

# NEPHROLOGY

# Rounds™

## Renal Artery Stenosis

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Stenosis in one or both main renal arteries or their branches can lead to hypertension that may be difficult to control and/or chronic kidney disease (CKD) that can progress to end-stage renal failure. Although noninvasive screening tests are widely available, the exact incidence, prevalence, and natural history of renovascular disease are still unclear. Studies that have examined therapy for renal artery stenosis (RAS) are flawed and there is no consensus regarding optimal treatment. At the present time, some practitioners have little enthusiasm for screening, whereas others actively seek out and revascularize these patients. This issue of *Nephrology Rounds* examines the epidemiology and physiology, as well as the natural history, signs, and symptoms of RAS, and also focuses on the diagnostic modalities and management of this increasingly common illness.

### Epidemiology of renal artery stenosis

Atherosclerosis is the major cause of RAS, accounting for 65%-70% of all cases, while fibromuscular dysplasia, which occurs most commonly in 25- to 50-year-old females, accounts for approximately 30% of lesions. Atherosclerotic RAS mainly affects those aged >50 years. Males are more commonly affected than females and it is often seen in conjunction with vascular disease in other beds, including peripheral vascular disease, coronary artery disease, or aortic disease.<sup>1</sup> Smoking and hyperlipidemia are commonly associated with atherosclerotic RAS.<sup>2</sup>

### Pathophysiology of RAS: hypertension and ischemic nephropathy

#### Hypertension

Pressure gradients and changes in blood flow develop when obstruction reaches 70%-80% of the luminal area. Renal perfusion pressure declines, which activates the renin-angiotensin system. Pathogenically, the development of hypertension is influenced by whether the lesion is unilateral or bilateral.

The classic Goldblatt models; the two-kidney, one-clip (2K-1C) and the one-kidney, one-clip (1K-1C) model both lead to hypertension, but by different mechanisms (Figure 1). Following clipping, renin, angiotensin, and aldosterone increase,<sup>3</sup> leading to sodium retention and a rise in blood pressure.<sup>4</sup> In the 2K-1C model, renin secretion is suppressed and sodium excretion enhanced in the contralateral kidney via the pressure natriuresis effect. In the chronic phase, hypertension is associated with increased sensitivity to angiotensin II, increased vasopressin, and increased activity of the sympathetic nervous system.<sup>5,6</sup> Compensatory hypertrophy of the vessel walls also helps to sustain the hypertension.

In the 1K-1C model, the contralateral kidney is removed, producing a model of global ischemia akin to bilateral RAS. Without a contralateral kidney to excrete salt, volume expansion persists, renal perfusion pressure increases, and renin/angiotensin levels return to normal.<sup>7</sup> If the renal artery clip is removed early in either model, hypertension can be cured. Likewise, early angiotensin II blockade normalizes blood pressure; however, if performed later in the course, normotension is much less likely.<sup>8</sup>

#### Ischemic nephropathy

When perfusion pressure drops below the range of autoregulation, the kidney is subject to ischemia that ultimately leads to collapsed glomeruli, tubular atrophy, and interstitial fibrosis. A proposed mechanism involves diminished ATP production, endothelial cell dysfunction, the release of various cytokines, and inflammatory mediators with subsequent necrosis and fibrosis.<sup>9</sup> Implicated inflammatory mediators include angiotensin II, endothelin-1, and transforming growth factor alpha (TGF- $\alpha$ ).<sup>10</sup> Interestingly, fibromuscular dysplasia rarely leads to ischemic nephropathy despite similar degrees of obstruction.

