SEMINARS IN
NEPHROLOGY

Renovascular Hypertension: Current Concepts

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Hypertension produced by renal artery occlusive disease is an important secondary form of hypertension. Clinicians commonly encounter forms of renal arterial disease of varying severity, many of which are of little hemodynamic significance when first detected. Experimental studies emphasize that transient activation of the renin-angiotensin-aldosterone system is necessary for initiation of renovascular hypertension. At some point, angiotensin II activates additional mechanisms responsible for sustained increased blood pressure including sodium retention, endothelial dysfunction, and vasoconstriction related to production of reactive oxygen species. Widespread application of agents that block the renin-angiotensin system, including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, render many patients with unilateral renal arterial disease manageable primarily by medical means for many years. In the setting of high a priori likelihood of renovascular disease, recognizing the potential for disease progression during medical therapy and individually evaluating the risks and benefits of renal revascularization are important tasks. Recent prospective studies show limited, but real, benefit regarding blood pressure control for patients with atherosclerotic disease. Whether earlier renal revascularization offers benefits regarding improved morbidity and mortality from cardiovascular end point reduction is an important question to be addressed in multicenter, prospective, randomized trials. Our paradigm stresses the fact that patients with renovascular hypertension require intensive blood pressure control and cardiovascular risk factor intervention, both before and after revascularization. Hence, management of such patients requires close attention and periodic review regarding restenosis and progression of vascular disease.

Semin Nephrol 25:261-271 © 2005 Elsevier Inc. All rights reserved.

KEYWORDS Hypertension, renal artery stenosis, renovascular hypertension, renin, angiotensin II, oxidative stress

Few clinical questions provoke more controversy among nephrologists and cardiologists than how best to manage patients with hypertension and renal artery stenosis. Advances in imaging and interventional techniques combine to amplify these questions, especially as more patients are identified with renovascular disease now than ever before. Even more importantly, the introduction of effective antihypertensive drugs including those that block the renin-angiotensin system has reduced and deferred the impetus for detecting renal artery disease to reduce the risk for uncontrolled blood pressure as compared with a decade ago.

Informed clinicians from different subspecialties hold widely divergent opinions regarding the role of renal revascularization, particularly for atherosclerotic renal artery stenosis (Fig 1). Some of those from interventional subspecialties (primarily interventional radiology and cardiologists) emphasize the major benefits now available from endovascular procedures, including the use of stents. They argue that revascularization offers the potential to improve or reverse renovascular hypertension, to salvage or preserve the renal circulation and renal function, and to improve the management of patients with refractory forms of congestive heart failure.[1] A recent review of the use of percutaneous renal artery procedures among Medicare beneficiaries confirms an increase from 7,660 claims in 1996 to 18,520 claims in 2000, primarily because of a 2.8-fold increase in procedures by interventional cardiologists.[2] Many in the nephrology community review the same published literature and reach nearly opposite conclusions. They argue that recent prospective studies fail to show major benefits of blood pressure control related to renal revascularization and that the risks for complications from interventional procedures are substantial, in-

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doi:10.1016/j.semnephrol.2005.02.010

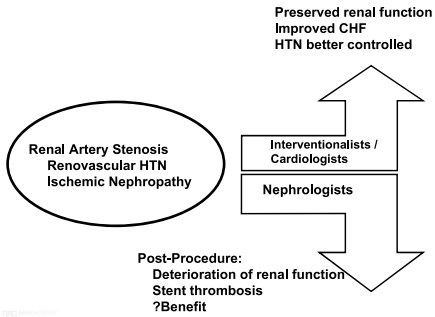

Figure 1 Levels of enthusiasm regarding endovascular intervention for atherosclerotic renal artery stenosis. Advances in imaging and stent technology have produced both increased awareness and interest among cardiovascular specialists in the hope of protecting the kidney and improving blood pressure (see text for more detail). Conversely, the nephrology community has lost enthusiasm over the past decade, in part because of disappointing clinical outcomes and occasional major adverse consequences.

cluding uncommon but sometimes devastating loss of renal function caused by atheroembolic disease.[3] Despite a wave of enthusiasm in the early 1990s to identify and reverse ischemic nephropathy for patients with advanced kidney disease, disappointing results after intervention have made many nephrologists more conservative toward renal intervention than before.[4]

What are the limitations of our current understanding of renovascular hypertension? This discussion focuses primarily on the issue of hypertension, including the results of recent treatment trials. Issues surrounding ischemic nephropathy and refractory congestive cardiac failure are beyond the scope of this review and have been reviewed recently.[5] More than ever, clinicians caring for patients with renal arterial disease need to balance carefully the risks and benefits of both medical management and the timing of renal revascularization. This review summarizes the current state of renovascular hypertension from this perspective.

Epidemiology and Prevalence

Some of the major conditions that produce the syndrome of renovascular hypertension are summarized in Table 1. These can include unusual conditions that impair perfusion to segments of renal tissue such as intrarenal tumors, cysts, renal artery aneurysms, infarction, and others. Any clinical condition that leads to reduced perfusion pressure can activate the sequence of events, leading to an increase in systemic pressures.[6] The most common causes of renovascular disease include fibromuscular diseases and atherosclerosis.

