustained hypertension. Surgical revascularization only became technically feasible in the 1960s, with the emergence of effective medical therapy and endovascular procedures in the 1980s and 1990s. The application of effective medical therapy, including statins, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-receptor blockers (ARBs), have led to clinical equipoise that is the basis for prospective, randomized trials comparing optimal medical treatments with or without revascularization, beginning around 2005. *PTRA*, percutaneous transluminal renal angioplasty; *CORAL*, cardiovascular outcomes for renal atherosclerotic lesions; *NITER*, nephrotherapy ischemic therapy; *ASTRAL*, angioplasty and stent for renal artery lesions; *STAR*, stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function; *RADAR*, randomized, multicenter, prospective study comparing best medical treatment versus best medical trearment plus stenting in patients with hemodynamically relevant atherosclerotic renal artery stenosis; *CHF*, congestive heart failure.

but identified relatively high associated morbidities and mortalities, particularly in patients with atherosclerotic disease.

In the 1980s and 1990s, further developments led to both improved medications and the introduction of endovascular procedures, including percutaneous angioplasty and stents. These both broadened the options for treating patients with vascular disease and raised new issues regarding timing and overall goals of intervention. Recent developments highlighted the need for intensive cardiovascular risk factor reduction and more stringent standards of blood pressure control. Antihypertensive medications have improved dramatically, both with regard to efficacy and tolerability. As emphasized in the following, the broad application of angiotensin-converting enzyme inhibitors and angiotensin-receptor antagonists for reasons other than hypertension alone changed the clinical presentation of disorders associated with renal artery stenosis.

Uncontrollable hypertension is now less commonly the reason to intervene in renovascular disease. Often, the main objective is the long-term preservation of renal function. In recent years, endovascular techniques make possible renal revascularization with relatively low morbidity in many patients previously considered unacceptable surgical candidates. The challenge for clinicians is how and when to apply these tools most effectively in the management of individual patients.[11]

DEFINITIONS AND CLASSIFICATION

The syndrome of renovascular hypertension (RVH) refers to hypertension primarily mediated by the reduction of renal artery perfusion pressure. The prevalence of renovascular hypertension is not known with precision, but available data suggest that it occurs in 0.5% to 5.0% of the general hypertensive population.[12] RVH can develop with a variety of arterial lesions, including arterial dissection, extrinsic compression, embolic infarction, or thrombosis (Table 42.1).

42.1 Lesions Producing Renovascular Hypertension and Ischemic Nephropathy

Causes of Renal Artery Stenosis
Atherosclerotic renal artery disease
Fibromuscular dysplasias
Medial fibroplasia
Perimedial fibroplasia
Intimal fibroplasia
Medial hyperplasia
Endovascular aortic stent graft crossing the renal artery
Acute arterial embolism/thrombosis (e.g., antiphospholipid syndrome)
Arterial trauma
Aortic dissection
Neurofibromatosis
Arterial aneurysm
Arteriovenous malformation/fistulae
Cholesterol emboli
Systemic necrotizing vasculitis
Polyarteritis nodosa

Atherosclerotic renal artery disease is the most common cause of renal artery stenosis, accounting for about 80% of renal arterial lesions. Fibrous renal artery diseases, as a group, account for less than 20% of renal arterial lesions. Reports of resistant hypertension suggest that when renovascular disease is a factor, more than 84% is atherosclerotic renal artery disease and 16% is fibromuscular renal artery disease.[13] Fibrous renal artery disease has been reported in 2% to 6% of potential renal transplant donors (usually normotensive individuals).[14,15] The vast majority of incidental renal artery lesions in angiographic series are atherosclerotic.

In addition to atherosclerotic and fibrous renal artery disease, a number of less common clinical entities can produce renovascular hypertension. These include acute arterial thrombosis or embolism, cholesterol emboli, aortic dissection, renal arterial trauma, arterial aneurysm, arteriovenous malformation of the renal artery, neurofibromatosis, polyarteritis nodosa, and Takayasu arteritis. Recent expansion of the use of endovascular aortic stent grafts, sometimes with structural impingement of the main renal arteries, is a new addition to the list of iatrogenic causes of renovascular hypertension.[4,16,17] Renal artery thrombosis occurring as a complication of umbilical artery catheterization has been recognized as causing renovascular hypertension in infants.[18] Transplant renal artery atherosclerosis, intimal hyperplasia, or vascular kinking may contribute to renal transplant renovascular hypertension (see Chapter 82).

Table 42.2 presents a classification of atherosclerotic and fibrous renal artery diseases with a description of their morphology and histology. These types of renal artery occlusive diseases represent a heterogeneous group of diseases, occurring in different age groups and behaving differently with regard to their individual natural history. An appreciation of these differences may be important for therapeutic decision making in patients with renal artery occlusive disease.

Fibromuscular Dysplasias

Fibromuscular dysplasia (FMD) lesions produce distortions of the luminal diameter of large- and medium-sized arteries due to nonatherosclerotic arteriopathies. The lesions usually involve the mid to distal vessel beyond the first 1 to 2 cm from the aorta (Fig. 42.3). The prevalence of clinically apparent renovascular FMD is estimated at 4 out of 1,000, with lower prevalence of cerebrovascular involvement (1 out of 1,000). Observations from screening angiographies in normotensive potential kidney donors indicate that some degree of FMDs can be observed in 3% to 6% of otherwise healthy, normotensive individuals.[15] Clinically apparent FMDs are most common among young females between the ages of 15 and 50 years. It may be familial in 10% of cases and tends to involve both renal arteries. It has been associated with subclinical carotid fibromuscular disease in first-degree relatives, which, in some cases, is consistent with an autosomal dominant inheritance. Renal arteries are involved with FMDs in 65% to 70% of cases, whereas 25% to 30% involve cerebral vessels. Both sites are involved in approximately 15% of patients. FMDs may develop in association with hereditary disorders of the connective tissue, such as Ehlers-Danlos and Marfan syndromes.

The lesions of FMD develop as disruptions of vascular wall components with abnormal deposition of collagen

42.2 Histologic Classifications of Fibromuscular Dysplasia and Angiographic Appearance

Type	Frequency	Histology	Angiographic Appearance
Medial		Alternating ridges of collagen/ loss of elastic membrane	String of beads Medial: bead diameter is larger than lumen diameter Perimedial: bead diameter is smaller than lumen diameter Medial hyperplasia: smooth stenosis without beads
Medial fibroplasia	85%–100% most common		
Perimedial fibroplasia	Rarer (10%–15%)	True smooth muscle hyperplasia: no fibrosis	
Medial hyperplasia	Rarest		
Intimal	<10%	Circumferential deposition of collagen in intima: fragmented or duplicated internal elastic lamina	Concentric smooth stenosis: long, smooth vessel narrowing
Adventitial	<1%	Dense collagen replaces fibrous tissue in adventitia and surrounding tissue	Smooth stenosis or diffuse attenuation of vessel lumen

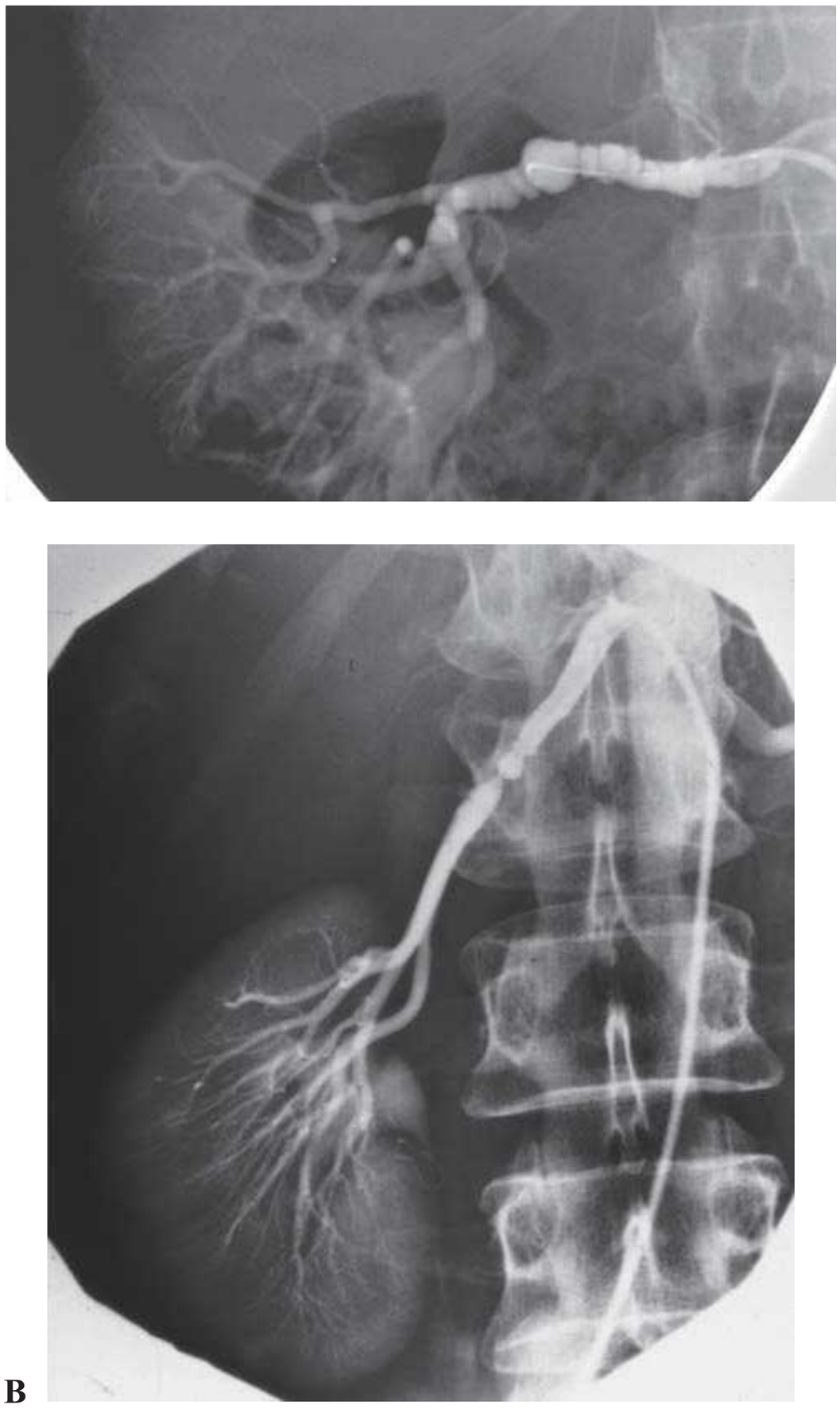


FIGURE 42.3 Examples of fibromuscular disease of the renal artery. **A:** An image of the string of beads appearance that is typical of medial fibroplasia with aneurysmal bulging beyond the artery. **B:** An image of a tight, focal lesion that is typical of intimal hyperplasia in a young male.

in bands, sometimes with disruption of the vascular elastic membrane. The molecular basis for these disruptions is unknown, although several candidate genes have been proposed. The primary subtypes of FMDs are designated as medial fibroplasia, intimal fibroplasia, and periadventitial fibroplasia, defined initially on the basis of histologic analysis of surgically resected vessels. Medial fibroplasia is the most common phenotype, and often manifests as a string-of-beads appearance with alternating stenoses with apparent luminal dilations, as summarized in Table 42.2. The other phenotypes appear as focal or elongated vascular occlusions. Medial fibroplasia affects the distal half of the main renal artery, frequently extends into the major branches, is often bilateral, and angiographically gives the appearance of multiple aneurysms wherein the diameters of the aneurysms are wider than the apparently unaffected portion of the main renal artery (Fig. 42.3A). Most cases of medial fibroplasia are diagnosed in women between the ages of 30 and 50 years. Although medial fibroplasia progresses to higher degrees of stenosis in about one-third of patients, complete arterial occlusion and/or ischemic atrophy of the kidney ipsilateral to the renal artery stenosis are rare. The stenotic lesions in medial fibroplasia are secondary to thickened fibromuscular ridges replacing the normal structure of the intima and the media of the artery. These thickened ridges alternate with thinned areas that may not have an internal elastic membrane, thereby becoming aneurysmal.

Perimedial fibroplasia (subadventitial fibroplasia) accounts for approximately 15% of fibrous renal artery lesions. This lesion also occurs predominantly in women, typically between the ages of 15 and 30 years. Angiographically, it is often characterized by a small string-of-beads appearance, with the beads being of similar or of smaller diameter compared to the diameter of the apparently unaffected portion of the renal artery. This lesion typically affects the distal half of the main renal artery, is frequently bilateral and highly stenotic, and may progress to total arterial occlusion. Collateral blood vessels and renal atrophy on the involved side are commonly observed.[19,20]

Medial hyperplasia and intimal fibroplasia account for only 5% to 10% of fibrous renal artery lesions. Intimal fibroplasia occurs primarily in children and teenagers and angiographically appears as a localized, highly stenotic, and smooth lesion with poststenotic dilation. It may occur in the proximal portion of the renal artery and when it does, it can resemble atheroma. Intimal fibroplasia is progressive and is occasionally associated with dissection or renal infarction and renal atrophy (Fig. 42.4C). Medial hyperplasia, also rare, is found predominantly in teenagers, and angiographically also appears as a smooth, linear stenosis, sometimes appearing as though a ligature were tied around the renal artery. There is considerable difficulty in distinguishing between intimal fibroplasia and medial hyperplasia by angiography alone, and these two types of fibrous artery disease are sometimes grouped together in the literature.[21]

Renal artery aneurysms can develop in up to 50% of these lesions, which sometimes produce local dissection and/or occlusion (Fig. 42.4C). Arteriovenous fistulae and thrombosis can also occur.

Rates of progression differ between histologic subtypes and are poorly understood. Many lesions remain below hemodynamic thresholds and have minimal clinical importance. Others progress to produce hypertension and occasional thrombosis, particularly in women, although this happens far more commonly with atherosclerotic lesions. Smoking appears to be the major risk factor for progressive disease in young women.

Takayasu arteritis is a variant form of systemic vasculitis that affects large arteries such as the aorta and its main branches, including the renal arteries. It mainly affects young women. It can cause discrete stenosis of the aorta

FIGURE 42.4 **(A)** and **(B)** Illustrate the ability of percutaneous transluminal renal angioplasty (PTRA) to open otherwise tight fibrous bands and successfully reverse renovascular hypertension in a young athlete. **C:** Fibromuscular disease complicated by a renal artery aneurysm that produced a segmental infarction and renovascular hypertension not amenable to renal revascularization.

and its main branches, including the common carotid, and the subclavian and the renal arteries.[22] Renal artery involvement is not uncommon in Asian and African patients and is a major cause of renovascular hypertension in these countries.[23] Koide[24] reported renovascular hypertension in 278 (18.8%) of 1,475 patients in a Japanese nationwide survey of Takayasu arteritis. Takayasu arteritis is a common cause of renovascular hypertension in Southeast Asia, including India and China, and accounts for between 20% and 60% of RVH cases.[23,25]

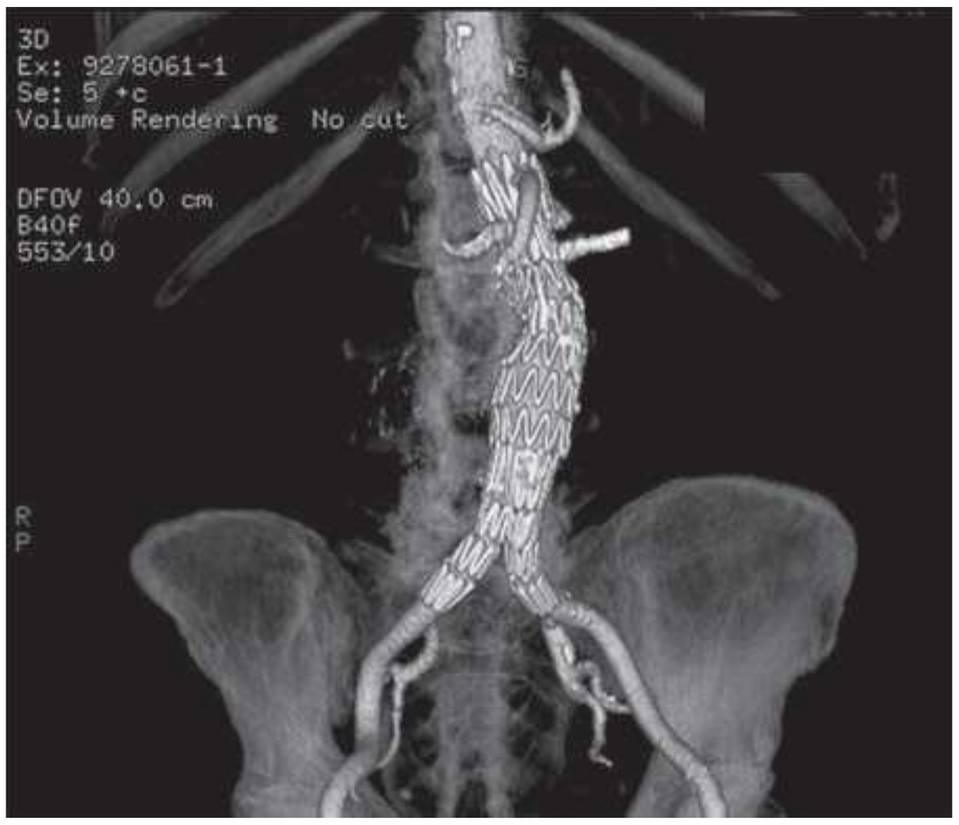
A recent expansion in the use of endovascular procedures for aortic aneurysm repair (EVAR) has produced a new clinical source of renal artery occlusion (Fig. 42.5A). Many of these stent grafts are placed in close proximity to the origins of the renal arteries. Occlusion of the renal arteries is observed in up to 6% of these procedures, sometimes related to migration or inadvertent coverage of the vessels.[4,26] Some grafts are designed for deliberate extension of uncovered struts above the renal arteries for anatomic reasons. Remarkably, the frequency of renal artery compromise is modest, and current endovascular procedures can restore luminal patency if promptly recognized.[27] Identifying and treating vascular occlusion due to aortic stent grafts is important, because failure to achieve patency is associated with a clinically important loss of kidney function in up to 20% of subjects.[28]

Acute and chronic renal artery occlusion secondary to renal artery emboli, aortic or renal artery dissection, neurofibromatosis, arterial trauma, arteriovenous malformations, and polyarteritis nodosa are discussed elsewhere in this book.

Atherosclerotic Renal Artery Stenosis

Atherosclerotic renal artery stenosis (ARAS) most often develops in older patients (> 50 years of age) and is associated with systemic atherosclerosis. ARAS is the most common

FIGURE 42.5 Examples of atherosclerotic renal artery stenosis. **A:** An aortic aneurysm repair using an endovascular stent graft with an extension to cover portions of the renal arteries, which represents a new form of treatment-associated renovascular compromise. (See Color Plate.) **B:** High-grade bilateral renal arterial stenoses from ostial lesions and **(C)** a total renal occlusion to the right kidney and high-grade stenosis to a solitary functioning kidney. Such lesions are becoming more common because effective antihypertensive drug therapy may be delaying the identification of ARAS until later stages with deteriorating kidney function and blood pressure control.



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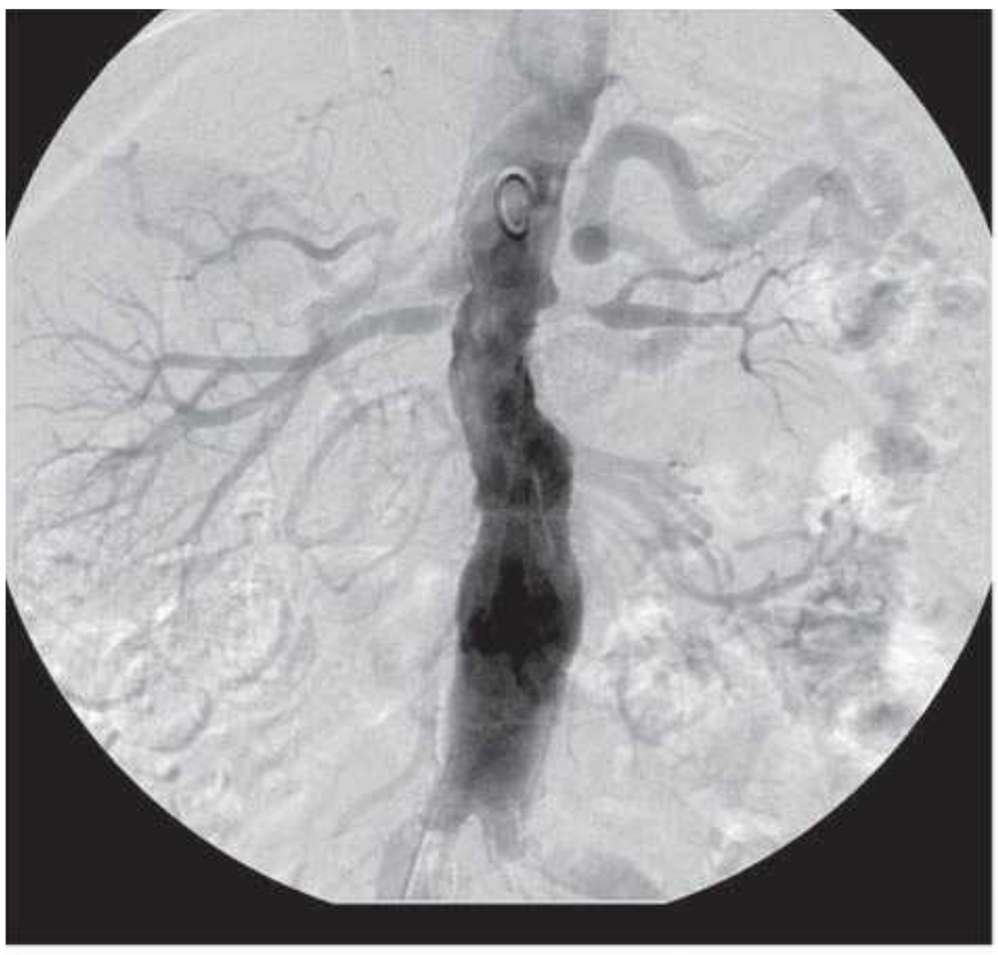

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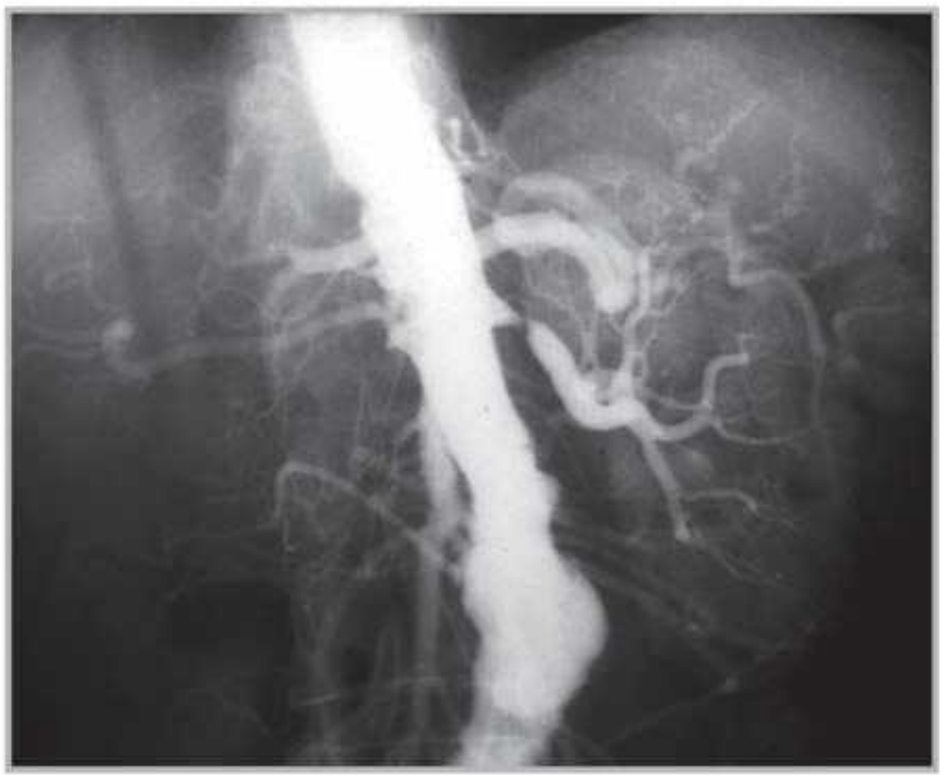


C

cause of RVH and can contribute to a loss of renal function leading to ESRD (Fig. 42.5B,C). Atherosclerotic plaque often arises in the first 1 to 2 cm of the renal artery or may extend directly from the aorta into the renal ostium. Aortic and renal vascular calcification is often present. Some 75% to 80% of patients with renal artery atherosclerosis and renovascular hypertension have ostial atherosclerotic lesions, and 25% to 30% of lesions are in the nonostial location. ARAS is a manifestation of systemic atherosclerotic disease and is associated with coronary, cerebrovascular, peripheral vascular, and aortic disease.[29,30] The prevalence of ARAS appears to be increasing. This probably reflects the fact that more people are living long enough for atherosclerotic vascular disease in the visceral abdominal vessels to reach critical levels, thus aggravating hypertension when the kidney is affected. In a recent systematic analysis of patients undergoing an angiography of the peripheral or coronary circulations, ARAS was found in 11% to 42% of cases.[30] Predictors of ARAS include a history of hypertension, the presence of renal functional impairment, coexisting vascular or coronary artery disease, the presence of abdominal bruits, and a history of smoking. Renal artery lesions are bilateral in 20% to 40% of such patients. Estimates of the prevalence of ARAS depend on the population screened. One population-based study of a cohort of 870 patients older than 65 years screened with renal artery duplex sonography found a 6.8% prevalence of ARAS, defined as greater than 60% stenosis. No differences in prevalence were detected between African Americans and Caucasians,[31] although reported rates for surgically corrected renovascular hypertension are lower for African Americans.[32] Men are affected more often than women, but this gender difference declines with advancing age. Recent series indicate a distinct shift toward women in series referred for revascularization.[33,34] Several studies suggest that atherosclerotic renal vascular disease is associated with adverse coronary events[33,35] and increased mortality. Autopsy series report an overall prevalence of 4% to 20%, with progressively higher rates for those older than 60 years (25% to 30%) and 75 years (40% to 60%). These studies suggest that ARAS leading to renal artery stenosis is the single most common cause of secondary hypertension in patients older than 50 years.[36] It also commonly leads to systolic hypertension with wide pulse pressures. Furthermore, renal artery stenosis has been reported to contribute

to the decline in renal function in 15% to 22% of patients reaching ESRD.[37,38]

Adaptation and Progressive Vascular Occlusion in Atherosclerotic Renal Artery Stenosis

With improved antihypertensive drug therapy and the recognized potential for advanced ARAS to lead to reduced kidney function, clinicians need to consider the potential for progressive renovascular occlusion during medical therapy. This has been a controversial subject. Initial retrospective studies of serial angiograms suggested that progressive occlusion could develop in 40% to 50% of subjects[37] with 15% progressing to total occlusion over periods between 3 to 5 years.[39] A series of studies in the 1990s with ARAS followed prospectively with high-resolution Doppler ultrasound indicated that measurable hemodynamic progression occurred in nearly 50% of subjects over 5 years,[40] although the rates of clinical progression defined by changes in kidney size (24%), loss of GFR, and/or progression to total occlusion were much lower.[41] The 3-year cumulative incidence of renal artery disease progression for 295 renal arteries initially classified as normal, less than 60% stenosis, and greater than or equal to 60% stenosis, was 18%, 28%, and 49%, respectively. In this prospective series, the early progression to total occlusion occurred only in nine arteries (3%), all of which had a baseline reduction in lumen diameter greater than 60% (Fig. 42.6). The cumulative incidence of progression to total occlusion in patients with baseline stenosis of 60% or more was 4% at 1 year, 4% at 2 years, and 7% at 3 years. Factors associated with the risk of renal artery disease progression during the time of monitoring included systolic blood pressure (BP) greater than or equal to 160 mm Hg, diabetes mellitus, and high-grade stenosis (more than 60%) in either the ipsilateral or contralateral renal artery.[37] One of the prospective treatment trials from Europe suggested that 16% of subjects treated without revascularization developed total occlusion, based on renography.[39] Recent prospective treatment trials indicate far lower rates of disease progression. BP control and statin therapy in these trials have been more effective and more widely applied than before, with crossover rates from medical therapy to renal revascularization below 10% over reporting periods between 3 and 5 years.[42] It should be emphasized that the epidemiologic and clinical hazard of progressive stenotic disease is closely related to the level of initial stenosis. For lesions that are more than 75% occluded, further progression is not only far more likely to occur, but the consequence regarding tissue ischemia and loss of functioning tissue is more severe (see Pathophysiology, which follows).

