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## State of the Art: Renovascular Hypertension and Ischemic Nephropathy

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### Abstract

Renovascular disease remains among the most prevalent and important causes of secondary hypertension and renal dysfunction. Many lesions reduce perfusion pressure including fibromuscular diseases and renal infarction, but most are caused by atherosclerotic disease. Epidemiologic studies establish a strong association between with atherosclerotic renal artery stenosis and cardiovascular risk. Hypertension develops in patients with renovascular disease from a complex set of pressor signals, including activation of the renin-angiotensin system, recruitment of oxidative stress pathways, and sympatho-adrenergic activation. Although the kidney maintains function over a broad range of autoregulation, sustained reduction in renal perfusion leads to disturbed microvascular function, vascular rarefaction and ultimately development of interstitial fibrosis. Advances in antihypertensive drug therapy and intensive risk factor management including smoking cessation and statin therapy can provide excellent blood pressure control for many individuals. Despite extensive observational experience with renal revascularization in patients with renovascular hypertension, recent prospective randomized trials fail to establish compelling benefits either with endovascular stents or surgery when added to effective medical therapy. These trials are limited and exclude many patients most likely to benefit from revascularization. Meaningful recovery of kidney function after revascularization is limited once fibrosis is established. Recent experimental studies indicate that mechanisms allowing repair and regeneration of parenchymal kidney tissue may lead to improved outcomes in the future. Until additional staging tools become available, clinicians will be forced to individualize therapy carefully to optimize the potential benefits regarding both blood pressure and renal function for such patients.

### Keywords

Renovascular Hypertension; renal artery stenosis; renin; BOLD MR; angioplasty; stent; atheroemboli

### Introduction

Management of patients with hypertension and renovascular disease has never been more complex—or ambiguous. Continued emphasis on achieving lower goal blood pressures to reduce cardiovascular risk forces clinicians caring for hypertensive patients to intensify therapy and consider secondary factors, such as renovascular occlusive disease, more than ever before. At the same time, however, a confusing array of prospective, randomized clinical trials published in the prominent general medical literature fail to establish major benefits from revascularizing patients with atherosclerotic renal arterial disease<sup>1;2</sup>. Many of these trials are seriously flawed<sup>3</sup>. While these trial results indeed reflect major improvements in medical management and antihypertensive drug therapy, most clinicians in

the field recognize the need to optimize both endovascular and medical interventions for renovascular disease. In some cases, critical opportunities to preserve renal function are missed, allowing patients to drift into advanced kidney failure. The goal of this review is to summarize the current state of affairs regarding renovascular hypertension and ischemic nephropathy for the clinician with a major interest in hypertension.

## Definition and epidemiology

Renovascular hypertension refers to the rise in arterial pressure attributable to reduced perfusion of the kidney. Most often this is from main renal arterial obstruction from either atherosclerotic occlusion or fibromuscular dysplasia. A variety of other lesions can produce the same syndrome, however, some of which are identified in TABLE 1. As a clinical phenomenon, these lesions sometimes produce an unexpected rise in blood pressure in younger subjects, e.g. less than 30 or contribute to resistant hypertension in previously normotensive or treated hypertensive subjects. Recent imaging studies indicate that “incidental” vascular lesions can be identified in 3-5% of normotensive subjects, e.g. potential living kidney donors with normal kidney function and blood pressure<sup>4</sup>. Hence, radiographic identification of a vascular occlusive lesion alone does not establish its physiologic role.

A variety of fibromuscular lesions are recognized, most commonly in young women. These sometimes first appear as unexplained rises in arterial pressure, e.g. during pregnancy. These lesions may have varied appearance including the “string-of-beads” associated with medial fibroplasia or focal banding in the mid-renal artery<sup>5</sup>. Remarkably, these lesions often trigger renin release without loss of renal parenchymal volume or glomerular filtration rate unless they lead to dissection or thrombosis of the entire kidney.

By far the most common renovascular lesion is atherosclerotic renal artery stenosis (ARAS). Atherosclerosis leading to elevated arterial velocities suggesting more than 60% stenosis can be detected in 6.8% of community based subjects above age 65<sup>6</sup>. The prevalence of ARAS rises with age and with clinically manifest disease in the coronary arteries (18-20%), the aorta, or peripheral vascular beds (35-50%), as recently reviewed<sup>7</sup>. Development of atherosclerotic disease relates to the magnitude of cardiovascular risk factors, including smoking, dyslipidemia, diabetes and age, among others. Epidemiologic associations have been proposed to suggest that individuals with refractory congestive heart failure and/or end-stage renal disease may have demonstrable ARAS in 40-50% of cases<sup>7</sup>. Whether these lesions are active causal factors in these conditions or represent an associated “biomarker” of atherosclerosis remains controversial. Development and use of aortic endovascular stent grafts, often placed adjacent to the renal arteries has produced a new class of patients with “acquired” renal artery stenosis related to occlusive effects of the stent graft<sup>8</sup>. This may become more common as these devices become more widely used in patients at ever older age ranges.