Fibromuscular diseases of the renal artery are identified in 3% to 10% of normal kidney donors.[7,8] These sometimes progress, particularly in smokers, to disrupt blood flow sufficiently to trigger or accelerate an increase in blood pressure. Most commonly, lesions of medial fibroplasia develop in the middle or distal segments of the renal arteries, and may be the site of aneurysm formation. There is a predilection toward the right renal artery and most interventional series contain a predominance of women, in whom fibromuscular diseases were detected through an abrupt onset of hypertension at relatively young ages.[9] Some of these patients are identified with pregnancy-associated hypertension. Recent interventional studies contain some patients with combined atherosclerotic and fibromuscular disorders, however, and the average age of individuals treated for renovascular hypertension of all causes is increasing.

Atherosclerosis comprises nearly 85% of the causes of renovascular hypertension in recent series.[10] Population-based studies indicate that hemodynamically significant stenosis (>60% lumen occlusion based on Doppler flow studies) is common (6.8% of individuals >65 years; more common in men [9.1%] as compared with women [5.5%]).[11] Renal artery stenosis caused by atherosclerosis is common especially in individuals undergoing coronary angiography (18% to 20%)[12] and undergoing peripheral vascular angiography for occlusive disease of the aorta and legs (35% to 50%).[13] The vast majority of patients with atherosclerosis have hypertension, which is an independent predictor of the presence of renal arterial disease in most series.[14]

How often are increased blood pressures in these studies caused by, or even remotely related to, the presence of renal artery lesions? This question continues to plague clinicians and complicates decision making. Many individuals with atherosclerotic renal artery lesions have years of pre-existing hypertension, active smoking histories, and coexisting diabetes mellitus.[14] The age of interventional series has increased progressively over the past decade as we have pointed out.[15] Many of those identified in their 70s and 80s surface because of reduced mortality related to coronary and cerebrovascular diseases observed over the past 30 years. These issues be-

Table 1 Examples of Vascular Lesions Producing Renal Hypoperfusion and the Syndrome of Renovascular Hypertension

Unilateral disease (analogous to 1-clip-2-kidney hypertension)
Unilateral atherosclerotic renal artery stenosis
Unilateral fibromuscular dysplasia
Medial fibroplasia
Perimedial fibroplasia
Intimal fibroplasia
Medial hyperplasia
Renal artery aneurysm
Arterial embolus
Arteriovenous fistula (congential/traumatic)
Segmental arterial occlusion (posttraumatic)
Extrinsic compression of renal artery (eg, pheochromocytoma)
Renal compression (eg, metastatic tumor)
Bilateral disease or solitary functioning kidney (analogous to 1-clip-1-kidney model)
Stenosis to a solitary functioning kidney
Bilateral renal arterial stenosis
Aortic coarctation
Systemic vasculitis (eg, Takayasu's, polyarteritis)
Atheroembolic disease

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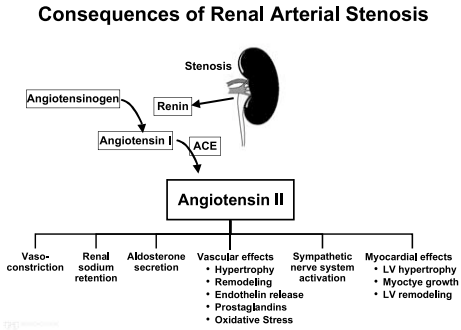

Figure 2 Reduced renal artery perfusion beyond a stenotic lesion leads predictably to activation of the renin-angiotensin system, at least initially. Increased levels of angiotensin II activate numerous additional pathways, leading to an increase in arterial pressure including sodium retention (via direct renal effects and production of aldosterone). Recent studies emphasized the role of additional mechanisms producing an increase in vascular resistance including increased neurogenic tone and production of reactive oxygen species (oxidative stress).

come central to estimating the likelihood of benefit regarding renal revascularization and the practicalities of managing older patients for whom competing risks, which may be so great as to outweigh the benefits of moderately improving blood pressure control.

Pathophysiology of Renovascular Hypertension

The seminal studies of Goldblatt et al[16] in the 1930s showed that reduction of perfusion to the kidney can produce a sustained increase of arterial pressure. Later work identified activation of the renin-angiotensin-aldosterone system as a central component of this process, as shown in Figure 2.[17,18] Soon after the first orally active angiotensin-converting enzyme (ACE) inhibitor, captopril, was introduced, experimental studies confirmed that 2-kidney-1-clip renovascular hypertension in the rat could be prevented indefinitely by blocking this system.[17] Recent studies in knock-out mice confirmed that renal artery clipping requires effective angiotensin type 1 receptors to develop 1-kidney-1-clip hypertension.[19] These observations led to a large body of work directed at confirming increased plasma renin activity as a diagnostic study[1] to identify possible cases of renovascular hypertension and[2] to confirm lateralization of renin release to justify surgical renal revascularization.[20,21] Understanding the transient nature of this process is important to recognize the limitations of these studies in practice today.