PATHOPHYSIOLOGY OF CLINICAL SYNDROMES WITH RENOVASCULAR DISEASE

Renovascular Hypertension

Renovascular occlusive disease from any cause that reaches a "critical" level can activate pressor mechanisms that tend to raise systemic arterial pressure and restore renal artery

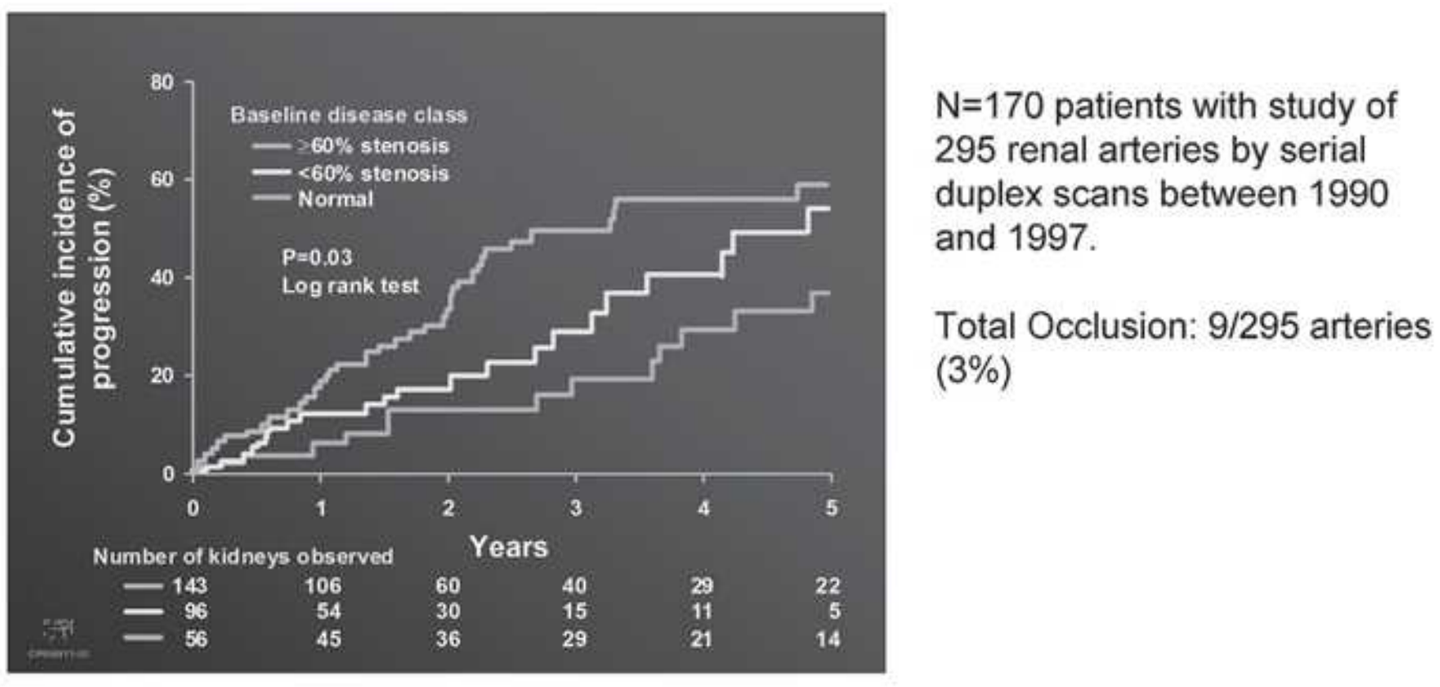


FIGURE 42.6 The progression of atherosclerotic renal artery stenosis (ARAS) of varying severity during a serial follow-up by Doppler ultrasound. There were 295 arteries that were followed sequentially at 6-month intervals for 5 years. Measurable hemodynamic progression (defined as an increase in peak systolic velocity of at least 100 cm per second) was identified in 31% by 3 years, and more than 50% of the group with more than 60% at baseline. Importantly, clinical progression was uncommon (defined by a change in serum creatinine, loss of kidney size, or total occlusion). Predictors of progression included systolic blood pressure, age, and diabetes. (Adapted from Caps MT, Perissinotto C, Zierler RE, et al. Prospective study of atherosclerotic disease progression in the renal artery. *Circulation*. 1998;98:2866–2872.) (See Color Plate.)

perfusion pressures. Luminal occlusion of less than 60% (cross-sectional area) rarely produces any measurable gradient for either pressure or flow. Hence, a fall in renal perfusion pressure sufficient to initiate RVH occurs only when luminal occlusion is relatively severe, usually in the 70% to 80% cross-sectional occlusion range (Fig. 42.7). When critical stenosis develops and reduces renal perfusion pressure, multiple mechanisms are activated in the kidney to restore renal blood flow. Foremost among these pathways is the release of renin from the juxtaglomerular apparatus, leading to the activation of the renin-angiotensin-aldosterone system (RAAS). Release of plasma renin occurs only after poststenotic pressures fall by at least 10% to 20% compared with aortic pressures.[43] This is mediated in part by the stimulation of neuronal nitric oxide synthase and cyclooxygenase 2 in the macula densa. Blockade of the RAAS at the time an experimental renal artery lesion is created prevents the development of hypertension. Animals genetically modified to lack the angiotensin (Ang 1) receptor fail to develop two-kidney one-clip hypertension.[44] Experiments using kidney transplantation from AT1 receptor knockout mice indicate that both systemic and renal angiotensin receptors participate in additive fashion to blood pressure regulation.[45]

In the presence of an intact RAAS, systemic arterial pressures increase until renal perfusion is restored. Studies in both experimental models and humans indicate that additional mechanisms add to long-term elevation of blood pressure in the presence of renal artery stenosis, including activation of the sympathetic nervous system, impairment of nitric oxide generation, and release of endothelin as well as hypertensive microvascular injury to the nonstenotic kidney.

Although there are differences among species (rat, dog, rabbit) in experimental renovascular hypertension, two basic models of Goldblatt hypertension are recognized: the two-kidney, one-clip (2K-1C) model (in which one renal artery is constricted and the contralateral renal artery and kidney are left intact) and the one-kidney, one-clip (1K-1C) model (in which one renal artery is constricted and the contralateral kidney is removed). These two experimental models of renovascular hypertension are diagrammed in Fig. 42.8A,B. Mechanisms responsible for sustained RVH differ according to whether one or both kidneys are affected. Both of these models depend initially on impaired renal perfusion and activation of the RAAS with sodium retention. However, the presence of a normal contralateral kidney allows pressure natriuresis to occur, by which the elevated perfusion pressure produces sodium excretion in the nonstenotic kidney. Because the nonstenotic kidney eliminates excess sodium and volume, the level of perfusion pressure to the stenotic side remains reduced, leading to the ongoing activation of the renal artery underperfusion and RAAS stimulation. This sequence of events producing angiotensin II (Ang II)–dependent hypertension and secondary aldosterone excess with hypokalemia is summarized in Fig. 42.8A.

By contrast, 1K-1C hypertension represents a model in which the entire renal mass is exposed to reduced pressures

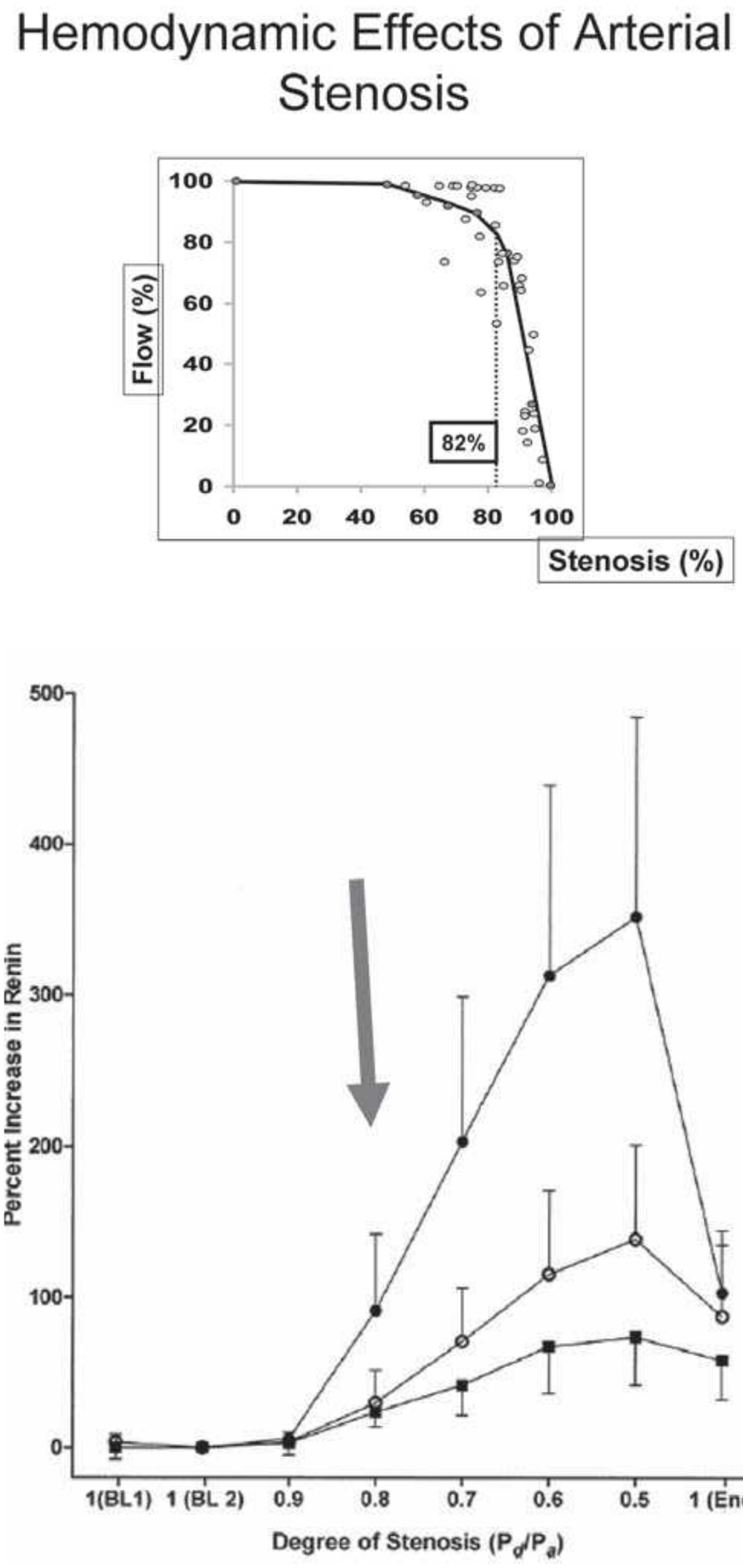


FIGURE 42.7 **A:** Arterial pressure depicted as a function of degree of luminal occlusion. These data highlight the fact that no change in postlesion pressure or flow can be identified until cross-sectional occlusion is severe, usually more than 70% to 80%. These experimental data in dogs are consistent with measurements in human subjects **(B),** wherein renal vein renin release was not detected during balloon occlusion until translesional gradients between the aorta and renal artery of at least 10% to 20% were produced. MAP, mean arterial pressure. (Data from May et al.[229] and De Bruyne et al.[43])

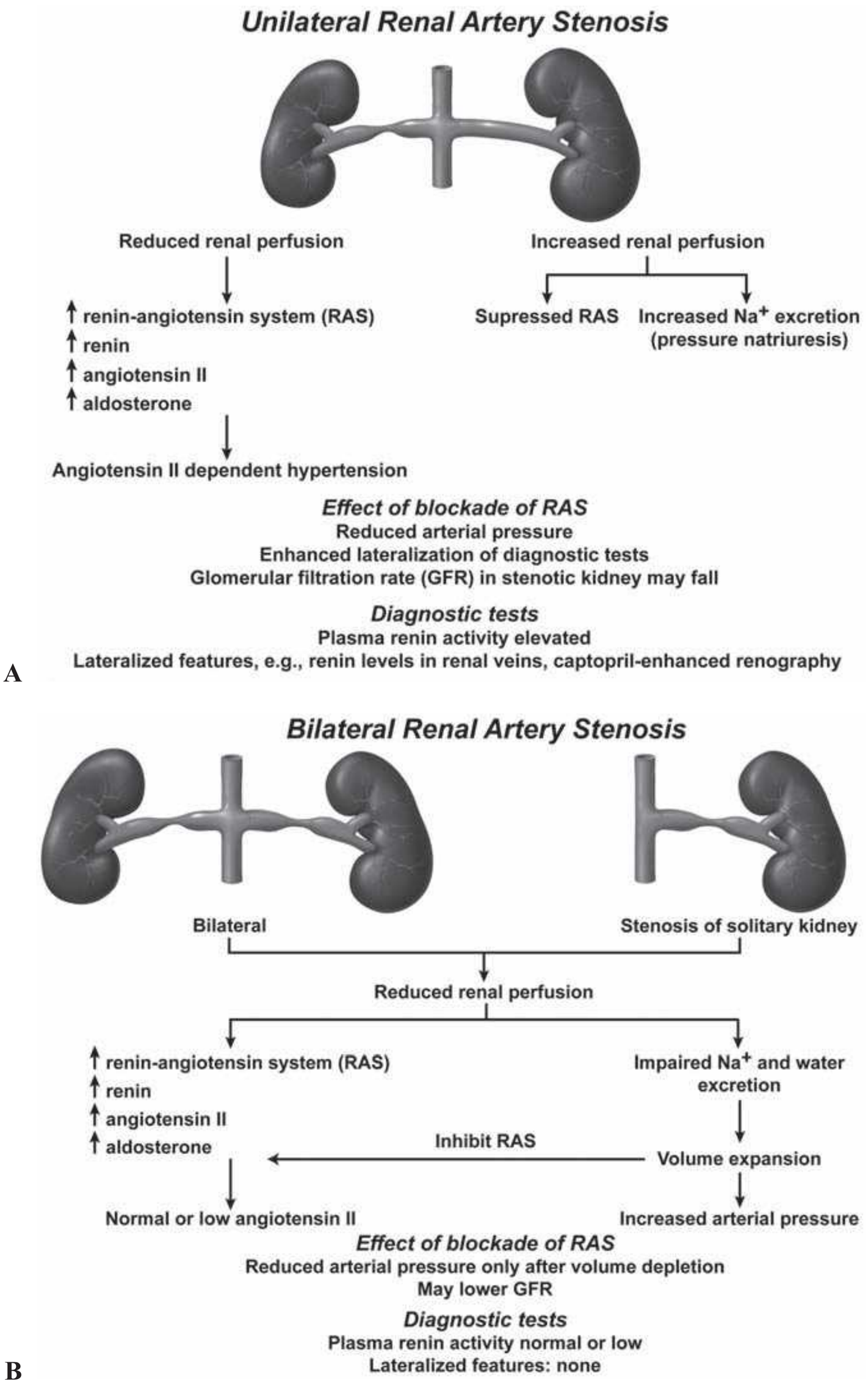


FIGURE 42.8 A: A schematic illustration of hormonal and hemodynamic effects of unilateral renal artery stenosis to produce renovascular hypertension. Unilateral disease is identified as 1-clip-2-kidney Goldblatt hypertension and manifests with the activation of the renin-angiotensin system so long as the contralateral kidney continues to undergo pressure natriuresis (see text). (Adapted from Safian and Textor[91].) Panel **(B)** illustrates the sequence of events with 1-clip-1-kidney Goldblatt hypertension, wherein no normal contralateral kidney is available to excrete sodium and volume in response to rising arterial pressures. In this model, the initial activation of the renin-angiotensin system is temporary due to volume expansion.

beyond a stenosis. There is no normal or nonstenotic kidney to counteract increased systemic pressures. As a result, sodium is retained and the blood volume is expanded, which eventually feeds back to inhibit the renin-angiotensin system (RAS) (Fig. 42.8B). Therefore, 1K-1C hypertension is typically not angiotensin dependent unless the removal of volume is achieved that reduces renal perfusion pressure and again activates the RAAS.

Most renovascular disease in humans is asymmetric and is thought most often to resemble 2K-1C renovascular models. The mechanistic differences between these forms of RVH have clinical implications regarding diagnosis and treatment. Many diagnostic studies classically used to evaluate the functional significance of renal artery lesions depend on comparisons of the different physiologic response of the two kidneys, which may not be evident if both kidneys are affected or if only one kid ney is present. Furthermore, diagnostic tests that depend on differences in responses to alterations in sodium status (such as the measurement of renal vein renin levels after sodium depletion or individual

kidney sodium reabsorption) may be problematic, because high levels of Ang II and aldosterone stimulate sodium reabsorption in both the stenotic and nonstenotic kidney.

The Phases of Renovascular Hypertension

Many of the primary physiologic drivers, such as activation of the RAAS, underlying renovascular hypertension manifest differently at various points in time. These changing manifestations complicate defining primary pathogenic mechanisms and establishing whether renovascular lesions are actually causal in hypertension. Rarely is it known exactly when critical levels of stenosis are attained. In experimental models, these observations have been summarized by separating two-kidney renovascular hypertension into sequential phases.[46] In phase 1, renal ischemia and activation of the RAS are central and the BP elevation is renin dependent. The acute administration of Ang II antagonists or angiotensin-converting enzyme (ACE) inhibitors, removal of the renal artery stenosis (i.e., removal of the clip), or removal of the stenotic kidney normalizes the BP. In the absence of these maneuvers, a transition phase (phase 2) subsequently develops, bridging the acute (phase 1) and chronic (phase 3) phases of experimental renovascular hypertension. This transition phase variably lasts from a few days to several weeks depending on the experimental model and animal species. During this transition phase, plasma renin levels gradually fall, but the BP remains elevated. Salt and water retention are observed as a consequence of the effects of hypoperfusion of the stenotic kidney, augmented proximal renal tubular reabsorption of sodium and water, and secondary aldosteronism.[47,48] In addition, the high levels of Ang II stimulate thirst, further contributing to an expansion of the extracellular fluid volume. The expanded extracellular fluid volume results in suppression of peripheral plasma renin activity (PRA). During this transition phase, the hypertension is still responsive to removal of the unilateral renal artery stenosis, to Ang II blockade, or to unilateral nephrectomy, although these maneuvers do not normalize the BP as promptly and consistently as in the acute phase. These changes may depend on the recruitment of additional mechanisms of Ang II action, including the generation of reactive oxygen species,[49,50] the quenching of nitric oxide,[51] and the generation of endothelium-derived substances such as endothelin[52,53] and thromboxanes.[54] Some of these mechanisms depend on slowly developing effects of Ang II at levels that do not reverse rapidly with direct Ang II blockade.[55] Additional mechanisms recruited over time that sustain BP elevation and induce tissue injury are summarized in Table 42.3.

After several days or weeks, a chronic phase (phase 3) evolves, wherein the removal of the stenosis by unclipping the renal artery in the experimental animal or nephrectomy of the stenotic kidney fails to reduce the BP to baseline levels. The mechanism maintaining elevated arterial pressure—that is, the failure of "unclipping" to lower the BP in this chronic phase of 2K-1C hypertension—is multifactorial but is thought to reflect widespread arteriolar damage in the contralateral kidney consequent to elevated systemic pressure and the initial high levels of Ang II. The BP remains elevated even though the PRA has returned to a normal level. The pressure natriuresis of the contralateral kidney blunts the extracellular fluid volume expansion initially generated by the stenotic kidney (Fig. 42.8A), but because the contralateral kidney suffers vascular damage from prolonged exposure to the increased BP, its excretory function diminishes and

42.3 Interactive Mechanisms Underlying Hypertension and Kidney Injury in Atherosclerotic Renal Artery Stenosis

Tissue Underperfusion	Recurrent Local Ischemia
Activation of the renin-angiotensin system	ATP depletion
Altered endothelial function: (endothelin, NO, prostaglandins)	Tubulointerstitial injury
Sympathoadrenergic activation	Microvascular damage
■ Increased reactive oxygen species	Immune activation
■ Cytokine release/inflammation (NF-κB, TNF, TGF-β, PAI-1, IL-1)	Vascular remodeling
■ Impaired tubular transport functions	Interstitial fibrosis
Apoptosis/necrosis	Activation of the renin-angiotensin aldosterone system
	Sympatho-adrenergic activation
	Endothelin
	Disturbances of "oxidative stress" Oxidized-LDL

NO, nitric oxide; NF-κB, nuclear factor kappa B; TNF, tumor necrosis factor; TGF-β, transforming growth factor-beta; PAI-1,plasminogen activating factor inhibitor; IL-1, interleukin 1; ATP, adenosine triphospate; LDL, low-density lipoprotein. From Textor SC. Atherosclerotic renal artery stenosis: overtreated, but underrated? J Am Soc Nephrol. 2008;19:656–659, with permission.

extracellular fluid volume expansion persists. In phase 3 of 2K-1C hypertension, acute blockade of the RAS fails to lower the BP. Sodium depletion may ameliorate the hypertension, but does not normalize it.

Exactly how and whether this sequence of events applies directly to humans is not known. All of these features obscure the diagnosis of true renovascular hypertension and limit predictability of the BP response to revascularization. Not surprisingly, a documented history of a brief duration of hypertension suggests a more favorable response to revascularization procedures.[56]

There are additional important clinical correlates of this process. First, many of the diagnostic studies that depend on the lateralization of effects have only modest predictive value when results are negative. As a general rule, these tests are most useful when results are positive, meaning that high-grade lateralization of renin release, differences in renal function, and changes in the glomerular filtration rate (GFR) after the administration of an ACE inhibitor most accurately predict improvement after revascularization when results are markedly positive. A negative test result, however, may also be associated with a beneficial outcome. Second, coexistent intrarenal disease, such as arteriolosclerosis with glomerulosclerosis, is usually associated with persistent hypertension despite the correction of renal artery stenosis, particularly for patients with ARAS.[57] In such patients, a long duration of hypertension favors the development of arteriosclerotic lesions and renal injury in the contralateral kidney. Thus, older age and a long duration of hypertension for more than 3 to 5 years predict a poorer clinical BP outcome after renal revascularization. Most older patients with ARAS also have impaired renal function that itself predisposes one to long-term hypertension.[11]

The Pathogenesis of Ischemic Nephropathy

The activation of pressor mechanisms producing RVH often occurs with a minor loss of renal size or function, particularly with fibromuscular disease.[58–60] Conversely, improved BP control after revascularization sometimes may be achieved without an appreciable improvement in kidney function. However, the more common clinical scenario with ARAS involves both increasing severity of hypertension and deteriorating renal function, often with a loss of renal size. Hence, the decision to consider renal revascularization commonly combines consideration of both the likelihood of salvage or the preservation of function, in addition to possible benefits regarding BP control.

