Review Paper

Atherosclerotic Renal Artery Stenosis and Renovascular Hypertension: Clinical Diagnosis and Indications for Revascularization

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Atherosclerotic renal artery stenosis (RAS) is relatively common and often associated with reversible hypertension, progressive renal insufficiency, and/or coronary-independent pulmonary edema. Not all RAS is associated with renovascular hypertension. Historical and physical findings may suggest renovascular hypertension and warrant investigation for RAS. Noninvasive diagnostic imaging options include renal artery duplex ultrasonography, magnetic resonance angiography, computed tomographic angiography, and CO_2 angiography, with each method having its own advantages and limitations. Functional tests of renal flow, which characterize RAS significance, include captopril-stimulated plasma renin activity and captopril renography. To date, no single approach has shown clear superiority either in diagnosis or identification of patients most likely to benefit from revascularization. Revascularization of RAS is recommended for severe/drug-refractory hypertension, preservation of renal function, recurrent flash pulmonary edema, or recurrent severe heart failure. Intervention response is variable, but the ongoing Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, comparing medical therapy with and without stenting, should provide management guidance. (J Clin Hypertens. 2006;8:502–509) ©2006 Le Jacq Ltd.

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Atherosclerotic renal artery stenosis (RAS) is more common than typically appreciated, with an incidence of 6.8% reported in an elderly group of patients.[1] This figure is higher in individuals with coronary artery (15%–23%), aortoiliac (28%–38%), and peripheral vascular (45%–59%) disease.[2–4] The disorder is associated with reversible hypertension and progressive renal insufficiency[5,6]; RAS is identified as the primary etiology in 1%–5% of hypertensive Americans[7] and in 2%–14% of newly diagnosed cases of end-stage renal disease. The prevalence of RAS is higher in Caucasians than in African Americans.[8]

Two pathophysiologic processes can lead to RAS. More than 90% of cases are due to atherosclerosis, with stenoses typically involving the proximal renal artery.[9] Risk factors are similar to those for atherosclerosis of other vascular territories and include advanced age, diabetes mellitus, hypertension, hyperlipidemia,[10] male sex, and smoking.[11] The remaining 10% of cases of

RAS are due to fibromuscular dysplasia, wherein characteristic "beading" in the distal two thirds of the renal artery is seen in these typically young female patients.[12] The focus of this discussion is atherosclerotic RAS.

Not all cases of atherosclerotic RAS are clinically significant. In a retrospective review of aortograms, about one half of patients with a >50% renal artery lesion did not have hypertension.[13] Subcritical RAS may progress to total occlusion. In a study performed before the widespread use of angiotensin-converting enzyme (ACE) inhibitors and statin drugs, up to 39% of patients developed 100% occlusion. Those with a >75% reduction in lumen diameter were most likely to occlude.[14] Lower rates of RAS progression have been noted since the 1990s. In a study of 295 vessels in patients followed with serial Doppler examinations over a period of 4–5 years, likelihood of progression depended on the initial grade of stenosis. Follow-up increased Doppler velocities (indicating stenosis progression) were noted in 31% of vessels, with only 3% progressing to total occlusion.[15] In a study of 1189 patients found to have RAS at cardiac catheterization, only 11% were subsequently found to have progressive disease. Recently reported rates of progression, notably lower than previously reported, may be related to wider use of ACE inhibitors and statin drugs.[16]

Clinical manifestations of atherosclerotic RAS are hypertension (often severe and/or refractory to standard medical therapy), renal failure (ischemic nephropathy), recurrent congestive heart failure, and episodic ("flash") pulmonary edema.[9,17]

The renin-angiotensin-aldosterone system is important in the development of renovascular hypertension (RH). RH begins with increased renin release in response to diminished perfusion to the affected renal afferent arterioles. Renin production in the contralateral kidney (in unilateral RAS) is suppressed by the systemic hypertension. Eventually, total serum renin levels fall (but remain higher than predicted in the face of blood pressure elevation) as intravascular volume expands under the downstream effects of angiotensin and aldosterone.[18]

Although RAS is often bilateral, one side typically predominates physiologically. True bilateral RAS, or RAS to a solitary functional kidney, should be suspected when renal insufficiency is present or oliguric renal failure develops during therapy with an ACE inhibitor or angiotensin receptor blocker.[19]

Ischemic nephropathy results from a reduction in glomerular filtration with loss of renal mass and subsequent renal functional impairment.