Classic studies indicate that the role of the renin-angiotensin system in 2-kidney-1-clip differs from that of 1-kidney-1-clip models.[22] The contralateral kidney in 2-kidney-1-clip models excretes sodium in response to increasing arterial pressures fostering sustained renin release by the clipped kidney. By contrast, 1-kidney-1-clip models have lower levels of renin activity and fail to respond to blockade of angiotensin II. Sodium retention by the clipped kidney accounts for the sodium-dependent status of the model, which then suppresses renin-activity to normal with increased systemic pressures. Depletion of sodium with reduced intake and/or diuretic administration converts a sodium-dependent model of renovascular hypertension to an angiotensin-dependent model.[22] Hence, sodium and/or volume expansion is capable of suppressing the renin-angiotensin system, even in renovascular disease.

Studies of human beings tend to confirm this observation. Studies of renal vein renin activity indicate that a stimulatory maneuver, such as diuretic and/or vasodilator administration, increases renin activity in the affected kidney, which had been suppressed before the maneuver.[23] A large body of experience indicates that when renal vein renin levels do in fact lateralize, the likelihood of a blood pressure response to renal revascularization exceeds 90%. Remarkably, when these levels fail to lateralize, the likelihood of benefit still approaches 50%, most likely because of failure to standardize the studies sufficiently and to achieve sodium depletion. In point of fact, the ambiguity of these studies and the fact that sodium retention develops even more commonly in patients with renal dysfunction make measurement of renal vein renin levels of limited value in practice. Confirming lateralization of renin production does, however, support more drastic interventions, such as unilateral nephrectomy for a pressor kidney.[24,25] Aldosterone levels appear to be higher in patients with renovascular hypertension during the long term.[26] This hormone now is recognized to participate in the regulation of tissue fibrosis and left ventricular hypertrophy, in addition to its effects on sodium retention.[27]

Activation of the renin-angiotensin system in response to renal artery compromise is a transient phenomenon. In some models, renin activity returns to normal levels for a period of time during which removal of the renal artery lesion still allows recovery to normal blood pressure levels.[28] Recent studies in experimental models showed recruitment of additional vasoconstrictive mechanisms, including oxidative stress, that no longer depend directly on angiotensin II.[29] Some of these systems are shown in Figure 2. Recent work indicated that endothelial dysfunction, reflecting impaired vasodilation to acetylcholine, is found in human patients with renovascular hypertension. This dysfunction improves after successful renal revascularization.[30,31] Experimental studies in a pig model of renovascular disease emphasized that cholesterol feeding itself can produce endothelial abnormalities that are magnified in the presence of renal artery stenosis.[32] These data support the observation that complex interactions between vascular injury related to dyslipidemias, smoking, diabetes, and blood pressure itself accelerate target organ injury related to renovascular hypertension.

Angiotensin II is known to alter vascular oxidative-reduction pathways by changing the kinetics of reduced nicotinamide-adenine dinucleotide phosphate, leading to overproduction of reactive oxygen species, such as peroxynitrite, hydroxyl radical, and hydrogen peroxide.[33] In the pig model, the increase in arterial pressure correlates most closely with the increase in stable metabolites of these oxidative products,

such as isoprostanes.[32] This appears to be one of the mechanisms underlying the slow response to angiotensin observed during sustained, subpressor infusion. Over the long term, vascular resistance and blood pressures increase in these animals, which may be triggered by angiotensin II but does not respond to short-term blockade.

Other systems, including the release of endothelium-derived endothelin, appear to be activated during development of renovascular hypertension, particularly in the presence of atherosclerosis.[34] Increased activity of the sympathetic nervous system is observed commonly, potentially mediated by disturbed afferent signals from the underperfused kidney and/or augmentation of nerve stimuli in the presence of angiotensin II.[35]

Clinical Correlates

Some of the earlier discussed aspects translate into clinical manifestations of renovascular hypertension. Blood pressure variability is enhanced in renovascular disease as compared with essential hypertensive patients, reflected by larger SDs during 24-hour ambulatory blood pressure monitoring.[26] Target organ injury, including left ventricular hypertrophy, is more severe than that observed with essential hypertension, despite similar levels of casual blood pressure. Patients describe flushing, rapid blood pressure level swings, and autonomic instability sometimes suggestive of pheochromocytoma. Commonly, the usual nocturnal blood pressure decrease is absent, producing more sustained hypertension during the 24-hour period. When blood pressure increases rapidly in the presence of high angiotensin II levels, a syndrome of hyponatremia and malignant-phase hypertension has been reported.[36]

Activation of the renin-angiotensin system in human renovascular disease also is transient. Whether the reversibility of blood pressure increase attributable to renovascular disease diminishes over time is not certain. Clinical prediction models continue to indicate that short duration of hypertension is among the strongest predictors of clinical response to renal revascularization,[37] although the precise onset of renovascular disease in human beings is difficult to ascertain. Human studies of temporary renal artery occlusion show the sequence of renin activation similar to those observed in experimental models, although early blood pressure changes are minor. It seems clear that sustained hypertension with vascular damage takes time to develop and may require activation of additional pressor mechanisms beyond angiotensin II.[38] Conversely, patients sometimes achieve clinical responses only weeks or months after revascularization, suggesting a time-dependent reversal of vasoconstrictor mechanisms. The fact that late removal of a pressor kidney beyond total renal artery occlusion can produce major blood pressure reduction indicates these effects can persist for years.

