The Current State of Endovascular Therapy in the Evaluation and Management of Renovascular Disease

Praveen R. Anchala, B.A.,¹ and Scott A. Resnick, M.D.¹

ABSTRACT

Hypertension is the most common reason for physician office visits among nonpregnant adults in the United States; up to one-third of Americans over the age of 18 have been diagnosed with hypertension. Patients with physiologically significant renal artery stenosis often go unnoticed because hypertension can often be well controlled with antihypertensive medications. As a result, screening for renovascular causes of hypertension is rarely done. However, the likelihood of renovascular disease increases in patients with acute, severe, or refractory hypertension and should be explored in patients who fall into these categories. Renovascular disease is a crucial consideration in the management of hypertension due to its increasing incidence and its potential for reversibility. Although renovascular disease accounts for less than 1% of patients with mild hypertension, it is estimated that between 10 and 45% of white patients with severe or malignant hypertension have renal artery stenosis (RAS). In this population, diagnosing and treating RAS can have a profound and long-lasting effect on the treatment of hypertension.

KEYWORDS: Hypertension, renovascular hypertension, fibromuscular dysplasia, angioplasty, atherosclerosis

Objectives: Upon completion of this article, the reader should be able to understand (1) the etiologies of, natural history of, and pathophysiology of renovascular disease, (2) the indications for treatment of renovascular disease, (3) the options for diagnostic evaluation of renovascular disease, (4) the range of available treatment options for renovascular disease in both native and transplant kidneys, and (5) the role of antiplatelet therapy and the importance of noninvasive postprocedure follow-up in treated renovascular disease.

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Hypertension (HTN) is the most common reason for physician office visits among nonpregnant adults in the United States.¹ Some studies have reported almost one-third of Americans over the age of 18 have been diagnosed with HTN,^{2,3} and this number has been

steadily rising.^{2,3} Patients with physiologically significant renal artery stenosis (RAS) often go unnoticed because HTN can often be well controlled with antihypertensive medications. As a result, screening for renovascular causes of HTN is rarely done. However,

¹Department of Interventional Radiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Address for correspondence and reprint requests: Scott A. Resnick, M.D., Northwestern University Feinberg School of Medicine, 251 East Huron Street, Feinberg 4-710X, Chicago, IL 60611 (e-mail: sresnick@northwestern.edu).

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the likelihood of renovascular disease (RVD) increases in patients with acute, severe, or refractory HTN and should be explored in patients who fall into these categories.^{4,5} RVD is a crucial consideration in the management of HTN due to its increasing incidence and its potential for reversibility.⁶

RAS from atherosclerosis (two-thirds of cases) and fibromuscular dysplasia (FMD) account for nearly all RVD.⁷ Less common causes of HTN include renal artery emboli, renal artery aneurysms, renal artery dissection, hypoplasia of the renal arteries, and stenosis of the suprarenal aorta. Although RVD accounts for less than 1% of patients with mild HTN, it is estimated that between 10 and 45% of white patients with severe or malignant HTN have RAS.^{5,8} In this population, diagnosing and treating RAS can have a profound and long-lasting effect on the treatment of HTN.

ETIOLOGIES OF RVD

As discussed above, diseases leading to clinically significant RAS can be divided into three main groups: (1) atherosclerosis, (2) FMD, and (3) other etiologies. Nearly all RAS occurs from either atherosclerosis or FMD.⁷ Other etiologies for RAS include postoperative complications, neurofibromatosis, Takayasu's arteritis, radiation-induced stenosis, and aortic dissection. This chapter presents a review of treatment options for RAS secondary to atherosclerosis and FMD.

NATURAL HISTORY

Although HTN is the most common presenting symptom of RAS, it is estimated that between 25 and 50% of patients with RAS are not hypertensive.^{9,10} This highlights an often overlooked, yet extremely important, aspect of RVD. The effects of renal artery disease are much broader than HTN, and its implications likely have widespread systemic effects. In one study, concurrent atherosclerotic heart, cerebrovascular, and peripheral artery disease were present in 67%, 37%, and 56% of RAS patients, respectively.¹¹ These prevalence estimates were two- to fourfold higher than those without RVD. Approximately 9% of patients who underwent abdominal aortography immediately after coronary angiography were found to have at least 50% RAS, and almost 5% had greater than 75% stenosis.¹⁰ The presence of greater than 75% RAS was associated with a 4-year survival of 57% versus 89% in those patients without RAS.¹⁰ This same study also showed a decrease in 4-year survival that correlated with RAS severity.¹⁰ The presence of RAS in asymptomatic patients should be considered a marker for more diffuse cardiovascular disease and should lead to aggressive risk factor modification and causative factor treatment.