## Pathophysiology: Renovascular hypertension and the role of renin-angiotensin system

Seminal studies demonstrating the link between vascular perfusion to the kidney and the development of hypertension remain fundamental to the field of blood pressure research<sup>9-11</sup>. Models using renal arterial lesions have been reproduced in multiple species including rat, dog, rabbit and swine. Studies in these models facilitated discovery and elucidation of the renin-angiotensin system. Unilateral experimental renovascular disease with a functioning “contralateral kidney” that excretes sodium as function of “pressure natriuresis” (identified as 2-kidney-1-clip hypertension) remains a premier model of angiotensin-

dependent hypertension. When a solitary kidney is present or both kidneys are affected, angiotensin-dependence is temporary and dependent upon sodium depletion<sup>12</sup>. Targeted blockade of the renin-angiotensin system<sup>13;14</sup> or its activation in animals without angiotensin receptors protects against the development of renovascular hypertension<sup>15</sup>. Studies using kidney transplants from angiotensin receptor knockout mice indicate that both systemic and renal effects of angiotensin participate in pressure and target organ injury in this disorder<sup>16</sup>. Remarkably, activation of the circulating renin-angiotensin system is transient and leads to recruitment of additional pressor pathways, including oxidative stress, sympatho-adrenergic activation, and impaired vasodilatory responses both within the renal and systemic microcirculation<sup>17</sup>. It should be emphasized that the release of circulating renin depends upon a substantial reduction in kidney perfusion pressure. Studies using balloon occlusion in humans indicate that this process requires development of a gradient across the lesion such that distal pressures fall at least by 10-20% below aortic pressure<sup>18</sup>. Such pressure differences correspond to translesional peak systolic gradients of 15-25 mm and develop only when the cross-sectional area of occlusion approaches 70-80% as illustrated in FIGURE 1<sup>19</sup>. An important corollary of this observation is that vascular lesions that fail to generate such a gradient are unlikely to participate in renovascular hypertension and do not benefit from measures to open the vessel. Conversely, revascularization of vessels with lesions that produce a gradient does not invariably resolve hypertension and renal dysfunction, which may be caused by alternative or co-existing mechanisms.

The kidney is relatively overperfused relative to its metabolic requirements, a feature consistent with its role as a filtering organ. Hence, blood flow and filtration may fall considerably without jeopardizing tissue viability. Recent studies indicate that reduction of renal blood flow sufficient to reduce kidney size and produce renin release may develop despite preserving normal overall levels of both cortical and medullary tissue oxygenation<sup>20</sup>. These data imply that renovascular hypertension does not depend upon true renal “ischemia” per se.

Clinical manifestations of renovascular hypertension include high rates of target organ injury as compared to similar levels of “essential hypertension”<sup>21</sup>. Importantly, the presence of ARAS also increases cardiovascular risk<sup>22</sup>. Some target organ injury may be related directly to activation of the renin-angiotensin-aldosterone axis. For this reason, the U.S. Cardiovascular Outcomes for Renal Artery Lesions (CORAL) trial specifies angiotensin-blockade as part of medical therapy for all patients in the study<sup>23</sup>. Patients with ARAS commonly have disturbed day-night blood pressures with loss of nocturnal BP fall, increased sympathetic nerve traffic as measured in efferent nerve fibers, more severe left ventricular hypertrophy and lower glomerular filtration rate (GFR) as compared to essential hypertension with similar clinic blood pressures<sup>24;25</sup>.

## Loss of renal function and viability

Although the kidney overall receives more blood than needed strictly for its metabolic activity, impaired blood flow eventually leads to tissue fibrosis. Remarkably, parenchymal fibrosis rarely develops in patients with fibromuscular disease with the exception of those experiencing renal infarction. This suggests that activation of remodeling mechanisms in the post-stenotic kidney is related to the atherosclerotic milieu itself<sup>26</sup>. Recent experimental studies also underscore the development of renal microvascular changes distal to a stenosis in the renal artery<sup>27;28</sup>. An example of microvascular proliferation induced by cholesterol feeding (a surrogate for early atherosclerosis) and subsequent “rarefaction” of renal small vessels beyond a main renal artery lesion is illustrated in FIGURE 2. Numerous signaling pathways lead to upregulation of cytokines and inflammatory mediators, including

transforming growth factor (TGF)-beta, within the post stenotic kidney<sup>29;30</sup>. Over time, rarefaction of the distal arterioles develops, associated with fibrogenesis and loss of viable function<sup>31, 32-34</sup>. When vascular occlusion reaches severe proportions, overt tissue ischemia can be demonstrated as illustrated using Blood Oxygen Level Dependent (BOLD) magnetic resonance imaging (FIGURE 3).

For many of these patients, restoring kidney blood flow alone has little effect on improving kidney function, as emphasized by the results from recent clinical trials<sup>35</sup>. However, some injurious pathways responsible for renal remodeling can be modified using intensive therapy with either anti-oxidants or statins<sup>36</sup>, leading to improved blood flow, vascular integrity and reduced kidney injury<sup>32</sup>. Clinical observations suggest that statins slow the progression of tissue injury in ARAS and are associated with substantially less interstitial fibrosis in kidneys removed for total arterial occlusion<sup>33;34</sup>. Remarkably, infusion of autologous endothelial progenitor cells in a swine model produces increases in renal blood flow and glomerular filtration rate even without renal revascularization<sup>37</sup>. Whether additional maneuvers, such as delivering undifferentiated progenitor cells to the kidney or mobilization of resident kidney stem cells, can facilitate recovery of viable tissue in humans under these circumstances remains to be seen.