The degree to which treatment with agents blocking the renin-angiotensin system, such as ACE inhibitors and angiotensin-receptor blockers, delay or prevent the appearance of renovascular hypertension in human beings is not yet known. It is clear that since the introduction of these and other antihypertensive agents over the past 2 decades, most renovascular hypertension can be managed primarily using medications, as we have discussed previously.[39] This was not the case earlier, when fewer than 50% of individuals could be controlled adequately with the medications then available. The fact that patient age is increasing for patients appearing for renal revascularization may be related to delayed clinical manifestations of this disease.

Diagnostic Imaging and Functional Studies

The past decade has brought major advances in noninvasive imaging of the renal vasculature. A detailed discussion of these techniques is beyond the scope of this review. Several points merit emphasis regarding renovascular hypertension. Remarkably, many renal artery lesions are discovered incidentally during vascular imaging for other purposes. It may be argued that the major responsibility of the clinician is to decide responsibly when to follow through with additional studies and/or to proceed to further vascular intervention procedures.

Magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) provide detailed images of the aorta and renal arteries, often allowing identification of multiple vessels. Gadolinium has little nephrotoxicity and MRA allows the most detailed vascular imaging in patients with renal insufficiency without the hazard of contrast nephrotoxicity. Both CTA and MRA allow gross estimates of renal size, overall anatomy, and filtration. Several published series indicate that both MRA and CTA provide reliable identification of atherosclerotic renal artery disease of the proximal arterial segments with sensitivity and specificity exceeding 90%.[40,41] A recent prospective study of more than 300 patients subjected to both examinations and digital angiography suggested substantially lower sensitivity (64%). This observation must be tempered by the fact that nearly 38% of renovascular lesions identified were caused by fibromuscular dysplasia in medial and distal segments, areas known to be less well visualized by MRA.

Doppler ultrasound provides high specificity in highly competent laboratories. When vessels can be identified and studied correctly, a positive finding rarely is disproven by angiography. Although ultrasound provides only minimal information regarding the function of kidneys, it can provide reliable hemodynamic assessment of arterial lesions and identify gross structural abnormalities related to kidney size. Some investigators argue that Doppler examinations provide more physiologic and relevant information than even intra-arterial angiography and therefore should be considered the true gold standard.[42] Measurement of diastolic blood flow velocity (usually expressed as the resistive index) can provide an indication of small-vessel disease and parenchymal fibrosis. When this exceeds 0.80, the likelihood of improved blood pressure or improved renal function after renal revascularization is low.[43] Limitations of Doppler ultrasound often are related to inadequate examinations, particularly in obese

Table 2 Management of Renovascular Hypertension

- Medical management
  - Antihypertensive drug therapy
    - ACE inhibitors
    - Angiotensin-receptor blockers
    - Calcium-channel blockers
    - β-blockers
    - Central sympathetic agents
    - α-blocking agents
    - Diuretics
    - Vasodilators
  - Lipid-reducing agents
    - Statins
    - All others
  - Cardiovascular risk factor reduction
    - Withholding smoking
- Renal revascularization
  - Endovascular
    - PTRA
    - PTRA with stenting
  - Surgical procedures
    - 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)
      - Spleno-renal bypass graft
      - Hepatorenal bypass graft
      - Gastroduodenal, superior mesenteric, iliac-to-renal bypass grafts
  - Ablative surgery
    - Removal of a pressor kidney
    - Nephrectomy: direct or laparoscopic
    - Partial nephrectomy

Adapted from Textor.[91]

individuals. It is among the least expensive means of evaluating the vasculature and can be applied to serial measurements of stenotic vessels to monitor disease progression.

Captopril renography is applied widely but has limited value, particularly in patients with renal insufficiency. If lesions are bilateral, no differences between kidneys may be identified.

Drive-by angiography applies to aortography performed during another arterial catheterization study, most commonly for the coronary arteries. Because of the relatively high prevalence of coexisting coronary and renal arterial disease, some centers routinely view the renal arteries in hypertensive patients undergoing coronary angiograms. Examination of these patients indicates no specific differences in blood pressure, kidney function, or most other risk factors other than systolic blood pressure.[12]

The earlier-described studies, particularly MRA, CTA, Doppler, and intra-arterial angiography, primarily provide information about the presence or absence of vascular stenosis. They do not offer reliable information about the role of stenotic lesions in the regulation of blood pressure or the likelihood of benefit from revascularization.

Management of Renovascular Hypertension

Table 2 shows several forms of therapy applied to renovascular hypertension. These are listed to underscore the broad range of tools available. It should be emphasized that therapy must be highly individualized depending on the circumstances of the patient. Most patients will be treated with intensive medical intervention both before and after renal revascularization. Hence, clinicians face the responsibility mainly for establishing timing and risk/benefits of both follow-up evaluation and vascular intervention.

