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“Current Approaches to Renovascular Hypertension”

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Introduction

Understanding the mechanisms and implications of renovascular disease remains an important challenge for clinicians caring for patients with hypertension. “Renovascular hypertension” is defined as systemic hypertension resulting from renal arterial compromise, often due to occlusive lesions of the main renal arteries. In classical definitions, the conclusion that hypertension is related directly to an arterial lesion depends upon reversal of the hypertension after relief of the obstruction. In practice, obtaining complete “reversal” of hypertension is rarely possible. It is important to recognize that renovascular disease often accelerates pre-existing hypertension, can ultimately threaten the viability of the post-stenotic kidney and impair sodium excretion in subjects with congestive heart failure.

Major advances in vascular imaging allow non-invasive identification of vascular lesions more easily than ever before. At the same time, introduction of effective, well-tolerated antihypertensive drug therapy for renovascular hypertension allows more effective medical management of this disorder than ever before. While renovascular hypertension appears on lists of “curable” forms of hypertension, outcomes from recent, small prospective trials up to now fail to establish major benefits of revascularization, either performed by endovascular procedures or surgery (1). These observations leave both patients and physicians uncertain about how best to treat renovascular hypertension, particularly with regard to moving ahead with either endovascular or surgical intervention. In view of this “equipoise” between medical therapy and renal revascularization, the National Institutes of Health in the United States are supporting a major prospective, randomized trial comparing intensive medical therapy alone to intensive therapy plus renal revascularization regarding the Cardiovascular Outcomes for Renal Atherosclerotic Lesions (CORAL). Until these questions are more clearly answered, physicians dealing with complex hypertension are understandably uncertain about the value of embarking on expensive, sometimes hazardous, diagnostic workups and vascular intervention.

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This review examines the current status regarding prevalence, mechanisms, clinical manifestations and management of renovascular hypertension at this point in time. It should be viewed as a work in progress. As with most complex conditions, clinicians must integrate the results of published literature studies while considering each patient's specific features and comorbid disease risks. Beyond identifying renovascular disease as a cause of secondary hypertension, one must manage renal artery stenosis (RAS) itself as an atherosclerotic vascular complication. This disease warrants follow-up regarding progression and potential for ischemic tissue injury. These elements often determine the role and timing for revascularization. In this respect, atherosclerotic renal artery stenosis is analogous to progressive carotid or aortic aneurysmal disease. Because selection of imaging tools and further diagnostic studies related to management of this condition often depends upon the clinical commitment to act upon those results, the section on imaging and diagnosis is positioned after initial management.

Pathophysiology

Studies demonstrating that vascular occlusion to the kidneys produces a rise in systemic arterial pressure remain among the seminal observations regarding pathogenic mechanisms for hypertension (2). Experimental models of renovascular hypertension, including those in which a normal contralateral kidney is exposed to pressure natriuresis (2-kidney-1-clip) and those for which the entire functioning renal mass is beyond a vascular occlusion (1-kidney-1-clip) remain among the most widely studied models of hypertension. For the models with a normal contralateral kidney, hypertension is more predictably angiotensin-dependent. These models have been adapted to numerous species including mouse, rat, dog and pig (3). These are widely accepted as fundamental models of angiotensin-mediated hypertension for studies directed toward vascular remodeling, left-ventricular hypertrophy, small vessel occlusive disease and renal dysfunction. Table 1 lists several of the causes of renal artery obstruction recognized as producing this syndrome. While intrinsic renovascular disorders related to atherosclerotic and fibromuscular disease are most common, it should be recognized that any structural disorder reducing renal perfusion pressure to viable kidney tissue is capable of producing renovascular hypertension.