Table. Clinical Clues for the Diagnosis of Renovascular Hypertension

Historical and Physical Findings
Abrupt-onset hypertension after age 55
Increasing blood pressure in previously controlled hypertension
Increasingly difficult-to-treat hypertension
Malignant hypertension
Unexplained recurrent congestive heart failure
Recurrent "flash" pulmonary edema
Worsening renal function with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy
Epigastric bruit (systolic/diastolic)
Evidence atherosclerosis elsewhere
Tobacco use
Laboratory
Unexplained worsening renal function
Atrophic kidney or discrepancy in size between the two kidneys (>1.5 cm difference by sonography)
Secondary hyperaldosteronism
Elevated plasma renin, low serum potassium and sodium
Proteinuria usually moderate

Adapted with permission from *J Vasc Surg.* 1992;15:73–80.[21]

Therapeutic blood pressure reduction can further reduce renal perfusion pressure and, when a critical pressure is reached, renal blood flow, glomerular filtration, and urine output decrease.[19] Also, an ACE inhibitor or angiotensin receptor blocker may reduce renal function independent of blood pressure change, as glomerular filtration pressure can be critically dependent on high levels of angiotensin II (maintaining efferent arteriolar tone) in RAS patients.[20]

Recurrent episodes of congestive heart failure and "flash" pulmonary edema not secondary to acute coronary ischemia may occur with bilateral RAS or unilateral RAS to a solitary functional kidney. These clinical events usually improve following revascularization. Spontaneous diuresis is often observed soon after intervention.[17,21] Although the mechanism is not definitely known, this response suggests that fluid retention, perhaps with coexistent left ventricular diastolic dysfunction, is important.[22]

DIAGNOSIS

Clinical clues suggesting RH due to RAS include historical, physical, and laboratory findings (Table). Malignant hypertension (severe hypertension with acute central nervous system involvement), resistant hypertension (inability to reduce blood pressure to <140/90 mm Hg on at least three drugs that have different mechanisms of action), and sudden worsening of previously controlled hypertension, all

suggest RAS as a possible etiology.[23] An epigastric systolic bruit that persists into diastole suggests severe arterial narrowing and significant RAS.[24]

As discussed above, identification of atherosclerotic RAS does not indicate RH. Some clinical features (Table) exist in a significant number of hypertensive patients regardless of etiology. An initial noninvasive imaging (imaging assessment) screening study, if found to be abnormal, warrants further evaluation of renal perfusion (physiologic assessment) to clarify whether RAS is hemodynamically significant.[9]

The Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study[25] was performed to determine the prevalence of RAS in patients with drug-resistant hypertension and to assess the predictive value of clinical features and diagnostic tests on these patients. A clinical prediction rule for RAS was devised in which a patient was considered to have RAS when at least a single stenosis of ≥50% in a renal artery was found. Clinical characteristics of 477 patients with drug-resistant hypertension or an increase in serum creatinine associated with ACE inhibitor therapy were analyzed. A clinical prediction rule and mathematic equation for quantifying the probability of RAS was developed.[26] The strongest discriminating factors favoring RAS over that of essential hypertension in descending order were found to be an abdominal bruit, atherosclerotic vascular disease, smoking history, hypercholesterolemia, and older age (mean 57 years vs. 50 years, respectively).

Although contrast angiography remains the gold standard for diagnosis of atherosclerotic RAS, it carries the risk of vascular (bleeding, dissection, embolization, pseudoaneurysm) and renal (atheroemboli, toxic nephropathic) complications. Noninvasive imaging modalities to diagnose RAS include duplex ultrasonography, magnetic resonance angiography (MRA), and computed tomographic angiography.

Duplex ultrasonography (combining B-mode two-dimensional imaging with Doppler flow measurement) is a good test for detection of atherosclerotic RAS. In addition to assessment of the stenotic renal vessel, kidney size can be measured and other abnormalities (abdominal aortic aneurysm, ureteral obstruction) can be detected. This technique is highly operator-dependent and nearly impossible to perform in obese patients. When performed by an experienced sonographer on appropriate patients, however, a negative ultrasonic evaluation effectively excludes RAS.[27,28] A renal artery/aortic peak systolic velocity ratio >3.5 with a renal artery peak velocity >2 m/sec corresponds to a stenotic lesion >60%[29] and is considered diagnostic of RAS. In addition, calculation of a segmental renal artery velocity parameter, termed the resistance index (RI), is predictive of outcome from angioplasty or stenting of the renal artery.[30] The RI is calculated as:

RI = (PSV – EDV)/PSV (where PSV is renal artery peak systolic velocity and EDV is renal artery end-diastolic velocity).