The progression of renal artery lesions has been well documented.¹²⁻¹⁵ It is unclear what percentage of renal artery stenotic lesions lead to HTN and/or renal insufficiency. Few patients with incidentally discovered RAS progress to end-stage renal disease.¹⁵ Doppler ultrasonography revealed the incidence of any progression at 3 years was 28% among arteries with an initial stenosis less than 60% and 49% among arteries with greater than 60% initial stenosis.¹² Some studies suggest that progression to total occlusion occurs in 10 to 15% of stenotic renal arteries, and is much more common in lesions with greater than 75% initial narrowing.¹⁴

Significant stenosis carries a long-term risk of renal insufficiency, decreased renal mass, and refractory HTN. It can also indicate more widespread cardiovascular effects leading to increased mortality. Most of these changes have been described in relation to atherosclerotic disease. Although FMD can progress as well, total occlusion and renal failure are rare events in its natural history. In these instances, FMD-associated arterial dissection is often causative. Moreover, the demographics of FMD affected patients differ markedly from that of atherosclerosis.

PATHOPHYSIOLOGY OF RVD

Atherosclerosis characteristically produces stenosis at the main renal artery orifice, or ostium. These lesions usually consist of an atheroma originating in the aorta and extending into the renal artery. Although the atheroma can arise in the renal artery itself, this is less common. Similar to other manifestations of atherosclerotic arterial disease, RAS is most common among men over the age of 45.

FMD, on the other hand, typically involves the middle and distal third of the main renal artery, occasionally with involvement of proximal renal branch vasculature.¹⁶ The medial disease variety of FMD is by far the most common form, accounting for 85% of these lesions.¹⁶ The stenosis occurs as a consequence of concentric rings of hyperplasia projecting into the arterial lumen.¹⁶ FMD typically occurs in women under the age of 45 years.

Although there are differences between the pathogenesis of atherosclerotic RAS and FMD, the pathophysiology of the HTN caused is identical. Ultimately, the stenosis of the main renal artery leads to renal hypoperfusion. This hypoperfusion initiates the renin-angiotensin system as decreased blood flow through the juxtaglomerular apparatus stimulates renin release from the macula densa. Renin release from the kidney leads to a subsequent increase in angiotensin II, a potent vasoconstrictor that also stimulates the release of aldosterone from the adrenal gland. Aldosterone causes sodium and water resorption in the kidney leading to increased extracellular fluid volume. Thus, the effect of RAS on

blood pressure is twofold from both the vasoconstrictive properties of angiotensin II and aldosterone-mediated sodium and water retention.^{17,18}

Before diagnosis of RAS, many patients have already received angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as a treatment for HTN. In addition to its effects described above, angiotensin II, the product of interaction between angiotensin I and ACE, normally constricts the efferent arteriole, causing increased glomerular pressure. The use of ACE inhibitors or ARBs decreases angiotensin II levels, resulting in decreased glomerular perfusion pressure. This is compounded by the already diminished renal blood flow due to RAS, and this combination can result in renal insufficiency. Although drug-induced renal insufficiency is itself detrimental, ACE inhibitor-induced renal insufficiency is often the sentinel event that leads to an investigation of an underlying vascular etiology for the HTN being treated, and is thus often viewed favorably when it occurs as it suggests a potentially treatable hypertensive etiology.

INDICATIONS FOR EVALUATION AND TREATMENT

Because the incidence of RVD varies with clinical setting, it is generally not advised to screen all hypertensive patients. However, in patients with certain types of HTN or renal insufficiency, screening can be of great value.