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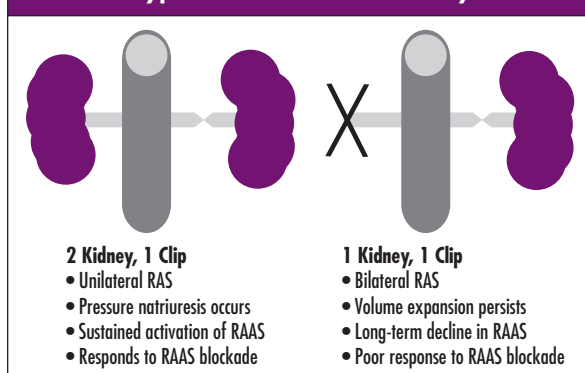
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**Figure 1: Classic Goldblatt models of hypertension and renal artery stenosis**



RAS = renal artery stenosis; RAAS = renin-angiotensin-aldosterone system

### Natural history of RAS

The natural history of RAS depends on the etiology. With fibromuscular dysplasia, stenosis most often affects the mid and distal renal arteries or branches and is bilateral in 60% of cases. Radiologically, a “string-of-beads” appearance is seen, representing multiple stenoses with interposed aneurysms. Only one-third progress to ischemic nephropathy; dissection, thrombosis, and total occlusions are rare. In contrast, atherosclerotic renal artery disease is most commonly proximal, often ostial and involves the aorta. Radiographically, these lesions appear as eccentric or concentric focal stenoses. Unlike fibromuscular dysplasia, anatomic progression is fairly frequent, with as many as 15% progressing to total occlusion.<sup>11</sup>

The exact incidence of end-stage renal disease (ESRD), as a consequence of ischemic nephropathy, remains uncertain. Some suggest that ESRD and dialysis dependence are rare,<sup>12,13</sup> however, in high-risk patients with bilateral disease, the incidence may approach 30%.<sup>14</sup> The reported incidence of RAS in dialysis populations varies from 2.1% to 15%.<sup>15,16</sup>

### Clinical presentation of RAS

RAS is relatively uncommon and is estimated to occur in only 0.5% to 5% of all hypertensives. Clinical features that suggest RAS include age (<30 years and >55 years), accelerated course, sudden onset, or refractory hypertension. Patients with underlying RAS may develop acute renal failure when treated with a renin-angiotensin system-blocking drug. An abdominal bruit, recurrent episodes of pulmonary edema, or worsening renal function suggest RAS, particularly in patients with other vascular disease.

### Diagnosing RAS

Many tests are available to diagnose RAS (Table 1). The choice depends on underlying renal function, pre-test probability, and the expertise and preference of the individual center.

#### Plasma renin studies

Measurements of plasma renin activity (PRA) can be helpful, but a peripheral PRA alone is neither sensitive, nor specific. An elevated PRA is found in only 50% of patients with renovascular hypertension.<sup>17,18</sup> A very low PRA, in the setting of normal urine sodium and the

absence of drugs that suppress renin, can virtually exclude renovascular hypertension.<sup>19</sup>

Renin secretion is inhibited by angiotensin II and angiotensin-converting enzyme (ACE) inhibition causes renin levels to increase. Patients with renovascular hypertension may have an exaggerated response to ACE inhibition.<sup>20</sup> The captopril stimulation test consists of pre- and post-captopril PRAs or a 60-minute post-captopril PRA.<sup>21</sup> This test has a sensitivity of 91% to 100% and a specificity of 84% to 95% when used to predict blood pressure response after intervention. The captopril stimulation test may be most useful to exclude RAS, as the negative predictive value is quite high.<sup>22</sup>

Comparison of the renin vein levels was often used to predict improvement after repair of a stenosis.<sup>23</sup> In unilateral disease, renal vein renin levels from the ischemic kidney should be elevated, while renin from the contralateral renal vein should be suppressed. However, a high false-negative rate was found,<sup>24</sup> and patients whose levels do not lateralize may still have significant stenosis, particularly with bilateral disease.