Activation of the renin-angiotensin system is an essential component of developing renovascular hypertension, at least in the initial stages. Studies in which animals are pre-treated with angiotensin-converting enzyme (ACE) inhibition indicate that development of hypertension is delayed so long as ACE inhibition continues. Genetic knockout animals without the angiotensin-1 receptor do not develop renovascular hypertension. Recent transplantation studies indicate that angiotensin receptors in both the systemic vasculature and kidney vasculature participate in this process (4;5). Measured components of the renin-angiotensin system, e.g. plasma renin activity, are elevated only transiently in renovascular hypertension. Observations in both experimental animals and human subjects indicate that renin-release is eventually reduced partly related to the rise in systemic, and thereby renal, arterial pressures and/or sodium retention. Recruitment of additional renovascular pressor mechanisms, such as release of endothelin, activation of the sympathetic nervous system, oxidative stress and others also produce sustained rises in arterial pressure that are not directly related to the renin-angiotensin system.

How much vascular occlusion is necessary to initiate the “syndrome” of renovascular hypertension? Recent studies confirm the observation that activation of renin-release depends upon the gradient between the aorta and the post-stenotic segments of the renal artery. No renin release can be detected until the gradient is between 10-20 mm Hg (6). Studies with latex casts of arterial segments indicate that reductions in pressure across an occlusive lesion require lumen obstruction in excess of 70-75% to be detected. Modern imaging studies frequently reveal “incidental” renal arterial occlusive lesions of lesser severity with only minor effects.

While the majority of clinical cases of renovascular hypertension are produced by main renal artery lesions from atherosclerosis or forms of fibromuscular dysplasia, it should be recognized that any lesion that reduces kidney perfusion pressures can lead to similar results. Less common cases include renal artery occlusion related to trauma (with or without arterial dissection), extrinsic compression such as a peri-vascular tumor, intrinsic obstruction such as produced by an aortic endograft that partially occludes the renal arteries, aortic dissection, etc (TABLE 1 and FIGURE 1).

Epidemiology and Clinical characteristics of Renovascular Hypertension

The hallmarks of renovascular hypertension include the onset and progression of blood pressure elevation outside the ranges typical of essential hypertension. Hence, hypertension appearing in younger individuals, e.g. children or young adults, or the recent onset of hypertension in previously normotensive older individuals above age 55 raises this diagnostic concern. Congenital anomalies and/or segmental infarction have been observed commonly in infants and children with hypertension. With the rise in childhood obesity, blood pressure elevations are now observed in more children than ever before. Hence, renovascular disease is not the single most likely cause of hypertension at any age. Prospective studies from a hypertension unit in the United Kingdom targeting 96 younger individuals identified secondary hypertension in 18.1%, most of which were renovascular hypertension (75%) (7). Actual cure rate was only 2 of 13 subjects (15% of renovascular cases) which represented only 3.2% of the screened population. Whether extensive diagnostic studies and renovascular intervention is always warranted in such cases remains controversial as discussed below.

Fibromuscular disease (FMD) affecting the renal arteries occurs in 3-5% of normotensive individuals presenting as potential kidney donors (8;9). It appears as a cause of hypertension most commonly in younger females, sometimes during pregnancy. Smoking is thought to lead to progression and worsening arterial pressures in this group. Rarely, FMD leads to complete or segmental occlusion (Figure 1a and b), but most individuals have normal kidney function and it rarely leads to loss of glomerular filtration rate.

The most common and problematic cause is atherosclerotic renovascular disease. Recent interventional series indicate that atherosclerosis constitutes 84% of patients identified with renal artery stenosis (10). (FIGURE 1c) Epidemiologic observations suggest that atherosclerotic lesions exceeding 60% occlusion (by Doppler ultrasound) affect the kidney in 6.8% of a community based sample of subjects above age 65 (11). When the renal arteries are studied as part of clinical angiography for other disorders, occlusive lesions are found in nearly 20% of patients with coronary disease and more than 35% in patients with clinically significant aortic or peripheral vascular disease (12). In this regard, the extent of renal arterial disease appears to reflect the overall disease burden related to atherosclerotic disease elsewhere. High-grade atherosclerotic renal artery disease predicts long-term survival based on several cohort studies, regardless of whether or not revascularization is undertaken (13).