HTN

In general, patients with more severe HTN should be evaluated for the presence of RAS. Some clinical indicators include HTN before the age of 40, onset of stage II HTN after the age of 55, refractory HTN, acute rise in blood pressure in a previously well-controlled patient and in patients with end-organ damage secondary to HTN such as kidney failure, enlarging heart, neurological damage, or retinal changes.

Renal Insufficiency

RAS places the kidney under stress as a result of hypoperfusion. Despite this, the kidney is typically able to maintain normal function, as indicated by a normal range creatinine level or glomerular filtration rate (GFR). The use of ACE inhibitors or ARBs leads to decreased glomerular perfusion pressure as described above. The additive effects of these two processes can lead to renal insufficiency. Thus patients with worsening renal function precipitated by ACE inhibitors or ARBs, as indicated by a rising creatinine level or a falling GFR, asymmetric kidney size, presence of a flank bruit, or

patients with renal insufficiency along with other manifestations of atherosclerotic vascular disease should be screened for RVD.

DIAGNOSTIC EVALUATION

Diagnostic evaluation of RVD should only be performed when a corrective procedure would be considered if clinically significant disease were detected, a policy consistent with the American College of Cardiology and the American Heart Association.^{19,20} The gold standard for the diagnosis of RAS is renal arteriography; however, a variety of less invasive tests have been used for screening purposes.^{21,22} Duplex ultrasonography, computed tomographic angiography (CTA), and magnetic resonance angiography (MRA) are the most commonly used screening tests for RAS. Plasma renin activity, captopril renograms, and intravenous pyelogram are no longer routinely considered due to their poor sensitivity and specificity.²⁰ Similarly, the use of renal vein renin sampling as a screening tool can lead to many false-positive and false-negative results^{5,23}—the exception is lateralizing which kidney contributes the most to HTN when bilateral stenoses is present.²⁴

DUPLEX ULTRASONOGRAPHY

Duplex ultrasonography is the least expensive of the above diagnostic tests for RAS.²⁵ One important advantage of duplex ultrasonography is that it provides both functional and anatomic assessment of the renal arteries. The duplex ultrasonography consists of direct visualization of the renal arteries as well as measurement of hemodynamic factors such as flow velocity, waveform analysis, and the aortorenal ratio that can indicate renal stenosis. Similar to other arterial exams, stenosis of the renal artery typically produces high-flow velocities at the level of the stenoses as well as flow disturbance distal to the stenoses. Although this sounds simple to evaluate, the exam is rarely so straightforward. Extremes of RAS can lead to a variety of waveform and flow velocity abnormalities. Additionally, to perform an adequate examination, the entire main renal artery must be visualized. This can be complicated by large patient body habitus and/or bowel gas artifact.^{26,27} A meta-analysis of 88 studies involving 9974 renal arteries indicated that sonography is a reasonable screening test for RAS, by showing elevated peak systolic velocity, and has an expected sensitivity of 85% and specificity of 92%.²⁵ In addition, it showed peak systolic velocity was the most accurate test characteristic, showing higher predictability than both the renal-aortic ratio and the acceleration index.²⁵

There are two main disadvantages of duplex ultrasonography. First, it can be very time-consuming, sometimes taking up to 2 hours to perform. The second

disadvantage is the technical difficulty in performing the test. It is often described as having a steep learning curve, and test characteristics are highly operator-dependent and can lead to widely varying results.^{24,28} The reliability of duplex ultrasonography can be improved by performing the procedure after ACE inhibitor administration.^{29,30}

CTA

CTA uses digital rapid scanning of the aorta, renal arteries, and kidneys during the peak arterial enhancement phase of an intravenous contrast bolus.^{31–37} Computer algorithms transform the data acquired from scans into a more angiographic view.^{36,37} Iodinated contrast requirements of this test limit its use in patients with renal insufficiency. CTA has demonstrated sensitivity and specificity in detecting RAS of 98 and 94%, respectively, when compared with arteriography. However, in patients with plasma creatinine concentrations above 1.7 mg/dL, sensitivity and specificity dropped to 93 and 81%, respectively.³⁸ CTA appears to be an excellent screening option for RAS in patients with normal renal function. In patients with renal insufficiency, the use of iodinated contrast material is a relative contraindication to performing CTA.