#### ACE inhibitor renography

In renography, technetium-labeled diethylenetriamine-penta-acetic acid (DTPA) or mercaptoacetyl triglycine (MAG<sub>3</sub>) are used to estimate glomerular filtration rate (GFR) or renal plasma flow, respectively. Because angiotensin II levels influence renal blood flow and GFR, administration of an ACE inhibitor (ACEI) exaggerates the differences in renal function between the ischemic and nonischemic kidney. An initial scan is performed after the administration of an ACEI and, if the post-ACE scan is abnormal, a non-ACE scan is performed. If alterations in renal function are exacerbated by ACE inhibition, significant RAS is felt to be present. Taylor reported a mean sensitivity of 92.5% with a specificity of 92.2% in 2,291 patients; however, this may be an overestimation since not all of the patients underwent angiography.<sup>25</sup> ACE inhibitor renography is most useful in patients with normal renal function, but it is less accurate in patients on ACE inhibition with nephropathy or bilateral disease.<sup>26</sup> The main problem is the high false negative rate.

#### Duplex ultrasound

Ultrasound with Doppler flow studies provides anatomic information about the kidneys and the renal arteries. In experienced hands, the sensitivity can reach 98% with a specificity of 98%. In a high-risk population (difficult-to-control hypertension, renal dysfunction, or vascular disease), the positive predictive value was 99%, with a negative predictive value of 97%.<sup>27</sup> Ultrasound is noninvasive and unaffected by medications, renal function, or whether the disease is unilateral or bilateral. Ultrasound cannot easily identify accessory arteries that may be important in some patients. A significant disadvantage is that the test is operator-dependent and each center must validate its own laboratory.

Radermacher et al<sup>28</sup> reviewed outcomes in 138 patients with RAS at >50% who underwent revascularization. There was little or no improvement in 35 patients with high renal resistive indices (RRIs), suggesting that such patients may not be good candidates for revascularization.

**Table 1. Comparison of tests for renal artery stenosis**

Study	Sensitivity	Specificity	Advantages	Disadvantages
Plasma renin activity (PRA)	75%-80%	Not available	Noninvasive, functional assessment	Affected by multiple medications, other factors
Captopril stimulation	91%-100%*	84%-95%*	Noninvasive, Improved sensitivity over PRA	Affected by multiple medications, other factors
ACEI renography	92.5%	92.2%	Noninvasive	May be inaccurate in chronic ACEI use and ischemic nephropathy
Duplex ultrasound	98%	98%	Noninvasive, anatomic assessment, no risk of renal damage	Highly operator- dependent
CT angiography	87%-98%	94%-98%	Widely available	Risk of contrast nephropathy
MR angiography	80%-90%	80%-90%	Widely available, no risk of renal damage	Overestimates degree of stenosis

\* for predicting response of blood pressure to intervention

However, the study was retrospective and included patients with only 50% stenosis that may not have had clinically important RAS. Therefore, it may be premature to exclude patients with a high RRI from revascularization.

### Computed tomographic angiography

Spiral computed tomography scans with intravenous contrast (CT angiography [CTA]) provides high-resolution images of the renal arteries less invasively than traditional angiography. Sensitivities vary from 87% to 98% with specificities of 94% to 98%.<sup>29,30</sup> CTA is a reasonable choice, particularly in patients with normal renal function, in whom the risk of contrast nephropathy is low.

### Magnetic resonance angiography

Magnetic resonance angiography (MRA) with gadolinium has a RAS sensitivity to 95%, but may overestimate the degree of stenosis as often as 21% of the time, especially in distal lesions. The rate of underestimation is approximately 14%<sup>31</sup> and branch vessels may not be well-visualized. MRA is noninvasive and less operator-dependent than ultrasound, but is contraindicated in patients with metallic implants.

### Angiography

Conventional angiography remains the gold standard for evaluating the renal arteries. Disadvantages include contrast exposure and the risk of cholesterol emboli. Contrast may be avoided by using carbon dioxide, but this is not available in all centers. Angiography also offers the possibility for concurrent treatment.

### Treatment of RAS

Intervention is generally accepted to be the treatment of choice for fibromuscular dysplasia; however, the optimal treatment for atherosclerotic RAS is a topic of debate. Although some patients benefit, it remains unclear whether, on average, revascularization is superior to medical therapy. The goals of therapy are stabilization or improvement in renal function, control of hypertension, and a reduction in cardiovascular events, including episodes of pulmonary edema.