Hypertensive specialists recognize that atherosclerotic renovascular disease is associated with accelerated and more severe target organ injury than essential hypertension. Careful studies of office and ambulatory blood pressure levels indicate that circadian pressure rhythms are commonly disturbed in subjects with RAS. Such individuals often lack a nocturnal fall in arterial pressure (therefore are classified as “non-dippers”) and may have paradoxically elevated nocturnal pressures (14). The severity of left ventricular hypertrophy, impairment of kidney function and other manifestations of vascular disease are increased for such patients. Increased adrenergic activity as measured by efferent sympathetic nerve traffic is common in this disorder and is associated with wider variability in blood pressure as compared with essential hypertension. Sometimes this appears as paroxysmal hypertension, easily confused with pheochromocytoma. Endothelial dysfunction with impaired vascular relaxation develops

in patients with renovascular hypertension (15). In experimental models, disturbances in endothelial function are magnified by cholesterol feeding as a manifestation of early atherosclerosis. All of these characteristics can improve after revascularization, and in some cases with statin therapy (16). Whether similar outcomes can be achieved using medical therapy that blocks the neurohormonal pathways activated with renovascular disease is not yet clear and is one of the major objectives of randomized controlled studies including CORAL.

Studies of Medicare claims indicate that individuals with newly identified renovascular disease develop other cardiovascular events at a higher rate than those without renovascular disease over a two year period (17). It should be emphasized that clinical events are most commonly related to new cardiovascular disease including coronary events, myocardial infarction, and heart failure. These are more common by far than reduction in kidney function in absolute terms. (FIGURE 2).

The role of renovascular disease limiting sodium excretion warrants special consideration. Structural occlusion of the renal artery sufficient to reduce renal perfusion pressure itself enhances sodium retention by slowing blood flow and filtration and enhancing peritubular forces leading to solute reabsorption. Activation of the renin-angiotensin-aldosterone system tends to retain sodium further. Angiotensin II directly increases sodium transport, an effect magnified by the reduction in blood flow related to its vascular effects. Aldosterone activates distal sodium retention by activating sodium-potassium ATPase. These combined forces have long been recognized as reducing sodium excretion in the post-stenotic kidney. In subjects with an intact contralateral kidney sodium excretion may be increased as a result of “pressure natriuresis” induced by systemic hypertension (18). Early studies using bilateral ureteral cannulation to examine individual kidney function confirmed that demonstration of lateralization of sodium excretion could predict improvement in renovascular hypertension after surgery (19). As the contralateral kidney becomes subject to intrinsic parenchymal injury or the effects of circulating sodium-retaining hormones, it may lose the ability to excrete sodium effectively. This form of functional sodium retention has been invoked to explain why the rise in plasma renin activity may be transient and why lateralization of renin secretion can only be demonstrated after sodium-depleting maneuvers. Hence, many of the early studies of renal vein lateralization depend upon administration of potent diuretics such as furosemide to identify the pressor role of the stenotic kidney. Perhaps even more importantly, bilateral renal artery disease (or stenosis to a solitary functioning kidney) limits kidney function and sodium excretion. This is sometimes manifest as transient episodes of severe hypertension and circulatory congestion that magnify left ventricular dysfunction and congestive heart failure, so-called “flash” pulmonary edema (20). The combination of reduced cardiac pump function and renovascular disease can be difficult to manage. While no controlled, prospective trials have been performed for such patients, several series suggest that recurrent hospitalizations for circulatory congestion can be reduced after renal revascularization (21). Thus, renovascular hypertension can present a broad range of neurohormonal pressor systems and impaired sodium and volume control.

Perhaps the most common presentation of renovascular hypertension is “resistant hypertension”. Recent consensus statements define this condition as failure to achieve goal blood pressures (usually considered <140 / 90 mmHg or lower for high risk conditions), despite optimal doses of three or more antihypertensive agents, including a diuretic. Common features to such patients include older age, systolic hypertension, obesity, obstructive sleep apnea and other manifestations of renal dysfunction (22). The fact that most such patients have multiple comorbidities makes it more difficult to assign a causative role for any specific condition, including renovascular disease.

