Renal Artery Stenosis in the Hypertensive Patient

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Abstract

- **Objective:** To review the diagnostic approach and therapeutic options for renal artery stenosis (RAS) in the patient with hypertension.
- **Methods:** Qualitative assessment of the literature.
- **Results:** RAS is a common secondary cause of hypertension. Factors associated with an increased risk for RAS have been identified. A useful diagnostic approach for evaluating the hypertensive patient at increased risk for RAS is noninvasive anatomic imaging followed by functional studies to determine the physiologic significance of identified lesions; however, no one diagnostic approach has been validated as best. Therapeutic options for RAS include pharmacotherapy and revascularization. The presence of RAS does not necessarily indicate that an invasive intervention is needed. Resolving the stenosis in individuals who have suspected long-term hypertension and who are likely to have pathology in the kidneys may not result in a dramatic benefit to the patient.
- **Conclusion:** Physicians entertaining the diagnosis of RAS face the challenge of accurately identifying patients who have hypertension and RAS and in whom correcting the stenosis will result in a meaningful improvement in health as well as those patients with incidental RAS who will derive insignificant gains from interventional procedures.

When a patient presents with hypertension, one of the challenges confronting the physician is to determine if genetics or environmental exposures are responsible for the disease (essential hypertension) or if the elevated blood pressure might be ascribed to an etiology that is remediable (secondary hypertension). Essential hypertension is overwhelmingly the most common cause of hypertension, but among the general population of persons who are hypertensive, secondary causes approach a prevalence of 10%, with renal artery stenosis (RAS) being among the most frequent etiologies [1]. Physicians entertaining the diagnosis of RAS face additional challenges, as controversy exists regarding the diagnostic evaluation of RAS and the degree of benefit afforded the patient by interventions to correct the narrowed artery or arteries.

CASE STUDY

**Initial Presentation**

A 52-year-old woman presents to the office for the first time after an initial visit to an employee health clinic where she complained of persistent headaches. At that visit she was observed to have an elevated blood pressure of 180/100 mm Hg. A calcium channel blockade agent was initiated, and she was instructed to be evaluated by a primary care physician.

**History and Physical Examination**

The patient states that her headaches have persisted since initiating the medication. She reports being seen by a physician only for upper respiratory infections in the past and otherwise has been healthy. She never consumes alcohol and has smoked 1 pack of cigarettes per day for 35 years. There is no family history of hypertension. On examination, she is 5’4” and weighs 122 lb. Blood pressure is 182/100 mm Hg in the right arm and 180/98 mm Hg in the left arm using an adult-sized cuff. An undilated funduscopic examination reveals the presence of arteriovenous nicking and arteriolar narrowing. Heart rate is 82 bpm and regular. Cardiac examination is significant for a nondisplaced but enlarged point of maximal impulse and the presence of an S4 sound without murmurs. Abdominal and extremity examinations are unremarkable. Femoral bruits are heard in systole in both groins.

**Laboratory Testing**

A 12-lead electrocardiogram demonstrates left ventricular hypertrophy but is otherwise normal. Her serum electrolytes are as follows: sodium 140 mg/dL, potassium 3.9 mg/dL, chloride 105 mg/dL, bicarbonate 24 mg/dL, and creatinine 1.1 mg/dL. Results of urinalysis are normal.

- **What is the prevalence of RAS? What are its causes?**

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There is no single definition that is accepted, but RAS is commonly defined as a greater than 50% reduction in the lumina of the renal arteries (although other definitions appear in the literature). The prevalence of RAS in the general population is uncertain, but autopsy-based studies of persons aged 50 years or older have reported estimates approaching 25% [2]. The largest cohort study to estimate the prevalence of RAS in the population included 1300 patients referred for cardiac catheterization and demonstrated that 15% had significant (>50% narrowing) stenosis—11% unilaterally and 4% bilaterally, of which 1.6% had bilateral stenoses greater than 75% [3]. A more recent population-based study [4] reported an overall prevalence of renovascular disease (stenosis > 60% narrowing) of 6.8% among 834 adults older than 65. However, uncertainty remains due to the lack of confirmation that these lesions were responsible for clinical disease.

