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Renal-Artery Stenosis

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Abstract

A 73-year-old former smoker with a history of hypertension and dyslipidemia presents to the emergency department with shortness of breath. His blood pressure is 160/75 mm Hg, heart rate 60 beats per minute, and respiratory rate 24 breaths per minute. Chest auscultation reveals diffuse rales, and there is 1+ pitting edema. The serum creatinine level is 1.4 mg per deciliter (124 μ mol per liter) (estimated glomerular filtration rate, 52 ml per minute), and urinalysis shows 1+ protein. His condition improves after treatment with intravenous diuretics, but his systolic blood pressure remains elevated, at 170 mm Hg. Magnetic resonance angiography (MRA) reveals a diseased aorta, a high-grade ostial lesion of the left renal artery that is consistent with atherosclerotic stenosis, and a normal right renal artery. How should he be further evaluated and treated?

THE CLINICAL PROBLEM

Renal-artery stenosis, defined as a narrowing of one or both renal arteries or their branches,¹ is most commonly caused by atherosclerosis. Less frequently, it is caused by fibromuscular dysplasia, and it rarely has other causes. Atherosclerosis and fibromuscular dysplasia have distinct presentations and clinical consequences, and whereas fibromuscular dysplasia appears to be effectively treated with balloon angioplasty, the optimal management of atherosclerotic renal-artery stenosis remains controversial (Table 1).

The reported prevalence of clinically manifested atherosclerotic renal-artery stenosis in the Medicare population is 0.5% overall and 5.5% among patients with chronic kidney disease.² Because patients are often asymptomatic, the true frequency of renal-artery stenosis is probably higher. In one community-based study that involved the use of duplex ultrasonography for screening in the elderly, the rate was 7%.³ Anatomical progression of atherosclerotic renal-artery stenosis may occur in more than one third of patients, but one study, conducted before statin therapy was available, showed that at 5 years of follow-up, stenosis had led to occlusion in only 3 to 15% of patients treated medically.⁴

Although hemodynamically significant renal-artery stenosis may result in refractory hypertension and end-stage kidney failure, these outcomes are uncommon in patients with atherosclerotic renal-artery stenosis that is treated medically.^{4–6} The frequency of hypertension resulting from renal-artery stenosis is unknown, and no test currently available reliably shows whether hypertension will improve after the correction of renal-artery

stenosis. Although impaired renal function (often called ischemic nephropathy) is common in patients with atherosclerotic disease, and although occlusion of the renal artery is associated with a substantial loss of renal size and function,⁷ there is little or no correlation between the severity of stenosis and renal function except for cases of occlusion in which renal function is compromised.^{8,9}

Regardless of whether hypertension and chronic kidney disease are direct consequences of the renovascular lesion, patients with atherosclerotic renal-artery stenosis are at increased risk for vascular events. In a retrospective analysis of a Medicare database,² patients with renal-artery stenosis had significantly increased rates of chronic kidney disease (25%, vs. 2% among those without renal-artery stenosis), coronary artery disease (67% vs. 25%), stroke (37% vs. 12%), and peripheral vascular disease (56% vs. 13%), after adjustment for other cardiovascular risk factors. Among patients with renal arteries that were assessed at the time of a cardiac catheterization, the incidence of cardiovascular events at 4 years of follow-up was much higher among patients with renal-artery stenosis than among patients without renal-artery stenosis, and there was an inverse correlation between the severity of stenosis and survival.¹⁰ In a cohort of almost 900 patients older than 65 years of age who were followed prospectively, the presence of renal-artery stenosis was associated with a risk of a coronary event that was increased by a factor of two, after adjustment for traditional risk factors. Renal insufficiency in patients with renal-artery stenosis is also associated with markedly decreased survival.¹¹ The explanation for the increased risk of cardiovascular events among patients with renal-artery stenosis is uncertain, but it may be related to concomitant atherosclerosis in other vascular beds,^{12–18} activation of the renin–angiotensin–aldosterone and sympathetic nervous systems, associated renal insufficiency, or all these factors.^{19–27}

STRATEGIES AND EVIDENCE

EVALUATION

The presence of chronic kidney disease, advanced age, and other atherosclerotic risk factors is associated with an increased prevalence of atherosclerotic renal-artery stenosis; however, these characteristics are also common in patients with essential hypertension.^{28,29} The classic clinical clues that suggest the diagnosis of renal-artery stenosis include the onset of stage 2 hypertension (blood pressure >160/100 mm Hg) after 50 years of age or in the absence of a family history of hypertension, hypertension associated with renal insufficiency (especially if renal function worsens after the administration of an agent that blocks the renin–angiotensin–aldosterone system), hypertension with repeated hospital admissions for heart failure, and drug-resistant hypertension (defined as blood pressure above the goal despite treatment with at least three drugs of different classes at optimal doses).