### Surgical options

The first surgical procedure was nephrectomy, which was only performed for intractable hypertension in

patients with a small renin-secreting kidney. Subsequently, endarterectomy was introduced, followed by various bypass procedures, and even autotransplantation has been used when in-situ repair is difficult.

Success rates depend on the outcome measure and the etiology of stenosis. In a 10-year experience in patients with atherosclerotic disease, Novick reported that 30.6% were cured, while 61.1% had improved blood pressure control. In patients who underwent surgery for preservation of renal function, there was improvement in 57.7% and stability in 31.1%. In 11.2% of patients, however, renal function deteriorated. Thrombosis or restenosis occurred 4.3% of the time. Because patients with RAS frequently have other vascular disease, the surgical risk can be high, with peri-operative mortality ranging from 2.1% to 6.1%.<sup>32,33</sup>

Surgical revascularization has also been reported to be an effective treatment for recurrent pulmonary edema. In one series of 17 patients with flash pulmonary edema and extreme hypertension, episodes of pulmonary edema ceased after surgical intervention.<sup>34</sup> Thus, surgical repair remains a potential treatment for RAS, although its relative utility as compared to percutaneous intervention and/or medical therapy is not known.

### Percutaneous transluminal renal angioplasty (PTRA)

PTRA has largely replaced surgery as the intervention of choice for RAS. When comparing surgery versus PTRA, surgery has higher initial rates of success and primary and secondary patency; however, there are ultimately no differences in blood pressure and renal function between surgical and PTRA groups.<sup>35</sup> Sos et al demonstrated that PTRA was effective in opening arteries narrowed by fibromuscular dysplasia or by unilateral, but not bilateral, atherosclerotic disease.<sup>36</sup> In one study with longitudinal imaging in all patients, the restenosis rate was 16%, which occurred more frequently in patients with severe aortic disease or ostial lesions.<sup>37</sup> The treatment of ostial lesions has improved by 10%-57% to 88%-100% with the introduction of stents. Restenosis occurs in approximately 11% to 14% of stented arteries versus 48% of unstented arteries at 3-24 months post-procedure.<sup>38,39</sup> There are no significant differences in complication rates for angioplasty with or without stents.

Although PTRA restores vessel patency, it is unclear if angioplasty improves outcomes in patients with athero-

sclerotic RAS. Three, small, randomized, controlled, clinical trials have been reported and all are significantly flawed. A recent meta-analysis that combined these trials found that patients treated with balloon angioplasty had a statistically significant and sustained decrease in the number of antihypertensive medications needed to control blood pressure, as well as a modest decline in blood pressure, as compared to medical treatment.<sup>40</sup> The clinical significance of this finding is uncertain and none of the trials to date have examined mortality or cardiovascular events (Table 2).<sup>41-43</sup>

Whether PTRAs result in better preservation of renal function is also unknown. In 55 patients undergoing angioplasty, Sos et al observed an initial decline in renal function in 26 patients, stable function in 19, and unsuccessful angioplasty with continued deterioration in renal function in 10. There was a 9% rate of major morbidity and mortality, including early need for dialysis.<sup>44</sup> In 17 elderly patients undergoing PTRAs primarily for ostial disease, 11 patients had stabilization of renal function. Of the 6 failures, 5 required dialysis and died a mean 33 days after the procedure.<sup>45</sup> Thus, PTRAs stabilize or improve renal function in some patients, while others experience immediate worsening, particularly high-risk patients with ostial lesions.

### Medical management

Regardless of whether an intervention is performed or not, patients with renal vascular disease should receive an intensive, multifaceted, medical regimen, including tight control of blood pressure, dyslipidemia, and diabetes; smoking cessation; administration of an antiplatelet agent; and attention to the complications of renal insufficiency (Table 3).