### Clinical manifestations and the Decision to undertake Diagnostic studies

Stenotic occlusive disease in the renal arteries is associated with a broad range of clinical manifestations as illustrated in FIGURE 1. Many of these lesions reflect incidental or modest disease with little clinical impact regarding renal perfusion, blood pressure or glomerular filtration. Results from recent trials underscore the fact that the severity of many vascular lesions, i.e. the degree of actual vessel occlusion, is overestimated from non-invasive diagnostic imaging, e.g. MR angiography, Doppler ultrasound or CT angiography. When subjected to quantitative angiography, many of these lesions remain below the threshold warranting vascular intervention. In the STent placement for Atherosclerotic Renal artery stenosis (STAR) trial, for example, 28% of stenotic lesions were not subjected to intervention despite assignment to this therapy, primarily due to identifying only clinically trivial disease after closer scrutiny during angiography<sup>2;3</sup>.

When reduced kidney perfusion activates pressor mechanisms, blood pressure often rises, sometimes leading to acceleration of pre-existing essential hypertension. As a result, the clinical manifestations of ARAS most commonly develop in previously treated hypertensive subjects. A rapid rise in arterial pressure can be associated with target injury such as a stroke, or when combined with reduced renal perfusion to the entire renal mass and enhanced sodium reabsorption can lead to rapidly developing circulatory congestion (sometimes termed “flash pulmonary edema”). Sodium retention in patients with left-ventricular heart dysfunction contributes to refractory congestive failure, particularly when both kidneys or the entire renal mass is affected. Finally, loss of blood flow produces irreversible kidney fibrosis as noted above. As a practical matter, the **decision** whether to initiate diagnostic studies often depends directly upon the clinical likelihood that renovascular disease is an important contributor to the disease state of the patient. It also depends upon whether these manifestations can be managed readily with medical therapy alone. It may be argued that if blood pressure and kidney function are treated satisfactorily and remain stable, little is to be gained by embarking on a path of expanded diagnostic studies. Hence, the decision to undertake expanded diagnostic testing should be based upon the commitment to consider renal revascularization if studies are positive. A commonly applied algorithm is summarized in FIGURE 4.

It is worth emphasizing that this approach is more conservative than proposed even a decade ago. Formal reviews of both the observational studies<sup>38;39</sup> and prospective trials emphasize that surgical and endovascular renal revascularization procedures carry expense and morbidity risks. Outcomes of these trials are summarized below (TABLE 2). The benefit to intensive investigation and vascular intervention for most patients is modest and should be reserved for those most likely to experience real clinical benefit.

## Diagnostic Studies for Renovascular Disease

Exhaustive consideration of vascular imaging of the kidney is beyond the scope of this review. Before initiating any of these procedures, clinicians would do well to define precisely the goals to be achieved, as we have discussed elsewhere<sup>40</sup>. In general, imaging procedures are undertaken to define the presence and/or bilateral location of hemodynamically important vascular occlusion. Optimally, one would like an estimate of the severity, accessibility, and location of these lesions, and the functional status of the kidney beyond. Even more importantly, one would like to define the degree to which these vascular occlusive lesions actually are responsible for the clinical manifestations present and the likelihood that restoring vascular patency would reverse this process. Achieving all of these goals is difficult with any single study.

Renal artery Doppler ultrasound is a widely available method that reliably defines velocity changes consistent with vascular narrowing. It requires attention to detail and varies considerably between institutions, particularly in light of operator expertise, patient preparation, and the time allowed for satisfactory study. Prospective series suggest sensitivity and specificity above 90% in dedicated laboratories<sup>41;42</sup>. Others have reported sensitivity in the 60% range with more than 20% technically inadequate studies, often due to obesity or poor preparation<sup>43</sup>. In our experience, duplex ultrasound rarely produces “false positives”, but can miss important vascular lesions, resulting in “false negatives”. It can be helpful to follow previously identified lesions regarding progression of disease. Identification of low resistive index in the affected kidney has been proposed as a marker of likely benefit from revascularization<sup>44</sup>, although this has not been observed universally<sup>45</sup>. Velocity thresholds for significant disease vary considerably (classically considered at 180-200 cm/sec Peak Systolic Velocity for “hemodynamically significant lesions” above 60% occlusion<sup>46</sup>). To avoid overdiagnosis of modest lesions some authors advocate setting the threshold at 300 cm/sec, currently the required threshold for enrollment in the Cardiovascular Outcomes for Renal Atherosclerotic Lesions (CORAL) trial in the U.S..

CT angiography (CTA) and MR angiography (MRA) provide ever more sophisticated imaging, allowing construction of three dimensional vascular images and estimates of individual kidney function. Use of contrast MRA in subjects with reduced GFR has fallen off drastically in this disease since the concerns regarding development of nephrogenic systemic fibrosis (NSF) and the putative role of gadolinium contrast<sup>47</sup>. While gadolinium contrast may be safe for patients with preserved GFR, newer techniques allow improved vascular imaging without gadolinium and may become more widely available<sup>47</sup>. CT angiography has both radiation and contrast exposure, but can provide excellent definition of both vascular tree and renal function.

## Functional testing based upon activation of the renin-angiotensin-system

Renovascular hypertension is more closely associated with activation of the renin-angiotensin system (RAAS) than any other form of hypertension. While intuitively attractive as diagnostic tools, measurement of plasma renin activity alone and/or the blood pressure response to angiotensin blockade are limited by interactions with drug effects, sodium



intake, renal dysfunction and possible alterations dependent upon age and the duration of renovascular disease.