Once renal-artery stenosis is suspected, confirmation of the diagnosis is typically made by means of imaging (Table 2), since biochemical tests such as the measurement of plasma renin concentrations lack specificity. Duplex ultrasonography is an excellent tool because it is noninvasive and has no apparent side effects.³⁰ Doppler measurement of renal-artery velocity³¹ provides a functional assessment of the severity of stenosis; higher velocity correlates with a greater pressure differential across the stenosis (Fig. 1). However, duplex

imaging is limited by abdominal obesity or bowel gas, is technically demanding, and is not available at all centers. Alternative methods include MRA and computed tomographic angiography (CTA) with the use of high-resolution multislice detector devices.³² These techniques can provide elegant images of the renal arteries and the abdominal aorta and can show images in multiple planes to enhance clarity (Fig. 2). However, equipment, technique, and reconstruction of the images may affect image quality, as can patient-related factors, including the presence of calcium, the presence of stents, and the ability to hold one's breath during imaging. In patients with chronic kidney disease, the use of MRA and CTA is limited by toxicity of the contrast medium: nephrogenic systemic fibrosis is associated with gadolinium,^{33,34} and nephropathy is associated with iodinated contrast dye. In experienced centers, high-quality digital-subtraction angiography with or without selective renal angiography may be performed with the use of small-diameter catheters and minimal amounts of contrast material in order to reduce the risk of vascular complications and contrast nephropathy (Table 2).

Although the degree of atherosclerosis of the aorta, the size of the kidney, the extent of poststenotic dilatation, and the rapidity of the appearance and washout of contrast material are useful in confirming or ruling out the diagnosis of renal-artery stenosis, no tests or findings conclusively establish the functional significance of the lesion or predict the response to revascularization. Physiological measures such as nuclear scintigraphy, renin sampling from the renal veins, determination of pressure gradients across stenoses, or ultrasonographic measurements may be useful in selected situations to determine whether a kidney supplied by an occluded renal artery is viable and is likely to be contributing to hypertension or whether stenosis within a renal artery is affecting intrarenal pressures.

TREATMENT OPTIONS

Medical Therapy—Medical therapy remains the cornerstone of treatment for renal-artery stenosis. No randomized, controlled trials have compared the effects of different medical regimens on outcomes in patients with renal-artery stenosis; recommendations for these patients are based on studies in other high-risk hypertensive populations. Multidrug regimens are frequently needed for blood-pressure control. Because the renin–angiotensin–aldosterone system is often activated in patients with renal-artery stenosis, a regimen including an inhibitor of this system is recommended in most patients. Additional agents may include an alpha-blocker or beta-blocker, a long-acting calcium-channel antagonist, and a diuretic. Although a renin–angiotensin–aldosterone system inhibitor may induce acute renal failure in some patients with bilateral severe stenosis, high-grade stenosis in one kidney, or advanced chronic kidney disease,³⁵ the probability of this complication appears to be low, and in most cases, it is reversible with the discontinuation of treatment. Moreover, recent data from a large cohort of patients with renal-artery stenosis suggested a reduced risk of death among patients treated with an angiotensin-converting-enzyme (ACE) inhibitor.³⁶ The demonstrated benefits of statins and antiplatelet therapy in general populations of patients with atherosclerotic disease provide support for the use of these agents in patients with renal-artery stenosis. Several case reports have described a reduction in the severity of renal-artery stenosis in patients treated with statins, and an association between statin use and improved survival was reported in a large case series of patients with renal-artery

stenosis who underwent stenting, although the study design precluded a conclusion that this association was causal.³⁷

Surgical Therapy—Surgical revascularization can result in durable relief of renal-artery stenosis, and in some patients, such therapy improves blood-pressure control and kidney function.³⁸ However, concerns have been raised about the safety of surgical revascularization, and recent data have indicated a 10% in-hospital mortality after this procedure among Medicare patients.³⁹ A randomized trial comparing balloon angioplasty with surgery in 58 patients with renal-artery stenosis showed that the two approaches resulted in similar rates of cure or improvement in hypertension and of stabilization or improvement in renal function⁴⁰; these findings provide support for nonsurgical revascularization as the preferred first-line approach if an intervention is planned.