In renal vascular hypertension, neurohumoral activation may contribute to adverse outcomes and specific drugs may suppress these pathways. Tullis et al found that blood pressures were lower in RAS patients who were taking an ACEI as compared to other antihypertensives.<sup>46</sup> Losito and co-workers reported that ACE inhibition was associated with improved clinical outcomes,<sup>47</sup> suggesting that renin-angiotensin-aldosterone blocking drugs should be used preferentially in these patients.

There is a well-described risk of acute renal failure with ACEIs or angiotensin receptor blockers (ARBs) in patients with global renal ischemia; however, this is relatively uncommon and usually reversible. There may also be rapid involution of the post-stenotic kidney with renin-angiotensin blockade, however, the contralateral kidney may be better preserved, as is the case for other forms of renal disease treated with ACE inhibition. In fact, the long-term effects of ACEI on kidney function in RAS patients have not been carefully evaluated. In one animal study, renal plasma flow and GFR were better preserved with an ARB than with an ACEI, however, this has not been confirmed in clinical trials.<sup>48</sup> Calcium

**Table 2: Clinical trials comparing renal artery angioplasty with medical therapy<sup>41-43</sup>**

Study (ref)	Number enrolled (N)	Follow-up (mon)	ΔBP (mmHg)	Anti-hypertensive drugs needed to control BP (N)
Webster <sup>41</sup> Uni RAS	med (13) pta (14)	6	-8/-6 -9/-5	↓
Webster <sup>41</sup> Bi RAS	med (12) pta (16)	6	-2/-2 -19/-4	↓
Plouin <sup>43</sup>	med (26) pta (23)	6	-8/-5 -12/-10	↓
Van Jaarsveld <sup>42</sup>	med (50) pta (56)	12	same	↓

UniRas = unilateral renal artery stenosis, BiRas = bilateral renal artery stenosis, med = medical therapy, pta = renal artery angioplasty

channel blockers are effective in renovascular hypertension and beta-blockers and diuretics should help prevent adverse cardiovascular events, but there are no data supporting their use in this setting. Most patients require ≥3 medications to reach recommended target pressures.

Although no specific evidence exists for patients with renovascular disease, lipid lowering can slow the progression of atherosclerosis in other vascular beds. Aggressive control of lipids is also recommended to reduce cardiovascular events.<sup>50</sup> Renovascular disease is considered a coronary artery disease-equivalent in terms of cardiovascular risk. The recommended goal for low-density lipoprotein (LDL) cholesterol is at least <100 mg/dL, with some suggesting that the target LDL should be <70 mg/dL.

A significant percentage of patients with atherosclerotic RAS will be diabetic and tight glucose control to a glycosylated hemoglobin of <7 mg/dL is recommended to reduce the incidence of micro- and macrovascular disease in these patients.

Smoking cessation is an important, but underemphasized, component of therapy for atherosclerotic RAS. It is postulated that smoking accelerates the course of RAS via promotion of atherosclerosis and cholesterol emboli.<sup>51</sup> In normotensive, nondiabetic, elderly patients with normal GFR, smoking worsened nonrenal atherosclerotic disease and this was associated with lower renal plasma flow, which likely resulted from ischemic nephropathy.<sup>52</sup>

Antiplatelet therapy with aspirin and clopidogrel or ticlopidine can result in a 22%-40% relative risk reduction in stroke and myocardial infarction in hypertensive patients and is likely to be beneficial in RAS patients as well.<sup>53</sup> Finally, many patients with RAS have some degree of renal insufficiency. Practitioners should follow the guidelines established by the National Kidney Foundation Kidney Disease Quality Initiatives ([www.kidney.org/professionals/doqi/guidelineindex.cfm](http://www.kidney.org/professionals/doqi/guidelineindex.cfm)) in managing the complications of chronic renal disease, including secondary hyperparathyroidism and anemia.