Medical Therapy of Renovascular Hypertension

Most patients with renal artery stenosis have pre-existing essential hypertension and other atherosclerotic disease. Hence, antihypertensive drug therapy, withholding tobacco use, and reduction of cholesterol level are important elements of treatment both before and after renal revascularization. Many older patients with renal arterial disease have reduced glomerular filtration rate (GFR), as shown in Figure 3. Current Joint National Commission Seventh Report (JNC 7) guidelines propose target blood pressure levels of less than 130/80 mm Hg for individuals with measurable loss of kidney function.[44] Some reports indicate that aggressive lipid reduction may lead to regression of atherosclerotic disease, which in fact has been observed sometimes in the renal arteries.[45] Many patients with renovascular disease will be candidates for ACE-inhibitor therapy (and/or angiotensin-receptor blocker) on the basis of other compelling indications such as diabetes, congestive heart failure, or high cardiovascular

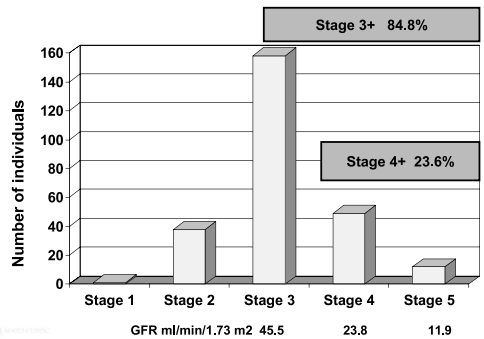

Figure 3 Stage of chronic kidney disease (chronic kidney disease as defined by the National Kidney Foundation) determined by estimated GFR (Modification of Diet in Renal Disease (MDRD)) in 258 patients subjected to endovascular stent therapy between 1996 to 2000. The mean age of this cohort was 71 years and the mean serum creatinine level was 1.6 mg/dL. These data underscore the fact that 84.8% have stage 3 chronic kidney disease or greater and have both high cardiovascular risk and other competing risks for mortality (see text for more detail).

risk. Clinical data suggest that the survival of patients with renovascular hypertension is better when ACE inhibitors are part of therapy than when they are not.[46] Importantly, most patients will continue to require complex antihypertensive regimens after successful renal revascularization.[47,48] Although some reports indicate that fewer drugs may be required, this is not observed universally. The major additional benefit of renal revascularization in many cases is the ability to achieve goal blood pressure levels at all. Whether those individuals already treated effectively to goal blood pressure levels gain much from revascularization is arguable.

Starting in the early 1980s, several trials evaluating the use of ACE inhibitors for the treatment of renovascular hypertension reported marked improvement in blood pressure control.[49,50] A major concern in the use of ACE inhibitors for renovascular hypertension is their potential to cause "functional acute renal failure."[51] The mechanism of acute renal failure relates to the inhibition of the compensatory mechanisms that develop beyond a stenotic lesion. Poststenotic reduction in renal perfusion pressures stimulates release of renin and angiotensin II, resulting in vasoconstriction of the efferent arteriole that preserves glomerular capillary filtration pressure. Administration of ACE inhibitors (or angiotensin II receptor blockers) and the subsequent relaxation of the efferent arteriole has the potential to reduce renal perfusion pressure, causing a decrease in the glomerular capillary hydrostatic pressure and glomerular ultrafiltration. This loss of filtration pressure produces an increase in serum creatinine levels. A distinctive feature of ACE inhibitors is their ability to decrease transcapillary filtration pressures and decrease the GFR without major changes in blood flow to the glomerulus.[52] Filtration usually recovers rapidly after discontinuation of the offending drug.[53] It frequently is ignored that a decrease in GFR is not specific to ACE inhibitors. Whenever antihypertensive drug therapy reduces systemic blood pressure sufficiently to impair blood flow beyond a stenotic lesion beyond the range of autoregulation, renal injury may result.[54] Remarkably, literature reports of ACE-induced irreversible renal insufficiency caused by renal artery thrombosis are rare.[55] Under these conditions, not only GFR but also blood flow seems to be compromised severely, resulting in irreversible renal damage. Consequently, it is essential that clinicians view the action of ACE inhibitors as a double-edged sword and exert caution when starting an ACE inhibitor in patients with known renal artery disease with close follow-up evaluation of kidney function and potassium levels.[56] Observing a significant decrease in GFR itself may be an important indication to proceed with renal revascularization.