Angiotensin is an important determinant of filtration pressure in the kidney. Most patients with renovascular disease tolerate RAAS blockade without evident adverse effects, although some fall in GFR may accrue inevitably from functional removal of the angiotensin II action that supports filtration<sup>48</sup>. This fall in GFR is exaggerated in the presence of pre-glomerular vascular disease and is the basis for examining changes in isotope renograms before and after captopril. Several series derived from clinically selected populations suggest that captopril renography can predict blood pressure and/or renal function improvements after renal revascularization with predictive values exceeding 75% and sensitivity above 90%<sup>49-51</sup>. These observations have not been confirmed when applied to larger populations and may be confounded by previous drug therapy, bilateral disease and reduced kidney function<sup>52;53</sup>. Captopril renography is less commonly used than before, but has advocates within the hypertension community<sup>54</sup>. It had little predictive value in the Dutch Renal Artery Stenosis Intervention Cooperative study group (DRASTIC) trial other than to identify individuals with progressive total occlusion<sup>53</sup>. Renography does provide functional data regarding blood flow and filtration, but no direct imaging regarding the renal vasculature itself. Hence, it provides an estimate of relative function when total occlusion is present that may validate consideration of nephrectomy of a “pressor kidney”, as recently revisited<sup>55;56</sup>.

Intra-arterial angiography and renal vein renin measurements remain the “gold standard”. Angiographic core laboratories indicate that visual estimates of stenosis commonly overstate the severity of vascular occlusive lesions. As a result, some authors recommend confirmation with transluminal gradient measurement using low profile pressure transducers<sup>57</sup>. Without a measurable gradient, it is hard to justify vascular intervention. While measurement of renal vein renin levels has fallen into less common use, a considerable body of data supports a predictive role of lateralizing values regarding the likely benefit of revascularization, at least regarding improved blood pressure control<sup>58</sup>. Careful studies of renal vein renin levels obtained after withholding drug therapy for two weeks indicate that lateralizing values (more than 1.7) accurately predict the fall in arterial pressure following nephrectomy in patients with total occlusion<sup>59</sup>. The authors argue that lateralization for non-occluded vessels performed best (by receiver operating curves) at a level of 1.55, which corresponded to a sensitivity of 54% with a false positive rate of 15%. In practice, many clinicians are unwilling to withhold drug therapy before testing and results may be less consistent. As with most diagnostic studies in this disorder, the results are most useful when positive. Failure to demonstrate lateralization can result for many reasons, including volume expansion commonly employed during angiography.

One might argue that ambiguous trial results should encourage more careful documentation and evaluation before undertaking renal revascularization procedures. There is a pressing need to refine the tools for defining the clinical impact of vascular occlusion in the kidney, as we have discussed<sup>40</sup>.

## Medical Therapy for Renovascular Hypertension and Ischemic Nephropathy

As noted above, much of the commitment for extensive diagnostic studies and vascular intervention depends upon the results of medical therapy as an initial step. Particularly for patients with accelerated or extreme hypertension, blood pressure reduction to safe levels should be achieved before invasive diagnostic procedures. Pharmacologic therapy of renovascular hypertension follows the basic principles of all antihypertensive drug therapy, but especially depends on effective blockade of the renin-angiotensin-aldosterone system

(RAAS). Italian and Canadian registry data suggest considerable survival advantages for patients able to employ angiotensin converting enzyme (ACE) inhibition or angiotensin receptor blockers (ARB's) as part of their regimen<sup>60;61</sup>. Few data address the role of direct renin inhibition, although this is a rational alternative. Analysis of subgroups from the HOPE and PEACE trials suggest the greatest clinical benefits from RAAS blockade accrue to those with some degree of renal dysfunction<sup>62;63</sup>. These groups are likely to include some patients with unrecognized atherosclerotic RAS. A clinically important fall in GFR associated with a rise in serum creatinine and potassium sometimes occurs with major preglomerular vascular occlusion that precludes the use of these agents. It should be emphasized that such a rise in creatinine develops both because blood flow is threatened and because angiotensin II supports filtration under those conditions<sup>64</sup>. Hence, the loss of GFR reflects a functional signal that blood flow is threatened and filtration requires the supportive action of angiotensin. Filtration can recover when blockade of RAAS is removed. A corollary of this observation is that other forms of antihypertensive drug therapy may also threaten blood flow, which in some cases constitutes a legitimate reason to move forward to restore renal blood flow. Remarkably, most patients with hemodynamically important ARAS tolerate RAAS blockade without difficulty. Withdrawal of ACE / ARB in the heart failure trials occurred in less than 5% of subjects<sup>65</sup>. Recommendations for the use of these agents include re-evaluation of serum creatinine and potassium level soon (within a week) after initiating therapy, particularly in patients with reduced kidney function<sup>48</sup>. It remains essential for the clinician to define what increase in serum creatinine can be tolerated, but some authors indicate that a rise of 30% may be expected<sup>66</sup>. Some investigators argue that the cardiovascular risk is magnified by the neuro-hormonal activation associated with ARAS<sup>57</sup>. As a result, the authors of CORAL advocate universal blockade of the RAAS as a central component of managing this disorder.

At least equally important is the intensive and rigorous management of atherosclerosis. Discontinuing tobacco use, statin therapy, aspirin, and diabetes management are major components that require attention. Most of the adverse outcomes for patients with atherosclerotic renovascular disease derive from non-renal vascular complications, including stroke, coronary events, and peripheral vascular disease<sup>67</sup>.