Basal energy requirements for the kidney are met with less than 10% of blood flow, consistent with its filtration function. The term ischemic renal disease should be used with caution in this context.[61] Under normal conditions, cortical blood flow provides vastly more oxygenated blood than is needed for tissue metabolism. Postglomerular vasa recta deliver a portion of kidney blood flow to the medulla. The major metabolic workload of the kidney takes place in medullary segments as a function of solute transport, leaving the medulla normally with substantial oxygen desaturation.[62] The balance between regional oxygen saturation within the cortex and the medulla is carefully maintained over a variety of conditions.[63] Remarkably, blood flow to the kidney can be reduced gradually to levels sufficient to reduce kidney volume, activate pressor mechanisms including the RAAS, and lower GFR without measurably disturbing cortical or medullary oxygenation.[64] Lowered GFR is associated with a reduced filtered load of solutes and thereby reduced requirements for solute reabsorption.[63] Venous oxygen levels from poststenotic kidneys therefore can be higher than those from normally functioning kidneys due to reduced metabolic oxygen consumption.[64] Measurements of cortical and medullary deoxyhemoglobin by use of blood oxygen level–dependent magnetic resonance in human subjects confirm that both cortical and medullary oxygen saturation can be well preserved over a wide range of renovascular occlusion.[65] These observations may explain the relative stability of kidney function observed in recent prospective treatment trials for ARAS for many years, despite an obvious reduction in renal blood flow beyond the stenotic lesion.

There are limits to the renal capacity for adaptation, however. When vascular occlusion is sufficiently severe, cortical blood flow and oxygenation falls.[66] This in turn overwhelms the adaptive capacity of the medulla, with expanding hypoxia and activation of fibrogenic and inflammatory pathways.

Mechanisms underlying parenchymal renal damage differ from those responsible for generating hypertension. Remarkably, parenchymal fibrosis rarely develops in patients with fibromuscular disease with the exception of those experiencing renal infarction. This suggests that the activation of remodeling mechanisms in the poststenotic kidney partly is related to the atherosclerotic milieu itself, which produces microvascular proliferation and abnormal endothelial function within the kidneys.[67] Recent experimental studies underscore the development of magnified renal microvascular changes distal to a stenosis in the renal artery in the context of atherosclerosis.[68,69] An example of microvascular proliferation induced by cholesterol feeding (a surrogate for early atherosclerosis) and the subsequent rarefaction of renal small vessels beyond a main renal artery lesion is illustrated in Fig. 42.9. Numerous signaling pathways lead to the upregulation of cytokines and inflammatory mediators, including transforming growth factor (TGF)-β, within the poststenotic kidney.[70,71] Over time, rarefaction of the distal arterioles develops and is associated with fibrogenesis and a loss of viable function.[72,73] The sequence of events underlying the transition from a reversible loss of function beyond a vascular lesion to irreversible tissue fibrosis is not well understood. Atherosclerotic and inflammatory pathways can produce disturbances in endothelial function in small vessels that parallel tissue injury and accelerate cytokine signaling pathways.[74,75] At some phase, microvascular rarefaction occurs that accompanies a fall in tissue oxygenation and activation of fibrogenesis.[75] An irreversible loss of viable

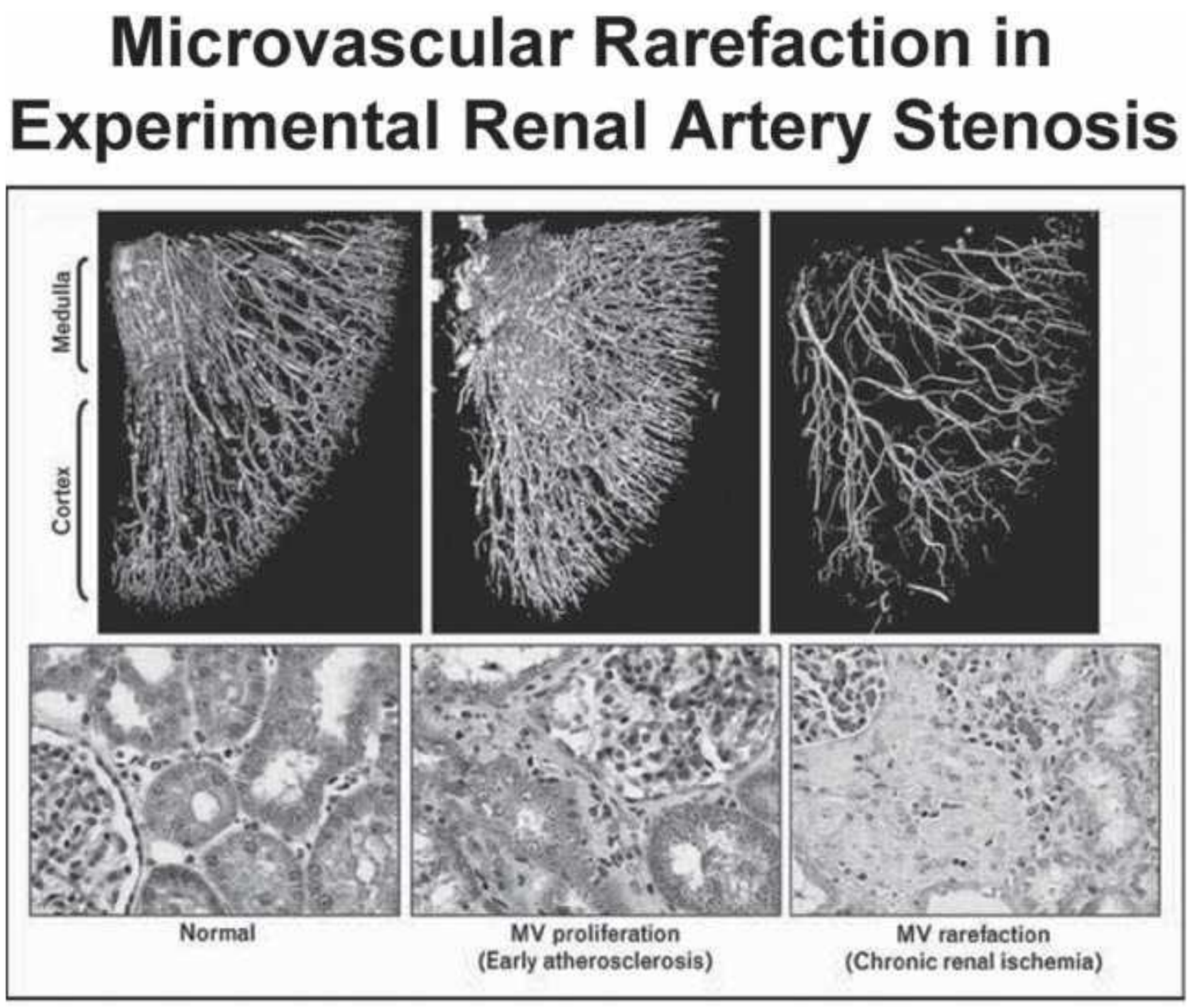


FIGURE 42.9 Reconstructions of the vascular structures using micro-computed tomography (CT) imaging in experimental renal artery stenosis. The atherosclerotic milieu produced by cholesterol feeding leads to microvascular (MV) proliferation and renders the animal especially susceptible to rarefication and obliteration of microvessels in the setting of high-grade renal artery stenosis. These changes eventually lead to interstitial fibrosis and a loss of kidney function. (From Lerman LO, Chade AR. Atherosclerotic process, renovascular disease and outcomes from bench to bedside. *Curr Opin Nephrol Hyper.* 2006;15:583–587, with permission.)

microcirculation may explain some of the limitations observed after the restoration of large-vessel patency (e.g., with renal revascularization). Occasionally, renovascular disease is associated with nephrotic range proteinuria that can regress after renal revascularization.[76] The mechanism of enhanced glomerular permeability in this context is unknown.

Circulatory Congestion and Flash Pulmonary Edema

Among other clinical manifestations, ARAS increasingly has been implicated in episodes of congestive heart failure and has been described as one of the cardiorenal syndromes.[47] Several mechanisms contribute to this disturbance, including (1) Impaired sodium excretion due to reduced renal perfusion pressure and activation of the RAAS that affects both stenotic and contralateral kidneys and (2) sustained, and sometimes rapid, increases in systolic arterial pressure can abruptly add to pressure overload of the left ventricle (Fig. 42.10).[77] Normally, the left ventricle compensates for changes in afterload with increased end-diastolic volume. This mechanism may be impaired, however, in patients with stiffened left ventricles due to left ventricular hypertrophy, precipitating in abrupt rises in end-diastolic pressure, left atrial, and pulmonary venous pressures. It is this abrupt rise in ventricular pressures that leads to sudden decompensation, often termed flash pulmonary edema, that was originally described by Pickering et al.[78] In addition, the activation of sympathetic nervous pathways magnifies these effects and alters the transcapillary capacities for gas exchange. Reports from several case series suggest that renal revascularization can interrupt this cycle and reduce reoccurrences.[79,80] In less dramatic cases, the presence of bilateral ARAS with reduced GFR may limit the effectiveness of diuretics and render congestive heart failure refractory to fluid removal short of external ultrafiltration.

Clinical Features of Renal Artery Stenosis

Renovascular Hypertension

In the 1970s, a cooperative study of RVH compared clinical characteristics of patients with surgically proven RVH with those of patients with primary hypertension. In this study, the average age of onset for fibrous renal artery disease as the cause of renovascular hypertension was 33 years, and 16% of these patients were younger than 20 years. For atherosclerotic renal artery disease as the cause of renovascular hypertension, the average age at onset was 46 years, and 39% of these patients were older than 50 years.[81] For these reasons, many argue that the clearly defined onset of hypertension below the age of 30 or above the age of 55 warrants the consideration of renovascular hypertension. Some features, such as the presence of an abdominal bruit, hypokalemia, and the absence of a family history of hypertension, were statistically more prevalent in RVH, but had little clinical predictive value. Recent studies suggest that for any level of office BP, patients with RVH may have higher nocturnal pressures and therefore higher overall pressure load as "non-dippers."[82] As a result, target organ manifestations are more severe, including left ventricular hypertrophy (Fig. 42.11). A series of patients with treatment-resistant hypertension indicate that elevated cholesterol, impaired renal function, lower body mass index (BMI), and smoking provide positive clues. In practical terms, none of these features is sufficiently sensitive or specific to offer diagnostic precision. As noted previously, RVH rarely may be associated with nephrotic-range

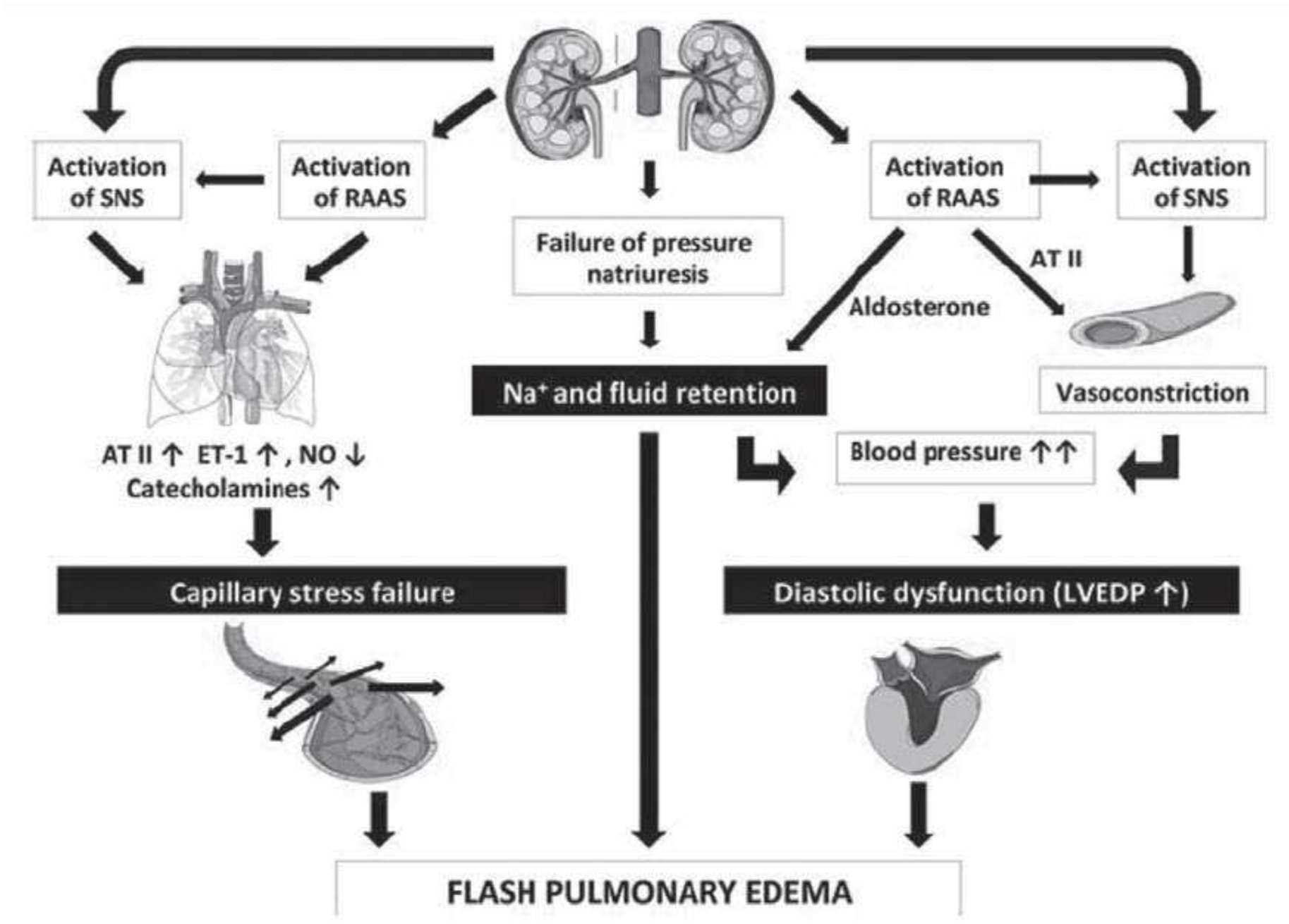


FIGURE 42.10 A schematic depicting the interplay of mechanisms leading to rapidly developing symptoms of left ventricular heart failure sometimes observed with renal artery stenosis. These include impaired volume excretion with bilateral atherosclerotic renal artery stenosis (ARAS), a rise in afterload and impaired left ventricular pump function, as well as disturbed capillary function within the pulmonary vasculature in part related to the activation of neurogenic and hormonal pathways. *SNS,* sympathetic nervous system; *RAAS*, renin-angiotensin-aldosterone system; *ATII*, angiotensin II; *ET-1*, endothelin 1; *NO*, nitric oxide; *LVEDP*, left ventricular end-diastolic pressure. (From Messerli FH, Bangalore S, Makani H, et al. Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering syndrome. *Eur Heart J.* 2011;32(18):2231–2237, with permission.)

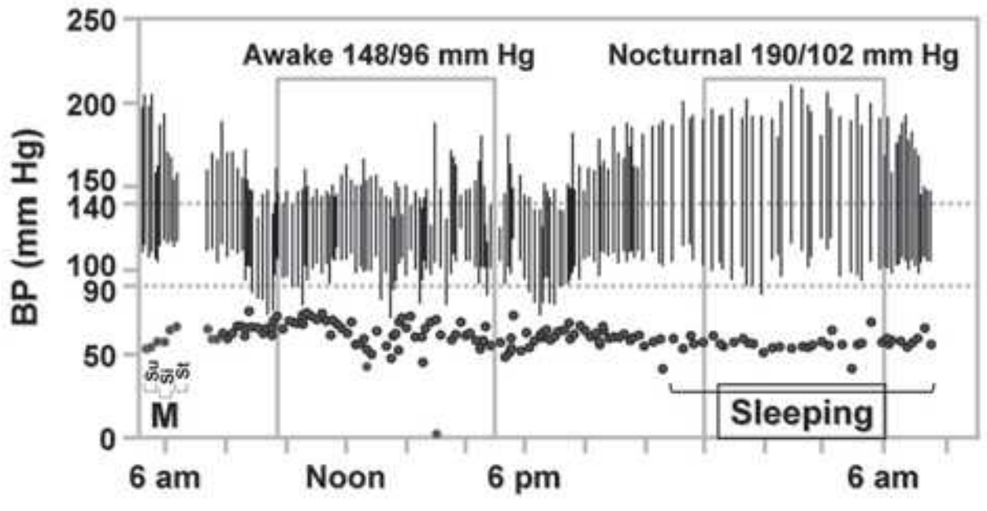


FIGURE 42.11 Ambulatory blood pressure (BP) monitoring in patients with renovascular hypertension commonly reveals a loss of nocturnal pressure fall, or in some cases, a complete reversal of the day–night pattern as shown here. This may be one of the features by which target-organ injury such as left ventricular hypertrophy is exaggerated as compared to patients with similar daytime blood pressure levels.[232]

proteinuria, which can regress with the correction of the vascular lesions.

BP elevations from RVH vary widely, often as a function of the rapidity of onset. Acute renal artery occlusion may only gradually produce an increase in pressure or it may produce a rapid increase in hypertension that may precipitate a hypertensive urgency or emergency. Before the current era of antihypertensive agents, 30% of Caucasian patients appearing in an emergency department with hypertensive urgency (defined as grade 3 or 4 hypertensive retinopathy) were ultimately found to have RVH. Hence, patients presenting with accelerated forms of hypertension should be considered candidates for renovascular hypertension (Table 42.4). Syndromes of polydipsia and accelerated hypertension with hyponatremia and hypokalemia, sometimes attributed to the dipsogenic actions of Ang II, also have been observed. Current antihypertensive medications have changed the clinical presentation of RVH, thus making them less severe.

Recent consensus documents regarding hypertension emphasize the need for effective populationwide BP control while limiting the number and expense of diagnostic studies.

42.4 Clinical Features Suggestive of Renovascular Disease

Clinical Clues

- Age at onset of hypertension (< 30 or > 55 years)
- Abrupt onset of hypertension
- Acceleration of previously well-controlled hypertension
- Hypertension refractory to an appropriate three-drug regimen
- Accelerated retinopathy
- Malignant hypertension/occasionally with hyponatremia
- Systolic–diastolic abdominal bruit
- Flash pulmonary edema
- Evidence of generalized atherosclerosis obliterans
- Acute renal failure with angiotensin-converting enzyme (ACE) inhibitor treatment

Laboratory Features of Renovascular Hypertension

- Early activation of renin-angiotensin-aldosterone system (RAAS)
- Paroxysmal symptoms: sympathetic nervous system activation
- Abnormal circadian rhythm: loss of nocturnal pressure fall
- Accelerated target organ damage
  - Left ventricular hypertrophy
  - Microvascular disease
  - Renal injury: fibrosis

Modified from Textor SC, Greco BA. Renovascular hypertension and ischemic renal disease. In: Floege J, Johnson RJ, eds. Comprehensive Clinical Nephrology. St. Louis, MO: Saunders/Elsevier; 2010: 451–468, with permission.

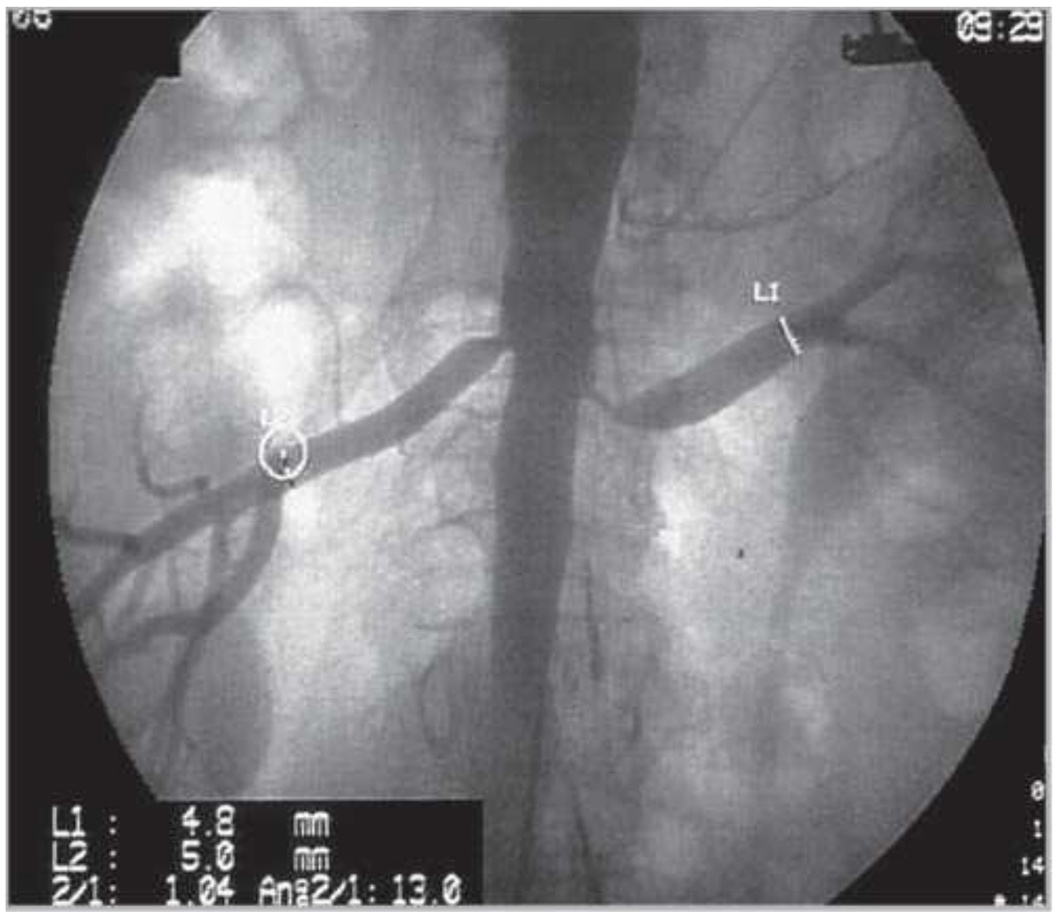


FIGURE 42.12 An aortogram revealing bilateral renal arterial disease performed during a coronary angiography. This individual was treated with antihypertensive drug therapy with excellent blood pressure (BP) control and normal kidney function and was identified only because imaging was included with coronary studies. Numerous series indicate that many such patients are otherwise never identified, but can be managed with medical therapy only. The number that progress to more advanced disease and/or loss of kidney function with current medical therapy may be less than 10% (see text).

When combined with the ambiguous results of prospective treatment trials in which medically treated individuals with ARAS fared as well as those treated with renal revascularization, some would argue that there is little evidence to support extensive diagnostic studies to identify all cases of renovascular hypertension. As a result, most patients with hypertension simply are treated and subjected to few laboratory investigations. For those who reach acceptable BP control without adverse effects, no further studies are performed. Hence, many if not most cases of true RVH are not detected (Fig. 42.12) unless hypertension becomes more difficult to treat or if renal dysfunction ensues. One important reason that RVH is less frequently detected is the availability of orally active antihypertensive agents that block the RAAS. Early studies beginning with captopril indicated that satisfactory BP control can be achieved in more than 86% of patients with RVH compared with less than 50% with previously available drugs. In recent years, the widespread application of ACE inhibitors and angiotensin receptor blockers (ARBs) for indications other than hypertension (e.g., congestive cardiac failure, diabetic nephropathy, and other proteinuric renal disease) increases the exposure of individuals with undetected renal artery stenosis to these drugs.

One result of these changes has been the emergence of distinctive clinical syndromes that merit a further evaluation in patients at risk for ARAS. These are summarized in Figure 42.1. As a result, patients who typically undergo a diagnostic evaluation and renal revascularization are a subset of the population of patients with RVH.

Deterioration of Renal Function During Antihypertensive Drug Therapy

The availability of effective and tolerable drugs for hypertension has meant that many patients are primarily treated with medical management (see the following). Because some patients with renovascular disease are functioning near the lower end of autoregulation, further pressure reduction may curtail blood flow further. Some authors argue that a rise in serum creatinine more than 30% above pretreatment levels should prompt the exclusion of large vessel ARAS.[83] The rapid deterioration of renal function following BP reduction with conventional antihypertensive agents or particularly following BP reduction with ACE inhibitors suggests the

presence of bilateral renal artery stenosis, or stenosis in a solitary functioning kidney.[84–88] In one series, more than half of patients demonstrating an acute elevation in the plasma creatinine concentration that was either unexplained or occurred shortly after the institution of therapy with an ACE inhibitor had main renal artery disease, whereas the remainder presumably had a disease of the intrarenal vessels due to nephrosclerosis.[88] Remarkably, most patients with renal artery stenosis tolerate ACE inhibition or ARB Rx with few adverse effects.[89]

Diagnostic Testing for Renovascular Hypertension and Ischemic Nephropathy

Goals of Evaluation

Given the array of diagnostic studies available and the need to focus the evaluation on patients most likely to benefit, it behooves clinicians to consider carefully the objectives of initiating expensive and sometimes ambiguous studies beforehand. As with all tests, the reliability and value of diagnostic studies depend heavily on the pretest probability of disease.[90] Furthermore, it is helpful to consider from the outset exactly what objective is to be achieved. Is the major goal to exclude high-grade renal artery disease? Is it to exclude bilateral (as opposed to unilateral) disease? Is it to identify stenosis and estimate the potential for clinical benefit from renal revascularization? Is it to evaluate the role of renovascular disease in explaining deteriorating renal function? The specific diagnostic studies may differ depending on which of these is the predominant clinical objective (Table 42.5).

Noninvasive diagnostic tests for renovascular hypertension and ischemic nephropathy remain imperfect. For the purposes of this discussion, diagnostic tests fall into the following general categories (Table 42.6): (1) physiologic and functional studies to evaluate the role of stenotic lesions particularly related to activation of the RAS, (2) perfusion and imaging studies to identify the presence and degree of vascular stenosis, and (3) studies to predict the likelihood of benefit from invasive maneuvers, including renal revascularization.