An index >80 identifies patients not likely to show improvement in blood pressure or renal function following vascular intervention and may be indicative of renal small vessel structural disease.[30] Duplex ultrasound has a sensitivity of 84%–98% and a specificity of 62%–99% in diagnosing RAS (vs. contrast angiography).[29] It should be noted that this study result has not yet been reproduced, and further validation of this technique is needed.

Three-dimensional MRA using gadolinium-based contrast agents (not nephrotoxic and safely used in renal insufficiency) usually visualize the major renal arteries well. Distal renal, intrarenal, and accessory renal arteries may not be adequately visualized; therefore, significant lesions within these vessels could go undetected by this method.[31–33] However, MRA can measure renal blood flow and glomerular filtration rate, allowing for assessment of RAS significance.[31] Compared with angiography, the sensitivity of MRA is 90%–100% and specificity is 76%–94%.[34,35]

A very useful screening test for renal artery lesions in patients with normal renal function is computed tomographic angiography (Figure 1); however, this modality requires iodinated contrast media and radiation exposure, with their attendant risks. Its accuracy appears better than that of duplex ultrasound, with a sensitivity and specificity of up to 98% and 94%, respectively,[36,37] and it is less operator-dependent.

CO_2 angiography can be used with minimal risk in patients with renal insufficiency. Its sensitivity (83%) and specificity (99%) compared with angiography is good.[38] Imaging of posterior structures within a vessel may be suboptimal, and the technique requires both rapid image acquisition (as CO_2 dissolves quickly) and vascular catheter placement (with risk of atheroembolization).[39] Resolution is not as good as with traditional contrast angiography.

One of the earliest functional studies for RAS was the hypertensive IV pyelogram, which uses kidney size, delayed time to caliceal appearance of

contrast, and renal accumulation of contrast in the delayed films as diagnostic criteria for RAS. This procedure is rarely performed now due to its relatively low sensitivity and specificity and attendant contrast risk.[40]

Plasma renin activity measurements are not diagnostically helpful, since patients with RH may have low, normal, or elevated random levels.[41] Oral captopril loading (50 mg), followed by delayed (1 hour) plasma renin activity measurement, improves sensitivity somewhat, but still leaves this approach lacking in patients with renal insufficiency, bilateral RAS, or RAS due to a single functioning kidney.

Captopril renography compares baseline radionuclide tracer scanning images with labeled hippurate (measuring renal flow) or technetium-99m diethylenetriamine penta acetic acid (DTPA) (measuring glomerular flow) with delayed images taken after oral captopril (25 mg) administration. With captopril, activity transiently decreases in the involved kidney only.[42] This procedure requires pretest discontinuation of medications that affect renin production (β blockers, clonidine, ACE inhibitors, angiotensin receptor blockers). Criteria for diagnosis include delayed time to maximal nuclide activity of the involved kidney, different peak activities between kidneys, retention of nuclide within the cortex, and reduced glomerular filtration rate of the involved kidney. Although the sensitivity and specificity is good for diagnosis of significant RAS, predictive value falls markedly in the presence of bilateral RAS or elevated serum creatinine.[43,44]

Thus, most noninvasive studies, whether functional or anatomic, demonstrate some degree of operator dependency and/or require interpreter experience, while the accuracy of others is limited in certain clinical circumstances. Selection is largely dependent on the local experience of technicians and interpreting physicians. If the clinical setting strongly suggests RAS but one or more noninvasive studies are inconclusive, contrast angiography should be considered if the potential benefit justifies associated risks. Whether any patients should bypass noninvasive evaluation and undergo standard angiography as an initial procedure is debatable, as revascularization is rarely, if ever, an emergency procedure, and the risk of contrast nephropathy and atheroembolization is greatest in patients with the most severe compromise of renal function.