## The role of Renal Revascularization

Restoring blood flow to kidneys that actively trigger pressor mechanisms in renovascular hypertension is an intuitively rational approach<sup>68</sup>. Indeed, both surgical or endovascular revascularization occasionally produce normalization of arterial pressures in such cases, leading to "cure". Most cases of fibromuscular dysplasia producing hypertension in younger individuals can be considered for angioplasty at low procedural risk, so long as no aneurysms are present. Considering the potential need for many years of antihypertensive therapy and the limitations on using either ACE inhibitors or ARBs in pregnancy, most clinicians favor angioplasty as initial therapy for younger women, who are most likely to be treated for this disorder. It is important to recognize that even with FMD, rates of "cure" are limited. Recent series suggest that achieving normal blood pressures without antihypertensive drug therapy occurs in less than 30% of subjects, although some improvement may occur in an additional 50% or more<sup>5</sup>. Complex disease including aneurysmal dilatation should be approached using either surgical or medical therapy primarily. Restenosis may occur with FMD and lead to repeat procedures in 11-23%<sup>5;69</sup>.

Atherosclerotic RAS poses a different set of concerns, as noted above. These lesions primarily develop in subjects with pre-existing hypertension, so revascularization rarely lowers blood pressure to normal. Nonetheless, restoring blood flow to kidneys at critically reduced perfusion offers the potential to recover kidney function, protect from further

degradation, and improve blood pressure control. Observational studies including both surgical and endovascular repair emphasize that important improvements in kidney function and reduced antihypertensive drug requirements can be obtained in such patients<sup>70-74</sup>. A formal review from the Agency for Health Quality Research (AHQR) indicates that while prospective studies fail to define unequivocal strategies for management of atherosclerotic RAS, clinically important improvements in kidney function and reversal of hypertension developed only in patients with successful revascularization<sup>38</sup>. Major improvements do not occur frequently, however, and these procedures have both costs and risks. Because the advances in medical therapy have been substantial, numerous prospective, randomized trials comparing intensive medical therapy with and without renal revascularization procedures have been undertaken in recent years<sup>39</sup>. Some of these have been completed and published. The main results from these trials are summarized in TABLE 2. It is notable that these trials vary enormously in size and power estimates, ranging from less than 100 to more than 1000 for target populations. Because patients with ARAS are older and commonly have widespread atherosclerosis, clinical events are subject to major confounding with other comorbid diseases. Some authors argue that such populations are inherently so heterogeneous as to be impossible to study as a single population<sup>75</sup>. A major limitation of these initial trials including STAR<sup>2</sup> and ASTRAL<sup>1</sup> has been the inconsistency in defining “critical” vascular occlusion and the degree of stenosis. Hence, the power of several trials has been undermined by realization that patients selected for treatment often have trivial disease. Another key observation has been the recognition that current optimal medical therapy appears to allow stabilization of atherosclerotic disease and renal dysfunction to a much greater degree than originally predicted. Hence, the ability to achieve reasonably good blood pressure control has been much better than reported in studies a decade ago<sup>76</sup>. Perhaps for these reasons, the results of the recent trials fail to demonstrate major advantages to renal revascularization as a primary intervention. The largest and most carefully performed study in this field in the U.S., the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), remains in progress and will not provide outcome data for several more years.

It must be recognized that revascularization procedures carry some risks, although modern techniques have reduced these substantially. Moderate complications including bleeding, local dissection, and branch occlusion can develop, but are reported in less than 10% of cases<sup>77</sup>. Restenosis remains a concern and can develop in 10-15% of subjects<sup>78</sup>. ARAS lesions commonly develop as part of generalized atherosclerosis, particularly in the abdominal aorta. As a result, either surgical or endovascular manipulation carry some risk of releasing atheroemboli. While a small amount of embolic debris may be released in nearly any vascular procedure, including guidewire placement<sup>79;80</sup>, the incidence of clinically important renal infarction or systemic atheroemboli remains low, reported between 1 and 4%<sup>77;81</sup>. When the full syndrome of systemic emboli occurs, however, it can be devastating. Risk factors for emboli include extensive aortic plaque and/or aneurysm, uncontrolled hypertension, and direct renal artery manipulation<sup>82</sup>. In a series of 43 patients developing advanced renal failure from this procedure, 31 required long-term dialysis and 33% did not survive the first year. Of those requiring dialytic support, only 12 (28%) ultimately recovered sufficiently to withdraw from dialysis. Whether use of embolic protection devices will improve these outcomes is uncertain. Results from a recent trial suggest that simply having the device in place during the procedure offers little benefit for recovery of kidney function after renal artery stenting<sup>83</sup>. Many embolic events develop in a “stuttering” fashion for days and weeks after the procedure, suggesting that temporary vascular protection will have limited value.



## Future Developments to recover renal function

ARAS initiates complex changes by which disturbed signaling pathways activate inflammatory and fibrogenic processes at different times<sup>29;30</sup>. Although the kidney microvasculature is complex and remarkably resilient despite local environments with reduced oxygen tension, it is likely that either recurrent or critical levels of ischemia participate in triggering some of these responses. While restoring large vessel perfusion alone is rarely sufficient, future studies may elucidate a role for adjunctive or alternative measures that overcome hypoxic stimuli and allow for restoring the microvasculature. Some may also support regeneration of functional cells to repair injured tubules and glomeruli. Experimental studies suggest that undifferentiated cells, either local progenitor cells or those recruited from elsewhere in the body, may foster a microenvironment where such repair can occur. We are optimistic that newer tools to monitor tissue conditions and improved technology to stimulate local repair mechanisms will play an important role in this process.