**Hypertension Related to RAS**

Goldblatt first developed a model of RAS in dogs while intending to investigate mechanisms that contributed to the development of essential hypertension [5]. Renin, the primary effector of the 2-kidney 1-clip model of hypertension, has been confirmed to also explain elevated pressures in human studies [6]. With the elevation of angiotensin II by renin, peripheral vascular resistance is increased and retention of sodium from elevated aldosterone levels occurs, all collectively producing elevated blood pressures. Ultimately, the hypertension, if not corrected, will cause glomerulosclerosis in the kidney and fibrotic changes in other vasculature that is irreversible and contributes to the chronicity of hypertension.

**Causes of RAS**

Atherosclerotic disease is the most common cause of RAS [7]. Typically, these lesions occur in the proximal aspect of the renal arteries and may be propagations of plaques that originate from inside the abdominal aorta. Fibromuscular disease is the next most common cause of RAS [8]. These lesions tend to occur in the more distal aspects of the renal arteries and affect other branches of the aorta as well. Fibromuscular disease usually is in the media of the arteries but uncommonly may also be limited to the intima or to the adventitia. There are notable clinical differences between atherosclerotic and medial fibroplastic lesions. The former tends to occur in persons older than 50 years and these plaques tend to progress; the latter occurs more commonly among younger women and are less likely to progress.

**Clinical Predictors of RAS**

The ability of physicians to discriminate among hypertensive patients according to the presence of RAS would limit the number of individuals who are tested and minimize the costs of providing care for persons with a prevalent chronic disease. Factors associated with an increased risk of RAS have been identified (Table). Hypertensive individuals who have an onset of disease before age 30 or after age 50 years, have a significant smoking history, or have recurrent episodes of pulmonary edema or difficult to control pressures have a higher prevalence of RAS. On examination, an abdominal bruit that is systolic-diastolic (as opposed to a bruit limited to systole) increases the likelihood of RAS. Indications of other vascular disease such as carotid bruits and decreased pulses in the peripheral extremities may be further indicators of atherosclerotic disease within the renal arteries. Results of incidental blood tests, such as hypokalemia, have been associated with RAS but lack sensitivity [9,10]. One study compared clinical characteristics of 131 individuals confirmed to have RAS-related hypertension with a set of persons who had essential hypertension [11]. Several characteristics were associated with the risk of having hypertension secondary to RAS: abdominal bruit increased the risk more than fivefold, whereas a family history of hypertension decreased the risk by less than approximately 40%. In this investigation, the only characteristic that had a high prevalence was having a family history of hypertension, which was present in 71% of persons with essential hypertension. It is worth noting, however, that 46% of persons with RAS had a family history of hypertension as well.

The response of a hypertensive patient to the administration of an angiotensin-converting enzyme (ACE) inhibitor or to angiotensin II receptor blockade (ARB) has been utilized by physicians as a possible diagnostic marker of RAS. Inhibition of the increased production of angiotensin II or
blockade of this effector binding to its receptor may reduce systemic pressures dramatically and abruptly. Further, the dependency of glomerular filtration rates on elevated angiotensin II levels results in elevated serum creatinines when ACE inhibitors or ARBs are instituted in the setting of bilateral RAS and in the rare situation of a solitary kidney with RAS. These responses to interference with the renin angiotensin axis unfortunately have very limited discriminative value given the low prevalence of RAS and the attributable proportion of hypertension to RAS. The abrupt decline of systemic pressure may also be observed in individuals who have renin-mediated hypertension, and the decline in renal function also may occur in patients who have elevated glomerular filtration rates to compensate for reduced nephron mass from chronic renal disease.