Management of Renovascular Hypertension

Optimizing antihypertensive therapy and overall cardiovascular risk is an essential initial step in managing renovascular hypertension. (TABLE 2) Much of the impetus for embarking on further diagnostic and therapeutic maneuvers depends upon whether blood pressure control and renal function can be maintained readily. Because actual “cure” of hypertension is rarely achieved (defined as normal blood pressure without requiring antihypertensive therapy), it may be argued that if blood pressure and renal function are managed easily, little is to be gained by elaborate diagnostic procedures. Conversely, failure to achieve acceptable levels of arterial pressure adds strength to the potential benefit of even partial improvement achievable with successful renal revascularization. Hence, the response to therapy is an important element in deciding on the benefits of renal revascularization when high-grade arterial lesions are present.

The role of angiotensin blockade

Blockade of the renin-angiotensin system is now established as an important element in the treatment of renovascular hypertension. Before agents such as angiotensin-converting enzyme (ACE) inhibitors were available, renovascular hypertension commonly presented as “untreatable” hypertension. Series of emergency room patients with hypertensive emergencies routinely appeared with accelerated phase hypertension, later identified as renovascular in origin (23). A few small series of patients with episodic, malignant-phase hypertension were identified that were subjected to bilateral nephrectomy as life-saving measure (24). With the introduction of agents now capable of interrupting this system, such measures are rarely necessary. Based upon the potential adverse effects of angiotensin to magnify vascular injury, myocardial damage and remodeling and increase the risk of adverse cardiovascular outcomes, many argue that administration of ACE inhibitors should be part of managing nearly all patients with significant cardiovascular risk, based on data from the HOPE trial and others (25). These observations have been extended to angiotensin-receptor blocking agents (ARB's) based upon results from studies directly comparing ACE inhibition with angiotensin receptor blockade (26). Whether neurohormonal disturbances resulting directly from renovascular disease are a major factor in the cardiovascular risk intervention in these patients remains an important question. As a result, blockade of the renin-angiotensin system is a core element in determining the effects of renal revascularization. All patients participating in the CORAL trial are provided an angiotensin receptor blocker as a cornerstone of therapy. Whether direct renin-inhibition with agents such as aliskiren will have the same effect is logical, but as yet unproven. Blockade of the renin-angiotensin system is therefore important, but often not sufficient, to control hypertension in patients with renovascular hypertension. Therapy with additional antihypertensive agents, particularly diuretics, is essential.

It must be emphasized that removal of the renin-angiotensin system is not without drawbacks. Initial consensus regarding application of ACE inhibitors was difficult to achieve, in part because of the well-recognized potential of these agents to lower glomerular filtration rate as a result of loss of angiotensin II effects at the efferent arteriole. As noted above, renin release can be observed when sufficient lumen obstruction to produce a pressure gradient between the pre- and post-stenotic segment of 10-20%. This can occur with only a minor disruption of blood flow to the kidney that requires less than 10% of its blood flow for metabolic demands. Early studies in the dog demonstrated that as renal blood flow becomes reduced with a progressive occlusion, sustaining trans-capillary filtration pressures depend upon maintaining efferent arteriolar constriction. This constriction is modulated largely by the vascular effects of angiotensin II. Blockade of angiotensin II production (with the use of an ACE inhibitor) or its receptor (with an angiotensin receptor blocking drug) reduces efferent arteriolar tone and allows blood flow past the capillary surface with insufficient pressure to form urine. As a result, the post-stenotic kidney may develop “functional acute renal insufficiency”, despite having adequate blood flow for metabolic demands.

When arterial obstruction is extreme, simply reducing perfusion pressure sometimes can reduce post-stenotic blood flow beyond that required for metabolic demands in the kidney. This can develop with any form of antihypertensive therapy and is not limited to agents that block the renin-angiotensin system (27). Early experimental studies in rats emphasized the potential for irreversible damage to the kidney to develop beyond a renal artery clip in animals treated with ACE inhibitors, leading some to refer to such therapy as “medical nephrectomy” (28). These experiences highlight the potential for renovascular disease to both activate pressor mechanisms and to ultimately threaten the post-stenotic kidney with insufficient blood supply. Surveys of pharmacy records related to administration of agents that block the renin-angiotensin system indicate that while these drugs allow effective blood pressure control and reduced clinical events such as stroke, death, congestive heart failure and initiation of permanent dialysis, they are associated nonetheless with a definite incidence of acute renal failure, sometimes leading to drug withdrawal (29). Post-marketing surveys indicate that risk factors for adverse events include older age groups, pre-existing renal dysfunction, episodes of acute illness leading to volume depletion (such as diarrhea or reduced intake during diuretic administration) (30).