## Summary: An integrated view of managing renovascular disease

Renovascular disease remains one of the most prevalent and important causes of secondary hypertension and renal dysfunction. Advances in antihypertensive drug therapy and intensive risk factor management including statin therapy can provide excellent blood pressure control in many individuals. Despite these advances, timely recognition of vascular occlusive disease is important to avoid progressive renal functional loss. Recent studies emphasize important interactions between large vessel occlusive disease and changes in the milieu or microvascular environment in the kidney. Changes in microvascular disease appear to activate multiple mechanisms of tissue injury and repair that remain incompletely understood<sup>31;84</sup>. Improved therapy for this disorder will depend upon more precise definition of the role of post-stenotic kidneys in sustaining hypertension and identification of kidneys that are threatened by vascular occlusive disease but remain viable and salvageable. Based on the ambiguous results of prospective treatment trials to date, clinicians will need to examine each patient closely to consider if limited net benefits warrant the expense and potential hazard of invasive procedures and vascular repair. We anticipate the need for more refined tools to define the degree of actual tissue ischemia within an individual subject and the role of adjunctive maneuvers to assist in tissue repair. Effective patient care for renovascular disease likely will benefit from close collaboration among clinicians directly managing medical therapy and those providing vascular intervention.

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Figure 1: (A)

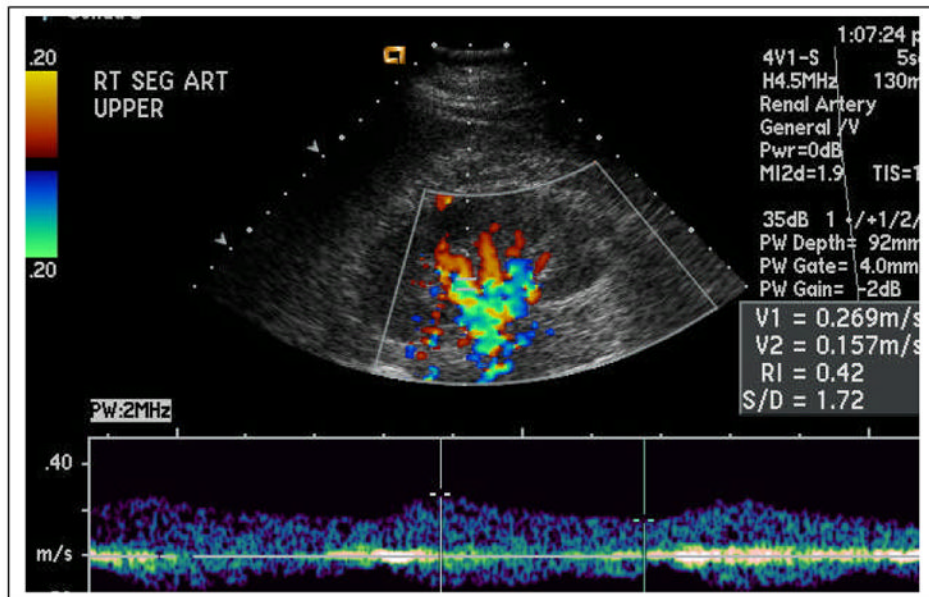
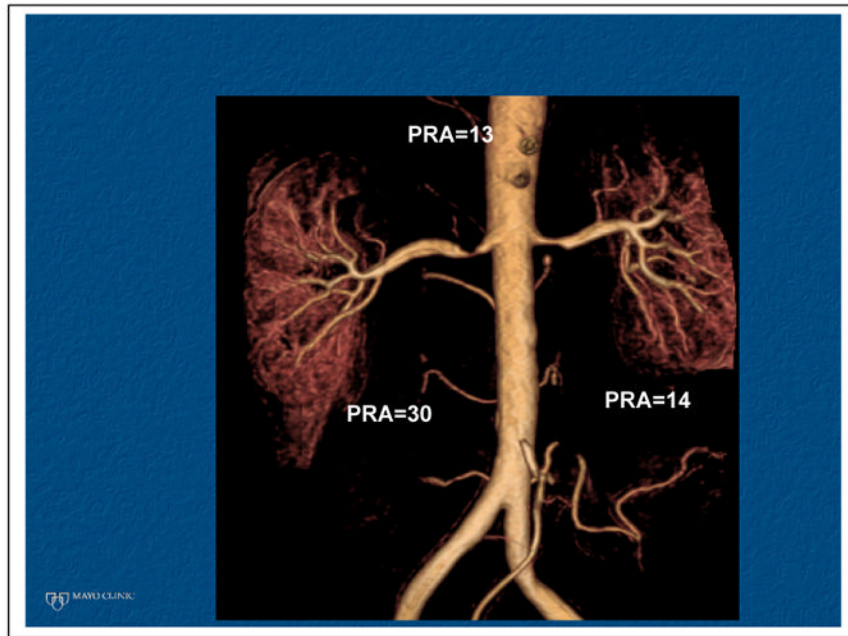


Figure 1 (B)