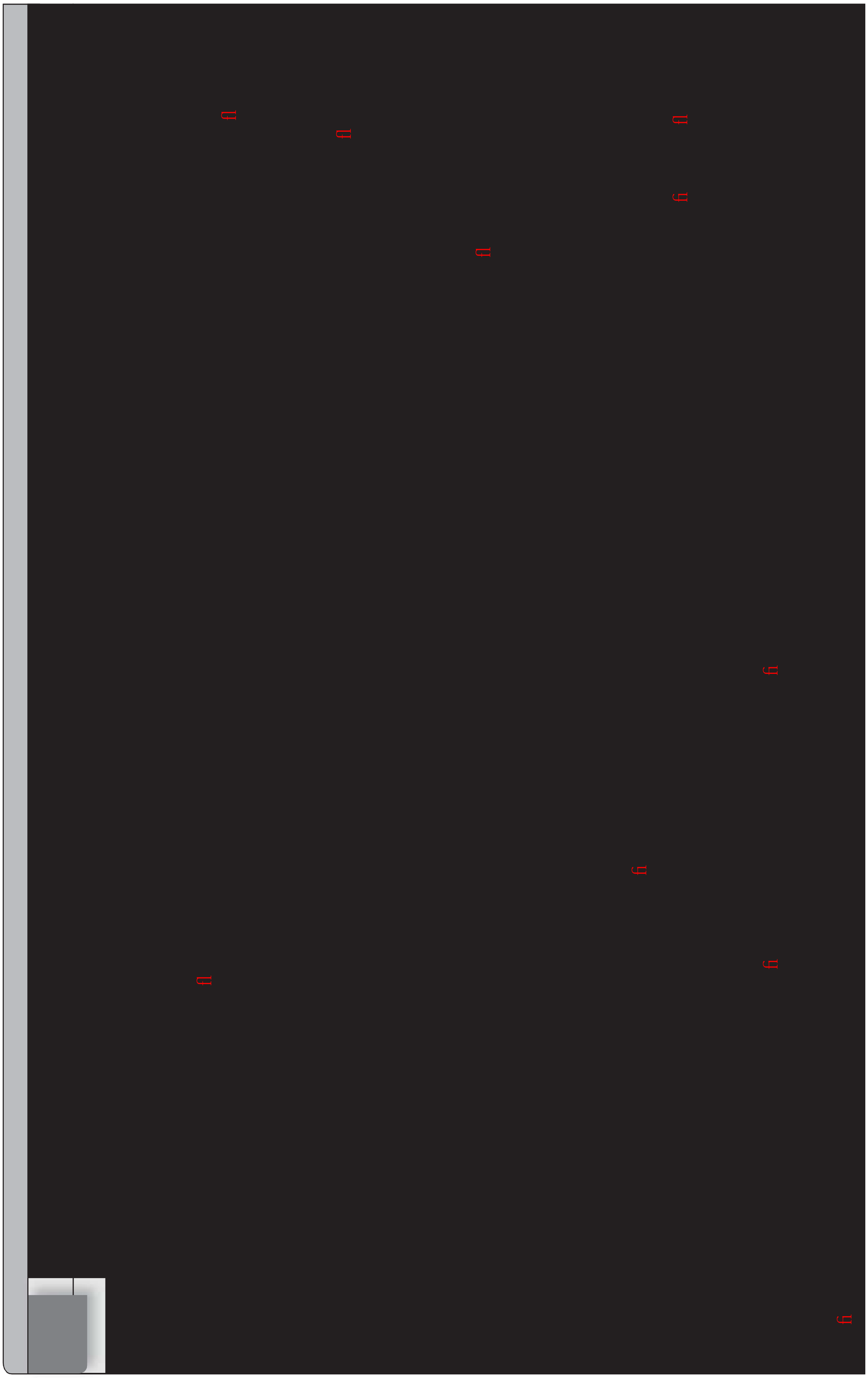
Physiologic and Functional Studies of the Renin-Angiotensin System

Efforts have been made for many years to link the measurement of activation of the RAS as a marker of underlying renovascular hypertension. Although these studies are promising when studied in patients with known renovascular hypertension, they have lower performance results as diagnostic tests when applied to wider populations, as we and others have reviewed.[91–93] PRA is modified by changes of sodium intake, volume status, renal function, and many medications. The sensitivity and specificity of measuring PRA are heavily dependent upon the a priori probability of renovascular hypertension. Although unilateral hypersecretion of renin is an expected finding in hemodynamically significant renal artery stenosis when renovascular hypertension is eventually proved, baseline PRA is elevated in only 50% of patients with renovascular hypertension.[92] Tabulation of the number of patients whose hypertension was cured or improved by surgical renal revascularization indicates that probably no more than 50% of patients with renovascular hypertension have elevated PRA.[94,95] In practice, the major utility of these studies often depends on their negative predictive value, specifically the certainty with which one can exclude significant renovascular disease if the test is negative. Because negative predictive value rarely exceeds 60% to 70%, these tests offer limited value in clinical decision making.

There are several reasons for the relatively low specificity and sensitivity of peripheral PRA in the diagnosis of renovascular hypertension. Most high-renin hypertension is not renovascular in origin; increased renin substrate can

42.5 Goals of Diagnostic and Therapeutic Intervention in Renovascular Hypertension and Ischemic Nephropathy

Goals of Diagnostic Evaluation
Establish presence of renal artery stenosis: location and type of lesion Establish whether unilateral or bilateral stenosis (or stenosis to a solitary kidney) is present Establish presence and function of stenotic and nonstenotic kidneys Establish hemodynamic severity of renal arterial disease Plan vascular intervention: degree and location of atherosclerotic disease
Goals of Therapy
I. Improved Blood Pressure Control Prevent morbidity and mortality of high blood pressure Improve blood pressure control and reduce medication requirement
II. Preservation of Renal Function Reduce risk of renal adverse perfusion from use of antihypertensive agents Reduce episodes of circulatory congestion ("flash" pulmonary edema) Reduce risk of progressive vascular occlusion causing loss of renal function: "preservation of renal function" Salvage renal function (i.e., recover glomerular filtration rate)



be due to estrogen intake, pregnancy, cortisol excess, intrarenal microvascular ischemia (parenchymal disease), or accelerated or malignant hypertension, and the 15% to 20% of patients with primary (essential) hypertension and high renin levels constitute the majority of high-renin hypertensives. Renin secretion fluctuates widely and is influenced by sodium intake, posture and sympathetic tone,[96] a variety of drugs, age, sex, and race.[97] The utility of peripheral PRA is reportedly enhanced when measured in the morning with the patient in the seated position and when indexed against urinary sodium excretion; when measured under these exacting circumstances, a high peripheral PRA is found in 75% to 80% of patients with proven renovascular hypertension.[98] Other investigators, measuring peripheral PRA under similar circumstances, failed to demonstrate significantly increased sensitivity of the peripheral PRA in predicting either the presence of ARAS and the response to therapy.[92,99,100]

The measurement of renal vein renin levels is a means to determine the role of a specific pressor kidney and has been widely applied in planning surgical revascularization for hypertension. Because surgical revascularization entails greater risks than those associated with current endovascular procedures, a substantial effort in the 1970s was directed to identify patients most likely to benefit.[101] These measurements are obtained by sampling renal vein blood and inferior vena cava blood individually. The level of the inferior vena cava is comparable to the arterial levels into each kidney and allows for the estimation of the contribution of each kidney to total circulating levels of plasma renin activity. Lateralization is defined usually as a ratio exceeding 1.5 to 2.0 between the renin activity of the stenotic kidney and the nonstenotic kidney. Some authors propose a detailed examination not only of the relative ratio between kidneys, but also the degree of suppression of renin release from the nonstenotic or contralateral kidney.[101] In general, the greater the degree of lateralization, the more probable that clinical BP reductions would follow after surgical revascularization. Results from many studies support the observation that large differences between kidneys identify high-grade renal artery stenosis. In 1976, Marks et al.[102] reviewed 21 published series encompassing 468 patients with unilateral renovascular disease who had been subjected to a broad spectrum of renin-stimulating maneuvers (e.g., sodium depletion, upright posture). They concluded that a lateralizing renal vein renin ratio predicted surgical cure or substantial improvement in the BP in 93% of patients. Remarkably, 57% of patients with a nonlateralizing renal vein renin ratio (less than 1.5 ipsilateral to contralateral) also benefited from surgery.[102] This later expanded to a review of 58 studies that suggested a ratio of 1.5 or more (stenotic kidney to contralateral kidney) as the diagnostic criterion predicting renovascular hypertension had a sensitivity of 80% and a specificity of 62%.[103] These observations have been extended recently through studies of renal vein measurements prior to considering a nephrectomy for refractory hypertension and advanced renovascular occlusive disease.[104] As with many tests of hormonal activation, study conditions are crucial and can change the interpretation of these tests. Strong and colleagues[105] demonstrated that nonlateralization can be changed to strongly lateralizing measurements by the administration of diuretics between sequential studies. A number of measures to enhance renin release and magnify differences between kidneys have been proposed, including sodium depletion with diuretic administration, hydralazine, tilt-table stimulation, or captopril.[106,107] Volume expansion with intravenous saline poses particular limitations due to the near universal application of this maneuver to limit nephrotoxicity associated with contrast imaging, which is usually performed with renal vein sampling.[108] Because of this variability with different testing conditions, recent series[109,110] concluded that the overall sensitivity of renal vein renin measurements was no better than 65% and that positive predictive value was 18.5%. For these and other reasons, renal vein assays are performed less commonly than before. A major additional factor is that the goals of renal revascularization have shifted substantially and are often directed toward the preservation of renal function, rather than BP control, per se. Nonetheless, the sum of cumulative data regarding renal vein renin determinations indicate that the renal vein renin ratio has a strong positive predictive value in forecasting favorable blood pressure responses to renal revascularization. On the other hand, many patients (at least 50%) demonstrating a nonlateralizing renal vein renin ratio have a marked improvement or cure of their hypertension following an intervention for the renal artery stenosis.

Many more patients are seen with bilateral renal arterial lesions in which both are suspected of participating in a loss of renal function. The most marked asymmetry is seen in patients who have complete occlusion of one renal artery, wherein renal vein renin levels from the side of the occluded artery may represent a combination of low flow through the kidney in addition to hypersecretion of renin.[111] In cases for which it is important to establish the degree of pressor effect of a specific kidney or site, such as before considering a nephrectomy of a pressor kidney, measurement of renal vein renin levels can provide strong supportive evidence. It may be argued that recent trials that suggest limited benefits from renal revascularization may prompt more extensive testing, including formal measurements of individual renin secretion before moving to interventional procedures.

Studies of Individual Renal Function

Serum creatinine, iothalamate clearance, and other estimates of total GFR are measures of overall renal excretory function and do not address differences between separate kidneys. A large body of literature addresses the potential for individual split renal function studies to establish the functional importance of each kidney in renovascular disease.

Split renal function studies classically utilized separate ureteral catheters to allow individual urine collection for the measurement of separate GFR, renal blood flow, sodium excretion, concentrating ability, and the response to blockade of

Ang II.[112] These studies demonstrate that the hemodynamic effects of renal artery lesions in fact do translate into functional changes, such as avid sodium retention, before major changes in blood flow occur. They emphasize that the autoregulation of blood flow and GFR can occur over a wide range of pressures in humans and may be affected in both stenotic and contralateral kidneys by the effects of Ang II. These studies require urinary tract instrumentation and provide only indirect information regarding the probability of benefit from revascularization. They are now rarely performed.

Separate renal functional measurements can be obtained less invasively with radionuclide techniques. These methods use a variety of radioisotopes (e.g., 99mTc-mercaptoacetyltriglycine [99mTc-MAG3] or 99Tc-diethlyene triamine penta-acetic acid [DTPA]) to estimate fractional blood flow and filtration to each kidney. The administration of captopril beforehand magnifies differences between kidneys, primarily by delaying excretion of the filtered isotope due to the removal of the efferent arteriolar effects of Ang II. Some authors advocate such measurements to follow progressive renal artery disease and its effect on unilateral kidney function as a guide to consider revascularization.[113] Serial measurements of individual renal function by radionuclide studies may allow a more precise identification of progressive ischemic injury to the affected kidney in unilateral renal artery disease than can be determined from the overall GFR. Recent studies indicate that single kidney GFR measurements by this method accurately reflect changes in three-dimensional volume parameters measured by magnetic resonance imaging (MRI).[114] These authors argue that demonstrating well-preserved parenchymal volume with a disproportionate reduction in single kidney GFR supports the concept of "hibernating" kidney parenchyma and might provide a predictive parameter for the recovery of kidney function after revascularization.[114]

Imaging of the Renal Vasculature

Advances in Doppler ultrasound, radionuclide imaging, magnetic resonance arteriography (MRA), and computed tomography (CT) angiography continue to improve the field of renovascular imaging. The details of these methods are beyond the scope of this discussion. They are addressed more fully elsewhere. What follows is a discussion of some of the specific merits and limitations of each modality as they apply to renovascular hypertension and ischemic nephropathy.[90]

Current practice favors limiting invasive arteriography to the occasion of endovascular intervention (e.g., stenting and/or angioplasty). Although for many, angiography remains the gold standard for evaluating the renal vasculature, its invasive nature, potential hazards, and cost make it most suitable for those in whom intervention is planned, often during the same procedure. As a result, most clinicians favor preliminary noninvasive studies. When noninvasive studies are equivocal, arterial angiography may be warranted to establish the presence of transstenotic pressure gradients, as recommended for treatment trials.[115,116]

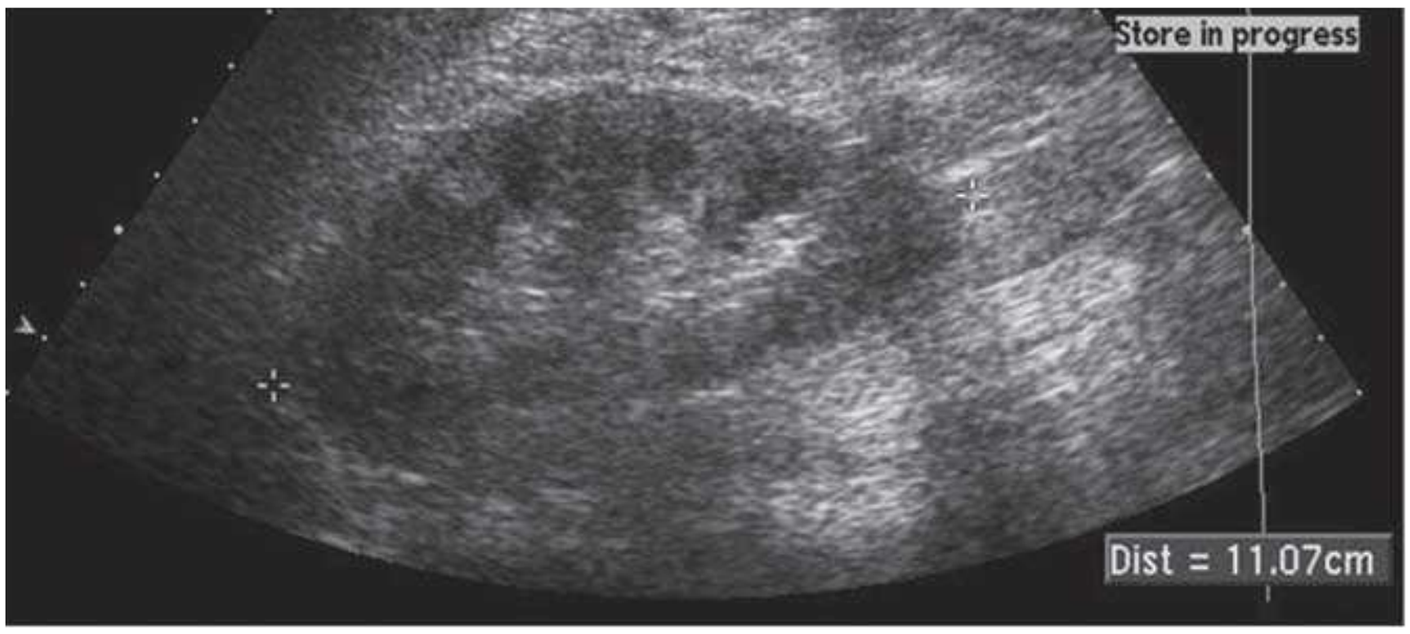
Noninvasive Imaging

Doppler Ultrasound of the Renal Arteries

Duplex interrogation of the renal arteries provides measurements of localized velocities of blood flow. This technique is available in most institutions and provides an inexpensive means for measuring vascular occlusive disease at sequential time points, both to establish the diagnosis of renal artery stenosis and to monitor its progression. After renal revascularization, Doppler studies are commonly used to detect restenosis and target vessel patency (Fig. 42.13A, B).[117,118] Its main drawbacks relate to the technical difficulties of obtaining adequate studies in obese patients and in those with complex vessels. The usefulness and reliability of Doppler ultrasound depend partly on the specific operator and the time allotted for optimal studies. These factors vary considerably between institutions. In our experience, results are most useful when positive (i.e., when a high grade renal artery velocity can be documented). Failure to identify a velocity increase (i.e., a negative duplex study) sometimes reflects an incomplete localization of the renal vessels.

Traditional primary thresholds for renal artery studies are a peak systolic velocity above 180 cm per second and/or a relative velocity above 3.5 as compared to the adjacent aortic flow.[119] Using these criteria, sensitivity and specificity with angiographic estimates of lesions exceeding 60% can surpass 90% and 96%, respectively, although not universally.[120] Increasing the threshold for peak systolic velocities reduces the rate of false positive estimates of stenosis. When main vessel velocities cannot be determined reliably, segmental waveforms within the arcuate vessels in the renal hilum can provide additional information. Damping of these waveforms, labeled as parvus and tardus, have been proposed as indirect signs of upstream vascular occlusive phenomena.[121] Recent studies challenge the use of angiographic estimates of stenosis as representing a gold standard altogether.[122] These authors argue that Doppler velocities correlate highly ($R = 0.97$) with a truer estimate of vascular occlusion, specifically stenosis, as determined by intravascular ultrasound.

Positive Doppler velocities in an artery clearly identified as the renal artery are rarely proven to be negative later. False negative studies are more common. In subjects with accessible vessels, Doppler ultrasound provides the most practical means of following vessel characteristics sequentially over time. A drawback of renal artery Doppler studies includes frequent failure to identify accessory vessels. Because the correlation between velocity and the degree of stenosis is only approximate, clinical trials such as Cardiovascular Outcomes for Renal Atherosclerotic Lesions (CORAL) have raised the diagnostic threshold for peak systolic velocity to 300 cm per second. This seems warranted, particularly when the risk of overdiagnosis of renal arterial lesions is high, as in the Stenting for Atherosclerotic Renal artery stenosis (STAR) trial, in which 18 out of 64 patients assigned to stenting were not treated because of insignificant renovascular disease at the time of angiography despite noninvasive estimates to



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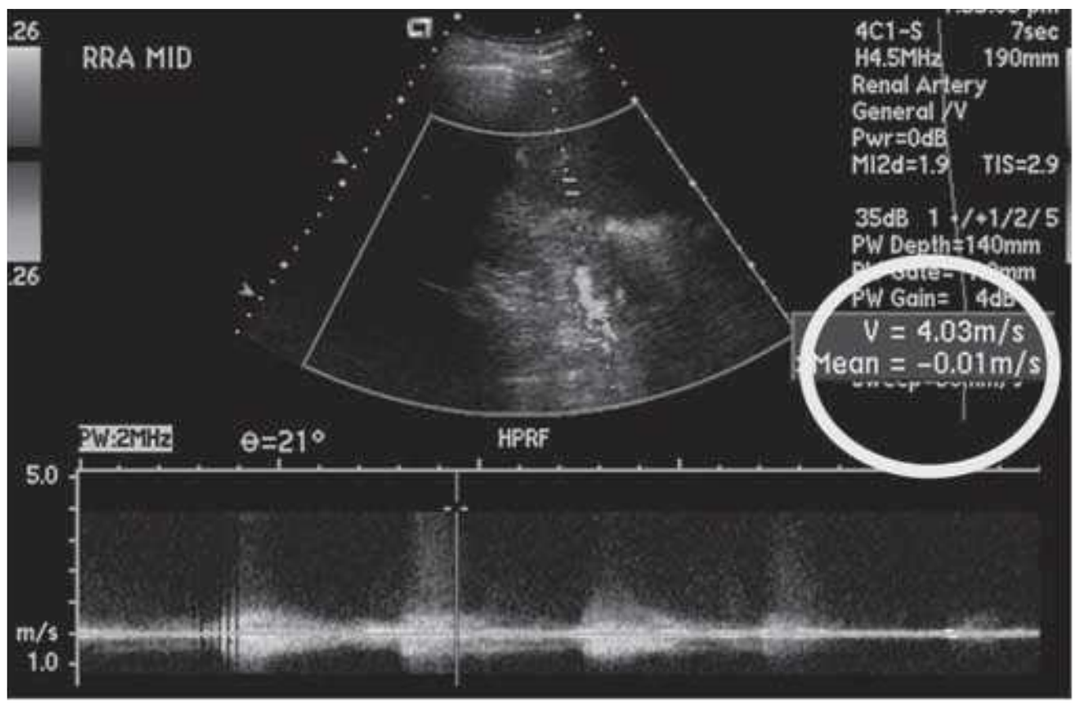

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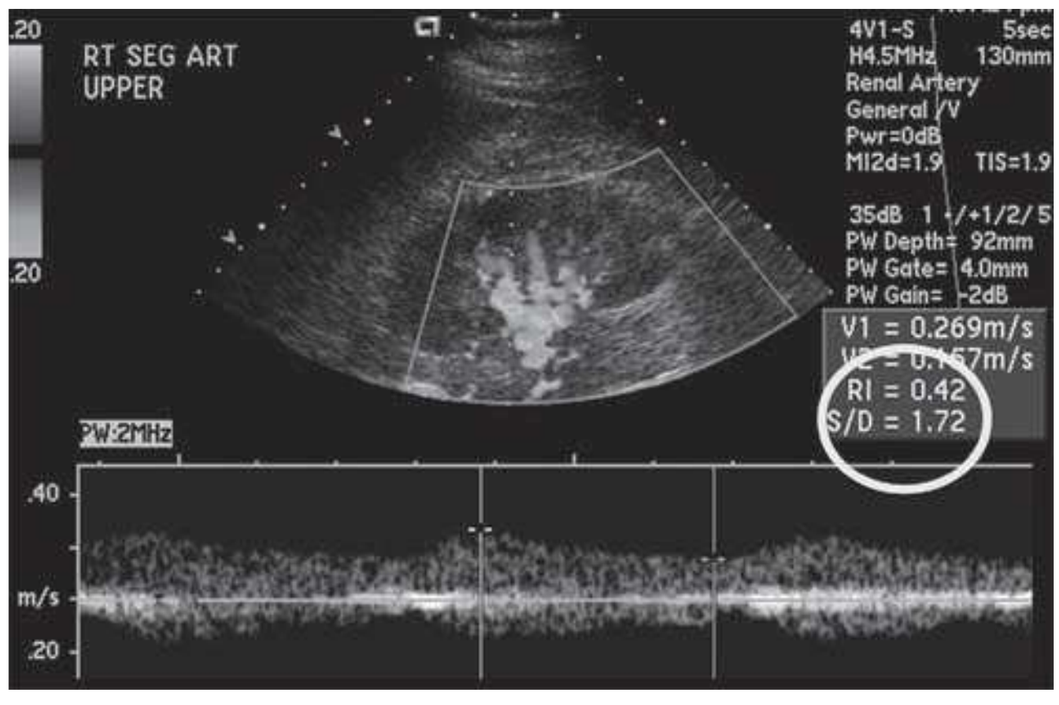


C

FIGURE 42.13 A and B: High-grade renal artery stenosis in a normal-sized kidney characterized by high peak systolic velocity (4.03 m per second) at the origin of the main vessel. **C:** Doppler velocity measured in the distal renal artery segments of the same kidney, illustrating delayed arrival with a blunted pulse wave (parvus and tardus) appearance characteristic of proximal stenosis. The sustained flow during diastole in this instance is expressed as low resistive index (RI) suggestive of favorable intrarenal hemodynamics (see text). (See Color Plate.)

the contrary.[123] A recent report suggests that a correlation with quantitative estimates of renal artery occlusion above 60% correlate best with velocities above 300 cm per second for native vessel disease and somewhat higher (395 cm per second) for in-stent restenosis.[124]

An additional feature of Doppler ultrasound allows for the characterization of small vessel flow characteristics within the kidney. The resistive index (RI) provides an estimate of the relative flow velocities in diastole and systole. In a study of 138 patients with renal artery stenosis, a RI above 80 provided a predictive tool for the identification of parenchymal renal disease that did not respond to renal revascularization (Fig. 42.14).[125] A sizable portion of the group with an elevated RI eventually progressed to renal failure. An RI less than 80 was associated with a more than 90% favorable BP response and stable or improved renal function. The authors emphasize that accurate predictive power depended on using the highest RI observed, even when present in the nonstenotic kidney. A subsequent study of 215 subjects with mean preintervention serum creatinine levels of 1.51 mg per deciliter failed to confirm the predictive value of RI measurements. Of 99 subjects with improved renal function after 1 year, 18% had an RI above 0.8 before intervention, whereas 15% of 92 subjects with no improvement had an index above 0.8 (not significant). In this series, the preintervention level of serum creatinine itself was the strongest predictor of improved renal function.[126] Additional studies indicate an overlap between levels of RI in those with and without clinical improvement after stenting. Nonetheless, low RI remained a predictor of clinical BP benefit after adjusting for age, sex, duration of hypertension, and other conditions.[127] In a series of 106 patients with ARAS undergoing revascularization, 70% of patients with an RI below 80 had a clinical benefit, as compared with only 20% of those with an RI above 80. Most clinicians agree that detecting a low RI indicates well-preserved vasculature within the kidney.[128]