TREATMENT

Measurement of renal vein renin concentrations may predict postrevascularization improvement in blood pressure,[45,46] but is not useful as a diagnostic screening tool. After imaging has discovered anatomic RAS, renin samples are obtained from both renal veins and from the inferior vena cava, both above and below the renal vein junction. Sampling is performed at baseline and then again after administration of IV furosemide or captopril, which stimulate renin release. An increase in renin production from the involved kidney, coincident with a decrease in renin release on the unaffected kidney (in a ratio of >1.5:1) is considered diagnostic.[45] Note that patients must not be taking medications that affect renin production at the time of testing.

While also not a useful screening tool, an elevated brain natriuretic peptide level (>80 pg/mL) in

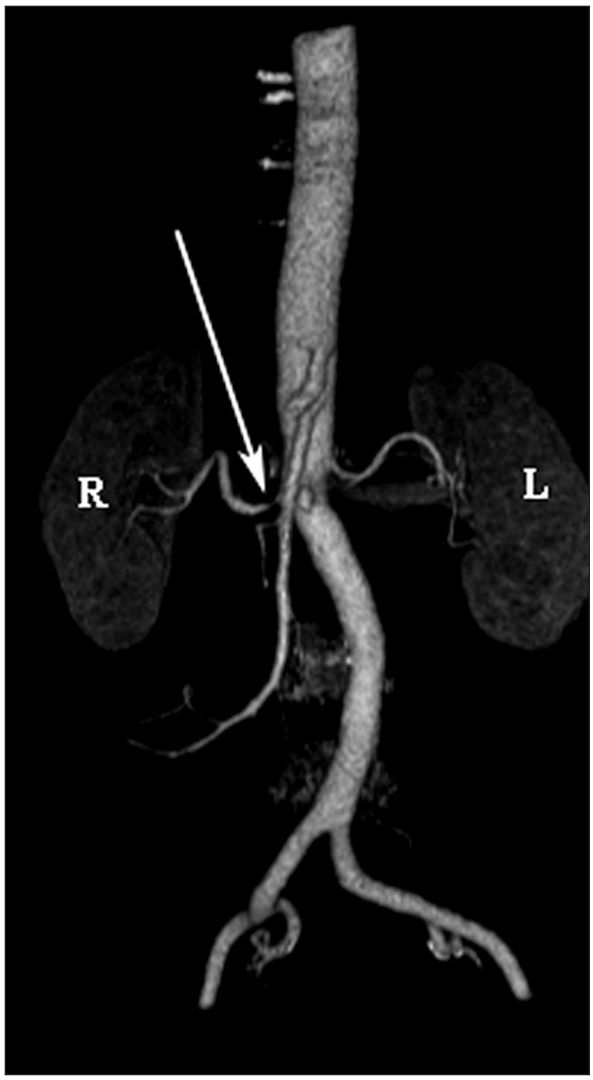

Figure 1. Computed tomographic angiography of a 68-year-old woman with progressively difficult-to-treat hypertension. A high-grade proximal right renal artery stenosis (arrow) was found. Although not "curative" of hypertension, balloon dilation and stenting of the lesion resulted in a reduction in blood pressure medications and dosages.

patients with RAS (in the absence of other conditions associated with such elevation) may identify patients who will obtain blood pressure reduction after stent revascularization.[46] This study has not yet been reproduced.

Direct measurement of an RAS gradient helped facilitate degree of stenosis severity but had no correlation with systemic blood pressure, renal function, or blood pressure medication requirements.[47] In a more recent study, however, 38 patients with RAS had a good correlation between the gradient and stenosis severity, renal function, and systemic blood pressure.[48] When the measured stenosis was a 50% reduction of lumen diameter, the gradient was about 22 mm Hg. A rapid progression of the gradient was noted with an increasing stenosis. These investigators found that with direct intra-arterial infusion of nitroglycerin, the gradient increased further across a significant stenosis.

Several studies have been performed comparing percutaneous intervention to medical therapy. In the DRASTIC study, patients were randomized if they had a ≥50% stenosis and were followed for 1 year. By 3 months, 44% of the medical groups crossed over to renal angioplasty.[49] Data were analyzed on an intent-to-treat basis. Stenting was not an option in this study. Restenosis occurred in 48% of patients randomized to angioplasty. Hypertension was cured in 7% of the angioplasty group and none in the medical therapy group. Both treatment arms only resulted in a mean blood pressure of ≈160/90 mm Hg.