Management of atherosclerotic disease risk

As a practical matter, much renovascular hypertension develops in the setting of pre-existing cardiovascular risk, including essential hypertension, dyslipidemia, diabetes and smoking. Because the major causes of morbidity and mortality remain related to cardiovascular outcomes including stroke and coronary events, management includes intensive efforts to reduce these risks. These include discontinuation of smoking, initiation of statin therapy, low dose aspirin, weight and diabetes control as appropriate. It must be recognized that identification of involvement of the renal vessels with atherosclerosis itself predicts higher mortality and intensifies the importance of risk management. The CORAL trial specifically seeks to address the additive effects of renal artery revascularization regarding cardiovascular events after assuring adequate and intensive management of these risk factors. For that reason, drug therapy to block angiotensin and statins to lower cholesterol is provided and each treatment site is provided “report cards” related to adequacy of risk factor control.

The role of renal revascularization

In the past, renovascular hypertension was often viewed as a secondary cause of hypertension that warranted diagnosis specifically with the goal of restoring blood flow to the kidney to “cure” hypertension. Although logical, this argument has not been supported by studies of clinical outcomes. Clinicians caring for patients with hypertension must balance the pros and cons of vascular intervention carefully, as summarized by a recent American Heart Association symposium (TABLE 3). These sometimes relate directly to the expertise available locally for either endovascular or surgical intervention within a specific institution or region. Previous studies emphasize that rates of peripheral arterial intervention differ by up to 14 fold within different regions of the country (31). Few prospective trial data are available to define either the populations most likely to benefit or the true risk/benefit profiles for these procedures.

The reasons for this ambiguity are complex. Rapid expansion of both imaging and interventional expertise has led to more common diagnoses of renal arterial lesions and a greater enthusiasm for endovascular procedures than ever before. Medicare claims data indicate a rise of more than four-fold between 1996 and 2005 as we have reviewed (32). These developments led the Centers for Medicare and Medicaid Services to commission a review of the data to support these procedures published in 2006. It concluded “available evidence was neither adequate nor sufficiently applicable to current practice to clearly support one treatment approach over another...” (1).

Fibromuscular dysplasias

Most clinicians favor considering endovascular intervention in the form of PTRAs for fibromuscular disease affecting the main renal arteries. This disorder often produces hypertension in younger individuals, most often women. A recent series of 69 subjects indicated that PTRAs achieved patency over 90% initially and 87% during follow-up over six years, although repeat procedures are needed in up to 25% of patients (33). The potential for relief of hypertension (although rarely complete cure) is substantial and this approach may reduce long-term antihypertensive therapy requirements. It must be emphasized that FMD can extend into smaller branch vessels and may not be amenable to intervention for technical reasons. Similarly, these lesions have a predilection for developing aneurysms that should not be stressed mechanically. In some cases, embolization of the aneurysm or surgical resection should be considered (34). Normally, stents are not suitable for FMD unless needed to repair a vessel dissection. Recent surgical series for complex anatomy or failed PTRA intervention indicate 27% with effective “cure” and improved in 67% (34). Most recent series suggest that up to 74% will have improved blood pressure levels following PTRAs. Kidney function is most often normal in subjects with FMD and does not materially change after PTRAs.

Atherosclerotic disease of the renal arteries presents a more complex picture. With the widespread application of endovascular stenting, most (95-98%) lesions can be successfully dilated to restore blood flow. Atherosclerosis commonly involves both the aorta and orificial components of the renal arteries. Dilation of these plaques commonly releases atheroembolic debris of varying sizes. Ex-vivo studies suggest that many steps of an interventional procedure, including initial placement of guidewires, are capable of releasing microembolic material (35). The results of restoring renal artery patency in these cases are not completely predictable. Previous studies with both surgical and endovascular procedures indicate that blood pressure control may be more easily achieved, sometimes with fewer medications. Current goal levels for blood pressure nearly always require further antihypertensive drug therapy, so complete cure without residual treatment is rare. In some patients with reduced glomerular filtration rate, kidney function may improve substantially with restoration of main vessel patency. This occurs in 25-28% of cases depending upon the definition for “improvement”. Most patients have no discernible change in kidney function. Most series report a smaller group of patients, ranging between 12-20%, that experience a loss of kidney function after renal artery revascularization, most often attributed to atheroemboli (36). In such cases, loss of renal function can progress rapidly and may progress to end-stage renal disease (ESRD) requiring dialysis. As a result, the appropriate application of endovascular stenting procedures for atherosclerotic renal artery disease remains controversial.

