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REVIEW

# Indications for Renal Artery Stenting

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## ABSTRACT

Renal artery disease (RAD) is a relatively common condition in the elderly, especially in the setting of concomitant vascular disease in other anatomical sites and is most often of atheromatous origin. Rarely is it encountered in young women as a result of fibromuscular dysplasia. RAD with significant renal artery stenosis is considered responsible for refractory or accelerated hypertension, progressive loss of renal function and deterioration of patients' cardiovascular status, with episodes of angina or pulmonary edema disproportional to the extent of coronary artery disease and left ventricle functional capacity, dominating the clinical presentation. This article summarizes the pathophysiological implications and diagnostic methods and attempts a review of the current literature on indications and efficacy of the available therapeutic options for renal artery stenosis, focusing on interventional treatment.

KEY WORDS: *renal artery stenosis; fibromuscular dysplasia; interventional treatment; renovascular hypertension; pulmonary edema; renal insufficiency*

## INTRODUCTION

Renal artery disease (RAD) is most commonly due to atherosclerosis (≈90%) or fibromuscular dysplasia (10%) and rarely to extrinsic compression, neurofibromatosis type I or Williams syndrome. Fibromuscular dysplasia (FMD) predominates in young women (30-50 years old), is a nonatherosclerotic, noninflammatory vascular disease that causes stenosis in medium and small arteries, most commonly involving the distal 2/3 of the renal artery and carotid arteries. Atherosclerotic renal artery stenosis is usually encountered in males over 55 years old and often occurs at the ostium or the proximal 2 cm of the artery.[1,2] Refractory hypertension, progressive renal function deterioration and recurrent episodes of decompensated heart failure or flash pulmonary oedema are the most common clinical manifestations of the disease.[1] Both conservative and interventional treatment has been proposed and applied with comparable efficacy in the case of atherosclerotic disease and thus certain controversies have arisen regarding the treatment of choice.[3]

**ABBREVIATIONS**
ATP = Adult Treatment Panel
CAD = coronary artery disease
CETP = cholesteryl ester transfer protein
HDL-C = high-density lipoprotein cholesterol
IDL = intermediate density lipoprotein
LDL-C = low-density lipoprotein cholesterol
NCEP = National Cholesterol Education Program
VLDL = very-low density lipoproteins

## EPIDEMIOLOGY

The true epidemiology of RAD is less well-known,[4] because the majority of such data are derived from studies of patients undergoing other procedures, mainly cardiac catheterization. The prevalence of RAD in the elderly has been reported to be 6.8%.

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In individuals with coronary heart disease, RAD coexists in 15-23% and in cases of aortoiliac or lower extremity vascular disease, it is found in 28-38% and 45-59% respectively.[4-7] In the most extensive study so far,[4,8] 11% of patients undergoing cardiac catheterization had greater than 50% unilateral narrowing of the renal artery, 2.4% had bilateral 50-75% and 16% had >75% bilateral stenoses. In this study the severity of the disease was predicted by old age, gender, peripheral vascular disease, congestive heart failure, renal insufficiency, smoking and the degree of coronary artery involvement.

## CLINICAL IMPLICATIONS

Renal artery disease has two cardinal pathophysiological consequences. A) It leads to renin-angiotensin-aldosterone system activation [in unilateral (Goldblatt) stenosis] and B) reduces glomerular filtration and salt and water extraction (bilateral artery stenosis or stenosis of the renal artery of a solitary kidney). Most patients remain clinically asymptomatic due to the large kidney functional reserve. Incidental RAD is usually identified during imaging of other vessels, i.e. while performing coronary or peripheral vessel angiography. Hypertension usually with abrupt onset in persons <30 years of age could be a manifestation of fibromuscular dysplasia. If the diagnosis is first made in the age over 50, atherosclerotic RAD should be considered. Accelerated, malignant or resistant hypertension should point the diagnostic view towards RAD.[1,4] Patients developing progressive renal failure which may be ischemic or drug induced (administration of ACEI or ARBs), as well as unexplained hypokalemia (secondary aldosteronism), ought to be examined for RAD. The presence of flank bruit or atherosclerotic disease elsewhere in the body may be supportive findings. Kidney size is also an important parameter. It has been reported that 71% of patients with an atrophic kidney (length <7cm) have severe stenosis of the renal artery ipsilateral to the small kidney.[1] Three studies have shown that, if a discrepancy in size between the 2 kidneys of greater than 1.5 cm exists, there is a 60% chance that the contralateral renal artery (normal sized kidney) is severely stenotic.[1,9] Finally, recurrent episodes of congestive heart failure and flash pulmonary edema, in the absence of significant myocardial ischemia or impaired left ventricular systolic function can result from bilateral renal artery stenoses or unilateral to a single functioning kidney.[1,9,10] Tables 1 and 2 summarize the clinical manifestations of the disease.