**Probability of RAS in This Patient**

The cardiac examination and the abnormal electrocardiogram indicate that this patient has had hypertension for a longer duration then suspected, given her recent onset of headaches and elevated blood pressures. The extensive use of tobacco and presence of femoral bruits also suggest the possibility of renal arterial disease as a cause of her hypertension. The physician increases the calcium channel blocker and adds a diuretic to the blood pressure regimen.

- How is RAS diagnosed?

**Diagnostic Testing**

Once a physician has determined that the hypertensive individual is at increased risk of having RAS as the cause of their elevated blood pressure, the next challenge is to determine if the main or accessory renal arteries are narrowed and if the stenoses are physiologically responsible for the hypertension [7]. A strategy for evaluating the hypertensive patient for RAS is shown in the Figure. There is no single diagnostic approach that has been validated as best. The strategy should be individualized according to characteristics of the patient and the attributes of the medical center.

**Anatomic Imaging**

The alternative forms of imaging can be classified as invasive or noninvasive. Commonly used noninvasive imaging techniques include Doppler ultrasound, magnetic resonance angiography (MRA), and computed tomography angiography (CTA). Ultrasound measures the size of the kidneys. A discrepancy of 1 cm or more between the 2 kidneys is suggestive of renal perfusion abnormalities. Assessment of renal artery blood flow by Doppler flow studies requires proficiency by technologists that is uncommon and generally limited to medical centers that evaluate large numbers of patients [12]. As many as 20% of U.S. procedures are unable to visualize renal arteries because of technologist-related factors or obscuring colonic air or are unable to locate posterior directed segments. The introduction of contrast agents with ultrasound that are nontoxic to the kidneys may improve the sensitivity of this technique [9,13]. MRA and CTA with contrast are reliable alternatives to visualize proximal renal vasculature but are limited in their capability to assess distal aspects, accessory renal arteries, and intrarenal artery stenosis. A concern related to CTA with contrast is the risk of contrast-induced nephropathy among individuals with chronic renal insufficiency. Currently, there are no well-designed studies that have sufficient power to detect important differences between the abilities of MRA and CTA to screen for RAS. A small prospective study enrolled 56 patients who underwent conventional angiography of the renal arteries to compare Doppler ultrasound and CTA [14]. Ultrasound had a much lower sensitivity (33%) for segmental artery stenoses as compared with stenoses in the main renal artery (63%). CTA was more accurate than ultrasound in detecting stenoses when present (96% versus 63%).

Contrast-enhanced angiography has been the gold standard for evaluating the extent of RAS, but it is generally
reserved for confirming the findings from other diagnostic tests. Concerns about the invasiveness of the procedure and the need for contrast support the argument that noninvasive imaging should be the initial test. Low osmolar contrast and the use of gadolinium may reduce the risk of contrast-induced nephropathy associated with angiography [15].

**Further Testing**

The patient undergoes an ultrasound evaluation and is discovered to have a right kidney 10.5 cm in length and a left kidney 10.0 cm in length. MRA demonstrates a 2-cm proximal lesion in the left renal artery as well as diffuse atherosclerotic disease in the abdominal aorta.

- **How is the functional significance of a lesion in the renal artery determined?**

**Functional Studies**

Once RAS disease has been identified by noninvasive imaging, the physiological significance of such lesions usually is clarified before procedures such as angioplasty or surgical revascularization are considered [16]. Again, there is no general consensus on the criteria that define a significant stenosis. A stenosis that reduces the cross-sectional lumen of a vessel more than 70% is generally proposed to be a hemodynamically significant lesion and one that warrants invasive evaluation to confirm the significance of the lesion (the presence of at least a 10-mm Hg gradient across the plaque). However, recent guidelines recommend that the clinical significance and the probability of the patient deriving benefit from revascularization should determine evaluation and treatment decisions rather than the morphology of the lesion or hemodynamic criteria [15].

