CASE PRESENTATION

A 63-year-old white man was referred for evaluation of hypertension. He had an elevated BP for approximately 10 years. Medications had been administered for approximately 7 years, but during the past 2 years, his BP had become more difficult to control, requiring increasing doses of metoprolol and lisinopril. Home monitoring of BP generally yielded values ranging from 150 to 180 mm Hg systolic and > 80 to 100 mm Hg diastolic. At the time of his most recent office visit, he was asymptomatic. His medical history disclosed that, other than hypertension, he had sustained a myocardial infarction 3 years previously with no subsequent complications. At the time, he was treated in an outlying hospital with tissue plasminogen activator. During that period, he had mild hypercholesterolemia and was administered simvastatin for its control. He had been a cigarette smoker, one to two packs per day, for 40 years until he stopped at the time of his cardiac event. Alcohol consumption was estimated at no more than one ounce daily. He also had occasional episodes of dyspepsia for which he was treated with antacids. There was no evidence of angina pectoris, and he denied the presence of significant dyspnea. Regarding the family history, his father and one of three brothers had been hypertensive. The father had died of an acute myocardial infarction at the age of 58 years. His mother was living and well at the age of 84 years. Current medications consisted of lisinopril, 40 mg/d; hydrochlorothiazide, 12.5 mg/d; metoprolol, 100 mg bid; simvastatin, 40 mg/d; and enteric coated aspirin, 325 mg/d.

Physical examination disclosed a BP of 160/95 mm Hg; heart rate was 65 beats/min. Height was 69 inches; weight was 160 lb. The patient appeared comfortable and normally developed. The neck was normal, and no bruits were audible. Cardiac findings disclosed a forceful apical impulse with a fourth heart sound. The sounds were otherwise normal. The lungs were clear. Abdominal examination disclosed no organomegaly, but a long systolic bruit was heard over the midepigastric area, with radiation laterally toward the left flank. Systolic bruits were also heard over both femoral arteries; however, the peripheral pulses were intact in the lower extremities.

Laboratory evaluation findings consisted of a normal CBC count and thyroid and liver profile. BUN was 35 mg/dL; creatinine, 2.0 mg/dL; fasting blood glucose, 84 mg/dL; cholesterol, 182 mg/dL; low-density lipoprotein [LDL], 105 mg/dL; high-density lipoprotein, 43 mg/dL; and triglycerides, 140 mg/dL. Serum electrolyte levels, including potassium, were normal. Urinalysis showed normal cellular content, and albumin excretion was calculated at 50 mg per 24-h period.

The ECG disclosed nonspecific ST-T segment abnormality with voltage criteria suggesting left ventricular hypertrophy. An echocardiogram demonstrated mild left ventricular hypertrophy (wall thickness, 1.4 cm) with normal chamber size and wall motion. The left atrium was mildly dilated (diameter, 4.3 cm). Otherwise, the findings were normal.

QUESTIONS FOR CONSULTANTS

1. What would be your overall clinical approach? Would you consider special tests in this patient to
seek renal artery stenosis (RAS) as a cause or contributor to the elevated BP and/or the reduced renal function? If you were to embark on such testing, which test or tests would provide the best method of screening for renovascular disease? If you prefer not to perform such testing, what would be your rationale for such restraint? What future medical management would you recommend, and how should this patient be followed up?

2. If renal angiography had been performed and an isolated area of severe stenosis were found in one renal artery, how would you manage such a situation? If an intervention were selected, which one would you prefer? If a procedure had succeeded in relieving such a stenotic area, what would be its likely effect on the BP? Would the possibility of improving or maintaining adequate renal function provide a reason for mechanical intervention? Are there any circumstances that might justify such treatment in the effort to preserve renal function?

COMMENTS BY CONSULTANTS
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The clinical history and physical findings are suggestive of the development of renovascular hypertension. It is clear that this patient has atherosclerotic vascular disease, and he illustrates the point that atherosclerosis is a systemic disease. He has multiple risk factors for atherosclerosis, including hypertension, a history of smoking for 40 years, hypercholesterolemia, a family history of heart disease, and of course his age and gender. He has a history of myocardial infarction. The history of recent difficulty in controlling the BP in an older man with atherosclerosis is another tip-off that the diagnosis is renovascular hypertension. Renovascular hypertension may occur as the sole cause for hypertension, but it may occur along with preexisting essential hypertension. This patient, despite multiple medicines for his hypertension, including lisinopril, hydrochlorothiazide, and metoprolol, has both systolic and diastolic elevations of his BP. So clearly his current medical regimen is not sufficient. He has evidence of target organ damage—physical findings, ECG, and echocardiogram showing left ventricular hypertrophy—so clearly his elevation in pressure has been long-standing and severe. His renal function is already compromised with an elevated BUN and creatinine, and this may be related to the hypertension, but ischemia could also be playing a role here. He has multiple bruits, and of course the epigastric and flank bruits are a tip-off to possible diagnosis of renovascular hypertension. The multiple bruits are again reminders that atherosclerosis is a systemic disease.