**TABLE1.** Clinical Manifestations of Renal Artery Stenosis

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| Poorly controlled hypertension refractory to medical therapy |
| Worsening renal function |
| Accelerated cardiovascular disease |
| Flash pulmonary edema |

**TABLE 2.** Clinical Clues to the Diagnosis of Atherosclerotic Renal Artery Stenosis

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| • Onset of hypertension after the age of 55 |
| • Exacerbation of previously well-controlled hypertension |
| • Malignant hypertension |
| • Resistant hypertension |
| • Epigastric bruit (systolic/diastolic) |
| • Unexplained azotemia |
| • Azotemia while receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blocking agents |
| • Atrophic kidney or discrepancy in size between the two kidneys |
| • Recurrent congestive heart failure or "flash" pulmonary edema |
| • Atherosclerosis elsewhere |

## DIAGNOSIS

Both imaging and functional assessment has been used in RAD evaluation. In cases of high clinical suspicion an imaging modality should be employed. Captopril renography, duplex ultrasonography of the renal arteries, spiral computed tomography with angiography (CTA), gadolinium magnetic resonance angiography (MRA) and contrast arteriography have been used (Table 3).

### CAPTOPRIL RENOGRAPHY

Captopril (or other ACEIs) magnifies the functional difference between kidneys reducing glomerular filtration rate (GFR) by 30% in the kidney with the stenotic artery. This leads to accumulation of radionuclide in the affected kidney. The test provides an indirect assessment of renal blood supply and presents a sensitivity of 85-90% and specificity of 93%, providing

**TABLE 3.** Diagnostic Modalities Used to Diagnose Renal Artery Stenosis

| Test | Sensitivity (%) | Specificity (%) |
|---|---|---|
| Captopril scan | 85–90 | 90 |
| Renal duplex | 98 | 99 |
| CT | 89–100 | 82–100 |
| MRI/MRA | 91–100 | 71–100 |
| Angiography | 98 | 100 |

CT = computed tomography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging

that one of the kidneys is normal. The presence of renal insufficiency (creatinine ≥2mg/dl) or bilateral renal artery stenoses severely influences the test's accuracy raising the likelihood of false positive scans.[1,10-12]

### DOPPLER ULTRASOUND

*Doppler ultrasound* of the renal arteries allows reliable serial estimation of flow velocities. A rise in velocity to more than 200 cm/sec or to a value higher than the aortic velocities with renal-aortic ratio ≥3.5 is considered predictive of more than 60% luminal narrowing.[1,10,13,14] Assessment of post-stenotic blood flow and vascular resistance within the kidney (resistive index) provides a guide to the potential salvageability of the kidney and the likelihood of blood pressure response post-interventionally. The method exhibits an 84-98% sensitivity and 62-99% specificity, is safe and cost-effective. However, it does not provide us with any functional assessment of the kidney, the method is technically demanding and time-consuming, some individuals are not suitable for the study and accessory renal arteries cannot be reliably identified.

### CT ANGIOGRAPHY

*CT angiography* (CTA) has an 89-100% sensitivity and 82-100% specificity.[10,15,16] Because it requires large amounts of nephrotoxic contrast medium, its use in azotemic patients is limited. *Gadolinium contrast MRA* provides visualization of the main renal arteries with high sensitivity (91-100%) and specificity (76-94%), and offers the most complete non-invasive imaging of the renal vasculature with a nonnephrotoxic agent. It is limited by cost, availability and by the fact that it may miss distal vascular lesions or accessory vessels.