MRA

MRA is increasingly being used as the first-line screening test for renovascular HTN as scanner technology and 3-D reconstruction has improved.^{39,40} Similar to CTA, MRA is based on intravenous injection of a gadolinium contrast bolus with rapid acquisition of a 3-D dataset. MRA has shown high diagnostic accuracy with sensitivity of 100% and specificity ranging from 71 to 97%.^{40,41} MRA has been shown to be a safe and non-invasive diagnostic test for main renal artery disease.⁴² The test characteristics of MRA can be increased with breath-hold MRA, which has shown sensitivity and specificity in detecting RAS of 100 and 98%, respectively.⁴³ In addition, MRA has been shown to be more reliable with less operator dependence than CT or ultrasound.⁴⁴

Initially, gadolinium, the contrast agent used in MRA, was thought to be safe and studies allowed MRA to be used in patients with renal impairment.^{45,46} However, recent data have come forth showing a strong link between gadolinium and nephrogenic systemic fibrosis with more than 95% of cases showing an association.^{47,48} This association was first discovered after gadolinium was found in skin biopsy tissue specimens of patients with nephrogenic systemic fibrosis.⁴⁹ As a result, it is advised to avoid the use of gadolinium in patients with a GFR less than 30 mL/min, patients with acute renal insufficiency of any severity due to hepatorenal syn-

drome, or in the perioperative liver transplantation period (FDA). The risk of nephrogenic systemic fibrosis from gadolinium has not been defined in patients who have an estimated GFR between 30 mL/min and 60 mL/min.

Unlike duplex ultrasound, most accessory renal arteries are detected with MRA. However, MRA has been characterized as unreliable in the detection of FMD due to the difficulty in visualizing lesions in the middle and distal portions of the main renal artery or in the branch vasculature.⁵⁰ One contraindication to the use of MRA is patients with claustrophobia; patients with metallic implants also limit applicability.

CONVENTIONAL ANGIOGRAPHY

As mentioned earlier, the use of conventional angiography is considered the gold standard in the diagnosis of RAS. The creation of noninvasive screening and diagnostic tests such as CTA and MRA has decreased the use of angiography. The use of contrast during conventional angiography is a significant risk for acute renal injury and has negative effects on health care costs and prognosis, occurring to some degree in almost 7% of patients.⁵¹ In a large retrospective study of more than 16,000 patients, the risk of death during hospitalization in patients requiring procedures using iodinated contrast and subsequently developing acute renal injury (defined as an increase in creatinine of at least 25%) was 34% compared with 7% in matched controls who did not develop acute renal injury.⁵²

Another method of performing angiographic evaluation is with the use of carbon dioxide (CO₂). Instead of mixing with blood, like iodinated contrast, CO₂ displaces blood and thus acts like a negative contrast agent. This difference between a blood vessel containing blood and containing gas can be evaluated using digital subtraction angiography. CO₂ quickly dissolves into the bloodstream and is excreted through gas exchange in the lungs. This elimination of iodinated contrast presents two main advantages: an absence of both nephrotoxicity and contrast allergy. In addition, the use of automated CO₂ injection machines and fully contained valved bag systems has virtually eliminated the risk of contamination of CO₂ injection with air. One disadvantage to the use of CO₂ for imaging is less detail in distal renal arteries. However, the vast majority of both atherosclerotic and fibromuscular dysplastic renal artery lesions involve the main renal artery or proximal branch vasculature. CO₂ angiography provides excellent imaging capabilities in this region. This provides an attractive alternative to the use of iodinated contrast in patients with renal insufficiency. Even if the entire exam cannot be performed using CO₂, use of this nonnephrotoxic contrast agent, augmented by iodinated contrast for select

images, can markedly decrease the total iodinated contrast load and thus substantively improve patient outcomes.

TREATMENT

The principal rationale for treatment of RAS is control of HTN. An additional well-accepted indication is significant renal insufficiency. There is also the possibility of preventing or minimizing the loss of renal mass due to hypoperfusion, although this latter rationale is somewhat controversial. Given the controversial nature of indications for RAS intervention, a brief discussion is warranted.