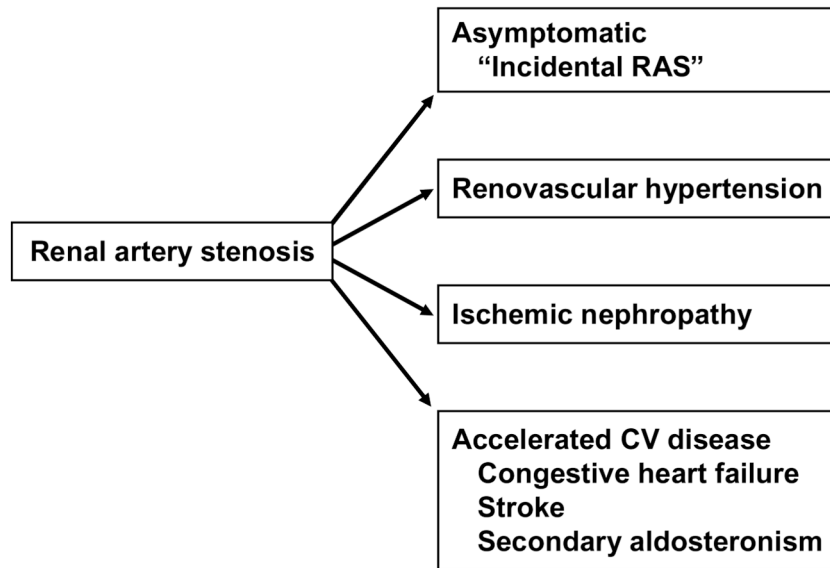


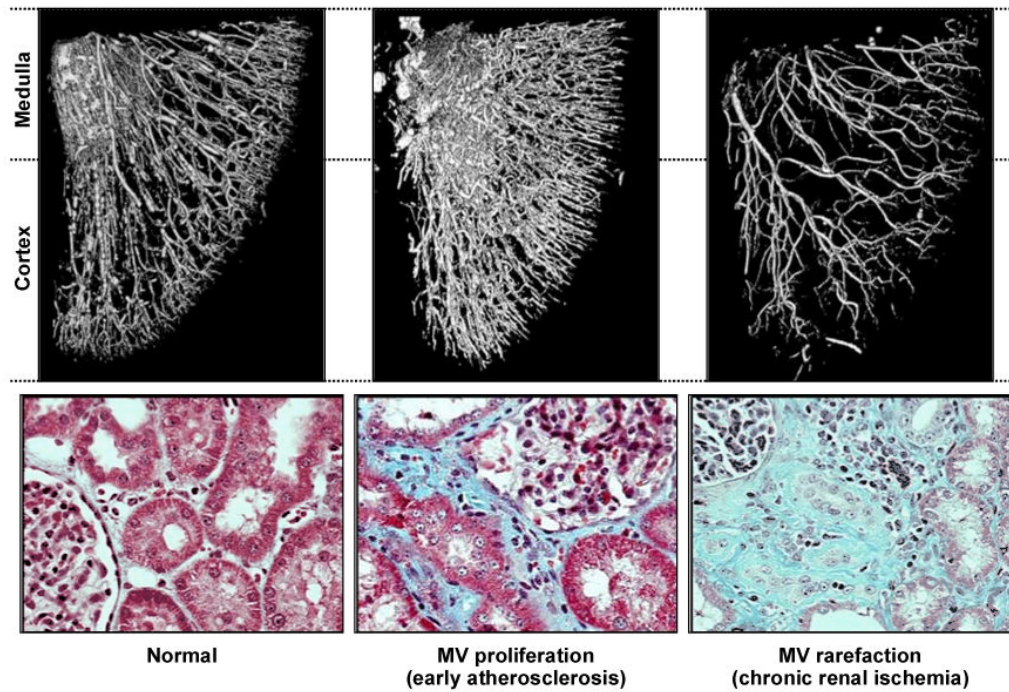
Figure 1(C)

**FIGURE 1.**

(a) MR Angiogram of High grade renal artery stenosis with renal vein renin measurements: lateralization suggests high probability of pressor activity.

(b) Renal artery duplex study of distal segments on the right kidney illustrating “parvus tardus” waveform and low resistive index (RI=0.42). These data suggest excellent distal blood flow “runoff” and limited parenchymal fibrosis. Severe hypertension had developed over a three month period that was reversed by successful revascularization.