Functional studies that require the use of radioactive tracers such as $^{99m}$Tc-MAG3 may be useful in patients who have greater than 50% of normal renal function. Impaired renal function results in delayed excretion of these tracers, limiting the usefulness of this test for evaluation of RAS, but for patients who have preserved renal function, captopril renography is a potential option. Among patients who have RAS, the renal perfusion in the affected kidney is preserved by elevated levels of angiotensin II. If production of this effector is blocked, then renal perfusion drops and the excretion of the tracer diminishes. A normal renal scan after administration of captopril indicates that the person is unlikely to have RAS or that previously detected renal stenosis by noninvasive imaging does not have functional significance, and intervention on these plaques will not improve hypertension. An abnormal captopril test should be followed by a subsequent renal scan performed without captopril to ensure that the decreased excretion of tracer is related to renin or is simply a static lesion [9].

Measurement of peripheral renin levels from blood sampling is generally not useful. The diurnal variation in renin, the response of renin release to body positions, and intravascular volume status are responsible for the low predictive nature of this test.

**Additional Studies in This Patient**

The patient has an initial captopril renal scan that demonstrates a marked decrease in renal perfusion and delayed excretion of tracer. One week later, a noncaptopril renal scan is interpreted as showing normal renal perfusion and tracer excretion. Based on the results from imaging and functional studies, the physician concludes that the left renal artery lesion is hemodynamically significant and might be responsible for the patient's hypertension.

- **What is the likelihood of the patient's RAS worsening?**

A physician might consider strategies to treat elevated blood pressures that do not address RAS. Before considering medical therapy alone, the physician should appreciate the natural progression of the stenosis as well as its ramifications on blood flow to the kidneys. A review of 5 studies of the angiographic evaluation of RAS suggested that RAS worsened among 49% of the 237 patients studied over a retrospective period of 6 to 180 months [17]. In a cohort of 170 patients, serial duplex scans detected reductions in the diameter of the renal artery among 35% of the cohort over a 3-year period [18]. The initial degree of stenosis appeared to be a factor determining the rate of progression, with an incidence at 3 years of 18%, 28%, and 49% for arteries classified as normal, less than 60% stenosis, and 60% or greater stenosis, respectively.

- **What are the therapeutic options for RAS-associated hypertension?**

**Pharmacotherapy**

ACE inhibitors or ARBs have been utilized to treat hypertension associated with RAS. For individuals who had a high grade of stenosis, ACE inhibitor use resulted in an increase of greater than 20% of serum creatinine for 57 individuals out of 108 enrolled into the study [19]. All instances of creatinine elevation resolved upon discontinuation of ACE inhibitors. It may be reasonable to attempt ACE inhibitor use among patients with less than 60% stenosis under the guise of monitoring of renal function as well as
kidney length. The kidney that is affected with RAS may atrophy from ACE inhibitor use [20], and any confirmed reduction in renal size should indicate consideration of a change from a strategy limited to medical therapy to the inclusion of an interventional procedure.

**Revascularization**

Percutaneous revascularization of the renal arteries by balloon angioplasty has been reported to be effective for 82% to 100% of persons who have fibromuscular dysplasia. In contrast to the 10% restenosis rate with these lesions, atherosclerotic disease has a restenosis rate of nearly 50% in certain series, but more often a 6-month restenosis rate of 30% is quoted. Non-ostial lesions have greater initial success (72%–82%) compared with lesions that arise from within the aorta (60%). A recent clinical trial randomized 106 patients with a diastolic blood pressure of 95 mm Hg or greater and with evidence of at least a 50% reduction in renal artery lumen to either angioplasty or medical therapy. One year after randomization, there were no significant differences in blood pressures or renal function between the 2 groups. After 3 months, 22 patients randomized to drug therapy underwent angioplasty because of poorly controlled hypertension. The significant crossover in this study leaves uncertain the benefit of angioplasty as an intervention to reduce blood pressure [21]. Stenting of lesions is an attractive alternative, but there are no long-term studies that have compared this strategy with angioplasty or surgery. Initially, the technical success rate is 99% to 100%, and initial patency rates are impressive, but by 6 months the patency rate of 80% for stents approaches that for angioplasty alone of ostial RAS [15,22].