Angioplasty and Stenting—In patients with fibromuscular dysplasia, balloon angioplasty remains the preferred form of therapy⁴¹; however, medical therapy alone may be appropriate in patients with well-controlled hypertension who are compliant with medical therapy. Although no data from randomized trials are available, data from single-center case series suggest high rates of improvement in blood pressure with angioplasty among patients with fibromuscular dysplasia, and many patients are able to discontinue all antihypertensive medications. Predictors of a favorable outcome of angioplasty include an age younger than 40 years at diagnosis, a duration of hypertension of less than 5 years, and a systolic blood pressure of less than 160 mm Hg.⁴¹

Balloon angioplasty appears to be less effective for atherosclerotic renal-artery stenosis than for fibromuscular dysplasia. In three multicenter trials of balloon angioplasty (without stenting), with up to 1 year of follow-up, there was no significant improvement in blood pressure, although a pooled meta-analysis of these trials suggested modest improvement in blood pressure with angioplasty, as compared with medical therapy.⁴² However, the interpretation of these findings, individually and in meta-analyses, has been controversial because of issues with patient selection, crossover from medical therapy to angioplasty, small samples of patients, and the use of angioplasty without stenting. Atherosclerotic stenoses are often ostial, and balloon angioplasty is suboptimal because of rates of restenosis that may be as high as 71% when assessed prospectively.⁴³

The use of stents, which limit elastic recoil, has led to improved restenosis-free patency as compared with angioplasty alone.⁴³ Improved blood-pressure control after stenting has been reported in single-center registries,⁴⁴ as well as in a multicenter registry of patients who underwent stenting after a technically inadequate result was achieved with balloon angioplasty.⁴⁵ In a case series of patients with renal-artery stenosis who underwent revascularization with stents or received medications, those who underwent revascularization had improved survival, improved blood-pressure control, and less impairment of renal function.⁴⁶

However, two randomized trials comparing stenting plus medical therapy with medical therapy alone for the preservation of renal function showed no significant benefits with the addition of stenting.^{47,48} The larger trial, Angioplasty and Stenting for Renal Artery Lesions

(ASTRAL) (Current Controlled Trials number, ISRCTN59586944), reported elsewhere in this issue of the *Journal*,⁴⁹ involved 806 patients with atherosclerotic renal-artery stenosis who were randomly assigned to undergo stent revascularization in addition to receiving medical therapy or to receive medical therapy alone. The rate of the primary outcome — the change in renal function, as measured by the rate of decrease in the reciprocal of the serum creatinine level — did not significantly differ between the study groups at the 5-year follow-up. Moreover, there were no significant differences between the groups in mean systolic blood pressure or in rates of renal or cardiovascular events or death; this was true even in the high-risk subgroup of patients with high-grade or bilateral stenosis or impaired or decreasing kidney function at study entry. However, because the study included many patients without clinically significant stenosis who were unlikely to benefit from intervention, and because there was limited power for the subgroup analyses, the validity of these conclusions is still uncertain. Likewise, the recently published Stenting in Renal Dysfunction Caused by Atherosclerotic Renal Artery (STAR) trial ([ClinicalTrials.gov](https://clinicaltrials.gov) number, NCT00150943), which included 140 patients, did not show a benefit of stenting plus medical therapy over medical therapy alone for the prevention of loss of kidney function, and stenting resulted in several serious procedure-related complications, including two procedure-related deaths (and an additional late death attributed to an infected hematoma).⁵⁰

These trials, however, are limited by imprecise definitions of renal-artery stenosis, inclusion of patients with clinically insignificant lesions, crossovers, and inadequate or loosely specified medical interventions. In addition, the trials primarily evaluated surrogate end points such as blood pressure and renal function, and they were not powered to assess differences in cardiovascular-event rates. Although revascularization would be expected to reduce the activity of the renin–angiotensin–aldosterone system and sympathetic nervous system,¹³ with possible cardiovascular benefits, pharmacologic therapy directed at these pathways may have similar benefits.

AREAS OF UNCERTAINTY

There is controversy regarding both diagnosis and treatment in patients with atherosclerotic renal-artery stenosis. Although the anatomical lesions are relatively easy to identify and some patients appear to benefit from revascularization, no method reliably predicts the response to revascularization. The optimal treatment strategy remains unclear. Data are lacking from randomized clinical trials comparing the effects of various medical regimens on outcomes in patients with atherosclerotic renal-artery stenosis. Whether angioplasty and stenting are more effective than medical therapy alone in patients with this condition remains unclear. The available data from randomized trials have not shown a benefit of revascularization plus medical therapy with respect to blood-pressure control and renal function; however, these trials had methodologic limitations, were not powered for the assessment of cardiovascular outcomes, and did not include quality-of-life assessments.