**Table 3: Optimal medical therapy for atherosclerotic renal artery stenosis**

Risk factor	Recommendation	Reference
Hypertension	Target BP $\leq$ 140/90; $\leq$ 130/80 with diabetes or proteinuria ARB as first-line agent; monitor potassium and creatinine	JNC VII 47,48
Dyslipidemia	Target LDL <100 mg/dL; consider <70 mg/dL	50
Diabetes	Target Hgb A1c <7 mg/dL; foot and eyecare	
Antiplatelet	Recommended, aspirin, agent clopidogrel or ticlopidine	53
Smoking	Cessation	51
Chronic kidney disease	Tight control of BP, dyslipidemia, diabetes. Manage anemia, hyperparathyroidism	NKF DOQI

BP = blood pressure, ARB = angiotensin receptor blocker  
LDL = low-density lipoprotein cholesterol; JNC VII = Seventh Joint National Committee; NKF DOQI = National Kidney Foundation – Disease Outcomes Quality Initiative

## Conclusion

Renovascular hypertension is likely to become more common as the population ages and the treatment of other illnesses improves longevity. While stenosis will often progress anatomically, it is uncertain how frequently this leads to ESRD. Percutaneous revascularization is usually technically successful and the treatment of choice for patients with fibromuscular dysplasia. However, there is no clear evidence that revascularization improves clinical outcomes in patients with atherosclerotic RAS as compared to medical therapy. For now, it seems reasonable to consider intervention in patients with rapidly declining renal function, intractable hypertension, or recurrent episodes of pulmonary edema. Patients with creatinines >3 mg/dL or small (<8 cm) kidneys are unlikely to benefit. A National Institutes of Health funded, prospective, multicenter, randomized clinical trial – the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) Study – will compare PTRAs and stenting with medical therapy versus medical therapy alone and should provide clearer insights into the optimal management of these difficult patients.

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## Abstract of Interest

### Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition.

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**BACKGROUND:** Patients with atherosclerotic renovascular disease (ARVD) are almost invariably treated by revascularization. However, the long-term outcomes of this approach on survival and progression to renal failure have not been investigated and have not been compared with that of a purely medical treatment. The aim of this observational study was to investigate factors affecting long-term (over 5 years) outcome, survival and renal function of patients with ARVD treated invasively or medically.

**METHODS:** ARVD was demonstrated angiographically in 195 patients who were consecutively enrolled into a follow-up study. Patient age was 65.6+/-11.2 years, serum creatinine was 1.74+/-1.22 mg/dL and renal artery lumen narrowing was 73.5+/-17.5%. A revascularization was performed in 136 patients, whereas 54 subjects having comparable characteristics were maintained on a medical treatment throughout the study; five patients were lost during follow-up.

**RESULTS:** The main follow-up was 54.4+/-40.4 months. The assessment of cardiovascular survival and renal survival at the end of follow-up revealed 46 cardiovascular deaths, 20 patients with end-stage renal disease (ESRD) and 41 patients with an increase in serum creatinine of over one-third. The multivariate analysis showed that renal revascularization did not affect mortality or renal survival compared with medical treatment. Revascularization produced slightly lower increases in serum creatinine and a better control of blood pressure. A longer survival was associated with the use of angiotensin-converting enzyme inhibitors (ACEIs) (P = 0.002) in both revascularized and medically treated patients. The only significant predictor of ESRD was an abnormal baseline serum creatinine.

**CONCLUSIONS:** On long-term follow-up, ARVD was associated with a poor prognosis due to a high cardiovascular mortality and a high rate of ESRD. In our non-randomized study, revascularization was not a major advantage over medical treatment in terms of mortality or renal survival. The use of ACEIs was associated with improved survival.

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## Upcoming Scientific Meetings

15-18 July 2006

**European Renal Association (ERA)**

**European Dialysis and Transplantation Association (EDTA)**

Glasgow, Scotland

CONTACT: [www.eraedta2006.org](http://www.eraedta2006.org)

15-19 September 2006

**28<sup>th</sup> Annual Meeting of the American Society for Bone and Mineral Research**

Philadelphia, PA

CONTACT: [www.asbmr.org](http://www.asbmr.org)

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