Captopril Renography

Imaging the kidneys before and after the administration of an ACE inhibitor (e.g., captopril) provides a functional assessment of the change in blood flow and GFR to the kidney, related both to changes in arterial pressure and the removal of the efferent arteriolar effects of Ang II. The most commonly used radiopharmaceuticals are 99mTc, DTPA, and MAG3. The latter agent has clearance characteristics similar to Hippuran and is often taken as reflecting renal

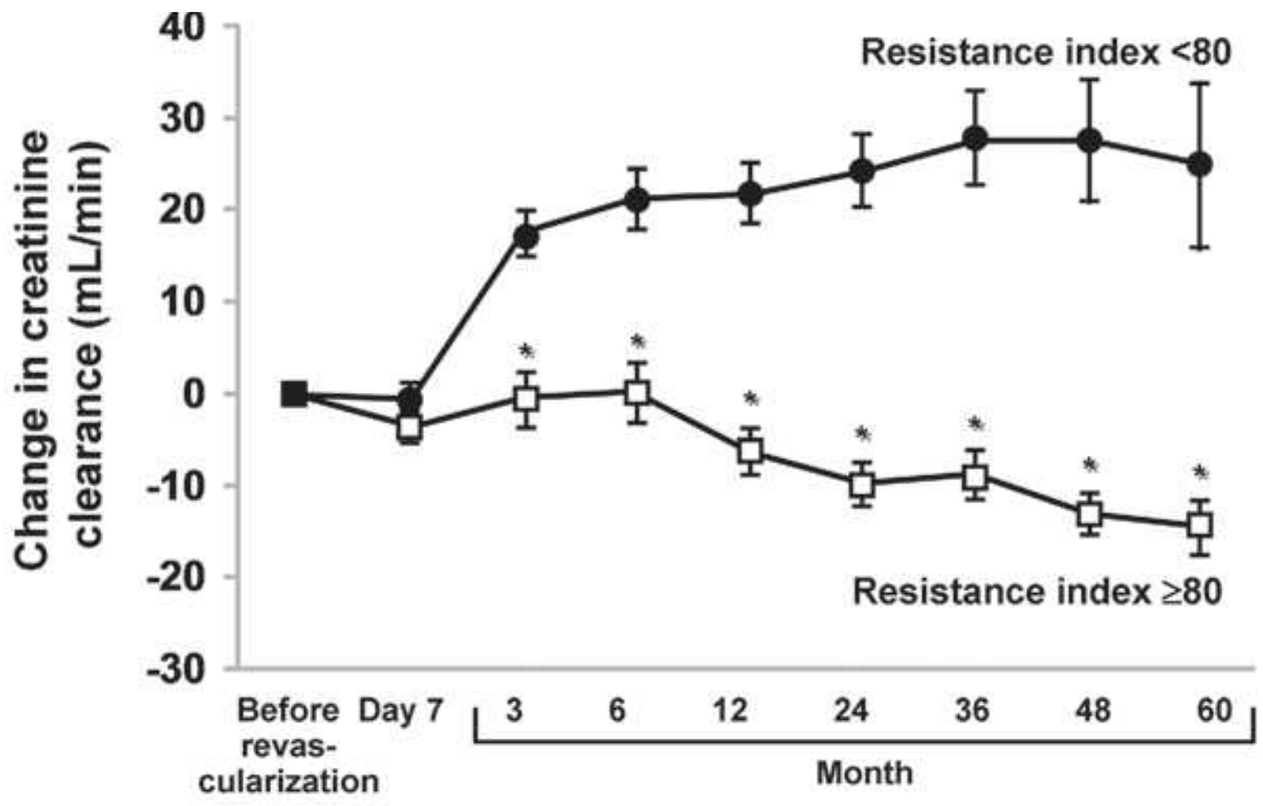


FIGURE 42.14 A resistive index (RI) obtained from 131 subjects undergoing renal revascularization. Those with relatively low resistive indexes (< 80) were more likely to have higher glomerular filtration rates (GFRs) during follow-up and were more likely to have a favorable blood pressure response than those with higher levels (> 80). These data suggest that preserved diastolic flow, which is the main determinant of RI, is a favorable sign for kidney recovery. (Adapted from Radermacher J, Chavan A, Bleck J, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med*. 2001;344:410–417, with permission.)

plasma flow. Both can be used, although specific interpretive criteria differ.[129] Both provide information regarding the size and filtration of both kidneys and the change in these characteristics after the inhibition of ACE allows inferences regarding the dependence of glomerular filtration on Ang II. Patient groups with the prevalence of renovascular disease rates between 35% and 64% of subjects suggest that sensitivity and specificity range between 65% and 96% and 62% and 100%, respectively.[129] Because of its high specificity, captopril renography can be applied to populations at low pretest probability with an expectation that a normal study will exclude significant renovascular hypertension in more than 96% of cases.[95] Some series report 100% accurate negative predictive values.[130]

These studies are less sensitive and specific for renovascular disease in the presence of renal insufficiency (usually defined as creatinine > 2.0 mg per deciliter). These performance characteristics deteriorate for patients who cannot be prepared carefully (i.e. withdrawal of diuretics and ACE inhibitors 4 to 14 days before the study).[129] It should be emphasized that renography provides functional information but no direct anatomic information (i.e., the location of renal arterial disease, the number of renal arteries, or associated aortic and/or ostial disease) (Fig. 42.15A,B). Some authors

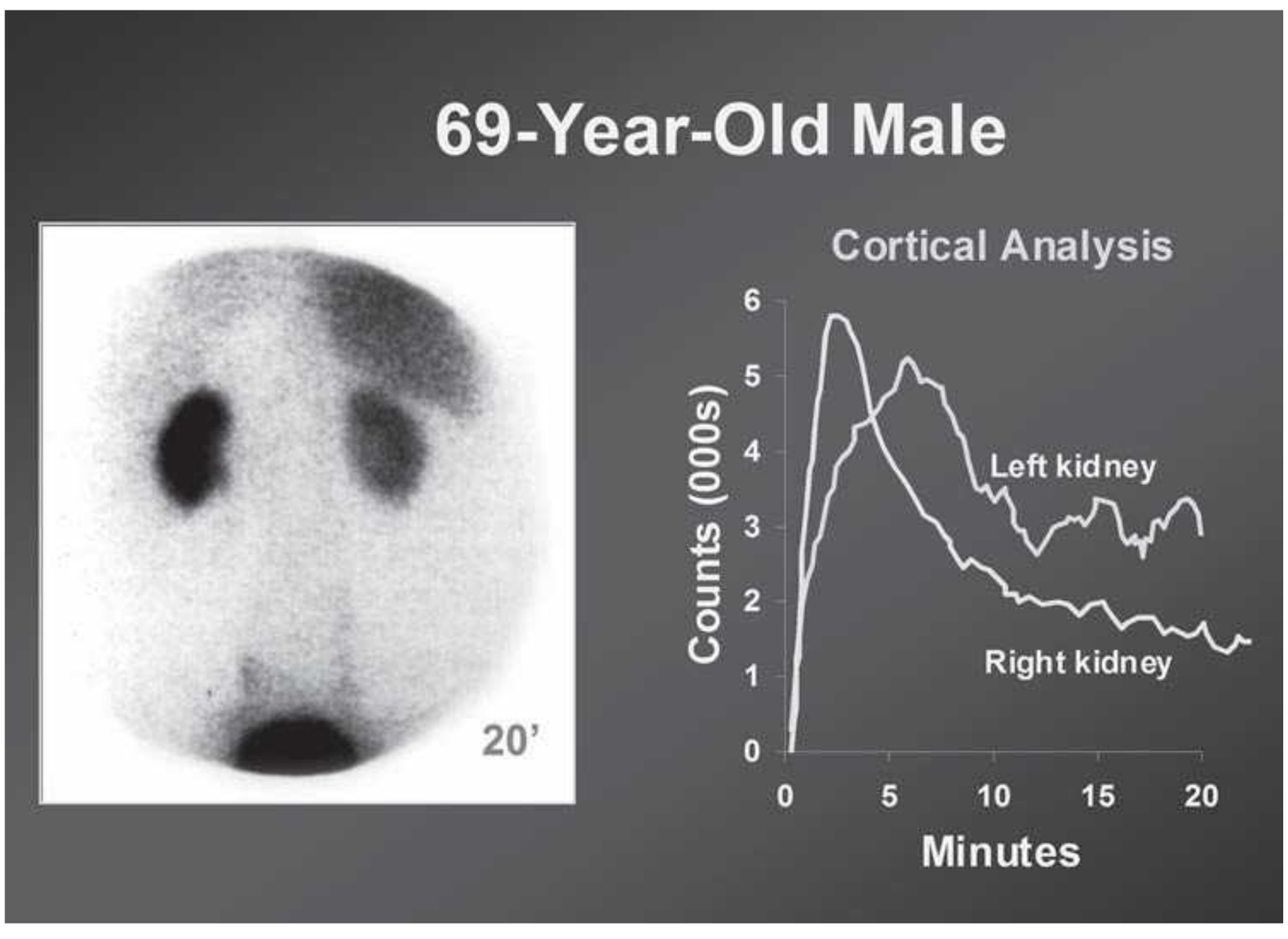


FIGURE 42.15 A radionuclide renogram illustrating asymmetry of flow and function between two kidneys in a patient with high-grade renovascular disease.

argue that renographic screening of patients using this technique is among the most cost-effective methods of identifying candidates for further diagnostic studies and superior to functional studies of the RAS. On the other hand, prospective studies of renovascular disease from the Netherlands did observe changes in the renogram during follow-up, but did not find captopril renography predictive of angiographic findings or outcomes.[39] A prospective study of 74 patients undergoing both renography and Doppler ultrasound evaluation before renal revascularization could identify only a limited predictive value of scintigraphy (sensitivity 58% and specificity of 57%) regarding BP outcomes.[131]

Under carefully controlled conditions, some authors argue that changes in renographic appearance correlate with changes in BP to be expected after revascularization. Changes in split renal function indicate that stenotic kidneys regain GFR after revascularization, sometimes with a decrement in contralateral GFR, thereby leaving overall kidney function unchanged.[132]

Computed Tomography Angiography

CT angiography using helical and/or multiple detector scanners and intravenous contrast can provide excellent images of both kidneys and the vascular tree. Resolution and reconstruction techniques render this modality capable of identifying smaller vessels, vascular lesions, and parenchymal characteristics, including malignancy and stones (Fig. 42.16A,B).[133] When used for the detection of renal artery stenosis, CT angiography agrees well with conventional arteriography (correlation 95%) and sensitivity may reach 98% and specificity may reach 94%.[134,135] Recent studies indicate that CT provides excellent accuracy regarding the evaluation of in-stent restenosis[136] and the evolving quantitative three-dimensional image analysis may improve on intra-arterial methods.[134] Although this technique offers a noninvasive examination of the vascular tree suitable for kidney donors with normal GFR, for example, it has the drawback of iodinated-contrast requirement. As a result, it is less than perfect for the evaluation of renovascular hypertension and/or ischemic nephropathy for patients with an impaired renal function. Concerns regarding toxicity associated with MRA contrast nonetheless encourage the wider use of multidetector CT as a diagnostic imaging test for patients suspected of renovascular disease. There are limitations, including the reduced visibility of vessel lumens in the presence of substantial calcium deposition. A single study comparing both CT angiography and MRA with intra-arterial studies in 402 subjects indicated substantially worse performance for the detection of lesions $>$ 50% stenosis.[137] In this particular study, CT angiography had a sensitivity of 64% and a specificity of 92%, whereas MRA had a sensitivity of 62% and a specificity of 84%. This was an unusual population with only 20% of the screened population having stenotic lesions, nearly half of which were FMD. The results of such studies reinforce the importance of careful patient selection for study and establishing in advance why imaging is being undertaken.[138]

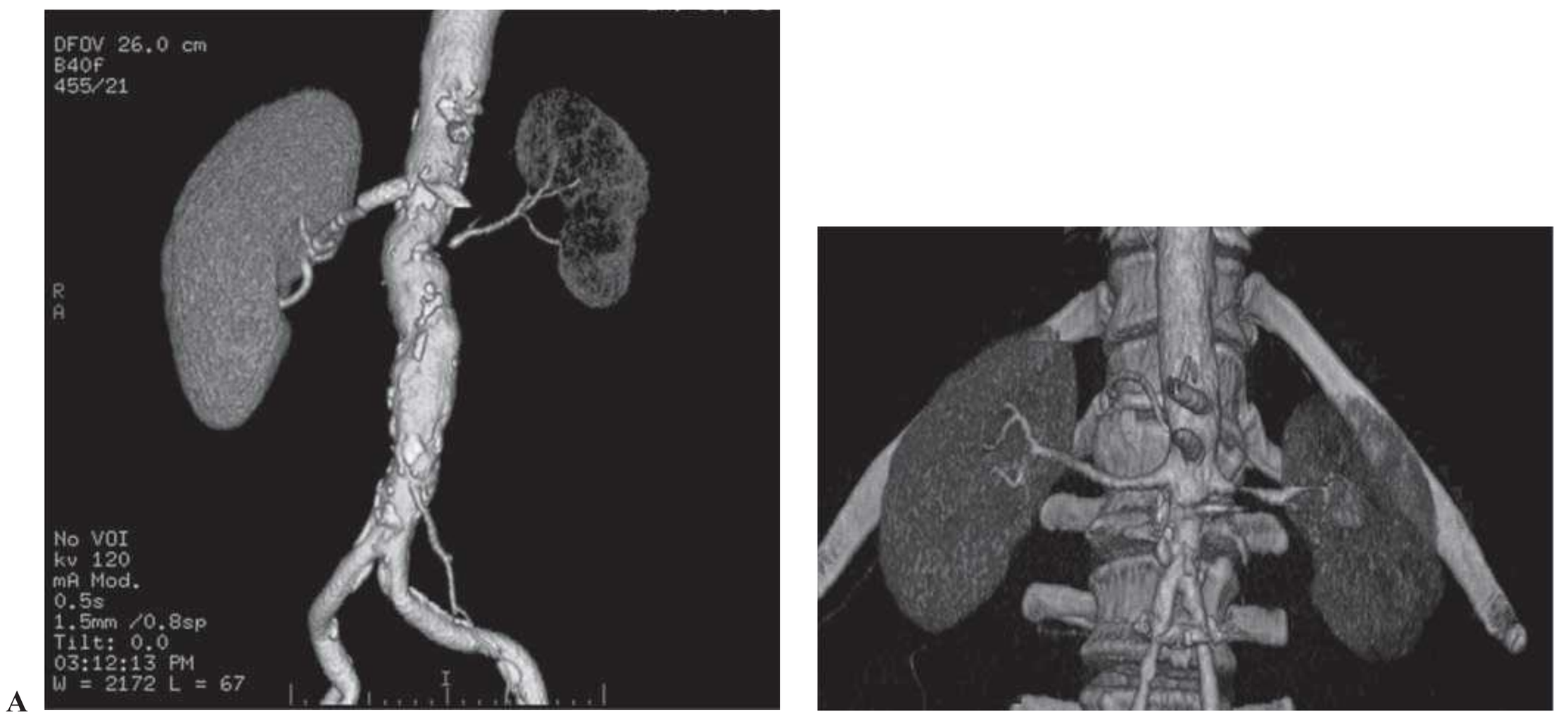


FIGURE 42.16 A and B: Computed tomography (CT) angiographic images with reconstruction can identify important elements of vascular anatomy and parenchymal function. **A:** A right renal artery stent with normal kidney parenchyma as compared with advanced renal artery stenosis affecting the left kidney, with evident loss of kidney size, perfusion, and function. **B:** A high-grade left renal artery stenotic lesion is evident with a moderate reduction in perfusion to the kidney as shown by its reduced size and the intensity of the nephrogram. (See Color Plate.)

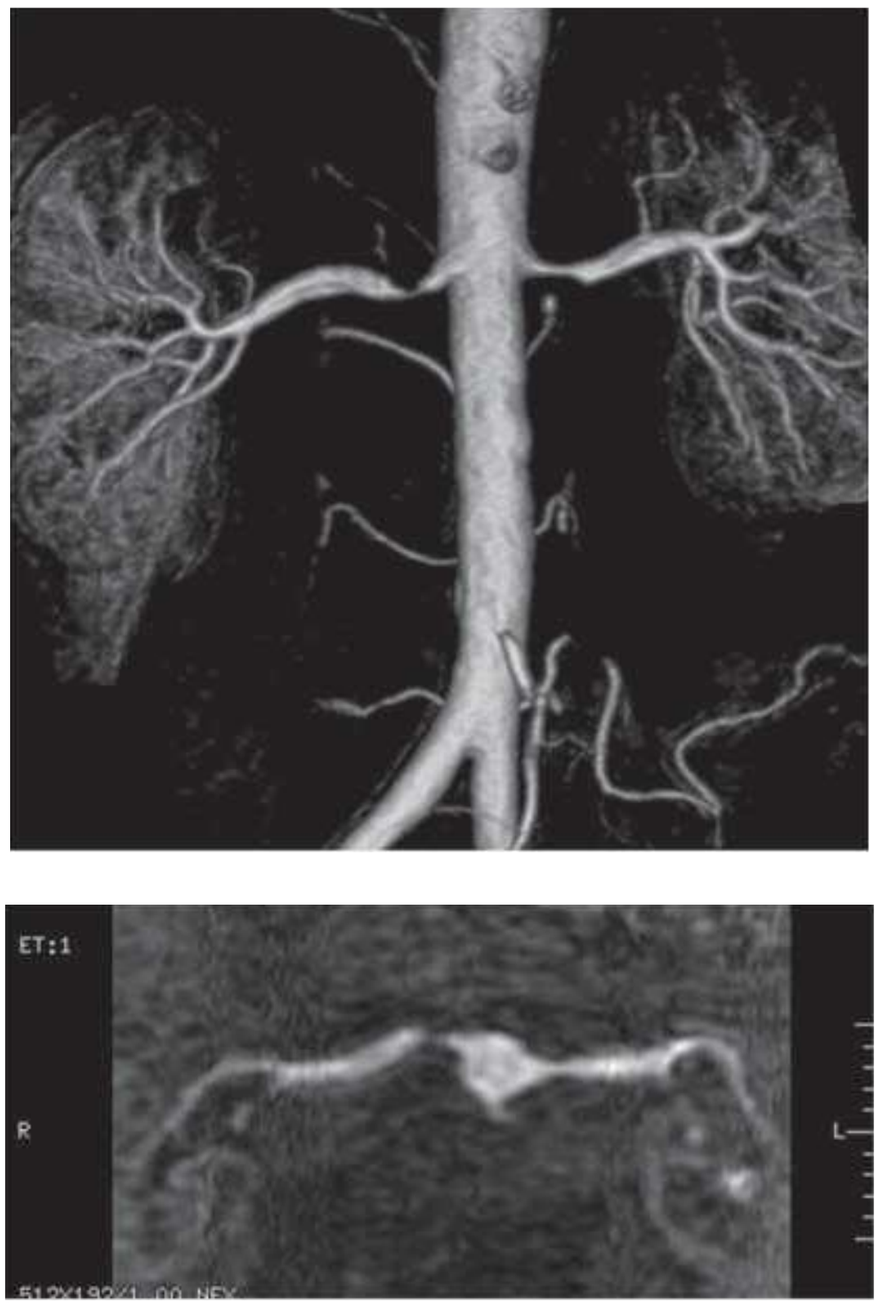
Magnetic Resonance Angiography

Gadolinium-enhanced images of the abdominal and renal vasculature have been a mainstay of evaluating renovascular disease in many institutions.[133,139] Comparative studies indicate that sensitivity ranges from 83% to 100% and specificity ranges from 92% to 97% in renal artery stenosis.[140,141] Meta-analyses of published literature[142] including 998 subjects support more than 97% sensitivity using gadolinium-enhanced imaging. The nephrogram obtained from gadolinium filtration provides an estimate of relative function and filtration, as well as parenchymal volume. The quantitative measurement of parenchymal volume determined by MRI appears to correlate closely with isotopically determined single kidney GFR in some institutions.[114] However, since 2006, concerns about the potential for gadolinium-based contrast to produce nephrogenic systemic fibrosis effectively have drastically reduced contrast-enhanced MR for patients with impaired kidney function in the United States.[143]

Technologic advances allow increasingly high-resolution vascular MRI without contrast in many patients. An example of MRA without contrast is shown in Fig. 42.17B. Drawbacks include the expense and the tendency to overestimate the severity of lesions, which in fact appear as a signal void.[144] The limits of resolution with current instrumentation make the detection of small accessory vessels limited, and quantitating fibromuscular lesions is difficult with current technology. Both of these are improving with newer generations of scanners. High spatial resolution three-dimensional contrast-enhanced MR scanners provide up to 97% sensitivity and 92% specificity for renal artery stenotic lesions.[145] Signal degradation in the presence of metallic stents renders MRA unsuitable for follow-up studies after endovascular procedures in which stents are used.

Functional Magnetic Resonance Imaging: Blood Oxygen Level–Dependent Magnetic Resonance

Blood oxygen level–dependent (BOLD) MR utilizes the properties of deoxygenated hemoglobin as a paramagnetic material that affects the local rates of magnetic polarization within tissues after a radiofrequency pulse (estimated as R2*).[146] These tools allow a real-time, noninvasive estimate of local oxygenation, which differs between the highly blood-perfused cortex and the much less perfused deeper medullary segments within the kidney.[147,148] Despite sufficient renal artery occlusion to reduce blood flow and GFR within the affected kidney by 30%, recent studies[61,64] indicate that overall cortical and medullary oxygenation in subjects treated with ACE inhibitors or ARBs maintain normal intrarenal patterns of oxygenation. In patients with more severe and/or long-standing reductions in blood flow, cortical oxygenation begins to deteriorate, reflecting overt hypoxia within the kidney associated with intrarenal fibrosis and inflammatory changes (Fig. 42.18).[66,149] Future studies hold the promise that such functional imaging may better identify those kidneys (1) at actual risk of ischemic injury and (2) that may benefit from restoring blood flow to recover function.[9]

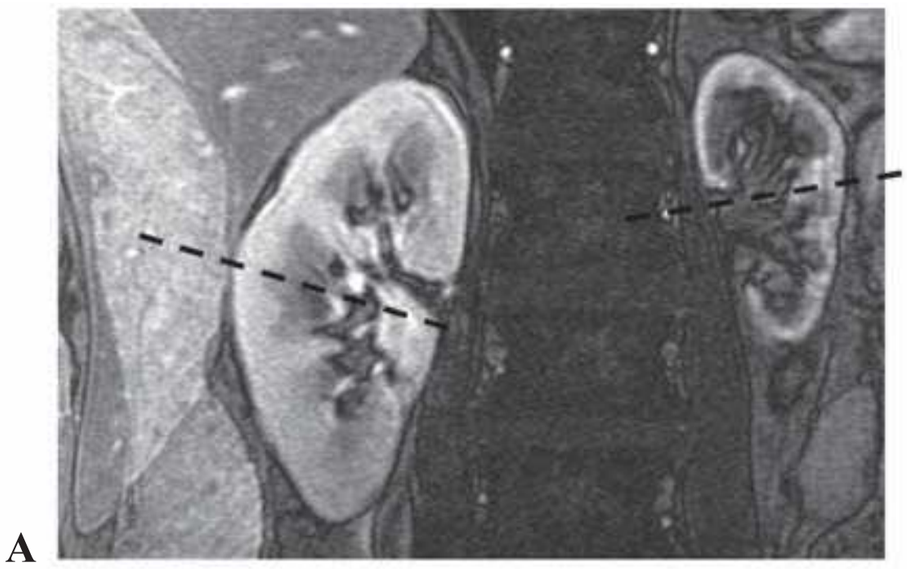


A **B**

FIGURE 42.17 Examples of magnetic resonance angiograms (MRAs) with **(A)** vascular reconstruction using gadolinium contrast. Continually improving MR imaging allows for the definition of smaller vessels with improved resolution and the definition of parenchyma without ionizing radiation. Use of gadolinium-based contrast agents has declined after concerns about nephrogenic systemic fibrosis (NSF) in patients with impaired glomerular filtration rates (GFRs). **B:** Time-of-flight imaging without contrast in the axial plane also can provide excellent definition of vascular occlusion, even at oblique angles from the aorta.

