Hypertension and renal artery stenosis: a complex clinical scenario

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Hypertension remains the most common reason for patients to visit physicians in the United States. Although awareness of hypertension among patients continues to increase, adequate control of hypertension remains poor. In addition, as the population of patients with hypertension ages, atherosclerosis becomes increasingly prevalent. Atherosclerotic renal artery stenosis is the most common secondary cause of hypertension and can cause hypertension to be difficult to control. Atherosclerotic renal artery stenosis may also result in chronic renal insufficiency. The physician must be aware of the clinical scenarios in which renal artery stenosis may occur, methods of diagnosis, and indications for intervention.

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Hypertension remains the most common atherosclerotic risk factor. Although physicians recognize the importance of hypertension in the pathogenesis of myocardial infarction, stroke, renal failure, and aortic dissection, control of hypertension remains poor. This paradox exists despite data demonstrating that aggressive reduction in blood pressure results in important clinical benefits.

In the Framingham Heart Study analysis of 10,333 participants followed from 1950 to 1989, the use of antihypertensive medications increased from 2.3% to 24.6% in men, and from 5.7% to 27.7% in women. During this time, the prevalence of significant hypertension decreased from 18.5% to 9.2% in men, and from 28.0% to 7.7% in women. Concomitantly, there was a significant reduction in electrocardiographic evidence of left ventricular hypertrophy, from 4.5% to 2.5% in men and from 3.6% to 1.1% in women.1

Based on the National Health and Nutrition Examination Survey III (NHANES III) data generated from 1991 to 1994, only 27.4% of patients with hypertension have consistent blood pressure measurements less than 140/90 mm Hg.2 Although the efforts of the National Heart, Lung, and Blood Institute have resulted in a positive impact on rates of cardiovascular events through publication of the reports of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, between the fifth and sixth reports, there has been a flattening of the age-adjusted rate of decline in coronary heart disease and a slight increase in stroke rates.3 This plateau is largely due to the poor control of hypertension among most patients.

In a recent series of 800 hypertensive men with an average duration of hypertension of 12.6 years, despite an average of more than six hypertension-related physician visits in 2 years, only 60% had a blood pressure measurement lower than 160/90 mm Hg.4 Several reasons account for hypertension remaining so poorly controlled despite the overwhelming preponderance of data supporting aggressive reduction in systolic and diastolic pressures. These reasons include the asymptomatic nature of disease, cost and side effects of antihypertensive agents, failure of patients to remain compliant with antihypertensive therapy (both lifestyle changes and pharmacologic therapy), and failure of physicians to recognize the importance of aggressive antihypertensive therapy.

Another important reason for failure to control hypertension is the lack of identification of an underlying secondary etiology. A number of medical disorders may result in elevation of blood pressure (Figure 1). If identified and treated, high blood pressure may be cured or improved. The most common secondary cause of hypertension in the adult population, especially with other risk factors for the development of atherosclerosis, is renal artery stenosis (RAS). Despite this secondary cause, two current articles on essential hypertension fail to mention the importance of this treatable disorder.5,6

Prevalence of renal artery stenosis

The prevalence of RAS in the general population is small. In the general population of hypertensive patients, 1% to 6% have some element of RAS.7 In selected patient populations, such as those undergoing diagnostic coronary arteriography, however, the prevalence rises to greater than 20%. In a prospective study of 1302 patients undergoing coronary arteriography, concurrent abdominal aortography demonstrated significant RAS in 15% of patients.8 The number of coronary arteries involved with atherosclerosis also predicted the likelihood of renal artery stenosis in this series. For example, if one coronary artery demonstrated atherosclerosis, the incidence of significant renal artery stenosis was 10.7%. If three coronary arteries demonstrated atherosclerotic involvement, the incidence of renal artery stenosis was 39.0%. Patients who undergo diagnostic arteriography in preparation for peripheral arterial revascularization have significant unilateral or bilateral RAS in 31% to 45% of cases.9,10