Asymptomatic (normotensive and normal GFR) lesions are rarely diagnosed and, if incidentally discovered, do not seem to merit correction. For the purpose of creating a treating algorithm, symptomatic renal artery stenoses can be divided into unilateral and bilateral lesions. Unilateral stenoses, when symptomatic, present as HTN. Unless there is underlying intrinsic renal disease, a unilateral RAS does not present with renal insufficiency. In the setting of unilateral RAS and renal insufficiency, renal artery intervention may still be indicated, but a nephrological evaluation investigating the underlying renal disease is warranted. Bilateral stenoses, when symptomatic, can also present with HTN, as well as chronic renal insufficiency, acute renal failure, or flash pulmonary edema. Bilateral stenotic arteries may require treatment, but only if the symptoms are not controlled with medical therapy. The mere presence of RAS in a hypertensive or renal-insufficient patient is not an indication for intervention. An appropriate trial of medical management should be applied and found to be suboptimal before correction of the underlying lesion(s) is undertaken. Unfortunately, classification of a medical regimen as suboptimal can be very subjective. In many instances, an antihypertensive drug regimen may provide adequate blood pressure management but produce significant side effects, resulting in poor patient compliance. It has been suggested by some authors that bilateral renal stenosis should be managed more aggressively than this regimen as progression of stenosis is more likely in bilateral lesions versus unilateral lesions.⁵³

Obvious, and noncontroversial, indications for intervention include the presence of unilateral or bilateral RAS in patients with refractory HTN, bilateral stenoses and associated renal insufficiency not related to intrinsic renal disease, and bilateral stenoses associated with recurrent episodes of flash pulmonary edema. Many clinicians also will elect to treat any uni- or bilateral atherosclerotic RAS in younger patients with recent-onset HTN and any nonatherosclerotic (FMD)-associated HTN. In these instances, the primary goal of treatment is to lower long-term anti-HTN medication use. All other cases of RAS should be considered

on a case-by-case basis with careful consideration of the benefits and costs of the procedure.

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

Percutaneous transluminal angioplasty (PTA) provides a nonsurgical method of returning blood flow through stenotic renal arteries. PTA has been known to be a safe procedure since the late 1970s,⁵⁴ and many studies have shown that PTA is associated with fewer complications compared with open surgery.^{55–58} Complications of PTA without stenting include access site hematoma (<3%), clinically known distal embolization (2.2%), cholesterol embolization (1.1%), and renal or other arterial injury requiring open surgery (2.5%).^{55–58} One multicenter study randomized patients with RAS to either medical therapy or angioplasty and showed that after 3 months, 44% of patients initially assigned to drug therapy required rescue angioplasty because of refractory HTN.⁵⁹ PTA has been shown to decrease the number of anti-HTN drugs needed.⁶⁰ Comparisons between PTA and open surgery show similar outcomes as almost all patients with restenosis can be treated with repeat PTA, and thus PTA is a reasonable first-line treatment.⁶¹

Technical results of PTA without stent in the treatment of atherosclerotic RAS have shown mixed results. The use of PTA is limited when the renal ostium is involved and has been shown to fail in up to 75% of cases.^{62–64} Treatment of unilateral atherosclerotic RAS with PTA has demonstrated a cure rate of only 8 to 20%, improvement of HTN in 50 to 60% of patients, and restenosis rate between 8 and 30%.²¹ Results in patients with bilateral disease are even less impressive.²¹ This is likely because of the aortic origin of many renal stenosing plaques and the nondurable displacement that occurs with PTA only. Following balloon withdrawal, the displaced aortic plaque is free to return to a position compromising the renal artery lumen. Results for the use of PTA for FMD are generally much better than atherosclerotic RAS. Once disrupted, the hyperplastic bands rarely cause recurrent stenosis. Between 50 and 85% of patients undergoing PTA for FMD are cured, 30 to 35% show improvement in HTN by requiring fewer medications, and less than 15% of procedures are considered failures.⁶⁵ This high success rate for FMD PTA is likely related to the fact that the FMD stenotic bands are quite delicate in nature and are usually disrupted with little force needed (Fig. 1).¹⁶