The most common cause of renovascular hypertension is atherosclerosis with stenosis in the proximal renal arteries. The majority of cases are men > 50 years old with a long history of hypertension. Fibromuscular dysplasia is the second most common cause and accounts for approximately 95% of pediatric cases. A common presentation of renovascular hypertension is hypertension that has been controlled and then becomes resistant even when the patient is receiving multiple medicines. Other features include newer onset of hypertension in an older person with the presence of coronary artery disease, peripheral vascular disease, or cerebrovascular disease. New-onset accelerated hypertension in a younger person, especially in women before the age of 30 years, may be suggestive, and here fibromuscular dysplasia may be contributing.

The “gold standard” for diagnosis of RAS is renal arteriography. (Of course, not all cases of RAS are associated with hypertension.) Noninvasive tests may be useful, including captopril renal scintigraphy, which examines renal uptake of a radioactive isotope and excretion of the isotope before and after captopril administration. A decrease of glomerular filtration rate after captopril administration, due to inhibition of angiotensin-mediated vasoconstriction of the efferent arteriole, is suggestive of renovascular stenosis. Sensitivity of this test is 80%, and specificity is 90%. Other noninvasive tests include a captopril test (with measurement of renin levels), which is less reliable in some subgroups of patients; Doppler duplex renal artery ultrasound, which can be useful but is highly operator dependent; and magnetic resonance angiography, which appears promising.

In the present case, this consultant would consider renal arteriography followed by placement of a stent (if significant stenosis of the renal artery was observed). What might be the result of this therapy? Most likely, the patient would still need to be receiving antihypertensives, and this approach might only transiently reduce the need for medicine and transiently protect renal function. A recent study by van Jaarsveld et al studied 106 patients with hypertension who had atherosclerotic RAS (luminal diameter stenosis ≥ 50%) and a serum creatinine level ≤ 2.3 mg/dL who were randomized to percutaneous transluminal renal angioplasty (PTRA) or drug therapy. At 3 months, BP was similar in the balloon angioplasty group (169/99 mm Hg) vs the drug group (176/101 mm Hg). However, the patients in the angioplasty group were receiving 2.1 daily doses of medicines while those in the drug therapy group were receiving 3.2 daily doses (p < 0.001). Twenty-two patients in the drug therapy group crossed over to balloon angioplasty after 3 months because of hypertensive despite three or more drugs or deteri-
oration of function. At 3 months, renal function was better in the angioplasty group. At 12 months, there were no differences in mean BP, daily drug dose, or renal function between groups.

In a separate analysis, in which improvement was defined as either a decrease of $\geq 10$ mm Hg in diastolic BP with no change or decrease in number of drugs, or a decrease in number of drugs without a change in diastolic pressure. Worsening was defined as either an increase of $\geq 10$ mm Hg in diastolic pressure with either no change or an increase in the number of drugs, or an increase in the number of drugs without a change in diastolic pressure. There were some differences between groups at 12 months. By this analysis, at 12 months, BP control had improved in 36 of 56 angioplasty patients (68%) and in 18 of 48 patients in the drug group (38%). BP control worsened in 5 patients in the angioplasty group (9%) and 16 patients in the drug group (33%; $p = 0.002$). Hypertension was cured in 4 of 56 angioplasty patients (7%) and in none of the patients in the drug-therapy group. At 12 months, the number of drugs required by the drug-therapy group was $2.4 \pm 0.9$ vs $1.9 \pm 0.9$ in the angioplasty group ($p = 0.002$).

Restenosis following balloon angioplasty of the renal arteries is common. Restenosis may be less common with placements of stents, but large long-term follow-up studies are needed. In one study, stenting did not improve BP or renal function after 6 months compared to angioplasty without stenting.

Another approach in this patient would be to further push medical therapy adding a calcium channel blocker or considering a centrally acting agent. Addition of an angiotensin-receptor blocker could be considered but potentially could worsen renal function, and potassium would need to be carefully monitored. This later medicine-only approach might be considered in those patients who were simply too ill or who are at risk of having contrast-induced renal insufficiency develop. I do not think our patient falls into that category. So, while the issue of stenting at this point remains somewhat empiric and we do not have the hard data of very large trials to know long-term outcome with stenting, I would still probably go this route.

If the patient received a stent, follow-up management would include aspirin plus a temporary course of another antiplatelet agent, such as clopidogrel. BP and renal function should be monitored closely; some utilize captopril renal scintigraphy or Doppler duplex renal artery ultrasound to follow up patients after renal artery intervention. The patient’s other risk factors should continue to be addressed. His LDL level was 105 mg/dL, and current National Cholesterol Education Program guidelines recommend an LDL level $< 100$ mg/dL for those with coronary artery disease. Thus, he may need adjustment of his lipid-lowering regimen.

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Taken together, this case presents the story of a relatively young man with recently progressive hypertension despite a three-drug regimen. There has been previous cardiovascular disease and impairment of renal function, with a serum creatinine level of 2.0 mg/dL.