Pathophysiology of hypertension in renal artery stenosis

Pathophysiology of hypertension in RAS begins with an increase in plasma renin activity. This increase results in an immediate increase in blood pressure. Subsequent elevation in plasma aldosterone results in an increase in salt and water retention, thereby potentiating the impact on hypertension. If unilateral RAS occurs, the contralateral normal kidney may compensate for the salt and water effects; however, this compensatory mechanism will not occur in the case of bilateral RAS. Other intrinsic renal effects involving the lipoxygenase pathway may play a significant role in the maintenance of hypertension in patients with RAS.11
Demonstrated progression of stenosis. In a pooled review of five arteriographic series, 39% of patients demonstrated progression of stenosis. In one independent arteriographic series, 39% of patients demonstrated progression of RAS. In a pooled review of five arteriographic series, 44% demonstrated progression of stenosis to occlusion, with progression occurring within the first 2 years in 46% of patients. Abnormal renal artery, whose therapy did not involve revascularization, were included. Of 149 renal arteries with baseline stenosis of less than 50%, 69% demonstrated no significant progression of stenosis; however, of 18 renal arteries with baseline stenosis of 75% to 99%, 39% progressed to occlusion on sequential arteriography. Finally, deterioration in renal function as measured by increase in serum creatinine when there was no progression of disease ($P<.02$). Renal size decreased in 70% of patients with progressive disease and in only 27% of patients without increasing stenosis ($P<.001$).

In one of only two prospective natural history studies of RAS, Dean and colleagues followed 41 patients with RAS whose treatment was medical, that is, control of hypertension and correction of any coexisting renal diseases, if possible. Progression of RAS occurred when blood pressure was well controlled; an increase in serum creatinine levels developed in 40% of patients, and 37% of patients had a decrease in renal mass. The second prospective study involved the use of renal artery duplex ultrasonography (RADIUS). In this study, 84 patients with at least one abnormal renal artery, whose therapy did not involve revascularization, were included. Of 139 renal arteries, during the course of a mean follow-up of almost 13 months, the cumulative incidence of progression of RAS as documented by RADIUS was 42% ±14% at 2 years. The occlusion rate at 2 years was 11%±6%. The overall progression rate was 20%.

Diagnosis of renal artery stenosis

The identification and the treatment of atherosclerotic RAS have gained considerable attention during the past decade. With improved diagnostic modalities and therapeutic alternatives, RAS is now being discovered frequently. The optimal method of diagnosis, however, is the presence of clinical clues to the diagnosis (Figure 2). Other modalities, including RADIUS, magnetic resonance arteriography, and captopril-stimulated nuclear renal flow scanning, all have some ability to confirm or refute the diagnosis of RAS.

Therapy of renal artery stenosis

The three options for therapy in patients with hypertension and RAS include medical therapy (control of blood pressure and modification of other atherosclerotic risk factors); surgical revascularization; and endovascular techniques (percutaneous transluminal angioplasty, with or without stents). The zeal with which physicians are now searching for RAS, however, is based on the technology of renal artery stenting.

Surgical revascularization

Surgical revascularization techniques have improved significantly. In one series of 323 surgical renal artery revascularization (RAR) procedures spanning 15 years, the overall mortality rate from the procedure was 5.6%. In those surgical cases that avoided the aorta, the mortality rate was 4.1% versus 8.1% with grafts arising from the aorta. Major postoperative complications occurred in 5.9% of patients with aortorenal bypass alone and in 21.4% of patients with combined aortic replacement and aortorenal bypass. Early (<30-day) graft failure occurred in 2.1% of combined procedures and 17.6% of aortorenal bypass cases.

The clinical impact of surgical RAR has also been extensively reported. In Hansen and associates’ series of 291 surgical RAR procedures, cure of hypertension was seen in 21%, and improvement in control of hypertension occurred in 70% of survivors. Surgical RAR improved renal function in 49% of survivors, caused no change in 36%, and resulted in deter-
Proliferation in 15% of patients. This beneficial impact on hypertension control and renal function has also been shown in patients with diabetes and RAS. Of 54 patients undergoing surgical RAR, cure or improvement in hypertension was seen in 72%, and 40% of patients had improved renal function.21

Medical therapy for renal artery stenosis
The impact of medical therapy for RAS has evolved over time. In the 1970s, 32% of patients with severe hypertension were found to have RAS22; however, antihypertensive therapy in patients with atherosclerotic RAS was quite ineffective in the 1970s, offering adequate control in fewer than 50% of patients.23 With the advent of angiotensin-converting enzyme inhibitors and calcium channel antagonists, more than 80% of patients in several series have demonstrated excellent blood pressure control.24 In fact, bilateral nephrectomy as urgent therapy for uncontrollable hypertension, formerly considered a viable therapeutic option, is now rarely, if ever, performed. Therefore, RAR for “cure” of true renovascular hypertension is an uncommon scenario in present-day medicine.