STENT

One way to improve the efficacy of angioplasty in the treatment of RAS (especially atherosclerotic ostial lesions) and diminish the rate of restenosis is through insertion of a stent in association with balloon dilation of

Figure 1 (A) Thirty-eight-year old white female patient with poorly controlled hypertension and midright main renal artery typical-appearing fibromuscular dysplasia; preangioplasty. (B) Post 3.3-mm angioplasty showing much improved lumen caliber.

the renal artery. The deployment balloon provides an initial radial force to displace the stenosing plaque, and the stent affords subsequent long-term hoop strength that maintains arterial patency by offsetting the elastic recoil force of arteries and atherosclerotic plaque resistant to simple PTA treatment.⁶⁶ A randomized trial comparing PTA with renal artery stenting showed higher technical success rates (57% versus 88%), higher 6-month patency rates (29% versus 75%), and similar complication rates.⁶⁷ Stent placements show a success rate of 65 to 80% with restenosis due to intimal hyperplasia within the stent occurring in 11 to 39% of patients.^{68–71} Although stent placements have been a successful treatment of RAS,^{68–71} many argue the principal benefit from stent placement, like PTA, is to decrease the requirement for anti-HTN medica-

tions.^{68–71} In addition, the plasma creatinine concentration improved in patients with renal insufficiency following stent placement, and the decreased renal function while using ACE inhibitors was reduced.⁷¹ Stenting is recommended for all ostial atherosclerotic lesions, but balloon angioplasty without stent placement is the primary treatment of FMD (Fig. 2).²⁰

The technical complication rate of angioplasty with or without stent placement has been shown to be between 5 and 15%.^{59–61,68,69,72} The majority of these are minor complications such as access site hematoma and non-flow-limiting renal artery dissection; however, major complications such as renal artery thrombosis, renal artery rupture (Fig. 3), branch vessel wire perforation with bleed, acute renal failure from embolism, and/or contrast load are also possible. Still, the need for a

Figure 2 (A) Sixty-eight-year-old white male patient with elevated creatinine and previously stable hypertension, which has recently become difficult to control. High-grade ostial atherosclerotic appearing lesion bridging the right adrenal artery. (B) Post 6-mm balloon-expandable stent placement. No residual stenosis.

Figure 3 (A) Fifty-six-year-old African-American female patient with poorly controlled hypertension. High-grade left renal artery stenosis secondary to eccentric calcified atherosclerotic plaque. Pre-stent deployment. (B) Immediately following stent deployment; renal artery rupture with contrast extravasation tracking in the retroperitoneum, cephalad from the treatment site, parallel to the aorta.

surgical salvage procedure is less than 1%.^{73,74} Stent infection can infrequently occur; therefore, some authors suggest stent placement should be preceded by an intravenous dose of appropriate antibiotics.^{75,76} As a routine, this seems unnecessary, however, if the renal intervention is prolonged or if the access site seems heavily colonized, then a single dose of antibiotic directed toward skin flora can be considered. As in most procedures, technical experience greatly limits complication rates. One study showed a decline in complication rates from 20% in the first hundred patients to 13% in the second hundred.⁷⁷ Overall, the combined incidence of 30-day mortality, loss of kidney, rupture of renal artery, occlusion of main renal artery, and need for surgical operation should be less than 4%.^{73,74,78,79} It is important to remember, however, that complication rates are also somewhat dependent upon case selection.

Atheroembolization following angioplasty has traditionally been considered uncommon.^{70,80} However, studies describing atheroembolic disease may be routinely underestimating its incidence. Studies involving the use of embolic protection devices during angioplasty and stenting describe gross embolic material in 45 to 60% of cases,^{81,82} which could be a more accurate estimate. Embolic protection devices have been used more frequently in recent years to limit this phenomenon, but results have not been convincing.^{81,82} These devices are designed for use in the carotid circulation and deployment occurs remote from the target lesion. The available length of renal artery must be long enough to accommodate both the deployed protection device and the dilating balloon catheter. The relatively short length of many main renal arteries and the design specifics of many available devices preclude their routine use. This seemingly high frequency of atheroembolic disease could increase the risk of performing revascularization proce-

dures.⁸³ Currently, the use of embolic protection devices should be considered on a case-by-case basis. If a renal artery specific device were to become available, then consideration for routine use would be warranted.