Concerning overall clinical approach, several points are worth emphasizing. First, this is an ominous combination of vascular disease and renal failure with a high likelihood of further cardiovascular morbidity/mortality over the next 5 years. Second, the combination of progressive hypertension, vascular disease, and renal dysfunction raises a strong possibility of RAS. However, this degree of renal dysfunction cannot be explained by unilateral renal arterial disease alone. Either the disease is bilateral (or affects a solitary functioning kidney) or additional disease (eg, nephrosclerosis) affects the contralateral kidney if unilateral RAS is identified. An important corollary to this discussion is that the likelihood of meaningful improvement in renal function from revascularization is low, if intrinsic renal disease affects both kidneys. Third, before embarking on more complex drug therapy, I believe it is important to exclude high-grade RAS, particularly if bilateral. For that reason, I would favor evaluation of the renal vasculature. Our method of choice in patients with impaired renal function is magnetic resonance angiography using gadolinium contrast in this instance. The contrast is nonnephrotoxic and provides excellent vascular imaging and an estimate of kidney size and function.

Concerning renal angiography and management, there are several possible outcomes of renal artery imaging in this case. The following are the most likely, although not exclusive, possibilities:

1. Normal renal arteries (or less than high-grade disease): In this instance, further drug therapy to more effectively control volume is warranted (the dose and choice of diuretic is inappropriate for this level of glomerular filtration rate).

2. High-grade, bilateral RAS: This is associated with more resistant hypertension, more likely progressive renal dysfunction and volume retention with circulatory congestion. Furthermore, the likelihood...
of recovery or “stabilization” of renal function is best if revascularization is undertaken before advanced renal failure (creatinine level > 3.0 mg/dL) develops. In this instance, renal revascularization would be justified. Whether this is best achieved with renal artery stenting or surgical revascularization is controversial. My choice would depend on other comorbid disease risks and their prognoses. It should be emphasized that surgical revascularization has a proven record of durability and effectiveness, which has yet to be defined for renal stenting.

3. High-grade, unilateral RAS: This is the most controversial possible result. Three prospective, randomized studies1–5 (albeit small patient numbers) have found only modest benefits regarding BP control with PTRA in such patients. A fourth randomized comparison of PTRA with PTRA plus stenting confirmed improved vascular patency using stents, but remarkably little difference in clinical outcomes, either regarding BP or renal function.3 It should be emphasized that intensive medical therapy will be required in any event. Improvement in renal function based on unilateral renal artery revascularization is not likely, although further loss of renal parenchyma might be avoided. Current methods entail a small but genuine risk of worsening renal function, usually explained by atheroemboli. Patients with creatinine levels > 2.0 mg/dL face a 20% risk of further deterioration of kidney function with revascularization by either surgical or endovascular procedures. However, 28% of patients improve substantially and 52% have stable renal function (usually presented as 80% “stable or improved”).6 It could be argued that the decision about potential benefits in this patient could be deferred until adequate drug therapy with demonstrably improved volume control has been achieved. Our methods of evaluating volume control in patients with “resistant” hypertension include: (1) advancing diuretics until prerenal azotemia is evident, (2) a rise in plasma renin activity has been achieved, or (3) a change in thoracic bioimpedance is demonstrable, which reflects cardiopulmonary volume.

If BP control can be achieved with appropriate and tolerable drug therapy, it may be argued that renal revascularization offers little further benefit. However, if hypertension remains uncontrolled despite appropriate therapy and/or contralateral renal arterial disease develops, then renal revascularization offers real benefits and should be considered.

Follow-up Information and Concluding Remarks

In order to assess the likelihood of RAS, this patient was first subjected to Doppler duplex renal artery ultrasound evaluation. This study disclosed a probable high-grade narrowing of the left renal artery without evidence of critical disease on the right. Both kidneys measured approximately 11 cm in length. Renal arteriography was then recommended. In order to prevent renal deterioration in response to the radiographic contrast agent, the diuretic was withheld for 3 days together with careful fluid volume augmentation. In addition, acetylcysteine, 600 mg, was administered orally twice daily on the day preceding and the day of radiographic contrast injection. This latter agent, presumably through its antioxidant action, has been shown to prevent worsening kidney function after contrast administration.7 Arteriography was then performed without deleterious effect on renal function and disclosed a proximal area of severe (90%) narrowing of the left renal artery. Luminal irregularities were noted in the right renal artery with a single zone of narrowing estimated at 50% of the luminal diameter.

This case and the discussions herein illustrate the various challenges encountered by the clinician in detection and treatment of renal arterial occlusive disease. The various diagnostic tests to screen for this disorder are enumerated above, and all have advantages and disadvantages. In our hands, duplex renal artery ultrasound evaluation has been reasonably accurate and was useful in this instance. The need for a good screening examination, however, depends on whether detection of RAS can allow one to alter the subsequent clinical course. If hypertension can be controlled adequately with medical treatment and renal function is normal, then there is little evidence that efforts to detect renal arterial disease would be of clinical benefit. Considerable difficulty in control of BP usually warrants efforts to detect such disease, especially if renal function is compromised. As pointed out, however, even with revascularization, hypertension usually persists and may require continued aggressive medical therapy. Renal function may be supported by revascularization, but as noted, the treatment of bilateral RAS would be generally required for one to anticipate such an effect.

References