In the Scottish and Newcastle study,[50] 55 (N=135) patients were randomized to medical therapy or angioplasty. Patients had a sustained diastolic blood pressure of ≥95 mm Hg on two or more antihypertensive medications. An RAS of ≥50% by angiography was necessary for inclusion. Patients with bilateral RAS randomized to angioplasty had a sustained significant decrease in blood pressure, whereas those with unilateral RAS had no improvement over those patients randomized to medical therapy.

The Essai Multicentrique Medicaments vs. Angioplastie (EMMA) trial[2] involved patients with a diastolic blood pressure >95 mm Hg on therapy with a ≥75% diameter narrowing or ≥60% with an abnormal functional study. Patients were randomized to drug therapy (n=26) or angioplasty with or without a stent (n=23). Subsequently, both groups had similar blood pressures, but the angioplasty group allowed for control with fewer antihypertensive drugs.

These three studies were relatively small and employed an interventional arm mostly without stenting. The Analysis of Stents versus PTA in Renal Arteries (ASPIRE-2)[51] evaluated the safety and effectiveness of the Palmaz balloon expandable stent (Cordis Corp., Warren, NJ) in the renal artery after failed angioplasty. ASPIRE-2 was a nonrandomized (n=208) study of renal stenting after failed renal angioplasty for RAS refractory to two or more antihypertensive medications. The primary end point was a 9-month angiographic or duplex ultrasound restenosis rate calculation, and secondary end points were renal function and blood pressure. Stenting was successful in 80% of patients with a restenosis rate of 17%. Blood pressure dropped from 168/82 mm Hg to 149/77 mm Hg at both 9 and 24 months. Serum creatinine in the group increased from 1.36 mg/dL to 1.40 mg/dL at 9 months and 1.46 mg/dL at 24 months. In the group with a creatinine ≥1.5 mg/dL, the mean level was 1.94 mg/dL at baseline and 1.87 mg/dL at 9 months and 1.93 mg/dL at 24 months. The group with bilateral RAS and stenting (n=43) showed the same degree of blood pressure improvement as the overall cohort. Similarly, as was noted in the unilateral RAS group, no significant effect was noted on long-term renal function.[52]

Thus, due to study limitations based on sample size, design, and/or interventional technology, fully evidence-based guidelines for revascularization are lacking. Present consensus recommends revascularization of flow-limiting RAS (≥70% stenosis of one or both renal arteries) for severe hypertension (Figure 2), preservation of declining renal function, or as therapy for recurrent acute pulmonary edema not associated with active coronary ischemia.[12]

Although patients with severe refractory RH often experience improvement with revascularization, only 10% of treated patients become normotensive without need for continued antihypertensive medications. Improvement will be noted in another one half of individuals (blood pressure reduced by ≥10 mm Hg on an unchanged medical regimen), while the remainder will have no change in blood pressure.[53] It does appear that a patient with RH refractory to medical therapy may benefit from revascularization.[54,55]

The National Institutes of Health (NIH)-sponsored prospective trial, Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), began in 2005 to determine whether renal artery stenting influences blood pressure, drug requirements, or outcomes in medically treated hypertensive patients.[56] This is a prospective, multicenter, randomized, two-arm trial assigning patients to renal stenting vs. medical therapy. The primary end point

of event-free survival will be analyzed on an intent-to-treat basis. It is a 5-year trial with an anticipated 1080 patient randomized enrollment. Inclusion criteria include systolic hypertension ≥155 mm Hg, on two or more antihypertensive medications, and one or more renal arteries stenosed ≥60% and <80% visually by angiography with a ≥20 mm Hg gradient or a ≥80% and <100% stenosis visually estimated at angiography.

Revascularization of RAS for chronic renal insufficiency has, on the whole, demonstrated no consistent improvement in renal function.[57,58] About one fourth of revascularized patients show significant improvement in serum creatinine, while half show no change and the remainder progressively lose renal function.[59] In patients with an RI >80 (see above), revascularization more often results in worsening renal function and no improvement in hypertension.[30] Revascularization to preserve renal function is recommended for patients with bilateral RAS and a serum creatinine >1.5 mg/dL, unilateral RAS and a glomerular filtration fraction ≤40%, or ACE inhibitor-induced renal failure. Conversely, medical therapy alone is recommended for patients with unilateral RAS with a serum creatinine >2.5 mg/dL, kidney length <7 cm, proteinuria >1 g/24 hours, diffuse intrarenal disease, and an RI >80.[60]