### CONTRAST ARTERIOGRAPHY

*Contrast arteriography* still remains the "gold standard" for diagnosing RAD, performed at the time of planned endovascular intervention (balloon angioplasty or stent deployment). The hazards include atheroembolic disease and contrast nephrotoxicity especially in older or diabetic patients. The use of non-toxic agents such as gadolinium or carbon dioxide may be beneficial in cases of renal insufficiency.[10,12]

Functional tests are used to establish whether a) hemodynamically significant lesions impair blood flow or activate renin release and b) correction of the vascular lesion can produce improvement in blood flow or renal function. They include plasma renin activity (PRA), captopril stimulated PRA, renal vein renin activity, intravenous pyelography, iodine-125 diethylenetriaminepenta-acetic acid (DTPA) scan (glomerular filtration assessment), captopril renography with Tc-mercaptotriglycylglycine, radionuclide scan with Tc 99m (renal blood flow assessment). These tests require comparison of a stenotic kidney with a presumed normal contralateral kidney, which is often actually abnormal. [10,17] Furthermore, indices of renal function (creatinine >3 mg/dl) and proteinuria are important in predicting recovery of kidney function after surgical or endovascular repair. [12]

## TREATMENT

Treatment decisions for the management of RAD should consider relative benefits and risks involved and must take into account the likelihood of blood pressure reduction and renal parenchyma preservation. In general, medical therapy is considered in cases of underlying advanced nephropathy with unilateral RAD and creatinine >2.5 mg/dl, renal length <7 cm, proteinuria >1 g/day, severe diffuse intrarenal disease and target kidney resistive index >80. Medical therapy includes antihypertensive, cholesterol-lowering and antiplatelet drugs. ACEIs, ARBs, calcium channel blockers and β-blockers are commonly used with proven efficacy and safety. However, a potential consequence of conservative therapy is disease progression as reported by small series,[18-20] potentially leading to renal artery occlusion, which makes even the endovascular therapy extremely difficult. Another consideration would be the possibility of progressively worsening renal function, leading to end-stage renal disease. Interestingly, a retrospective cohort evaluation suggests that serum creatinine levels remain stable for many years,[18,21] but the small numbers of patients observed makes it hard to base real clinical management decisions on such reports.

Revascularization is favoured in patients with bilateral renal artery stenoses and creatinine >1.5 mg/dl, unilateral renal artery stenosis and fractional glomerular filtration rate <40%, ACEI-induced renal failure, hypertensive crisis and non-ischemic pulmonary edema (Table 3).[10] Revascularization can be attempted by intraluminal intervention or surgery. The surgical techniques include aortorenal, hepatorenal or splenorenal by-pass.[22,23] Nowadays, medical and endovascular methods have become more established, but surgery still retains a role. Current indications for surgical revascularisation include: occluded renal artery with preserved renal parenchyma, RAD with Takayasu's arteritis, RAD with multiple small renal arteries or early primary branching of the main renal artery, branch disease from FMD that cannot be treated adequately with balloon angioplasty, especially in patients exhibiting complex disease that extends into the segmental arteries and those

**TABLE 4.** Indications for Renal Artery Revascularization

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|---|
| ≥50% stenosis |
| Trans-lesional systolic pressure gradient ≥15 mm Hg |
| Difficult-to-control hypertension |
| Worsening renal function |
| Nonischemic pulmonary edema |

having macro-aneurysms, recurrent stenosis after stenting or simultaneous aortic surgery (abdominal aortic aneurysm repair or symptomatic aortoiliac disease). Even in this last circumstance, it may be advisable to stent the renal artery first and then proceed with aortic reconstruction. The mortality rate of aortic replacement and renal artery revascularisation is higher than for either procedure alone.[22]

Current recommendations (ACC/AHA) for renal artery revascularization include:

- Asymptomatic RAD in case of bilateral or solitary viable kidney with a hemodynamically significant renal artery stenosis (class IIb, LOE C).
- Accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication in patients with hemodynamically significant renal artery stenosis (class IIa, LOE B).
- Progressive chronic kidney disease with bilateral renal artery stenoses or a renal artery stenosis in a solitary functioning kidney (class IIa, LOE B).
- RAD and chronic renal insufficiency with unilateral renal artery stenosis (class IIb, LOE C).
- Hemodynamically significant RAD and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema (class I, LOE B).
- Hemodynamically significant RAD and unstable angina (class IIa, LOE B).[24]

Single balloon angioplasty is the treatment of choice in fibromuscular dysplasia. However in atherosclerotic lesions, stent placement is indicated in order to minimize the risk of procedure failure and the restenosis rate. Van de Ven et al. performed a trial in 1999 comparing 42 patients undergoing renal artery angioplasty with 45 patients receiving angioplasty and stenting. They found that success as well as patency rates were significantly higher in the second group although the differencies in renal function or blood pressure were stasistically non significant. Similar results were reported by Rundback et al.[25,26]

## TECHNIQUE OF PERCUTANEOUS TRANSLUMINAL RENAL ANGIOPLASTY (PTRA) AND STENTING

Until the beginning of the 1990s, balloon angioplasty was the only method of percutaneous treatment of renal artery stenosis with satisfying acute and long-term results for angioplasty of stenoses caused by FMD and atherosclerotic stenosis of the renal artery trunk.[27-29] However, balloon angioplasty of ostial atherosclerotic lesions was limited by a low acute technical success rate (50–62%) and a high restenosis rate of up to 47% over the long-term because of the potential for dissection and elastic recoil or rigidity of the lesion.[30] The introduction of stenting has revolutionized percutaneous renal revascularization. Following promising single center reports,[31,32] two randomized studies proved the superiority of stenting over conventional balloon angioplasty[25,33] in the treatment of atherosclerotic ostial renal artery stenosis, the most common manifestation of renal artery stenosis. Nowadays using premounted low profile stent devices ("nested ring design"), atherosclerotic renal artery stenosis can be successfully treated in almost 100% of cases with restenosis rates ranging from 0% to 23% depending on the diameter of the renal artery.[29,34]

Currently, the guiding catheter technique is the procedure of choice with the lowest intervention and radiation time. Selective catheterization of the renal artery is usually performed through the guiding catheter using a steerable 0.014 or 0.018 inch stiff guidewire with a flexible tip. Except in case of subtotal occlusion, direct stenting is feasible in almost all cases of ostial renal artery stenosis using the new flexible low profile stent devices. In rare cases of unfavorable anatomy, the brachial approach is a reliable alternative. An alternative technique is the use of a guiding sheath or long preshaped sheath; this device (e.g., Vista Britetip IG, Cordis Corp., Miami, FL, USA) combines the traditional sheath with a guiding catheter. Adverse events reported in angioplasty studies included death by 30 days in up to 3% of patients, transient deterioration of kidney function in 1% to 13%, renal artery or parenchymal injury in up to 5%, and peri-procedural cardiovascular events in up to 3%. Other adverse events that have been reported are hemorrhage, hematomas, and renal artery occlusion. Seventeen studies of angioplasty with stent placement showed restenosis rates that ranged from 10% to 21% during follow-up of 3 to 40 months.[35-37]

The main causes of renal function deterioration after the procedure are embolism and contrast-induced nephropathy. To avoid renal embolism prior to selective renal angiography, the guiding catheter should be cleaned from debris by aspiration of blood through the gu iding catheter ("proximal protection"). This technique cleans the tip of the guiding catheter from debris collected during the engagement of the renal artery and therefore reduces the risk of renal embolization. The use of distal protection devices is limited by the anatomy of the renal artery, [29] but recently there have been reports about the use of such devices in renal intervention.[38] To avoid contrast-induced nephropathy, nowadays carbon dioxide or gadodiamide can be used as alternative contrast agents if digital subtraction technique is available.[39,40] Furthermore, the development of less nephrotoxic contrast agents such as iodixanol (an iso-osmolar, nonionic-iodinated contrast agent), nephroprotective agents, and pre- and post-interventional hydration of the patient have also led to a reduction of the frequency of contrast nephropathy.[29]