The role of surgical revascularization since the advent of percutaneous procedures may be limited to individuals who have atherosclerotic lesions that arise from the abdominal aorta and extend into the renal artery or that have lesions in the distal aspects of arteries that are not amenable to balloon catheters. Several small studies have compared the various options of medication, surgical revascularization, stenting, and angioplasty alone. Unfortunately, no conclusions can be made based upon the lack of power to detect clinically meaningful effects.

- **What are the goals of therapy?**

The presence of RAS, even bilateral disease, does not automatically indicate that an invasive intervention is needed and that the patient will benefit. Appreciation of the potential duration of undiagnosed RAS and hypertension should guide, in part, the decision to proceed with improving the patency of the stenosed vessel(s). RAS may be silent for sufficient time such that arterioles within the kidney are hyalinized and sclerosed, with significant fibrosis developing within the kidney(s) before impaired renal blood flow is detected. This is dissimilar to coronary artery stenosis, which typically results in symptoms before irreversible disease results. In the Honolulu Heart Study, 300 protocol autopsies revealed significant damage within the renal cortex among individuals with hypertension and diabetes, changes that are irreversible even with restored renal blood flow [23]. Resolving the stenosis in individuals who have suspected long-term hypertension and who consequently are likely to have pathology in the kidneys may not result in a dramatic benefit to the patient. Elimination of antihypertensive therapy is idealistic and likely unachievable in the individual who has evidence on clinical examination of end-organ damage. Amelioration of elevated pressures or the reduction in the number of medications is possible in patients who have a proportion of their hypertension that is attributable to RAS and that has not resulted in irreversible injury.

- **Which patients may benefit from an invasive procedure?**

Few studies have sought to develop rules that predict who is likely to have a reduction of elevated blood pressure as a result of an invasive procedure. In a prospective study of 5950 patients screened for RAS as a cause of hypertension, Doppler ultrasound was used in the 138 patients with RAS to measure resistance to flow in the segmental arteries, and a resistance index was calculated. Patients were then treated for stenosis with angioplasty with or without stenting or surgery. The resistance index was independently predictive of a therapeutic response (reduction of at least 10 mm Hg in mean arterial pressure) to the interventions. A resistance index of less than 80 had a positive predictive value of 94% and a negative predictive value of 97% of a response to the interventions. The mean arterial blood pressure declined by a minimum of 10% among individuals who had an index of less than 80 as a result of any invasive intervention [12].

**Intervention**

The patient is referred to a nephrologist. Based on the results of the studies, the nephrologist concludes that the patient has RAS likely from a single atherosclerotic plaque and that the reversible perfusion abnormality suggests that her hypertension likely will be improved by percutaneous angioplasty. The nephrologist discusses the case with the interventional radiologist at the local hospital who recommends that angioplasty without stenting be performed given the non-ostial location of the lesion. The patient agrees and undergoes angioplasty of her left renal artery without
complications. Her blood pressure responds and she is able to stop all her medications with a blood pressure of 128/84 mm Hg. Three months later, her blood pressure is elevated at her primary care physician office to 180/96 mm Hg. Reimaging of her renal arteries by MRA shows that her left renal artery restenosed. She undergoes angioplasty with stenting and remains on a single diuretic agent.

**Conclusion**

Management of this patient led to a successful outcome of reduction of elevated blood pressure. The challenge that persists for the clinician is to accurately identify patients who have hypertension and RAS in whom correcting the stenosis will translate into a meaningful improvement in health, as well as to correctly distinguish the patients with hypertension who have incidental RAS and who will derive insignificant gains from interventional procedures [7].

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**References**