In unilateral renal artery stenosis, the affected kidney frequently has reduced filtration.[57] However, changes in total GFR are minor, presumably caused by a compensatory increase in GFR by the contralateral kidney. Clinically significant loss of GFR during treatment with ACE inhibitors happens only in a fraction of treated patients, and usually in those who are at a particularly high risk owing to vascular stenosis that affects the entire functional renal mass (bilateral renal artery stenosis or stenosis to a solitary kidney). Initial studies reported renal failure in one fourth to one third of patients with either bilateral renal artery stenosis or stenosis to a solitary kidney that received ACE.[58] In a review 269 patients treated with captopril, Hollenberg[59] reported a lower incidence: of 136 (51%) patients with either bilateral renal artery stenosis or stenosis of the renal artery of a solitary kidney, only 8 (5.8%) patients developed progressive acute renal failure within the first month of treatment. In all but 1 patient, the changes in renal function were reversible with discontinuation of captopril. The efficacy and safety of ACE inhibitors were examined in a prospective, randomized, double-blind study of 75 patients with renovascular hypertension that compared an enalapril-based regimen versus triple therapy without an ACE inhibitor.[50] An increase in the serum creatinine level was observed in 10 (20%) patients in the enalapril group compared with 1 (3%) in the control group. No oliguric renal failure occurred in the enalapril-treated group, although the largest increase in creatinine level was noted in this group, specifically among the patients with bilateral renal artery stenosis and pre-existing renal insufficiency. Taken together, ACE inhibitors usually can be used for treatment of renovascular hypertension without important loss of GFR. In current practice, the emphasis is on early recognition of potential risk factors for ACE inhibitor–induced renal side effects and close monitoring of this group of patients.[60] In addition to pre-existing renal insufficiency, bilateral renal artery stenosis, or stenosis of the renal artery of a solitary kidney, another major predisposing risk factor is an activated renin-angiotensin system caused by volume depletion, diuretic or vasodilator therapy, and congestive heart failure. In high-risk patients and particularly those with heart failure, most investigators would agree that diuretics should be withheld before initiation of ACE inhibition.[61] Some patients with increased creatinine levels can be treated with discontinuation of diuretics rather than ACE inhibitors.[62] Intercurrent illnesses leading to volume depletion (vomiting, diarrhea) and consequent increase in creatinine level should be treated with saline infusion and discontinuation of ACE inhibitors during the acute illness. With reduction in perfusion pressure, renal blood flow becomes highly dependent on vasodilatory prostaglandins.[63] The concurrent use of nonsteroidal anti-inflammatory drugs should be discouraged strongly because acute reduction in renal function may ensue. Patients with congestive heart failure and coexisting renal artery stenosis represent a major therapeutic challenge. They often are treated with sodium restriction and diuretics and are prone to hypotensive episodes. Addition of an ACE inhibitor and decreasing the arterial blood pressure to less than the lower limit of renal blood flow autoregulation ($<$70 mm Hg)[64] can result in a precipitous deterioration of renal function. Volume management with the judicious use of diuretics and close monitoring of renal function is crucial during chronic treatment with ACE inhibitors in these patients.

Loss of poststenotic volume and function likely occurs as a result of decreasing blood pressure that, in renovascular hypertension, is achieved most effectively with ACE inhibitors. Therefore, an essential component of chronic therapy of hypertension in patients with known renal artery stenosis, regardless of the specific drug regimens, should include close

monitoring of their renal function and kidney size. Revascularization should be considered if early signs of renal impairment occur.

Endovascular Renal Revascularization: Angioplasty and Stenting

Uncontrolled observational studies of balloon angioplasty of the renal arteries provide the basis for applying endovascular procedures for renovascular hypertension. Numerous reports indicate that blood pressure levels in patients with refractory hypertension can improve.[65-67] An example of endovascular stenting is shown in Figure 4. The availability of these procedures allow patients to be treated with comorbid disease risks unacceptable for surgical revascularization. In some cases, renal function appears to improve and/or the progression to worsening renal function can be halted.[68] Unfortunately, endovascular procedures carry some risk also. Hence, the true risk/benefit ratio relevant to endovascular procedures in renovascular hypertension remains ambiguous.

Ramsay and Waller[69] reviewed several published series before the introduction of stents. Despite occasional successes, these investigators noted widely variable definitions of blood pressure control, uncontrolled use of antihypertensive drugs, definitions of technical and clinical success, and complications. They argued that the benefits had been overrated. In the 1990s many technical issues had been overcome, including the limitations posed by ostial lesions, which typically were not treated effectively because of elastic recoil immediately after angioplasty. The use of endovascular stents allowed much improved vascular patency[70,71] as compared with angioplasty alone. As a result, the use of endovascular procedures to restore vessel patency increased substantially between 1996 and 2000.[2] Multiple observational series have appeared in the literature, some of which have been reviewed. Isles et al[72] reported a combined review of 10 studies with 417 stented arteries and indicated that restenosis rates averaged 16% with "serious complications" in 9% to 11%. More recent series suggested fewer complications (7% to 9%), but with persistent restenosis in the 12% to 14% range.[73,74] Importantly, complications can include deterioration of renal function, sometimes related to atheroembolic disease, and death.[75]

Remarkably, only 3 randomized trials with a total of 210 patients have compared medical management versus percutaneous transluminal renal angioplasty (PTRA) in a prospective fashion.[76-78] These trials attempted to standardize blood pressure measurement before and after revascularization. The results of these trials are summarized in Table 3. When compared with retrospective reports, the results of these prospective studies indicate less benefits from angioplasty than expected (Fig 5). Taken individually, these studies show only minimal, if any, advantage of vascular intervention over medical treatment in blood pressure control. One trial showed improved blood pressure control in patients with bilateral,