Endovascular revascularization
Interest in nonsurgical methods of RAR began after Sos and coworkers25 published their initial series of 89 patients with RAS who underwent percutaneous transluminal angioplasty (PTA). The procedure was technically successful in 57% of patients with unilateral RAS and in only 10% of patients with bilateral RAS. Antihypertensive response was impressive, with cure or improvement in hypertension in 84% of patients with atherosclerotic disease. Sos and associates noted the lack of benefit of PTA on ostial atherosclerotic lesions by stating “[the ostial lesions] are, more precisely, lesions of the thickened aortic wall that encroach on the renal-artery ostium, rather than lesions in the renal artery itself.” Although an initial relief of the pressure gradient occurs after PTA of an ostial atherosclerotic lesion, “most of them probably return to their pre-angioplasty state within hours or days.”25

Canzanello and colleagues26 reported on the effect of PTA on blood pressure and renal function in 100 consecutive patients with 125 renal artery stenoses. Technical success ranged from 67.7% (solitary kidneys) to 76.2% (unilateral RAR). During a mean follow-up of 29 months, 59% of patients had improvement or cure in blood pressure. Patients with ostial RAS had the poorest benefit in blood pressure control (32.5%). Complications resulting from PTA occurred in 14% of patients, with two deaths as a consequence of the procedure. Acute renal insufficiency occurred in 26% of patients after PTA.

Because of the limitations of PTA in
effectively treating ostial atherosclerotic RAS, endovascular stent placement has emerged as a revascularization procedure that may prevent recoil and offer a more durable result. This procedure is technically sound, with one series demonstrating technical success in 100% of 92 renal arteries undergoing stent deployment.27 Henry and associates28 also demonstrated 100% technical success in 64 procedures, with a 6-month restenosis rate of 1.6% and a primary stent 1-year patency rate of 92%. Cure or improvement in hypertension was found in 76% of patients.

In a series of 100 patients with 133 renal artery stenoses, renal artery stent deployment was technically successful in 99% of cases.29 Cure or improvement in blood pressure control was seen in 76% of patients 6 months after the procedure. Restenosis occurred in 19% of cases at a mean follow-up of 8.7 months. No patients died as a result of the procedure, and only one stent thrombosis occurred. Two patients suffered contrast-induced acute renal failure, neither requiring dialysis. In this series, 76% of patients had normalization of the blood pressure on the same or fewer antihypertensive agents. No significant adverse effects on renal function were noted.

In a prospective series of 74 consecutive renal artery stenoses which were revascularized with stent deployment, technical success was 100%, with a restenosis rate of 11% after 60 months.30 No major complications occurred, and no patients required emergency surgery after the procedure.

Recent data in 163 patients who underwent renal artery stent placement and were followed up for 4 years revealed some important information.31 This study demonstrated a marked benefit in overall survival and reduction in progressive renal insufficiency if the baseline serum creatinine level before stent revascularization was less than 1.5 mg/dL, as compared with those patients whose serum creatinine level before stent placement was greater than 2.0 mg/dL.

Given all these data, how do we decide which patients with RAS and difficult-to-control hypertension truly require revascularization? Several factors must be considered, including the adequacy of the medical regimen, associated renal insufficiency, presence of concomitant aortic atherosclerosis, skill of the operator, and long-term life expectancy. Even in the “ideal” candidate, however, recent data challenge the short-term needs of renal revascularization. In a series of 68 patients with significant (>70%) RAS followed up without renal revascularization for 6 months, blood pressure did not increase; however, patients required a significant increase in antihypertensive medications to control blood pressure.32 In addition, in follow-up, four patients did require renal revascularization, and one patient required nephrectomy for blood pressure control.

A current clinical trial compared 106 patients with mild, moderate, or severe RAS (>50%) who were randomly assigned to percutaneous renal artery angioplasty or antihypertensive therapy.33 Although the authors conclude that medical therapy was as effective as angioplasty in controlling blood pressure, there were several serious flaws in this trial which make this conclusion inaccurate. In fact, after 12 months, patients assigned to medical therapy required a significant increase in the number of antihypertensive medications in order to control their blood pressure when compared with the group undergoing angioplasty (2.4 vs 1.9, P=0.002). During the course of the trial, 44% of patients assigned to medical therapy received angioplasty. Finally, the durability of renal angioplasty is not nearly as good as with renal artery stent deployment; yet, only two patients in the trial actually received a stent.

Comment
In patients with RAS and significant hypertension that cannot be controlled with appropriate antihypertensive medications at maximal doses, renal revascularization should be considered. In skilled hands, renal artery stenting appears to be the procedure of choice. The technical success of this procedure, low complication rates, durability, and impact on the improvement in blood pressure control are all favorable factors. The key to success in these complex patients, however, is a high index of suspicion for the presence of RAS (Figure 3).

References