Invasive Imaging

Intra-arterial angiography currently remains the gold standard for the definition of vascular anatomy and stenotic lesions in the kidney. Often, it is completed at the time of a planned intervention, such as endovascular angioplasty and/or stenting. What is the current role of including angiography of the renal arteries during imaging of other vascular beds, such as drive-by angiography during coronary artery imaging? Several studies confirm that the prevalence of renal artery lesions exceeding a 50% lumen occlusion in patients with hypertension and coronary artery disease is high, usually between 18% and 24%.[150] Some individuals (7% to 10%) will have high-grade stenoses above a 70% occlusion



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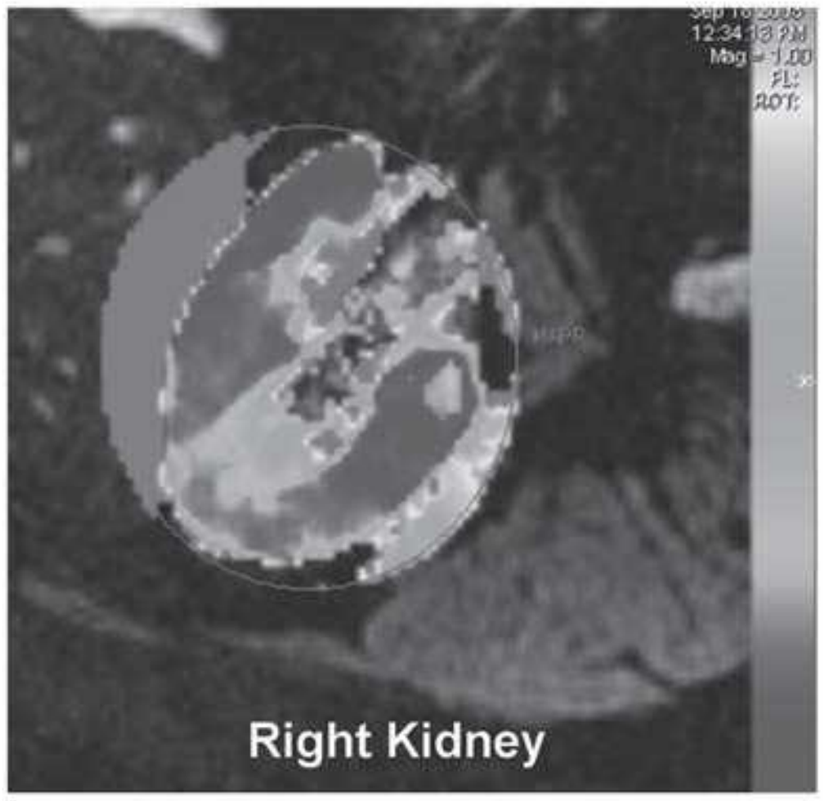

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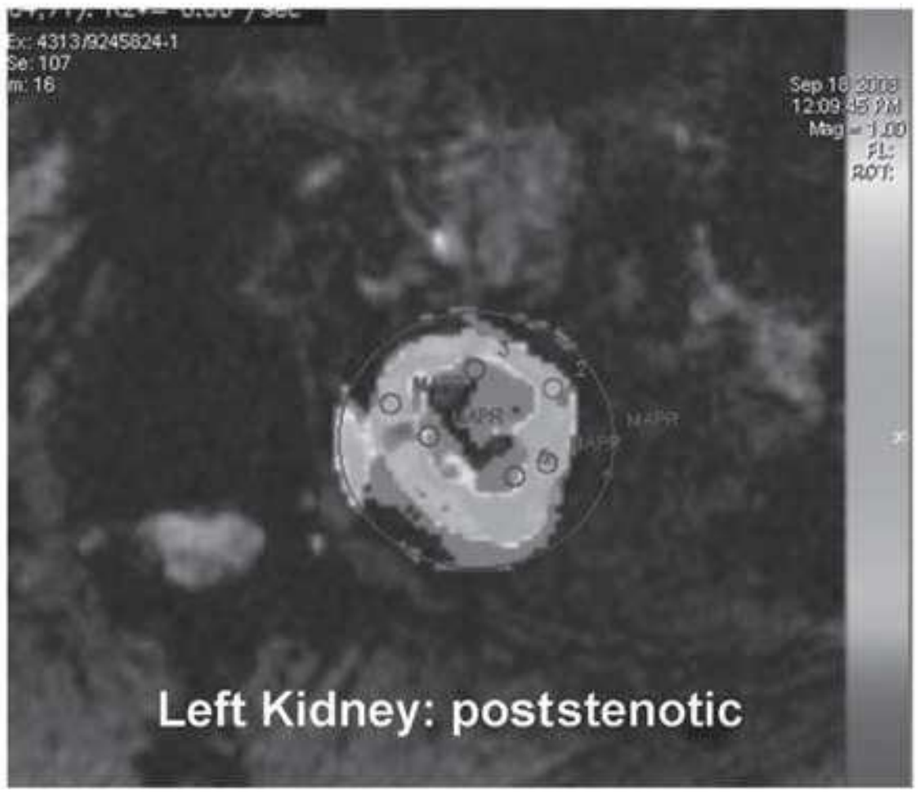

C

FIGURE 42.18 A, B, and C: Functional magnetic resonance (MR) using blood oxygen level–dependent (BOLD) imaging provides a measurement of tissue deoxyhemoglobin levels (expressed as R2* (sec^{-1})) illustrated in axial sections of a normal kidney **(B)** and the severely stenotic **(C)** kidney shown here. Maps of R2* in the normal kidney demonstrate abundant oxygenation in the kidney cortex (low R2* levels associated with blue-green regions) with a gradient to hypoxic regions in the medulla (higher R2* levels associated with orange-red). When blood flow is reduced sufficiently, cortical flow falls and the tissue becomes overtly hypoxic in the cortex and the zone of medullary hypoxia widens **(C)**. (Adapted from Reference (66) with permission.) BOLD MR represents one potential tool to identify vascular insufficiency leading to tissue hypoxia and may allow improved selection of patients for renal revascularization. (See Color Plate.)

and some will be bilateral. Accepting the fact that an arterial puncture and catheterization of the aorta and coronary vessels produces some risk, the added risk from including an aortography of the renal vessels appears to be small/almost negligible. Follow-up studies[12,151] of individuals with identified incidental renal artery lesions suggest that the presence of these lesions does provide an additive predictive risk for mortality. No data to this point suggest that combining screening angiography with renal revascularization changes that risk. Hence, endovascular procedures for such lesions should be confined to individuals with strong indications for renal revascularization, as even the most ardent advocates of catheter-based intervention have suggested.[150] Remarkably, studies of patients with identified ARAS during the preoperative screening indicate no increased risk for acute kidney injury (AKI) during or after cardiovascular surgery as compared to those without ARAS.[152]

Contrast toxicity remains an issue with conventional iodinated agents.[153] Intravascular ultrasound procedures have been undertaken using papaverine to evaluate flow reserve beyond stenotic lesions.[154] Various reports indicate that either a reduction or preserved flow reserve may identify a poststenotic kidney that may improve function after successful revascularization.[154,155] Previous studies of pressure gradients measured across stenotic lesions have failed to predict the clinical response to renal revascularization. Measurements using currently available low profile wire probes do, however, indicate a relationship between pressure gradients and the activation of the RAS.[43] Outcomes of patients with translesional pressure gradients measured after vasodilation suggest that a measurement of hyperemic systolic gradient above 21 mm Hg most accurately predicts high-grade stenosis (average 78% by intravascular ultrasound) and a beneficial response of BP after stenting.[156] The latter observation and the increasing reliability of technical measurements underscore the value of measuring gradients to establish a hemodynamic role for vascular lesions of marginal severity.

Management of Renal Artery Stenosis and Ischemic Nephropathy

Overview

Considering the variety of potential treatments and major differences in individual patient comorbid diseases and risks, clinicians need to formulate a clear set of therapeutic goals for each patient. Each treatment, ranging from medical therapy alone to surgical revascularization, carries both benefits and risks. The clinician's task is to weigh the role of each of these within the context of each patient's response and likely long-term outcome. Rarely is it obvious how best to proceed. In most cases, the long-term management of the patient with renovascular disease requires an integrated pharmacologic management of BP, treating cardiovascular risk factors, and the careful timing of renal revascularization. The objective of this section is to provide a framework by which to plan a balanced approach to the patient with unilateral or bilateral renal artery stenosis. It should be emphasized that the consideration of renal artery disease takes place in the broad context of managing other cardiovascular risk factors, including withdrawing tobacco use, reducing cholesterol levels, and treating diabetes and obesity.

Medical Therapy of Renovascular Disease

The overall goals of therapy are summarized in Table 42.5. Foremost among these is the statement by the Joint National Committee (JNC) of the National High Blood Pressure Education Program (NHBPEP): "The goal of treating patients with hypertension is to prevent morbidity and mortality associated with high blood pressure."[157] This task may include the effort to simplify or potentially eliminate long-term antihypertensive drug therapy. Several scenarios should be considered in the care of patients with renal artery stenosis and hypertension: (1) true renovascular hypertension, in which atherosclerotic or fibrous renal artery disease is the sole cause of the hypertension; (2) pure essential hypertension, in which atherosclerotic or fibrous renal artery disease is present but does not contribute to the hypertension at all; (3) essential hypertension with superimposed renal artery stenosis producing a renovascular contribution to the underlying essential hypertension; and (4) the hypertension of renal parenchymal disease, that is, chronic renal insufficiency with superimposed renal artery stenosis contributing to the hypertension (Fig. 42.19). Accordingly, the medical management of patients with presumed renovascular hypertension and renovascular disease is primarily an effort to control the BP. As will be summarized in the following, rarely does any specific revascularization procedure lead to the withdrawal of all antihypertensive therapy or to a true cure for hypertension. Hence, medical therapy at some level is a primary component of treatment for nearly all patients with renovascular disease. A second corollary is that a trial of medical therapy often becomes a practical test of the need for expanded diagnostic studies. Regarding this, some of the major criteria recommended by an American Heart Association writing group are summarized in Table 42.7.

A further goal is to prevent a loss of kidney function related to impaired renal blood flow. In some instances, renal revascularization is undertaken to allow for the improved management of salt and water balance in the process of managing patients with congestive cardiac failure. This may allow safer use of diuretic agents and ACE inhibitor/ARB classes of medication in patients with critical renal artery lesions to the entire renal mass. Because prospective, randomized trial information is limited and ambiguous for renovascular disease, each patient must be considered individually. What cannot be assumed is that renal revascularization prolongs

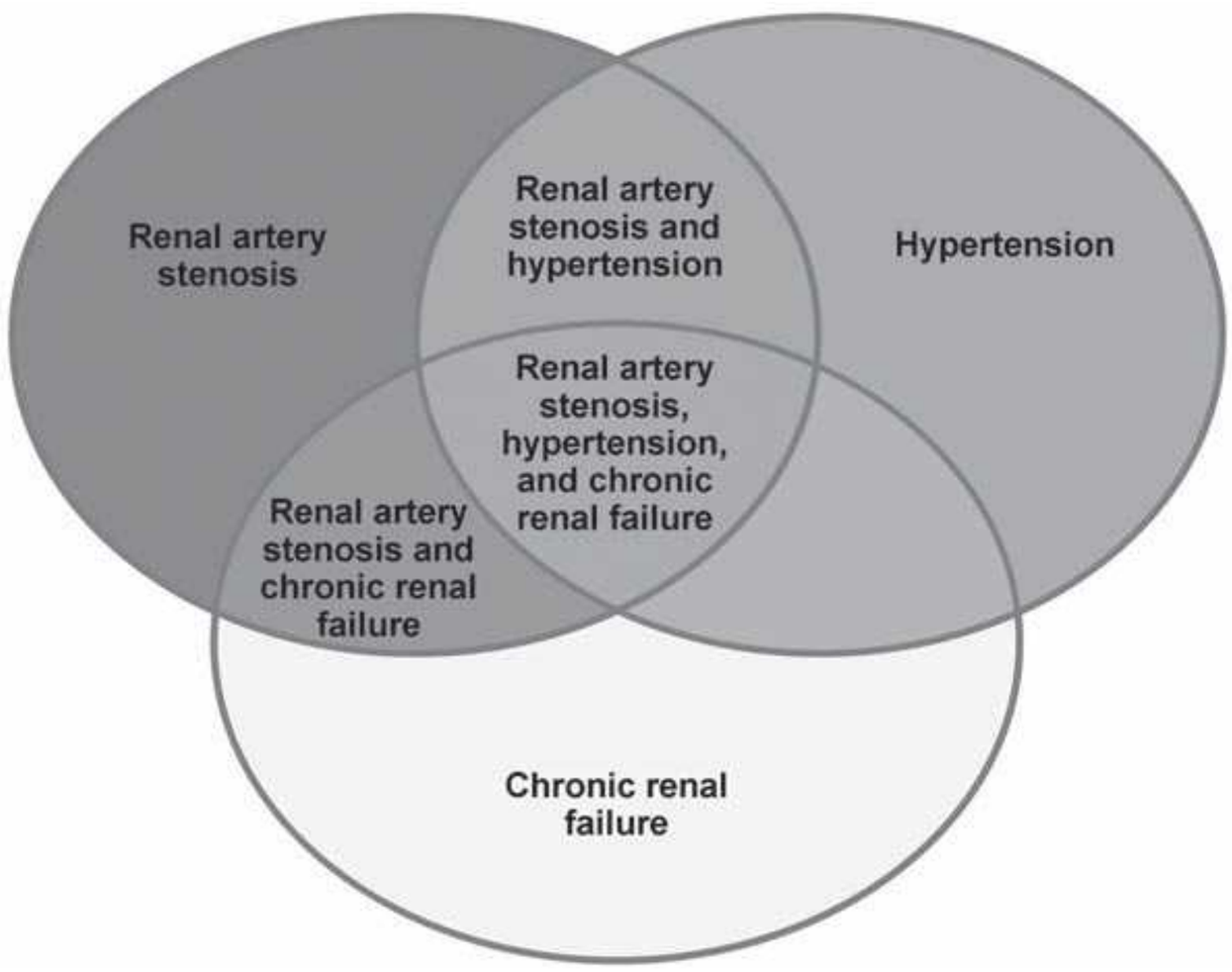

FIGURE 42.19 A Venn diagram illustrating the relationships between renal artery stenosis, hypertension, and chronic renal failure. The challenge to clinicians is to evaluate the relationship between these circles for an individual patient. Because all three are common and increase with age, it is no surprise that identifying patients with truly causal interconnections is difficult. In many respects, elucidating the role of renal artery stenosis remains a clinical judgment based on time, duration, and severity, in addition to the practical difficulties in managing both blood pressure and kidney function. (From Safian RD, Textor SC. Medical progress: renal artery stenosis. *N Engl J Med*. 2001;344:431–442, with permission.)

42.7 Classification and Therapies for Renal Artery Stenosis

A. Functional Classification for Atherosclerotic Renal Artery Stenosis

Grade I: Renal artery stenosis present, but no clinical manifestations (normal blood pressure and normal renal function)
Grade II: Renal artery stenosis present, but patients have medically controlled hypertension and normal renal function
Grade III: Renal artery stenosis present and patients have evidence of abnormal renal function, medically refractory hypertension, or evidence of volume overload

B. Factors Favoring Specific Therapies for Renal Artery Stenosis

Factors favoring **medical therapy and revascularization** for renal artery stenosis
- Progressive decline in GFR during treatment of hypertension
- Failure to achieve adequate blood pressure control with optimal medical therapy
- Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure
- Decline in GFR during therapy with ACE inhibitors or ARBs
- Recurrent congestive heart failure in a patient in whom the adequacy of left ventricular function does not explain the cause

Factors favoring **medical therapy and surveillance** of renal artery disease
- Controlled blood pressure with stable renal function
- Stable renal artery stenosis without progression on surveillance studies (e.g., serial duplex ultrasound)
- Advanced age and/or limited life expectancy
- Extensive comorbidities that make revascularization too risky
- High risk or previous experience with atheroembolic disease
- Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g., diabetic nephropathy)

GFR, glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker. Adapted from the writing group for Atherosclerotic Peripheral Vascular Disease Symposium.[5,234]

life or regularly prevents ESRD.[11,158] The Centers for Medicare and Medicaid Services (CMS) commissioned a formal review of strategies for managing atherosclerotic renal artery disease. The results were published in 2006 and concluded that "data were insufficient to conclude substantial benefit regarding blood pressure control, kidney function or mortality for atherosclerotic renal artery disease" in favor of either specific management strategy.[159] Since that review, several prospective randomized trials have been reported or remain in progress, albeit with limitations (see the following). None have provided compelling evidence supporting a major benefit for renal revascularization for all patients, although a subgroup of patients in each of these studies has benefited. As noted previously, the burden of atherosclerotic disease associated with renal artery stenosis is often widespread and the causes of death include a broad array of cardiovascular events. Both endovascular and surgical intervention in the aorta and renal vasculatures carry substantial risks that may accelerate morbidity and the loss of renal function. As a result, these measures must be considered within the entire context of patient management over time.

There is little question that the more severe the hypertension, the greater the likelihood that it has a renovascular component and the more one has to gain by successful revascularization to facilitate BP control. Furthermore, younger patients with fibromuscular renal artery diseases have less risk of procedural complications and may respond well to revascularization with either angioplasty or surgery. However, the results of renal revascularization in patients with atherosclerotic renal artery disease are less favorable, because many of these patients are older and almost certainly have coexisting primary or essential hypertension.[56]

Unilateral Versus Bilateral Renal Artery Stenosis

Consideration of these disorders differs in some respects. In this context, bilateral refers to the circumstances when the entire functional renal mass is affected by vascular occlusion. This may be associated either with bilateral stenoses or stenosis to a solitary functioning kidney. Not only are the putative mechanisms related to BP and volume control different in the presence of a nonstenosed, functioning contralateral kidney with unilateral disease (as outlined under pathophysiology, previously), but also the potential hazards of intervention and/or medical therapy differ. Patient survival is reduced in patients with bilateral disease or stenosis to a solitary functioning kidney. Progressive arterial disease in this group also poses the most immediate hazard of declining renal function. Patient survival depends on the extent of vascular involvement[160] regardless of whether renal revascularization is undertaken.

Management of Unilateral Renal Artery Stenosis. Most patients with atherosclerotic renal artery disease have preexisting hypertension. As a result, most are exposed to antihypertensive therapy before the lesion has been identified and may be treated successfully with only moderate medication use.[34,161] Such patients commonly come to clinical attention when recognizable clinical progression occurs or when imaging is undertaken for other reasons. Occasionally, clinical decision making is influenced strongly by concerns about the hazards of medical therapy and failing to achieve both BP control and failing to maintain adequate blood flow soon enough. Examination of the results of medical therapy alone is important before evaluating the role of vascular reconstruction or dilation.

Since the introduction of agents blocking the RAS, most patients (86% to 92%) with unilateral renal artery disease can achieve blood pressure levels < 140/90 mm Hg with medical regimens based on these agents. Recent treatment trials[162–165] for ARAS confirm that target BP levels often can be achieved with optimized medical therapy with or without renal revascularization. It must be understood that widespread application of these agents to patients with many forms of cardiovascular disease already ensures that many subcritical cases of renovascular disease are treated medically unbeknownst to the clinician. Several clinical reviews, including large administrative databases, suggest that treating renal artery stenosis with ACE inhibitors or ARBs is associated with a more favorable patient outcome than that observed with other antihypertensive regimens.[89,166,167] Comparing 1,857 (53%) patients given either ACE inhibitors or ARBs out of 3,570 patients treated for renovascular disease, Hackam and colleagues[166] reported lower rates of overall mortality, congestive heart failure, and chronic dialysis in the group treated with RAAS blockers. There were, however, slightly higher rates of hospitalization for acute renal failure (1.2 versus 0.6 events per 100 patient years).[166] An example of a patient with complex aortic disease and high-grade unilateral ARAS managed for many years with ACE inhibitor therapy and diuretics is illustrated in Fig. 42.20A.

Do the risks of treating unidentified renal artery stenoses with antihypertensive drug therapy pose a hazard to patients? This issue is at the crux of many clinical debates

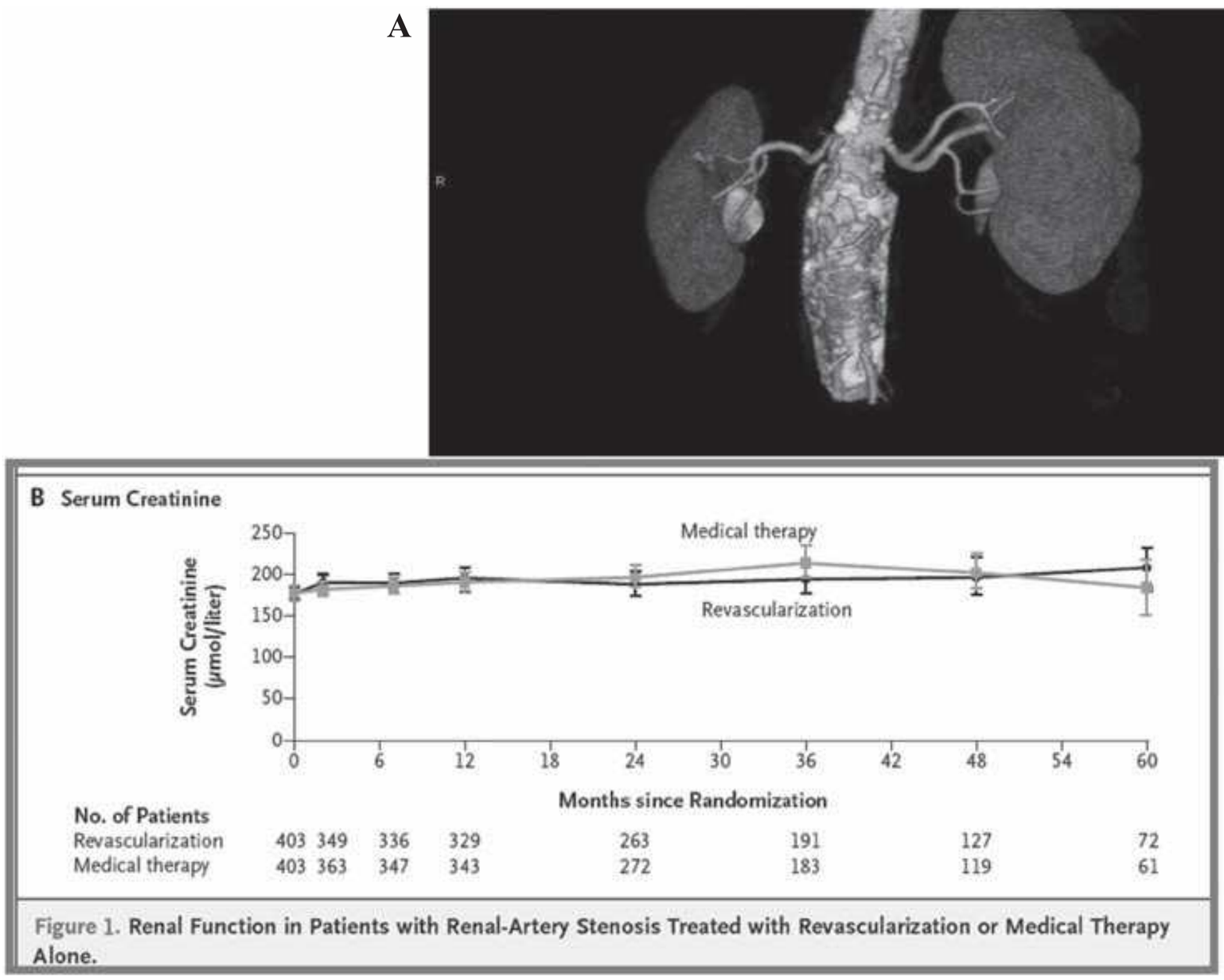

Figure 1. **Renal Function in Patients with Renal-Artery Stenosis Treated with Revascularization or Medical Therapy Alone.**

FIGURE 42.20 A and B: A computed tomography (CT) angiogram **(A)** obtained from a patient with high-grade renal artery stenosis leading to loss of parenchymal volume on the right kidney, but evidently normal blood flow and function on the left kidney. The aortic anatomy is complicated by an aneurysm formation and intramural thrombus that increases the hazards of endovascular stenting. This individual with unilateral renal arterial disease has been managed for years with stable renal function and blood pressure control with only modest antihypertensive drug requirements. Panel **B** reproduces the levels of serum creatinine for more than 400 patients in each group assigned to medical therapy with or without renal artery stenting in the ASTRAL trial. Patients assigned to this trial had moderate renal dysfunction that remained remarkably stable for the group as a whole during the follow-up approaching 5 years. Rates of progression to a renal endpoint were 16% to 20% in both groups. (From The ASTRAL Investigators. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med.* 2009;361:1953–1962, with permission.)

(and prospective, randomized clinical trials) regarding the management of patients with renovascular hypertension. Early studies with experimental clip hypertension emphasized renal fibrosis and scarring, which occur in the stenotic kidney in animals treated with ACE inhibitors. It is well recognized that the removal of the efferent arteriolar effects of Ang II pose the possibility of a loss of glomerular filtration in a kidney with reduced renal perfusion. Experimental studies in 2K-1C rats indicate that the loss of kidney function is sometimes irreversible, although survival is improved in ACE inhibitor–treated animals as compared to minoxidil-treated ones.[168] The unique role of ACE inhibitors and ARBs must be understood in this regard. Any drug capable of reducing systemic arterial pressure has the potential to lower renal pressures beyond a critical stenosis. As a result, successful antihypertensive therapy in renovascular disease has the theoretical result of reducing blood flow to the poststenotic kidney sufficient to induce vascular thrombosis. The unique feature of agents that block the RAS is the reduction of efferent arteriolar resistance sufficient to lower transcapillary filtration pressures, despite preserved blood flow to the glomerulus. This property is central to the benefits of this class of agents in hyperfiltration states thought to accelerate renal damage in other settings. In the presence of renovascular disease, the fall in glomerular filtration beyond a stenotic lesion can be observed despite relatively preserved plasma flows. The fall in GFR heralds an approaching degree of critical vascular compromise before blood flow itself is reduced.[169] Studies[170] in renovascular hypertensive animals confirm that despite a reduction in filtration, renal structural integrity can be preserved and recovered after the removal of the clip and/or the removal of the ACE inhibitor. Hence, it is unlikely that ACE inhibitors or ARBs themselves pose a unique hazard beyond that attributable to a reduction in renal blood flow.