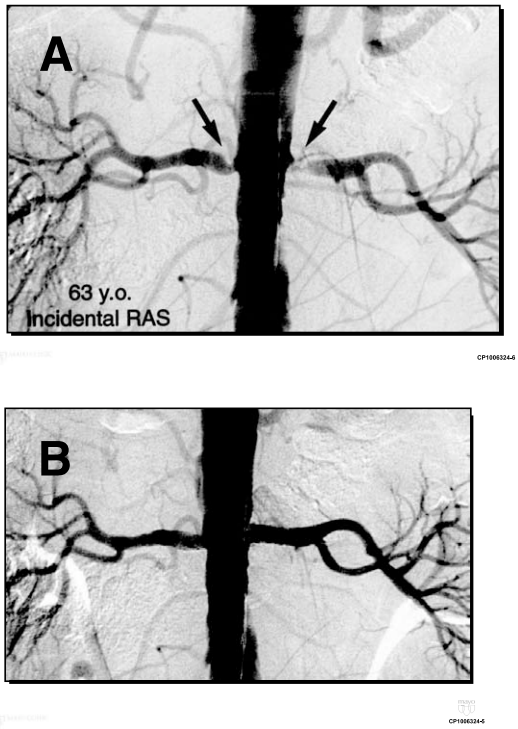

Figure 4 (A, B) Angiograms of an individual with high-grade renal artery stenosis identified incidentally as part of a coronary angiogram. (C) Blood pressure levels and renal function were managed easily with ā-blocker therapy for more than 2 years until a progressive increase in blood pressure prompted consultation with a hypertension specialist. Blood pressure control remained problematic despite the addition of amlodipine and diuretic therapy to the ā-blocker, leading to intervention with bilateral stent placement. Successful stenting allowed sustained improvement in blood pressure control, although continued triple-drug therapy was required. Management in this case underscores the need for vigilance and follow-up studies in patients with identified renovascular disease and the potential benefits of renal revascularization when progressive clinical events warrant. Reprinted with permission from Textor.[87]

but not unilateral, renovascular disease. The validity of this conclusion must be interpreted within the limitations of each of these trials. They included only a small number of patients, a relatively short follow-up period, and failure to report preenrollment changes in blood pressure and creatinine level

Table 3 Prospective Randomized Trials Comparing Medical With PTRA for Atherosclerotic Renal Artery Stenosis

Study, Duration	Classification Prerandomization	Medical Therapy Versus PTRA			Drug Regimen
		Number of Patients	Blood Pressure Outcome (mm Hg)	Serum Creatinine mmol/L or Creatinine Clearance mL/min	
Webster et al,[76] 12 mo	Unilateral	14 versus 13	161/88 versus 173/95 P = NS	160 versus 146 mmol/L, NS	Atenolol + diuretic + calcium-channel blockers ± methyldopa ± prazosin
	Bilateral	16 versus 12	171/91 versus 152/83 *P* < .005	152 versus 192 mmol/L, NS	ACEI inhibition not allowed
Plouin et al,[78] 6 mo	Unilateral	26 versus 23	141/84 versus 140/81 P = NS	74 versus 77 mL/min, NS	Nifedipine ± clonidine ± prazosin ± atenolol ± furosemide ± enalapril
Van Jaarsveld et al,[77] 12 mo	Unilateral and bilateral	50 versus 56	At 3 months: 163/88 versus 169/89 P = NS At 12 months: 162/88 versus 152/84 P = NS	At 3 months: 59 versus 70 mL/min *P* = .03 At 12 months: 62 versus 70 mL/min, NS	Amlodipine + atenolol or enalapril + diuretic

NS, statistically nonsignificant, p ≥ .05.

Figure 5 Changes in arterial pressure after renal revascularization from 1 report of observational registry data from 1,058 patients successfully subjected to stenting as compared with a meta-analysis of 3 prospective, randomized, controlled trials (n = 210 patients total) of angioplasty in atherosclerotic renovascular hypertension. The prospective trials used standardized, automated measures of arterial blood pressure before and after intervention. The outcome of the prospective trials showed considerably less change in arterial pressure (all 3 individually were considered to show no benefit in unilateral renal artery stenosis as compared with medical therapy). Which set of data most closely represents the likely results in clinical practice remains a subject of controversy (see text for more details). ■, Observational series; □, prospective series. Data from Dorros et al[84] and Nordmann et al.[79]

over time, which might have accounted for differences between the groups at the time of enrollment.[79] In 2 of these studies, 7 of 26 (27%) and 22 of 50 (44%) patients who initially were assigned to medical therapy crossed over to the PTRA group because of refractory hypertension or progressive occlusive disease. These patients were included in the medical group in each case for intention-to-treat analysis. From this point of view, these data support the role of PTRA for renovascular hypertension that is refractory to medical therapy. Two meta-analyses of these trials independently reported that, compared with medical therapy, PTRA was more effective in decreasing blood pressure. In 1 study, a comparison of the mean change (baseline to 6 months) between the groups showed greater reductions of both systolic (6.3 mm Hg, $P = .02$) and diastolic (3.3 mm Hg, $P = .03$) pressures in the angioplasty group.[80] No clear benefit in terms of serum creatinine level change from baseline was observed. Similarly, the other study reported that balloon angioplasty was more effective, with a weighted mean difference between the treatments of -7 mm Hg for systolic and -3 mm Hg for diastolic blood pressure.[79]

Surgery for Renovascular Disease

The frequency of renovascular surgical procedures for renovascular hypertension has been decreasing in the decade since the introduction of endovascular stenting.[2] Most centers rely on surgical reconstruction of the renal arteries primarily for individuals undergoing aortic revascularization or

for failed endovascular procedures. Although surgical techniques produce excellent restoration of blood flow with long-term patency, the initial procedure carries considerable morbidity and prolonged recovery.