The AHRQ review of published literature commissioned by CMS concluded that data were insufficient to consider the role of revascularization of proven benefit. At least four prospective, randomized trials of endovascular stenting for renal artery stenosis have been undertaken in the last several years. Preliminary results of the largest of these (the Angioplasty and Stenting in Renal Atherosclerotic Lesions (ASTRAL)) conducted in the United Kingdom have been presented in abstract form. This trial was intended to evaluate changes in renal function. Subjects were eligible if the clinicians were “uncertain” about optimal therapy. The mean serum creatinine was more than 2.0 mg/dL at entry and the average degree of stenosis was estimated to be 76% lumen occlusion. Remarkably, no differences between 806 patients assigned to medical therapy with or without stenting could be detected regarding blood pressure control, renal function, hospitalization for congestive heart failure or mortality (37) during a median follow-up period exceeding two years. More than 600 subjects with more stringent entry criteria have been enrolled in CORAL with a target date to finish enrollment of more than 1000 subjects by the final quarter of 2009.

How should clinicians interpret these results in the interim? As noted above, some patients develop functional acute renal insufficiency during antihypertensive drug therapy that can improve after successful revascularization. The AHRQ summaries acknowledged that occasional removal of antihypertensive drug therapy and recovery of kidney function were reported only in patients subjected to renal revascularization (1). It is inescapable that some patients derive major benefits from successfully restoring renal blood flow. What must be acknowledged is that these benefits are not universal (or even common) and do entail both risk and considerable expense. In this respect, we view them as important interventions similar to other vascular procedures such as those applied to aortic or carotid disease. Revascularization should be considered mainly for individuals with vascular disease likely to progress and likely to benefit from the procedure at acceptable levels of risk. How best to identify patients likely to benefit remains an elusive goal. To a great extent, this is defined by failure of medical therapy alone, as summarized in Tables 2 and 3).

Diagnostic Evaluation of Renovascular Hypertension

The hallmark of identifying renovascular hypertension is the demonstration of structural and functional occlusion of the renal vessels. How to achieve this optimally remains an elusive goal. We have argued that selection of imaging studies should reflect precisely the questions to be answered, since not all of these can be equally addressed with certainty (38). As a result, many patients undergo multiple non-invasive studies before reaching a diagnostic and/or therapeutic angiogram. Our own approach is to emphasize—in advance—the precise goals of the diagnostic study and the commitment to act upon the findings if positive.

Major advances in vascular imaging over the last decade allow positive identification of renovascular disease more easily than ever before. Although a detailed discussion of each technique is beyond the scope of this discussion, several points may be worth mentioning.

Renal artery duplex (Doppler) ultrasound—Remains among the most widely available and least costly studies to identify hemodynamically significant vascular lesions. Ultrasound examination is a proven technology for evaluating the kidney and reliably detects obstructive uropathy, asymmetry in size, cortical thickness, location and many parenchymal abnormalities. As such it remains among the first studies considered by nephrologists evaluating patients with reduced glomerular filtration. When used to evaluate renovascular disease, results remain operator- and center-dependent. The results are most useful when “positive”, i.e. when major flow accelerations are detected and verified in a major renal artery. Although moderate increases in velocity (above 180-200 cm/sec) generally correlate with stenosis above 60%, these are approximate. Recent modifications to allow entry into CORAL require velocities above 300 cm/sec (FIGURE 3), when confirmed by a central laboratory. Because the location and course of renal arteries can be complex, a negative study is less re-assuring that no lesion is present. Previous claims that resistive index, a measure of relative systolic and diastolic flow patterns, predict the clinical outcomes of renal revascularization have not been universally confirmed (39). Detection of a low resistive index, however, does suggest relatively preserved parenchymal blood flow.