Another future development is the use of drug-eluting stents for renal application. The GREAT trial found that the blood pressure and angiographic outcome at 6 months did not

show a significant difference between bare metal and sirolimus eluting stents, but the small number of patients examined may have influenced the results.[41] Thus, future studies with a larger patient population and longer angiographic follow-up are warranted to determine if there is a significant benefit of drug-eluting stents in treating ostial renal artery stenosis. However, an increased restenosis rate is only a matter of concern in small renal arteries with a diameter of 5 mm or less,[42] and drug-eluting stents may be indicated only for these vessels. Lower rates of mortality, stroke, myocardial infarction and azotemia, and better blood pressure control have been reported in patients receiving renal artery stenting compared to those treated only medically (87% 5-year survival vs 67%).[30,43] However, two recent studies (DRASTIC, Scottish) failed to prove the superiority of interventional treatment. The Scottish study was unable to demonstrate any benefit with respect to renal function or event-free survival. The DRASTIC study concluded that angioplasty has little advantage over medical therapy in individuals with hypertension and RAD, but the crossover of patients between the medical and angioplasty group was high so that the results are considered virtually uninterpretable.[19,20,44]

So far the available evidence is neither adequate nor sufficiently applicable to current practice to clearly support one treatment approach over another for the general population with RAD. Blood pressure (classified as cured, improved or unchanged) can be decreased adequately with combination antihypertensive medication but intervention may lead to better control, particularly in cases of bilateral vascular disease. Both medical and interventional approaches lower it, but almost all angioplasty studies report that some persons (≈18%) were cured of hypertension.[29,35] However, randomized studies regarding blood pressure control are seriously flawed. Although most practitioners consider significant a stenosis over 70%, the studies incorporated patients with stenosis >50%, which notably is consistent with the latest guidelines published by the American College of Cardiology (ACC). Crossover between persons randomized in the angioplasty or conservative branch[3,19] in two studies, makes their results rather confusing, neither supporting nor refuting the potential benefits of revascularization.

Most studies suggest no large differences in mortality rates, cardiovascular events or change in kidney function between patients treated only medically and those receiving angioplasty. Within the published studies of angioplasty, 8-51% of patients improved their kidney function, while approximately 31% worsened it.[35]

The existing trials so far have also failed to demonstrate hard evidence on kidney function improvement with either conventional or invasive therapy.[3] It is a fact that there is poor correlation between the degree of anatomic stenosis and glomerular filtration rate. Nuclear studies have shown that GFR in the non stenotic kidney is often the same or even lower than that in the kidney distal to a stenosis.[3,33] This phenomenon probably relates to the presence of ischemic damage in the post stenotic kidney and hypertensive injury to the non stenotic one, which also explains why filtration rate often fails to improve significantly after revascularization. Observational studies report that kidney function may stabilize or get better in some individuals. On the other hand, interventional therapy may itself cause declines in renal function either from contrast nephropathy or atheroembolic disease (Table 5). In a largest prospective randomized trial, there was no difference in kidney function in the two groups of patients one year later.[3]

Another clinical condition associated with RAD as already mentioned, is *flash pulmonary edema*. There are studies demonstrating decline of hospitalization for such reasons after renal artery stenting and NYHA class improvement, but the concomitant increase in the use of ACEI observed during the study may have contributed to the improved outcome.[3,36] The Scottish and Newcastle Renal Artery Stenosis Collaborative Group found no differences in event rates for congestive heart failure, stroke or myocardial infarction across 54 months of follow –up between the two groups.[20,35] Studies commenting on survival were generally too small to detect anything but large differences in mortality rates, and no large differences in mortality rates were found. Mortality rates greater than 40% within 6 years occurred mostly in studies of patients with high-grade stenosis (>75%) or bilateral disease.[35] Ischemic nephropathy is an important cause of end-stage disease and among patients who are receiving dialysis, those with renovascular disease have the lowest survival rate with a median