Few studies have compared in a prospective manner the surgical reconstruction of the renal arteries with other therapeutic modalities, namely PTRA[81] and medical management.[82] A direct comparison between PTRA and surgery showed similar patency rates after 2 years, 90% and 97%, respectively. Because PTRA was repeated in several patients for restenosis, the investigators recommended it as a first-line therapy, with a requirement of intensive follow-up evaluation and aggressive intervention when needed. A small trial comparing medical management with surgical revascularization in 52 patients with renal artery stenosis affecting the entire renal mass failed to show a difference in survival over a follow-up period of 8 years.[82]

Recent experience with laparoscopic nephrectomy may provide an alternative for patients with refractory hypertension and minimal residual function in the affected kidney. These procedures can be performed by experienced operators with minimal morbidity and usually allow rapid recovery within a few days.[83] When renography confirms loss of filtration function, nephrectomy can provide important advantages in blood pressure control.[25]

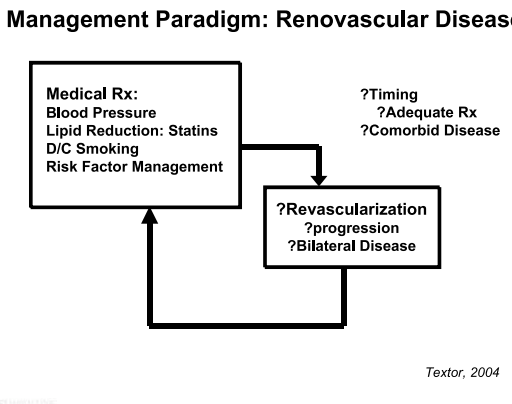

Figure 6 Simplified schematic for management of individuals with renovascular hypertension, primarily related to atherosclerosis. By using current guidelines, intensive blood pressure control and risk factor reduction is essential to reduce overall cardiovascular risk. The primary issue for clinicians is to determine the appropriate timing of renal revascularization, considering the risk for major adverse events and the potential for limited clinical benefit (see text for more details). Optimal management is directed at obtaining the most effective clinical benefit at the lowest risk, recognizing that continued medical therapy (and surveillance for recurrent vascular disease) is required in most cases.

A Paradigm for Managing Renovascular Hypertension

How should the clinician integrate these observations into rational, long-term management of patients with renovascular disease? As with most examples of complex diseases, management decisions must be highly individualized for each patient. It is essential to consider renal arterial disease as one aspect of atherosclerotic disease that also usually affects many other vascular beds. Recent studies of both interventional and noninterventional series indicate mortality rates between 25% to 30% over follow-up periods of 3 to 4 years.[84,85] Even after successful restoration of vascular supply to the kidney, mortality most often relates to cardiovascular disease events that closely relate to the postintervention level of renal function.[86] Although individual patients can recover lost renal function and may have substantial benefit regarding congestive heart failure and blood pressure control, it has been difficult to establish improved survival in large groups of patients.

Figure 6 shows our own approach with the emphasis on following-up these patients carefully and proceeding with vascular intervention when either blood pressure control or renal function is less than optimal. The case shown in Figure 4 shows that high-grade renal arterial disease can pose no problem regarding either kidney function or blood pressure for several years. At one point, however, blood pressure began to accelerate and did not respond to the addition of several antihypertensive drugs.[87] How often renovascular disease progresses remains controversial. Prospective studies in the 1990s showed measurable progression by high-performance Doppler ultrasound in 51% of patients with lesions exceeding 60% occlusion.[88] However, clinical progression to a reduction in kidney volume is lower, perhaps 20% over 3 years, with changes in serum creatinine levels of much less.[89] The actual progression of incidentally detected high-grade lesions to levels forcing vascular intervention in such series appears to be less than 10%.[85] However, recognizing the transition in such cases is an important element for nephrologists and other clinicians caring for such patients. Prompt vascular intervention in such cases can provide major improvements in blood pressure control and avoid adverse cardiovascular outcomes that are the leading cause of morbidity and mortality in this condition. We have argued that nephrologists have become overly conservative regarding renal revascularization, whereas some other subspecialists have become overly aggressive.[90]

Further prospective studies to characterize the timing and role of renal revascularization better in the management of patients with renovascular disease in the current era are needed urgently. This has been recognized by the National Institutes of Health and they recently approved and funded a multicenter prospective trial of Cardiovascular Outcomes in Renal Artery Lesions. The overall goal of this trial is to ascertain whether patients with high-grade, proven atherosclerotic lesions subjected to careful medical management gain additional benefit from endovascular stenting. The fact that such a trial is approved after careful peer review underscores the ambiguity of our current knowledge. Accepting this uncertainty and encouraging enrollment in prospective trials is an important obligation of all of those participating in the care of these patients.

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