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study (NCT00081731) is a large, multicenter, randomized, controlled trial funded by the National Institutes of Health and scheduled to be completed in 2011. This study comparing the effects of optimal medical therapy plus stent revascularization with medical therapy alone has a

composite end point of cardiovascular and renal events. Pending the results of the study, the best treatment for renal-artery stenosis and even whether to evaluate patients for this disease remain uncertain.

GUIDELINES

The American College of Cardiology–American Heart Association 2005 guidelines⁵¹ for the care of patients with peripheral-artery disease, including renal-artery stenosis, provide recommendations for screening patients and for medical treatment, including the use of ACE inhibitors or angiotensin II receptor blockers, calcium antagonists, and beta-blockers. The recommendations based on class I evidence (i.e., general agreement on usefulness) are for revascularization in patients with recurrent congestive heart failure or pulmonary edema. The recommendations based on class IIa evidence (i.e., conflicting opinions, but with the preponderance of evidence favoring usefulness) are for revascularization in patients with global renal ischemia and progressive chronic kidney disease, unstable angina, or hypertension that is worsening, resistant to medical therapy, malignant, or associated with an unexplained unilateral small kidney or in patients who cannot tolerate antihypertensive medication. However, these guidelines antedated the available randomized trials comparing medical therapy with stent revascularization and were based largely on case series and expert opinion.⁵² According to a recent comparative-effectiveness analysis by the Agency for Healthcare Research and Quality (www.effectivehealthcare.ahrq.gov/repFiles/RenalArteryStenosisFinalUpdateExecSum.pdf), it is still not clear whether medical treatment or revascularization is preferable for the management of renal-artery stenosis.

CONCLUSIONS AND RECOMMENDATIONS

A diagnosis of renal-artery stenosis should be considered in any patient with a history of severe or resistant hypertension, hypertension that is associated with renal insufficiency, or disease in other vascular beds. Initial examination should include measurement of kidney function and a lipid profile. An anatomical diagnosis may be made with the use of duplex ultrasonography; if high-quality duplex imaging is not available, then CTA or MRA may be appropriate. In patients with atherosclerotic renal-artery stenosis, such as the patient in the vignette, intensive medical therapy, including tight control of blood pressure with a regimen that includes a blocker of the renin–angiotensin–aldosterone system, is appropriate. Levels of serum creatinine and potassium should be closely monitored when such treatment is initiated and if the dose is increased. Administration of an antiplatelet agent and a statin and treatment of diabetes and chronic kidney disease, if present, with treatment aimed at currently recommended targets are also recommended. The role of revascularization in the treatment of atherosclerotic renal-artery stenosis is controversial. Since available data from randomized trials have not shown a benefit of revascularization over medical therapy, revascularization should be reserved for patients in whom aggressive medical therapy has failed and for patients who are participating in clinical trials.

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Figure 1. Duplex Ultrasonography in a Patient with Renal-Artery Stenosis

Panel A shows aliasing of color in the proximal left renal artery indicating high velocity and turbulent flow. Panel B shows the estimated velocity of blood flow in excess of 900 cm per second in the left renal artery near the aortic ostium; 90% stenosis was confirmed angiographically.

Figure 2. Magnetic Resonance Angiography of the Renal Arteries Showing Severe Bilateral Stenosis

The angiographically confirmed 70% ostial stenosis of the right renal artery (arrow) is associated with a systolic pressure gradient of 28 mm Hg, and the 40% ostial stenosis of the left renal artery (arrowhead) is associated with a pressure gradient of 13 mm Hg.

Table 1

Characteristics of Atherosclerotic Renal-Artery Stenosis and Fibromuscular Dysplasia.

Variable	Atherosclerosis	Fibromuscular Dysplasia
Age at presentation	Older (>50 yr)	Usually young (<40 yr)
Sex	Either	Usually female
Lesion location	Ostial, proximal, middle*	Middle or distal
Blood-pressure response to revascularization	Unclear	Normotension in most patients

* Locations are listed in descending order of likelihood (i.e., ostial is more likely than proximal, which is more likely than middle).

Table 2

Diagnostic Imaging Tests for Renal-Artery Stenosis.

Test	Advantages	Disadvantages
Duplex ultrasonography	Noninvasive	Requires a skilled technician; limited by obesity or bowel gas
Magnetic resonance angiography	Noninvasive	Risk of nephrogenic systemic sclerosis among patients with chronic kidney disease
Computed tomographic angiography	Noninvasive	Risk of contrast nephropathy among patients with chronic kidney disease; radiation exposure
Digital-subtraction angiography	Best image quality and anatomical information	Invasive, risk of contrast nephropathy among patients with chronic kidney disease, risk of atheroembolic events, risk of vascular complications at puncture site; radiation exposure