**TABLE 5.** Complications of PTRA ± Renal Artery Stenting

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| **Local renal (3–83%)** |
| 1. Contrast-induced acute renal failure (mild or severe) |
| 2. Atheroembolic renal failure (0.5%) |
| 3. Rupture of the renal artery |
| 4. Dissection of the renal artery |
| 5. Thrombotic occlusion of the renal artery (2%) |
| 6. Occlusion of a branch renal artery (0.5%) |
| 7. Balloon rupture or malfunction (may lead to inability to remove the balloon) |
| 8. Renal artery spasm |
| **Puncture site** |
| 1. Hematoma, hemorrhage or vessel tear (3–48%) |
| 2. Brachial plexus compression (axillary approach) |
| 3. Pseudoaneurysm (0.5%) |
| 4. Arterio-venous fistula (0.1%) |

PTRA = percutaneous transluminal renal artery angioplasty

survival of 25–34 months and a 5-year mortality rate of more than 80%. Left ventricular dysfunction, age, and a baseline creatinine level of more than 2.5 mg/dL are reported to be independent predictors of mortality.[29] The cause of death was congestive heart failure or myocardial infarction (73%), stroke (13.5%), and malignant disease (13.5%).[12]

In general, the existing data cannot establish the necessity for angioplasty in patients fullfilling the so far accepted indications without endorsement of additional criteria. Obviously some of them benefit from the interventional procedure while others do not or even experience deterioration of their clinical or laboratory status. The studies of diagnostic tests were inadequate to determine whether any such test may predict long-term outcome or guide best treatment approaches. Weak evidence suggests that patients with bilateral disease may preferentially benefit from angioplasty over medical treatment. Clinical symptoms and signs or laboratory values can also serve as predictive factors. Impaired kidney function predicts a higher mortality rate, poorer clinical outcomes including cardiovascular events and worse blood pressure control. On the other hand prior cardiovascular disease correlates with increased mortality rates and worsening renal function.[19,20,35-37,45-47]

Among the published studies four diagnostic tests have been evaluated to determine their value in predicting treatment outcomes in RAD. The DRASTIC study found that neither captopril test nor renography can predict kidney function or blood pressure control after treatment.[35,45] Two cohort studies evaluated the role of baseline resistive index of >80%. In the first one, people with elevated resistive index were most likely to benefit after angioplasty and stenting in terms of blood pressure and renal function, while in the second the same individuals were more likely to have worsening renal function and poorer blood pressure control after angioplasty with or without stenting.[48,49] Another study reported that non spiral flow on MRA predicts significantly worse kidney function outcomes.[50]

What becomes evident from this discussion is that until now there are no undoubted evidence to either prove interventional approach's superiority compared to medical therapy or determine the subgroup of patients which is likely to benefit from one or the other treatment option. More large randomized prospective controlled trials are needed in order to provide hard evidence on these controversial issues. Three ongoing studies are expected to enlighten this field. The CORAL and the STAR studies are comparing the effects of PTRA with stent placement and optimal medical therapy, to medical therapy alone on a composite end-point of adverse cardiovascular and renal events.[51,52] The 3R study aims at comparing the effect of endovascular revascularization versus medical therapy in 300 patients.[53] Their results will probably address many of the deficiencies in current evidence about revascularization and medical treatment comparison and may provide useful information on the value of different diagnostic tests on determining which therapeutic method is best for individual patients. However, more studies are necessary to avoid a spontaneous generalization of those trials' results, which may lead to inappropriate treatment, misallocated resources and worse outcomes in case that these finding be applied to patients with different characteristics from those incorporated in the studies.

## CONCLUSIONS

RAD is a rather common condition that threatens the quality of life as well as the survival of patients. The therapies endorsed so far are of no undoubted effectiveness and interventional approach may hold advantage for certain suitable individuals although the existing evidence is not enough to establish this fact. Renal artery stenting is a particularly promising revascularization technique but further studies are needed to prove its superiority over medical treatment alone. The aim of the clinician must therefore be the primary and secondary prevention of renal atherosclerosis, the achievement of an earlier diagnosis and the selection of the appropriate treatment (conservative vs interventional) considering the overall prognosis of the patient.

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