In-stent restenosis can occur in anywhere between 11 and 39% of patients undergoing stent placement.^{68–72,83} Management of restenosis is of ongoing controversy. Many approaches have been attempted, including repeat angioplasty either as a stand-alone therapy or augmented with the use of drug-eluting, bare metal, or covered stents. Cutting-balloon angioplasty, cryotherapy angioplasty, and atherectomy have been attempted as well. There is little evidence providing guidance of treatment for patients with in-stent stenosis. The benefit from restenting is not significant when compared with conventional angioplasty.^{84,85} In addition, 43% of those who received bare metal stents for this indication showed restenosis after 12 months and 17% restenosis for covered stents compared with 71% for conventional angioplasty.⁸⁴ Drug-eluting stents have been used because it is thought they lead to lower rates of restenosis, but data supporting their use over angioplasty alone or bare metal stents are lacking. In fact, the GREAT trial showed no advantage of drug-eluting stents over bare metal stents.⁸⁶ Additionally, the currently available drug-eluting stent sizes are rarely applicable to normal-sized main renal arteries.

Other Techniques for In-stent Stenosis

In some patients, simple balloon angioplasty may not provide adequate dilation of the in-stent stenotic renal artery, and cutting balloon angioplasty may be used to facilitate treatment.⁸⁷ These balloons contain blades oriented longitudinally on its surface, which disrupt the fibroelastic rings within the hyperplastic intima,

preventing recoil and allowing the artery to be dilated more than traditional balloon angioplasty. Recurrent restenosis is also thought to be limited compared with traditional angioplasty since intimal injury is directed with microincisions instead of generalized with hoop stress along the artery.⁸⁸ Complications of cutting balloon angioplasty have been rare. Thus, cutting balloon angioplasty is thought by some authors to be better than traditional angioplasty by creating larger vessel lumens.⁸⁸ Other authors have found cutting balloon angioplasty to have higher restenosis rates compared with traditional angioplasty.⁸⁴ Additionally, owing to the embedded atherotomes, cutting balloons are quite rigid and present a large crossing profile compared with conventional balloons, or even some balloon-mounted stents. Technically, device delivery to the target lesion can limit applicability, and predilation to allow cutting balloon access is the norm. However, conventional angioplasty with or without stent placement can be technically difficult in many restenotic stented renal arteries as the inflated balloon tends to slide off of the dense intimal hyperplastic mound. This phenomenon can make repeat stent placement highly inaccurate. Cutting balloon angioplasty prior to repeat stent placement can obviate this problem and, therefore, may be used not only as a stand-alone procedure but also applied prior to restenting. Although the use of this device for the treatment of in-stent stenosis is not uniform, it remains a commonly applied niche application.

There are little data discussing the use of cryoplasty for renal artery in-stent stenosis. Studies comparing cryoplasty of the iliofemoral, femoral, and popliteal artery and traditional angioplasty have shown no added benefit.^{89,90} Thus there is no current evidence supporting the use of cryoplasty for renal artery restenosis.

Another proposed method of treating in-stent restenosis is the use of covered stents. The stent-associated polytetrafluoroethylene-derived graft layer creates a mechanical barrier between the arterial lumen and wall, theoretically improving patency. This method of treatment prevents exposure of the vessel wall to constituents of blood that may initiate the intimal hyperplastic process such as macrophages and platelets, which may reduce the incidence of in-stent restenosis.⁹¹ Another method of utility could be the inhibition of neointimal hyperplasia by the physical barricading of intimal, smooth muscle, and fibroblastic advancement.⁹¹ One longitudinal study following patients receiving covered stents showed a 12-month patency rate of 73%.⁹² Early studies of the use of covered stents are promising, but larger studies are needed.⁸⁴

RENAL ALLOGRAFTS

Stenosis in transplant renal arteries has been described in up to 23% of transplant recipients.^{93–95} This very high rate of disease is likely due to both increased detection due to routine imaging and vascular injury associated with immunosuppressive agents.⁹⁵ The etiology of stenosis varies based on where the lesion occurs. Preanastomotic lesions are more likely to be from atherosclerosis or clamp injury, and anastomotic lesions tend to be caused by intimal hyperplasia or reaction to suture material. Postanastomotic lesions can be caused by immunologic reaction or turbulent blood flow, and distal lesions are likely from transplant rejection. The physiological significance of stenosis is difficult to determine, especially with potential associated pathology occurring within the renal allograft. Renal insufficiency is more likely to be from rejection,