Recent studies of patients with ARAS treated with ACE or ARBs indicate that even with up to 30% reductions of renal blood flow beyond ARAS, actual tissue oxygenation can be remarkably well preserved. Gloviczki and colleagues[64] studied subjects under standardized conditions to measure regional blood flows within both stenotic and contralateral kidneys, as well as tissue oxygenation estimated by BOLD MR. Despite demonstrating high-grade stenosis with lateralizing renin activity and reduced blood flow in unilateral ARAS, both cortical and medullary levels of tissue oxygenation (as reflected by levels of deoxyhemoglobin) did not differ from either the contralateral kidney or from patients with essential hypertension under the same conditions. These authors argued that many such patients do not suffer true kidney hypoxia any more than essential hypertension or normal kidneys. Such observations support the relative safety of medical therapy and may partly explain the stability of kidney function during medical therapy over many years, as reported in recent trials such as Angioplasty and Stenting for Renal Atherosclerotic Lesions (ASTRAL) (Fig. 42.20B).[42] It should be emphasized that the same study format indicates that such an adaptation for oxygen delivery in a poststenotic kidney has limits. When the degree of vascular occlusion becomes sufficiently severe, cortical perfusion falls and overt hypoxia can appear in both the cortex and the medulla.[171]

It is important to recognize that the contralateral kidney supports total glomerular filtration despite reduced filtration in the stenotic kidney. Hence, changes in overall GFR may be small or undetectable. This may be interpreted in several ways. Some authors argue in favor of using split renal function measurements, such as radionuclide renal scans, to detect a loss of individual kidney function as a means of timing revascularization.[91] Depending on the circumstances, a loss of function in one kidney may be an acceptable price if one can assure the patient that the remaining kidney has adequate function and blood supply. The fall in GFR from a loss of one kidney represents a loss of GFR analogous to that of donating a kidney for renal transplantation or nephrectomy for malignancy. In such instances, the long-term hazard to the remaining kidney is small, although not negligible.[172,173] As the age and comorbid burden of the population at risk rises, the loss of one kidney may pose little additional hazard if overall glomerular filtration is adequate. The experience with ACE inhibition in trials of congestive cardiac failure is reassuring in this regard. Thousands of patients with marginal arterial pressures and clinical heart failure have been treated over many years with a variety of ACE inhibitors, and more recently, ARBs. These patients are at a high risk for undetected renal artery lesions as part of the atherosclerotic burden associated with coronary disease. Although a minor change in creatinine is observed in 8% to 10% of these individuals, a rise sufficient to lead to withdrawal of these agents under trial monitoring conditions occurs in only 1% to 2%.[169,174] Data from patients with a high risk of cardiovascular disease treated with ramipril included patients with creatinine levels up to 2.3 mg per deciliter. Those with creatinine levels between 1.4 and 2.3 mg per deciliter were at a higher risk for cardiovascular mortality and had a major survival benefit from ACE inhibition. A close follow-up of kidney function indicated that the withdrawal of ACE inhibition due to a deterioration of renal function was less than 5% and no greater than placebo.[175]

Should patients be evaluated for ARAS before major surgery, such as coronary artery bypass grafting (CABG)? Some raise concerns that these patients may be at a higher risk for AKI. A report[176] of 798 patients undergoing CABG surgery after having a diagnostic aortogram to detect renal artery stenosis indicated no increase in AKI related to the presence of ARAS.

Progressive Renal Artery Stenosis in Medically Treated Patients. The potential for vascular occlusive disease to worsen is central to the management of patients with renovascular disease. It may be argued that failure to revascularize the kidneys exposes the individual to the hazard of undetected, progressive occlusion, potentially leading to

total blood flow and/or an irreversible loss of renal function. A firm understanding of the data regarding progressive atherosclerotic disease of the kidney is important for planning both endovascular and surgical revascularization.

Atherosclerosis is a variably progressive disorder. Managing disorders of the carotid, coronary, aortic, and peripheral vasculatures all recognize the potential for progression, which occurs at widely different rates between individuals. Medical therapy of all of these disorders should incorporate measures aimed at an intensive reduction of risk factors, of which smoking cessation, BP control, and correction of dyslipidemias are paramount. Treatment of these risk factors reduces mortality rates related to cardiovascular disease.[177]

How does progressive renal artery occlusive disease affect the management of renovascular hypertension? Moderate anatomic progression alone does not reliably predict functional changes in terms of deteriorating BP control or renal function. In serial reports[41] of Duplex ultrasound studies from Seattle, a decrement in measured renal size by 1 cm (renal atrophy) developed in 5.5% of those with normal initial vessels and in 20.8% of those with baseline stenosis > 60% during a follow-up interval of 33 months. Changes in serum creatinine were infrequent but did occur in a subset of patients, particularly those with bilateral renal artery stenosis. These are in general agreement with early studies during medical therapy of renovascular hypertension in which 35% had a detectable fall in measured renal length, but only 8 out of 41 (19%) had a significant rise in creatinine levels during a follow-up of 33 months. The follow-up of the medical treatment arms during short-term studies fails to show major changes in kidney function, although the occasional loss of renal perfusion by radionuclide scan is observed.[39]

How often does the management of renal artery stenosis without revascularization lead to clinical progression, either in terms of refractory hypertension or advancing renal insufficiency? A follow-up of patients with incidentally identified renal artery stenosis is helpful in this regard. Review of peripheral aortograms identified 69 patients with high-grade renal arterial stenoses (> 70%) who were followed without revascularization for more than 6 months. Their long-term follow-up identified generally satisfactory BP control, although some required more intensive antihypertensive therapy during an average of 36 months follow-up.[178] Four patients eventually underwent renal revascularization for refractory hypertension and/or renal dysfunction. Five developed ESRD, of which only one was thought to be related to RAS directly. Overall, serum creatinine levels rose from 1.4 mg per deciliter to 2.0 mg per deciliter. These data indicate that many such patients can be managed without revascularization for years and that clinical progression leading to urgent revascularization develops in 10% to 14% of such individuals. Expansion of this data set to 160 individuals allowed for a comparison of different antihypertensive regimens. The rates of progression did not appear related to the introduction of ACE inhibitors, although the level of BP control improved in later years.[179] These observations are supported by a report of 126 patients with incidental renal artery stenosis compared to 397 patients matched for age. Measured serum creatinine levels were higher, and calculated (Cockcroft-Gault) GFR was lower in patients with RAS who were followed for 8 to 10 years. However, none of the patients progressed to ESRD.[180]

What Can We Learn From Prospective Randomized Trials of Medical Therapy in Renovascular Disease? As noted previously, advances in both medical therapy for hypertension and revascularization procedures have shifted the balance for therapy enormously. No fewer than six prospective, randomized trials conducted in several countries have attempted to address the relative advantages of medical therapy as compared to revascularization for ARAS, either with endovascular or surgical methods. Most of these trials have been small with short-duration follow-ups and inconclusive. Results of two recent trials have appeared in the general medical literature, including the largest single trial of 806 patients from the United Kingdom in ASTRAL.[42,123] The major results of these trials are summarized in Table 42.8. Although the number of antihypertensive drugs were slightly lower in revascularized groups, BP levels often did not differ. Kidney function was unchanged overall in these trials. Procedural complications, although not common, were occasionally severe. Overall, these data fail to demonstrate clinically important benefits to renal revascularization in the patients enrolled during follow-ups between 2 and 5 years. The U.S. trial addressing overall cardiovascular outcomes, CORAL, which completed enrollment at the beginning of 2010, is the largest and is the most stringent regarding entry criteria. Data from CORAL are not expected until late in 2012 at the earliest.

Negative conclusions from these trials have been unsatisfying and widely criticized.[1,2,181] Recruitment for randomized controlled trials (RCTs) has been difficult, in part due to intense preconceptions of practicing clinicians. Many of the patients enrolled in these trials were found to have mild—sometimes trivial—vascular disease, clearly reducing the power of the study. In the STAR trial, for example, nearly a quarter of patients assigned to renal revascularization did not have the procedure performed because of a lack of clinically evident vascular stenosis at the time of angiography.[123] It is clear that many patients with high-grade disease, sometimes to a solitary functioning kidney, were not included in these trials out of a conviction on the part of the clinician that revascularization should or should not be considered. The largest trial to date, ASTRAL, excluded those "that required surgery" or were "likely to need" revascularization within 6 months. No contemporary registry of exclusions is available, nor is there any defined criteria for requiring intervention. Some authors have argued that atherosclerotic renal artery stenosis, in particular, is confounded so heavily with other individualized patient factors and comorbid disease risks that it cannot be addressed responsibly in a prospective trial format.[182]

Some observations from these trials warrant comment, however. The size (Table 42.8) and power estimates on

42.8 Characteristics of 1,208 Patients Included in Prospective, Randomized Trials for Atherosclerotic Renal Artery Stenosis Subjected to Meta-Analysis[235]

	EMMA	SNRASCG	DRASTIC	ASTRAL	STAR	NITER
Total Number Pts.	49	55	106	806	138	43
Inclusion	HTN/ unilateral	Resistant HTN/CKD	Resistant HTN	HTN/CKD/ Uncertainty	CKD	Resistant HTN/CKD
Age (mean)	59.4	61.1	59.9	70.5	66.5	72
F/U mos (mean)	6	12	12	33.6	24	43
Initial creatinine	1.2	1.8	1.3	2.0	1.7	1.7
Bilateral (%)	0	51	23	53	48	52
BP change (SBP/DBP)						
Med + PTRA	−12/−10	−15/−10	−19/−11	−6/−3	−10/−7	−5/−3
Med only	−8/−10	−6/−1	−17/−1	−8/−4	−9/−4	−6/−7

EMMA, Essai Multicentrique Medicaments vs Angioplastie, France 1998; SNRASCG: Scottish and Newcastle Renal Artery Stenosis Collaborative Group, UK, 1998; DRASTIC: Dutch Renal Artery Stenosis Intervention Cooperative study group, Netherlands, 2000; ASTRAL: Angioplasty and Stenting for Renal Artery Lesions, UK, Australia, New Zealand, 2009; STAR: Stenting for Atherosclerotic Renal artery lesions, Netherlands, 2009; NITER: Italy, presented in abstract form; HTN, hypertension; CKD, chronic kidney disease; Pts, patients; F/U, follow-up; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PTRA, percutaneous transluminal renal angioplasty.
These authors concluded that, taken together, blood pressure reductions with modest reductions in medication requirements were evident in revascularized patients. They could not identify differences in kidney function, cardiovascular events, or mortality in these trials between groups treated medically with or without revascularization. It should be emphasized that these trials were short in duration, mostly quite small and heterogeneous in their characteristics, and many patients were not treated as assigned (see text).

the part of planners reflect vastly different expected rates of progression and clinical events. The STAR trial reported results from 140 subjects, whereas the goal for CORAL based on overall cardiovascular outcomes was more than 1,000 subjects.[183] As often occurs in randomized trials, the event rates were lower than expected. Although average estimates for the severity of renovascular disease in ASTRAL exceeded 70% occlusion, the trial cohort included 40% of subjects between 50% and 70% occlusion, many of whom had only a minor disease. This was confirmed at the time of angiography, at which point 68 of 403 (17%) assigned to stenting failed to be treated, because many of them had only trivial vascular disease. Importantly, many patients in these trials achieved acceptable BP levels during medical therapy. Renal function was remarkably stable in both arms in ASTRAL over years of follow-up, thus reaffirming the observation that many patients can be managed for years. Crossover rates from medical to revascularization arms were between 6% and 24%, primarily due to treatment failures.

These observations extend and confirm results of prospective trials of medical versus surgical intervention started in the 1980s and extended into the 1990s.[184] No differences in patient survival or renal function could be identified. Taken together, all of these studies indicate that rates of progression of renovascular disease are moderate and occur at widely varying rates. Often, such patients can be managed without revascularization for many years. The clinical issue in a specific patient frequently hinges on whether or not the risks of revascularization are truly less than the risks of progression.

Although these reports are informative, they leave many questions unanswered (Table 42.9). How often does suboptimal BP control in renovascular hypertension accelerate cardiovascular morbidity and mortality? Does one lose the opportunity to reverse hypertension successfully by delaying renal revascularization? How often will the expense and morbidity associated with complex drug regimens lead to inadequate treatment and/or adverse outcomes compared to restoring blood flow? These issues will depend on more selective, long-term prospective studies. It is equally clear that for many patients with progressive disease, optimal long-term stability of kidney function and BP control can be achieved by successful surgical or endovascular restoration of the renal blood supply.

42.9 Limitations of Clinical Trials in Atherosclerotic Renal Artery Stenosis

1. Patient selection
   a. Most severe cases not considered for randomization
   b. Most severe hypertension and progressive renal disease not included
   c. Limited selection of antihypertensive drug therapy
      i. Role of renin-angiotensin system blockade
      ii. Nonstandardized measurement of outcomes: BP levels
   d. Nonstandardized therapy for dyslipidemia/comorbid disease
2. Outcome measurement
   a. Widely variable definitions of BP goals, achieved levels
   b. Variable measurement of renal function
   c. Circulatory congestion/volume control/drug selection
   d. Crossovers from medical to interventional arms: 20%–44%
   e. Short duration of follow-up
3. Confounders limiting interpretation
   a. Roles and magnitude of comorbid disease: diabetes, preexisting cardiovascular disease
   b. Age/timing of intervention/timing of detection of disease
   c. Intermixing degree of renal involvement/tissue at risk: roles of unilateral and bilateral disease unevenly addressed
   d. Rates of development of disease, including renal dysfunction/BP changes
   e. Definition of treatment resistance

BP, blood pressure.
From Textor SC, McKusick MA, Misra S, Glockner J. Timing and selection for renal revascularization in an era of negative trials: what to do? Prog Cardiovasc Dis. 2009;52:220–228, with permission.

ENDOVASCULAR RENAL ANGIOPLASTY AND STENTING

The ability to restore vessel patency in high-risk patients with renovascular hypertension and ischemic nephropathy using endovascular methods undoubtedly represents a major advance in this disorder. Stenting allows the reversal of major degrees of vascular occlusion in more than 98% of cases, as illustrated in Fig. 42.21A,B. The restoration of blood flow to the kidney beyond a stenotic lesion seems to provide an obvious means to improve renovascular hypertension and to halt progressive vascular occlusive injury. For clinicians experienced in the field of renovascular hypertension, these developments represented a major breakthrough that hardly required testing in a controlled trial. As one author[185] argued in 2005, "A recent report on the use of parachutes to prevent death and major injury after jumping out of airplanes emphasized the fact that the parachute has never been subjected to a randomized controlled trial, even though numerous reports of survival after jumping without a parachute have been published."

The past 2 decades have been characterized by a major shift from surgical reconstruction toward preference for endovascular procedures. The total volume of renal revascularization procedures registered for the U.S. Medicare population above age 65 rose 62% from 13,380 to 21,600 between 1996 and 2000. This change reflects an increase in endovascular procedures by 2.4-fold, whereas surgical renovascular procedures fell by 45%. The trend continued with an estimate of 35,000 endovascular procedures in 2005 (Fig. 42.21C).[9,186] The transition to endovascular procedures also has enlarged and reconfigured the physician pool engaged in making decisions about renovascular hypertension. Interventional cardiologists increased their activity in this field nearly fourfold during this interval.

Revascularization of the kidney carries both benefits and risks, however. With older patients developing renal artery stenosis in the context of preexisting hypertension in the present era, the likelihood of a cure for hypertension is small, particularly in atherosclerotic disease. The true risks and benefits of these procedures are sometimes difficult to ascertain from published literature. They may vary between institutions depending on the technical expertise available. As noted in the following, methods of reporting results regarding clinical outcomes are inconsistent. Although complications are not common, they can be catastrophic, including atheroembolic disease and aortic dissection. Wide variability in the experience with peripheral endovascular procedures is reflected by the observation that their use, combining renal and lower extremity vascular stents, varies more than 14-fold between regions in the United States.[187] The probability of renal angioplasty within 30 days of cardiac catheterization has been fourfold higher when cardiologists perform the procedure than when interventional radiologists are responsible. Knowing when to pursue renal revascularization is central to the dilemma of managing renovascular disease.

Angioplasty for Fibromuscular Disease

Most lesions of medial fibroplasia are located at a distance 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.[188] Some of these lesions (approximately 10%) develop restenosis for which repeat procedures have been used.[189] Clinical benefit regarding BP control has been reported in observational outcome studies in 65% to 75% of patients, although the rates of cure are less secure.[190] Cure of

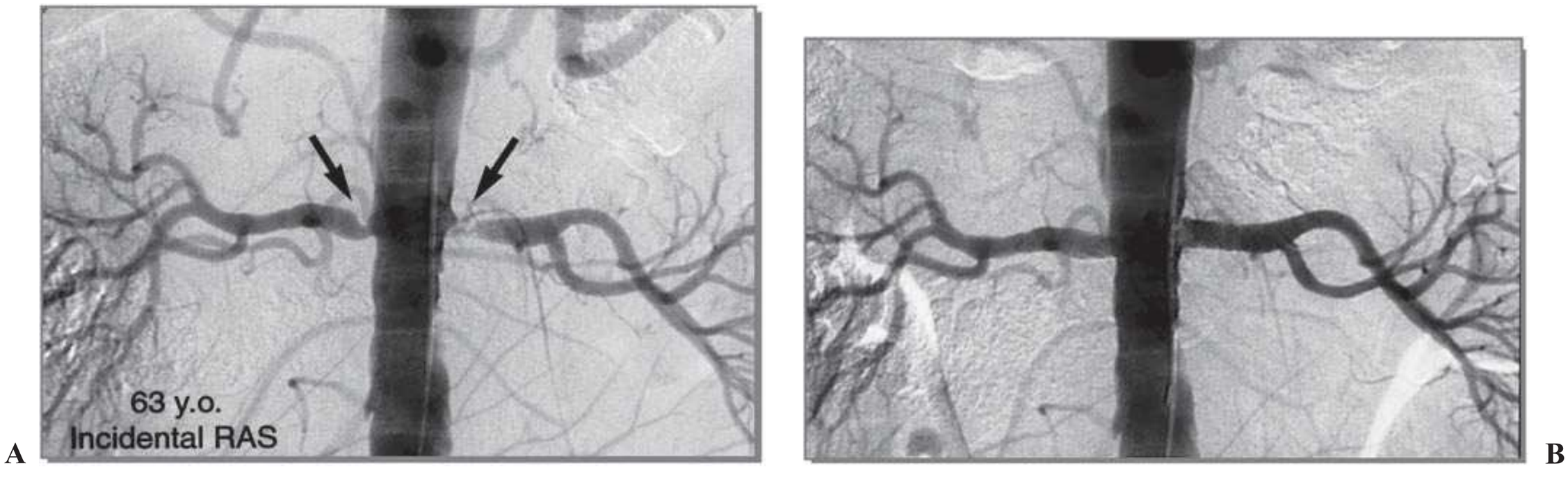

FIGURE 42.21 An angiogram obtained before **(A)** and after **(B)** renal artery stenting in an individual developing rapidly progressing renovascular hypertension. The ability to restore vascular patency using endovascular procedures has allowed many more patients to be treated than would have been considered for renovascular surgery. Development of these methods led to the striking expansion of renal artery stenting procedures, as reflected by the rise in Medicare claims submitted between 1996 and 2005 (see text) **(C).** *RAS*, renin-angiotensin system.

hypertension, defined as sustained BP 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 at 6 months and beyond after angioplasty) include lower systolic BP, younger age, and a shorter duration of hypertension.[191] A systematic analysis of treatment reports for fibromuscular dysplasia evaluated evidence from 47 series treated with angioplasty (1,616 patients) and 23 surgical series (1,014 patients).[192] Methods of evaluating BP outcomes and definitions of cure varied considerably in these reports. However, by selecting the criterion of BP $<$ 140/90 mm Hg after withdrawing antihypertensive drug therapy as a cure in contemporary terms, these authors found that only 36% of percutaneous transluminal renal angioplasty (PTRA)-treated patients and 54% of surgical patients achieved that response. Predictors of a favorable response included younger age and earlier date of publication. Major complications were lower with PTRA versus surgery (7% versus 15%). Hence, these authors concluded that renal revascularization even for FMD offers "moderate benefit."[192]

A large majority of patients with FMD are female. The age of detecting hypertension is usually younger than the series with atherosclerotic disease.[190] In general, such patients have relatively less aortic disease and are at less risk for major complications of angioplasty. Because the risk for major procedural complications is low and the potential antihypertensive drug treatment requirement is so long, most clinicians favor an 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

During the introduction of PTRA, it was soon evident that ostial lesions commonly failed to respond, in part because of extensive recoil of the plaque, which extended into the main portion of the aorta.[193] These lesions develop restenosis rapidly even after early success. Endovascular stents were introduced for ostial lesions in the late 1980s and early 1990s.[194]

The technical advantage of stents to achieve and maintain vessel patency is indisputable. An example of successful renal artery stenting is shown in Fig. 42.21. A prospective comparison between angioplasty alone versus angioplasty with stents indicates intermediate (6 to 12 months) vessel patency was 29% and 75%, respectively. Restenosis fell from 48% to 14% in stented patients.[193] 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%.[150,195]

The introduction of endovascular stents has expanded the practice of renal revascularization, in part because of the improved technical patency that is possible with ostial atherosclerotic lesions as compared to angioplasty alone. It should be emphasized that much of the shift to endovascular procedures relates to their applicability in elderly patients and the widespread availability of interventional radiology.

What are the reported outcomes of patients undergoing renal artery stenting? These are commonly considered in terms of (1) BP control and (2) the preservation or salvage of renal function in ischemic nephropathy. Results from observational cohort BP studies after stenting face the same limitations as observed with angioplasty alone. Results during the follow-up from 1 to 4 years are summarized for representative series in Table 42.10. These have been reviewed elsewhere.[196] Typically, a fall in BP levels are in the range of 25 to 30 mm Hg systolic, the best predictor of which was the initial systolic BP.[197] Some authors report a 42% improvement in BP with fewer medications needed, although cures were rare and renal function was unchanged.[198] A careful attention to the degree of residual patency led to more than 91% patency at 1 year and 79% at 5 years in 210 patients with stents.[118] BPs were cured or improved in more than 80% of cases. In some cases, angina and recurrent congestive cardiac failure subsides.[199,200] As noted under the trials summarized previously, prospective randomized controlled trials have been less impressive regarding the benefits of angioplasty. The ambiguity of BP responses in these studies has produced widely different recommendations. These range from "we are left with whether renal angioplasty should be considered at all"[201] to a general conviction expressed within the interventional community that "open renal arteries are better than closed renal arteries" and that nearly all renal artery lesions should be opened (and probably stented).[150]

What results regarding the recovery of renal function can be expected after endovascular revascularization? Table 42.10 summarizes some of the recent series. In general, changes in renal function for atherosclerotic renal artery stenosis, as reflected by serum creatinine levels, have been small.[158] Remarkably, the changes in renal function in azotemic patients after surgical reconstruction are similar.[202,203] As we and others have observed, overall group changes in kidney function can be misleading. A careful evaluation of the literature indicates that three distinctly different clinical outcomes are routinely observed for patients with reduced GFR. In some instances (approximately 27%), revascularization produces meaningful improvements in kidney function. For this group, the mean serum creatinine level may fall from a mean value of 4.5 mg per deciliter to an average of 2.2 mg per deciliter. There can be no doubt that such patients benefit from the procedure and can avoid major morbidity (and probably mortality) associated with advanced renal failure. The bulk of patients (approximately 52%), however, have no measurable change in renal function. Whether such patients benefit much depends on the true clinical likelihood of progressive renal injury if the stenotic lesions were managed without revascularization, as discussed previously. Those without much risk of progression gain little. The most significant concern, however, is the group of patients whose renal function deteriorates further after a revascularization procedure. In most reports, this ranges from 19% to 25%.[158,204] In some instances,

42.10 Observational Outcomes of Renal Artery Stent Placement: Hypertension[118,193,194,198,204,206,236–240]

	Cured	Improved	No change
14 series n = 678 patients 98% technical success	Weighted mean: 17% Range: 3–68	Weighted mean: 47% Range: 5–61	Weighted mean: 36% Range: 0–61
Renovascular hypertension n = 472	12%	73%	15%
Renal Artery Stents: Effect on Renal Function in Azotemic Patients			
	Improved	**Stabilized**	**Worse**
14 series reporting "impaired renal function" n = 496 patients	Weighted mean: 30% Range: 10%–41%	Weighted mean: 42% Range: 32%–71%	Weighted mean: 29% Range: 19%–34%
Ischemic nephropathy n = 469	41%	37% no change	22%

this represents atheroembolic disease, or a variety of complications including vessel dissection with thrombosis.[205] Although less common with improved techniques, some of the complications associated with renal artery stenting can be clinically significant, as identified in Table 42.11. Hence, nearly 20% of azotemic patients face a relatively rapid progression of renal insufficiency and the potential for requiring renal replacement therapy, including dialysis and/or renal transplantation.[203,206,207] Possible mechanisms for deterioration include atheroembolic injury, which may be nearly universal after any vascular intervention[208] and acceleration of oxidative stress producing interstitial fibrosis.[209] Whether improving techniques, including the application of distal protection devices for endovascular catheters, will reduce these complications is not yet certain.

Several studies suggest that the progression of renal failure attributed to ischemic nephropathy may be reduced by endovascular procedures.[204,210] Harden et al.[204] presented reciprocal creatinine plots in 23 (of 32 patients), suggesting that the slope of loss of the GFR could be favorably changed after renal artery stenting. It should be emphasized that 69% "improved or stabilized," indicating that 31% worsened; these results were consistent with other series. These reports and a guideline document from the American Heart Association promote the use of breakpoint analysis to analyze and report the results of renovascular procedures. Caution must be applied regarding the use of breakpoints using reciprocal creatinine plots in this disorder, however. This concern was underscored by a report attempting to use estimated GFR (eGFR) changes compared to measured iothalamate GFR values to follow sequential changes in kidney function in atherosclerotic disease. Madder and colleagues[211] found that the staging of kidney disease—and even the direction of change, whether improving or deteriorating—in 254 patients was discordant between 28% and 40% of cases. Vascular disease does not affect both kidneys symmetrically, nor is it likely to follow a constant course of progression, in contrast to diabetic nephropathy, for example. As a result, a gradual loss of renal function with subsequent stabilization can be observed equally with unilateral disease, leading to total occlusion as well as successful revascularization. Perhaps the most convincing group data in this regard derive from serial renal functional measurements 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 per deciliter. Follow-ups over a mean of 20 months indicate that the slope of GFR loss converted from negative (−0.0079 dL/mg/mo) to positive (0.0043 dL/mg/mo).[210] 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 (see previous).