Captopril renography—Remains widely available as an imaging technique. This method does not image the vasculature directly, but provides functional assessment of overall perfusion and function. Early studies indicated that entirely normal studies reliably excluded renovascular disease (40). Recent inclusion of renography in prospective trials failed to predict clinical outcomes (41;42). When renal function is abnormal, asymmetries in renal flow and function can develop for many reasons unrelated to renovascular disease. When considering nephrectomy or evaluating the relative contribution of a given kidney to overall glomerular filtration rate, renography can assess each kidney's level of function separately.

MR angiography—Although relatively expensive, MR imaging has become a major imaging tool to reliably evaluate size, structure and vascular anatomy. Gadolinium-enhanced imaging is now less commonly employed due to concerns about nephrogenic systemic fibrosis. Newer technologies promise to allow high resolution imaging of the major renal vessels without contrast, however, and allow definition of vascular patterns without radiation exposure. Both MR and CT angiography (see below) can reliably define “normal” major vessels, thereby assuring the patient that bilateral disease is not present. This fact can be critically important in planning long-term medical therapy

CT angiography—Application of multi-detector CT and rapid image acquisition now allow excellent vascular and parenchymal imaging with moderate radiation and contrast exposure (Figure 1a and b). Although expensive, CT angiography can provide detailed estimation of function, blood flow, anatomic variation and approachability.

Intra-arterial angiography—Remains the “gold standard” by which renovascular lesions are identified and subjected to quantitative assessment (Figure 1c). It is usually reserved for the time of planned endovascular intervention, although some centers include aortic imaging as part of coronary angiography. The additional contrast usually is minor and several studies indicate little incremental risk to imaging the renal arteries, so long as selective instrumentation is avoided.

When should an identified renovascular lesion be subjected to instrumentation and dilation, with or without stenting? This remains a troubling question. Prediction of a positive blood pressure response remains elusive—and less pressing in the era of effective antihypertensive drug therapy than it was two decades ago. We have proposed a series of criteria that may be addressed by both clinicians and patients that may facilitate this decision (TABLE 3).

A variety of biomarkers have been proposed to identify patients likely to have clinical improvement in blood pressure after renal revascularization. These include measurement of renal vein renin levels, brain natriuretic peptide (BNP) (43), captopril stimulated renin values and changes in glomerular filtration after ACE inhibition. Although useful when strongly positive, these strategies often fail to add critical information when applied to unselected populations. The strongest predictor of clinical benefit until now remains the short duration of hypertension.

Summary of Current thinking on Renovascular Hypertension

Taken together, it should be apparent that advances in medical therapy, vascular imaging and endovascular procedures have changed the landscape of renovascular hypertension. Many cases presenting simply as new-onset hypertension with normal kidney function can be treated simply with existing antihypertensive drug therapy, usually including agents that block the renin-angiotensin system. Renovascular disease remains an important predictor of cardiovascular risk and warrants intensive therapy to reduce this risk including aspirin, statins, tobacco withdrawal, diabetes and weight control, in addition to attention to blood pressure. For patients with complex disease, changing levels of kidney function, or failure to respond to antihypertensive therapy, further diagnostic studies with a commitment to restoring renal perfusion may be entirely appropriate. The magnitude of the risks and benefits remain controversial. They depend greatly upon the comorbid conditions of the individual subject. Further studies directed toward how best to estimate recovery potential for renal function and the long-term outcomes for specific patient groups will be essential for optimal application of newer interventional procedures.

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FIGURE 1.

a) and b): CT angiogram obtained in a 45 y.o. woman presenting with new onset renovascular hypertension. Aneurysmal dilation and vascular occlusion beyond a fibromuscular lesion is present in the right kidney associated with loss of perfusion to the entire upper pole of the kidney. Antihypertensive therapy in this instance can be achieved using agents that block the renin-angiotensin system. While such cases are unusual, they underscore the broad range of lesions that can produce the syndrome of renovascular hypertension.

c) Aortogram demonstrating high-grade stenosis affecting the left renal artery. Quantitative measurements indicated more than 86% lumen obstruction. This individual was randomized to medical therapy in the CORAL trial (see text)

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Figure 2.