Figure 4 (A) Thirty-six-year-old white male patient with right renal allograft (two renal arteries) and elevated creatinine. Duplex ultrasonography shows velocity of upper vessel is 89 cm/s and lower vessel is 450 cm/s. Renal parenchymal biopsy negative for rejection. Angiogram confirms high-grade stenosis of lower vessel. Pre-stent. (B) Post 5-mm balloon-expandable stent placement. No residual stenosis.

obstruction, or progression of intrinsic renal disease than due to transplant RAS.⁹⁶

Treatment modalities for transplant RAS have been shown to be beneficial, with surgical correction being successful in almost 92% of cases.⁹⁷ However, surgical arterial repair tends to be avoided in these patients as there is already damage to the renal artery from the original transplant procedure, as well as associated scarring around the transplant organ, which can make surgical revision of the arterial anastomosis technically challenging. For this reason, endovascular therapy is felt by many to be the first-line treatment option for these patients. PTA with or without stenting has been technically successful in 63 to 100% of patients (Fig. 4).⁹⁷⁻¹⁰⁰ These numbers are not dissimilar from the native renal artery intervention data.

ANTIPLATELET THERAPY

Stents are thrombogenic because they are made of components such as stainless steel or cobalt chrome alloys, which enable thrombus formation. Additionally, balloon dilation associated with stent placement results in a controlled injury exposing subintimal material to the bloodstream. Platelets will adhere to these subendothelial elements and become activated. This platelet activation is the first step in a process that can lead not only to acute thrombosis but also to fibrointimal hyperplasia and restenosis. Thus, the use of antiplatelet agents such as clopidogrel and aspirin is absolutely mandatory in any renal angioplasty or stenting procedure to prevent stent thrombosis and/or rapid restenosis. Patients undergoing stenting are recommended to receive aspirin 325 mg and clopidogrel 300 to 600 mg at least 2 hours before the endovascular procedure.¹⁰¹ Alternatively, these patients may be on both medications for a full week prior to the therapy to attain adequate blood level to assure appropriate antiplatelet effect. Furthermore, there is some worry of a blunted clopidogrel effects in patients who are already taking the medication, and it is recommended that, until further data are available, these patients take between 600 to 900 mg of clopidogrel prior to their procedure.¹⁰² Long-term 325-mg aspirin therapy has been shown to reduce the incidence of late stent thrombosis, and a complication of aspirin cessation is thrombosis in both bare metal and drug-eluting stents. Long-term clopidogrel therapy is 75 mg and is proposed to have similar long-term effects to aspirin. Many authors suggest a minimum of 3 months postprocedure combined aspirin/clopidogrel administration, followed with aspirin for life thereafter. Although the use of aspirin and clopidogrel do not eliminate the risk of stent thrombosis, they have been shown to be beneficial. Routine use of GP IIb/IIIa inhibitors is being studying for use in renal artery interventions, but currently, there are no data supporting their use in this role.

POSTPROCEDURAL FOLLOW-UP

The use of duplex ultrasonography for the postprocedural follow-up of patients has been shown to be a good method of accurately detecting in-stent restenosis.⁶⁹ Although angiography is the gold standard for visualizing lesions of the renal artery, it remains a more invasive choice. Concordance between ultrasonography and angiography in diagnosis of renal artery restenosis at 9 months was 87%, showing that duplex ultrasonography is a reliable test in detecting restenosis.⁶⁹ Although CTA is an excellent tool for evaluating potential restenosis, iodinated contrast issues remain. MRA imaging is limited following stent placement due to stent-induced artifact precluding visualization of the treated segment. There are no clear indications of when during the postprocedural period, how often, or for what duration to screen for restenosis. Clinical findings such as progressive HTN or renal insufficiency are insensitive indicators and should not be used as primary screening tools to detect stenosis.

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