42.11 Complications After PTRA and Stenting of the Renal Arteries[205,206,227]

Minor: (most frequently reported)
- Groin hematoma
- Puncture site trauma

Major: (Reported in 71/799 treated arteries (9%)[227]
- Hemorrhage requiring transfusion
- Femoral artery pseudoaneurysm needing repair
- Brachial artery traumatic injury needing repair
- Renal artery perforation leading to surgical intervention
- Stent thrombosis: surgical or antithrombotic intervention
- Distal renal artery embolus
- Iliac artery dissection
- Segmental renal infarction
- Cholesterol embolism: renal
- Peripheral atheroemboli
- Aortic dissection[205]

Restenosis: 16% (Range: 0%–39%)

Deterioration of renal function: 26% (range: 0%–45%)

Mortality attributed to procedure: 0.5%

Procedure-related complications: 51/379 patients in 10 series: 13.5% (206)

Surgical Treatment of Renovascular Hypertension and Ischemic Nephropathy

Early experience with vascular disease of the kidney was based entirely on surgical intervention, either nephrectomy or vascular reconstruction, with the objective of surgical curability.[10] For that reason, much of the original data regarding split renal function measurements were geared toward identifying functionally significant lesions as a guide by which patients should be selected for a major surgical procedure. Surgical intervention is less commonly performed in the current era, in part because age and comorbid risks of patients with atherosclerotic disease commonly favor endovascular procedures when feasible.

Methods of surgical intervention have changed over the decades. A review in 1982 emphasized the role for ablative techniques, including the partial nephrectomy. Use of ablative operative means was guided by the difficulty of controlling BP during this period. They are less common since the expansion of tolerable medication regimens, as noted previously. The recent introduction of laparoscopic techniques, including the hand-assisted nephrectomy, may return attention to nephrectomies as a means to reduce medication requirements with low morbidity in high-risk patients.

Surgical series from the 1960s and early 1970s indicated that the cure of hypertension was present only in 30% to 40% of subjects, despite attempts at preselection. The survival of groups chosen for surgery appeared to be better than those chosen for medical management. This likely reflected the heavy disease burden and preoperative risks identified in those for whom surgery was excluded. The Cooperative Study of Renovascular Disease in the 1960s and 1970s examined many of the clinical characteristics of renovascular hypertension. These studies identified some of the limitations and hazards of surgical intervention and reported mortality rates of 6.8%, even in excellent institutions. The mean age in this series was 50.5 years. Definitions of operative mortality included events as late as 375 days after the procedure and may have overestimated the hazard. Had the authors considered only deaths within the first week, for example, the immediate perioperative mortality was 1.7%.[107]

The subsequent development of improved techniques for patient selection, including screening for coronary and carotid disease, for renal artery bypass, and endarterectomy, and for combined aortic and renal artery repair, represent major elements in the history of vascular surgery.[10] Several of the options developed for renal artery reconstruction are listed in Table 42.12. Most of these methods focus on reconstruction of the vascular supply for the preservation of nephron mass. A transaortic endarterectomy can effectively restore circulation to both kidneys. It requires aortic cross-clamping and may be undertaken as part of a combined procedure with aortic replacement. The identification and treatment of carotid and coronary disease led to reductions in surgical morbidity and mortality. By addressing associated cardiovascular risk before surgery, early surgical mortality falls below 2% for patients without other major diseases.

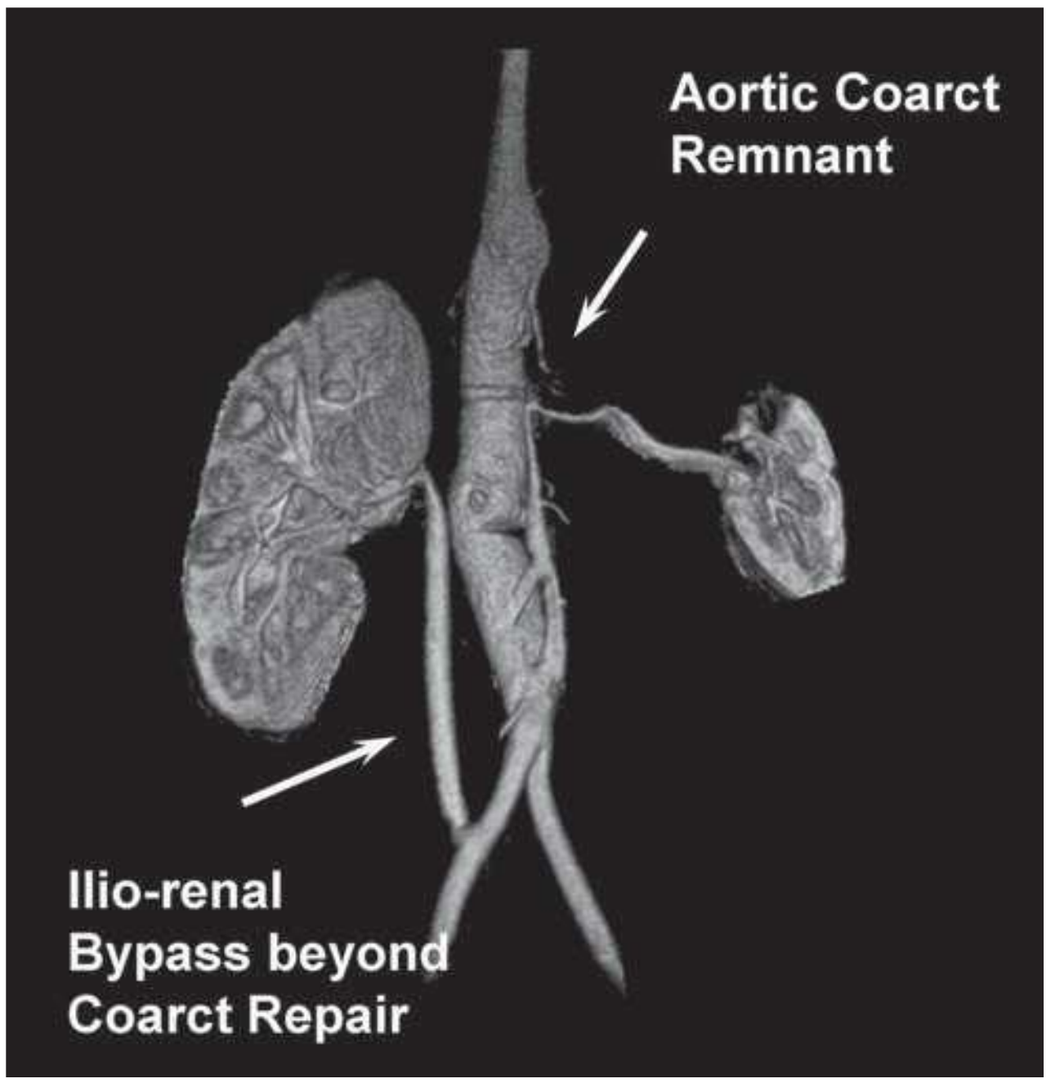

FIGURE 42.22 The surgical correction of renovascular disease. This is an example of late renal artery compromise after the correction of aortic coarctation in childhood. The tenuous status of renal circulation was corrected by construction of an ilio-renal bypass. These operative procedures now are reserved mainly for complex cases and repeated failures of endovascular stenting.

42.12 Surgical Procedures Applied to Reconstruction of the Renal Artery and/or Reversal of Renovascular Hypertension

Ablative Surgery: removal of a pressor kidney
- Nephrectomy: direct or laparoscopic
- Partial nephrectomy

Renal artery reconstruction (require aortic approach)
- Renal endarterectomy
- Transaortic endarterectomy
- Resection and reanastomosis: suitable for focal lesions
- Aortorenal bypass graft

Extra-anatomic procedures: (may avoid direct manipulation of the aorta)
- Require adequate alternate circulation without stenosis at celiac origin
- Splenorenal bypass graft
- Hepatorenal bypass graft
- Gastroduodenal, superior mesenteric, iliac-to-renal bypass grafts

Autotransplantation with ex vivo reconstruction

Modified from Libertino JA, Zinman L. Surgery for renovascular hypertension. In: Breslin DL, Swinton NW, Libertino JA, Zinman L, eds. Renovascular Hypertension. Baltimore, MD: Williams and Wilkins; 1982: 166–212.

Surgical reconstruction of the renal blood supply usually requires access to the aorta. A variety of alternative surgical procedures have been designed to avoid manipulation of the badly diseased aorta, including those for which previous surgical procedures make access difficult (Fig. 42.22). These include extra-anatomic repair of the renal artery using hepatorenal or splenorenal conduits, which avoid the requirement of manipulation of badly diseased aorta.[212] It should be emphasized that success with extrarenal conduits depends on the integrity of the alternative blood supply. Hence, a careful preoperative assessment of stenotic orifices of the celiac axis is undertaken before using either the hepatic or splenic arteries. The results of these procedures have been good, both in short-term and during long-term follow-up studies.[213] An analysis of 222 patients treated more than 10 years earlier indicated that these procedures were

performed with 2.2% mortality and low rates of restenosis (7.3%) and good long-term survival. The predictors of late mortality were age above 60 years, coronary disease, and previous vascular surgery.

The durability of surgical vascular reconstruction is well established. Follow-up studies after 5 and 10 years for all forms of renal artery bypass procedures indicate excellent long-term patency (above 90%) both for renal artery procedures alone and when combined with aortic reconstruction.[214] Results of surgery have been good despite increasing age in the reported series. Patient selection has been important in all of these reports. Although long-term outcome data are established for surgery, limited information is available for endovascular stent procedures, which are more prone to restenosis and technical failure. This proven record of surgical reconstruction leads some clinicians to favor this approach for younger individuals with longer life expectancies.

Some studies have compared endovascular intervention (PTRA without stents) and surgical repair. A single study of nonostial, unilateral atherosclerotic disease in which patients were randomly assigned to surgery or PTRA indicate that although surgical success rates were higher and PTRA was needed on a repeat basis in several cases, the 2-year patency rates were 90% for PTRA and 97% for surgery.[215] A prospective comparison of endovascular stents compared to open surgical renal revascularization argued that patency over 4 years was better with open surgical repair, but that otherwise, the outcome of the two procedures did not differ.[216]

In many institutions, surgical reconstruction of the renal arteries is most often undertaken as part of aortic surgery. Those with impaired renal function at the Mayo Clinic (creatinine ≥ 2.0 mg per deciliter) underwent simultaneous aortic and renal procedures in 75% of cases.[202] Recent experience indicates that combining renal revascularization with aortic repair does not increase the risk of the aortic operation. As with endovascular techniques, the results regarding changes in renal function include improvement in 22% to 26%, no change (some consider this stabilization) in 46% to 52%, and progressive deterioration in 18% to 22% (Fig. 42.23). Using intraoperative color flow Doppler ultrasound allows for the immediate correction of suboptimal results and improved long-term patency.[217] Despite good results, open operations for renal artery revascularization continue to decline. A review of the National Inpatient Sample indicates relatively high mortality rates (approximately 10%) overall, leading the authors to support lower risk endovascular methods where possible or a referral to high volume surgical centers.[218] For experienced centers using current techniques, operative risk is below 4% in good risk candidates.[219,220] Factors for higher risk include advanced age,

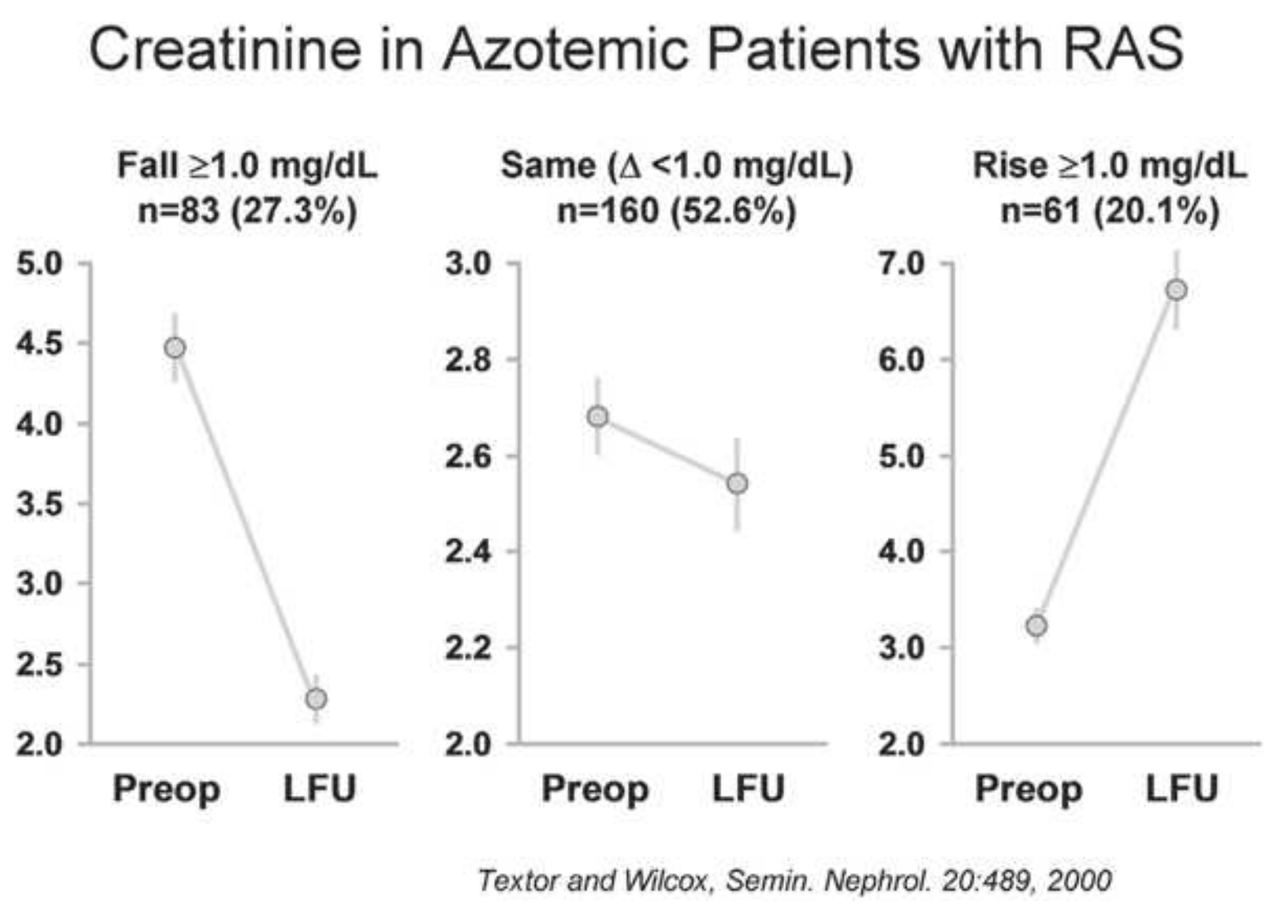

FIGURE 42.23 Renal functional outcomes following surgical revascularization of more than 300 patients with serum creatinine above 2.0 mg per deciliter. Although mean values for the entire group were unchanged, these figures obscured the fact that meaningful clinical improvement (defined as a fall in creatinine ≥ 1.0 mg per deciliter) was evident in 27.3%, and creatinine remained stable in 52.6% (thereby avoiding progression). These outcomes were counterbalanced in this cohort by 20.1% experiencing a distinct worsening of kidney function (defined as a rise in creatinine of more than 1 mg per deciliter). These outcomes have been remarkably reproducible in azotemic patients regardless of the method of revascularization and have been attributed to a variety of effects, including atheroembolic complications.[158] The identification of subjects likely to benefit from revascularization remains a primary challenge in this disorder. RAS, renal artery sclerosis; LFU, last follow-up. (From Textor SC, Wilcox CS. Renal artery stenosis: a common, treatable cause of renal failure? *Annu Rev Med.* 2001;52:421–442, with permission.)

elevated creatinine (above 2.7 to 3.0 mg per deciliter) and associated aortic or other vascular diseases. In some cases, nephrectomy of a totally infarcted kidney provides major improvement in BP control at low operative risk. The introduction of laparoscopic surgical techniques makes nephrectomy technically easier in some patients for whom vascular reconstruction is not an option. These series reflect widely variable methods of determining BP benefits, as discussed in the following.

Studies in patients with bilateral renal artery lesions or vascular occlusions to the entire renal mass indicate that the restoration of blood flow can lead to preservation of renal function in some cases.[221] Most often, this has been undertaken when a clue of preserved blood supply, sometimes from capsular vessels, is evident by renography. Occasionally, revascularization can lead to functional recovery that is sufficient to eliminate the need for dialysis.

Predictors of Likely Benefit Regarding Renal Revascularization

Identifying patients who are most likely to improve their BP and/or renal function after renal revascularization remains an elusive task. As noted previously, functional tests of renin release, such as the measurement of renal vein renin levels, have not performed universally well. Many of these studies are most useful when positive (e.g., the likelihood of benefit improves with more evident lateralization), but have relatively poor negative predictive value; that is, when such studies are negative, outcomes of vessel repair may still be beneficial. As a clinical matter, the recent progression of hypertension remains among the most consistent predictors of improved BP after intervention.

Predicting favorable renal functional outcomes is also difficult. Either surgical or endovascular procedures are least likely to benefit those with advanced renal insufficiency, which is usually characterized by serum creatinine levels above 3.0 mg per deciliter. Nonetheless, occasionally, patients with recent progression to far advanced renal dysfunction can recover GFR with durable improvement over many years. Small kidneys, as identified by a length less than 8 cm, are less likely to recover function, particularly when little function can be identified on radionuclide renography.[222] Reports of the renal resistance index as measured by Doppler ultrasound in 5,950 patients indicated that the identification of lower resistance was a favorable marker for both an improvement in GFR and BP, whereas an elevated resistance index was an independent marker of poor outcomes (Fig. 42.14).[125] None of these is absolute, and recent studies identify favorable outcomes in some patients with adverse predictors.[223] Some authors suggest that detecting abnormalities in fractional flow reserve, as measured by translesional flows and gradients after dilation with papaverine, may predict benefits of revascularization.[156,224] Recent deterioration of kidney function or hypertension portends a more likely improvement with revascularization.

Complications of Renal Artery Angioplasty and Stenting

Atherosclerotic plaque is commonly composed of multiple layers with calcified, fibrotic, and inflammatory components. The physical expansion of such a lesion applies considerable force to the wall of the artery and may lead to cracking and the release of small particulate debris into the bloodstream. Effective balloon angioplasty and stenting requires applying optimal techniques for limiting the damage to blood vessels during the procedure. A review[206] of 10 published series with 416 stented vessels indicated that significant complications arise in 13% of cases, not counting those that led to the need for dialysis. These include several of the events listed in Table 42.11, including hematomas and retroperitoneal bleeding requiring transfusion. Renal function deteriorated in these series on average 26% of the time and 50% of subjects (7 out of 14) with preprocedure creatinine levels above 400 mc/mol progressed to advanced renal failure requiring dialysis.[206] Most complications are minor, including local hematomas and false aneurysms at the insertion site. Occasional severe complications develop, including aortic dissection,[205] stent migration, and vessel occlusion with thrombosis.[225] Local renal dissections can be managed by the judicious application of additional stents. Mortality related directly to this procedure is small, but has been reported in 0.5% to 1.5% of patients.[206,223]

Restenosis remains a significant clinical limitation. Rates vary widely between 13% and 30%, most often developing within the first 6 to 12 months.[206,226–228] The most recent series reported 13% to 16% restenosis, sometimes leading to repeat procedures.

SUMMARY

Renovascular disease is common, particularly in older subjects with other atherosclerotic disease. It can produce a wide array of clinical effects, ranging from asymptomatic incidentally discovered disease to accelerated hypertension and progressive renal failure. With improved imaging and older patients, significant renal artery disease is detected more often than ever before. It is incumbent upon the clinician to evaluate both the role of renal artery disease in the individual patient and the potential risk/benefit ratio for renal revascularization. An algorithm to guide treatment and reevaluation of patients with atherosclerotic renal artery stenosis is presented in Fig. 42.24. The application of this strategy relies heavily on considering comorbid risks and the evolution of both BP control and kidney function over a period of time. Managing cardiovascular risks and hypertension are the primary objectives of medical therapy. For most patients, the realistic goals of renal revascularization are to reduce medication requirements and to stabilize renal function over time. Patients with bilateral disease or stenosis to a solitary functioning kidney may have a lower risk of circulatory congestion (flash pulmonary edema or its equivalent) and

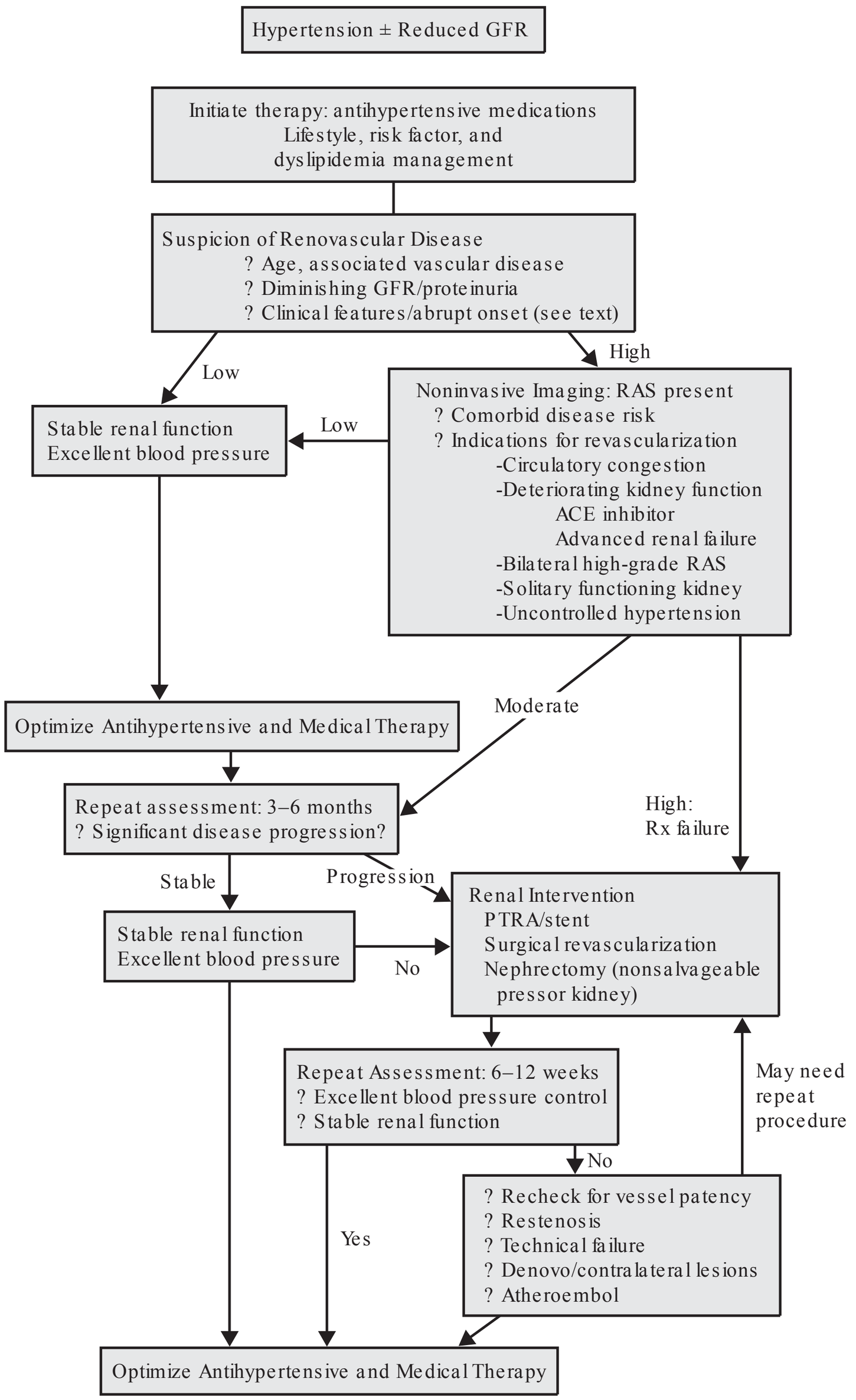

FIGURE 42.24 An algorithm proposed for the identification and management of renovascular disease and ischemic nephropathy. In general, antihypertensive drug therapy is a primary mode of therapy. If kidney function and blood pressure are stable and controlled with a tolerable regimen, there may be little to gain from an extensive evaluation for renovascular disease. If there is high suspicion for developing renovascular disease and/or a commitment to intervene, then more extensive imaging is appropriate. Indications for renal revascularization should be clearly defined before this process proceeds. If kidney function, blood pressure control, or circulatory congestion is inadequate and the individual is prepared to accept the hazards of revascularization, this may be appropriate. As with any vascular disease, periodic follow-up for disease progression and/or recurrence is warranted (see text). GFR, glomerular filtration rate; RAS, renal artery sclerosis; ACE, angiotensin-converting enzyme; PTRA, percutaneous transluminal renal angioplasty. (From Textor SC. Renovascular hypertension and ischemic nephropathy. In: Brenner BM, ed. *Brenner and Rector's: The Kidney*. Philadelphia, PA: Saunders; 2008: 1528–1566, with permission.)

a lower risk for advancing renal failure after revascularizing the kidney. It is essential to appreciate the risks inherent in either surgical or endovascular manipulation of the diseased aorta. These include a hazard of atheroembolic complications and the potential deterioration of renal function related to the procedure itself (estimated at 20% for patients with preexisting kidney dysfunction). Hence, the decision to undertake these procedures should include consideration of whether the potential gain warrants such risks. In many cases, improved BP and the recovery of renal function justify the costs and hazards completely. A follow-up of both BP and renal function is important, particularly because of the

potential for restenosis and/or recurrent disease. Optimal selection and timing for medical management and revascularization depend largely on the comorbid conditions for each patient.

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