Patients with recurrent bouts of acute "flash" pulmonary edema associated with markedly elevated blood pressures may benefit from renal revascularization.[17,21] Refractory congestive heart failure may improve after revascularization for bilateral RAS. The hospital readmission rate may decrease, and volume management may become less problematic.[21]

Since RAS is a defined peripheral vascular disease and coronary disease equivalent, its presence lowers the goal of lipid (low-density lipoprotein) therapy to <70 mg/dL based on the 2004 update to the National Cholesterol Education Program guidelines[61,62] and systemic blood pressure goal <130/80 mm Hg in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[63] on hypertension management. Although medical therapy to these goals are expected to reduce major adverse cardiovascular events globally, whether there is a difference in outcomes in the specific RAS population is yet to be rigorously tested. Similarly, whether antiplatelet therapy affords any additional or specific benefit to patients with RAS (perhaps by reducing local atheroembolic renal injury) compared with the overall benefit afforded to patients with other atherosclerotic manifestations also remains an untested hypothesis.

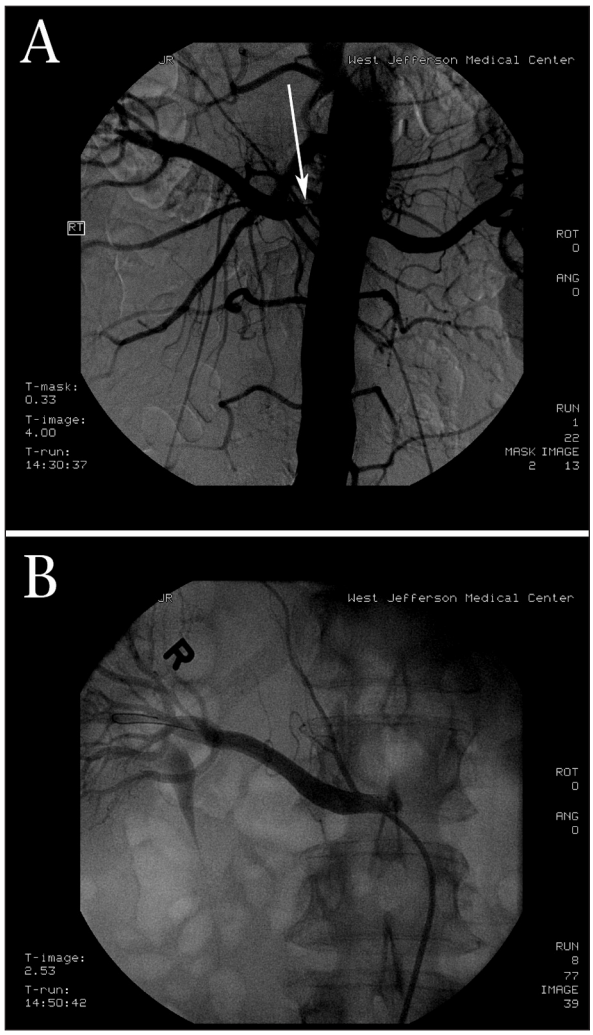

Figure 2. A 74-year-old man developed progressive severe hypertension. Despite therapy with three medications, his blood pressure remained elevated. A) Nonselective angiography reveals a high-grade proximal renal artery lesion (arrow). The right renal artery was then selectively engaged with a catheter, and the pressure gradient across the lesion measured 65 mm Hg. B) Selective angiography postdilation of the lesion by balloon angioplasty. Stenting was then performed.

CONCLUSIONS

RAS is a relatively common finding. It is not necessarily associated with RH. Several historical and physical findings may be suggestive and warrant a noninvasive investigation for RAS. Once identified, a functional study may help determine whether the vascular lesion is associated with RH. Indications for intervention include a ≥70% stenosis and either: 1) severe hypertension; 2) renal insufficiency; or 3) flash pulmonary edema or recurrent severe heart failure. Generally, revascularization of RAS has not been proven to have

better outcomes than medical therapy. The ongoing CORAL trial should provide clinicians with guidance in managing patients with RAS. Identifying which patient with RAS has RH, and also which patient will benefit from a revascularization procedure, remain subjects of continued investigation.

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