Incidence of new Medicare Claims within two years of diagnosis of atherosclerotic renal artery stenosis. Patients with renal artery disease are more likely to have new coronary, stroke, congestive heart failure, and chronic kidney disease (CKD) than those without renal arterial disease. Adverse cardiovascular outcomes are far more likely than those related specifically to kidney disease (data from Kalra, et.al, with permission (22))

Figure 3.

a) Doppler ultrasound velocity at the origin of the vessel was measured at 4.91 m/sec (or 491 cm/sec) consistent with vascular occlusion exceeding 85%. (b). Segmental artery Doppler waveforms demonstrate a delayed upstroke in the distal vessels (defined as “tardus parvus”), but excellent diastolic blood flow with a calculated “resistive index” of 0.69. Demonstration of a low resistive index has been proposed as a measure of the viability of the post-stenotic kidney and likely benefit from revascularization regarding kidney function and blood pressure. (see text).

Table 1
Major causes of Renovascular Hypertension

Atherosclerotic Renal Artery Stenosis
Fibromuscular disease
Medial Fibroplasia
Perimedial fibroplasia
Intimal fibroplasia
Medial hyperplasia
Extrinsic Fibrous band
Renal trauma
Arterial dissection
Segmental renal infarction
Page Kidney (perirenal fibrosis)
Aortic Dissection
Aortic Endograft occluding the renal artery
Arterial embolus
Other Medical Disorders:
Hypercoagulable state with renal infarction
Takayasu's arteritis
Radiation induced fibrosis
Tumor encircling the renal artery, e.g. pheochromocytoma
Polyarteritis nodosa

Table 2
Management of Renovascular Hypertension

-Antihypertensive Drug Therapy

Blockade of the Renin-Angiotensin System:

Angiotensin Converting Enzyme Inhibitors (ACE)

Angiotensin Receptor Blockers (ARB's)

Direct Renin Inhibitors? (Aliskiren)

Calcium Channel Blocking Agents

Diuretics

Mineralocorticoid Receptor Blockade

Additional Classes: Beta-Blockade, alpha-receptor blockade, sympatholytic agents, vasodilators

-Cardiovascular Risk Reduction:

Removal of tobacco use

Treatment of dyslipidemia: Statins, fibrates, others

Treatment of obesity: obstructive sleep apnea

Management of glucose intolerance / diabetes

-Renal Revascularization: Selected Cases

Endovascular revascularization

PTRA: primarily fibromuscular dysplasia

PTRA with stenting: Atherosclerotic disease

Surgical: Renal artery bypass / endarterectomy (now usually reserved for complex aorto-renal disease, aneurysmal disease, failed endovascular stent procedures, etc.

-Nephrectomy: open or laparoscopic removal of pressor kidney, usually nonfunctional

Table 3
Clinical Factors favoring Medical Therapy with or without revascularization for
Renovascular Disease

-
1	Favoring Medical therapy with Revascularization:
a.	Progressive decline in GFR during treatment of hypertension
b.	Failure to achieve adequate blood pressure control despite optimal medical therapy
c.	Rapid or recurrent decline in GFR associated with reduced systemic blood pressure
d.	Decline in GFR associated with ACE inhibition / ARB therapy
e.	Recurrent congestive heart failure out of proportion to left ventricular dysfunction
2	Favoring Medical Therapy and Surveillance without revascularization
a.	Controlled blood pressure with stable renal function
b.	Stable renal arterial disease without evident progression
c.	Advanced age and/or limited life expectancy
d.	Extensive comorbidity
e.	High risk or previous atheroembolic disease
f.	f. Other concomitant parenchymal renal disease likely to explain renal dysfunction, e.g. diabetic nephropathy
-

GFR=glomerular filtration rate. (Modified from American Heart Association Atherosclerotic Peripheral Vascular Disease Symposium recommendations {8267}.)