(c) Manifestations of renal arterial disease



**FIGURE 2.**

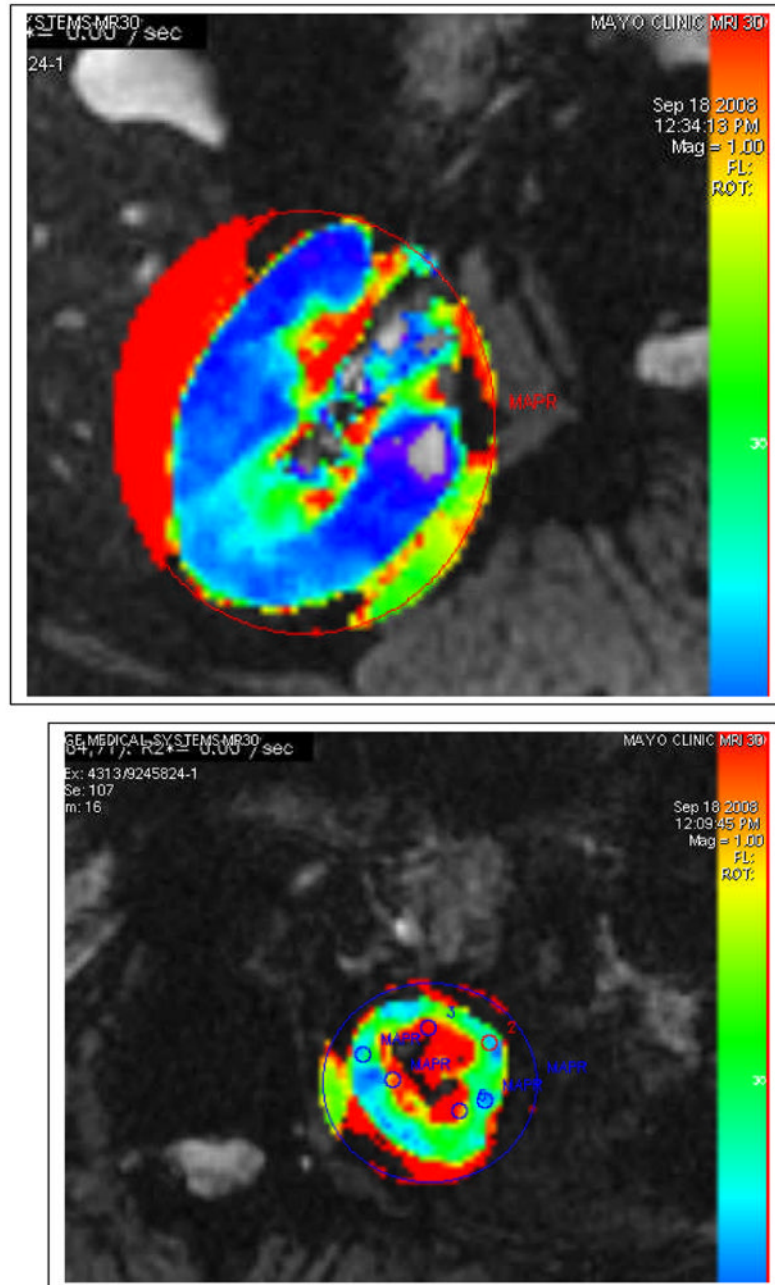
Micro-CT imaging of vascular casts obtained from a swine model of atherosclerotic renal artery stenosis. Atherosclerosis produced by cholesterol feeding induces small vessel proliferation and disturbed endothelial function (middle panel). The kidney beyond a main renal arterial occlusive lesion induced by copper stent experiences dropout (“rarefaction”) of small vessels within both cortex and medulla and accelerated tissue fibrosis. From Lerman and Chade, with permission<sup>90</sup>.

Figure 3 (A) and B)



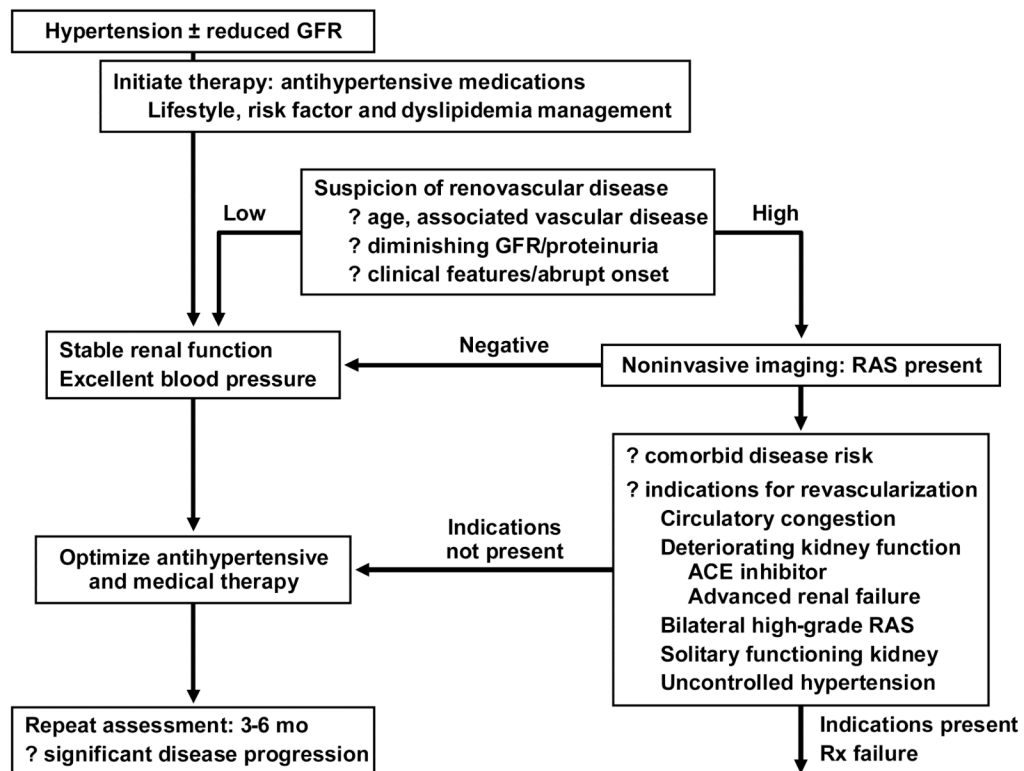


Figure 3 : (C) and (D)

**FIGURE 3.**

(a) T2 imaging by MR and CT angiogram demonstrating high grade renal artery stenosis to the left kidney and a normal nephrogram on the right (with a vascular stent in place and distal fibromuscular disease). (b) Parametric maps of  $R2^*$  (reflecting the level of deoxyhemoglobin) from Blood Oxygen Level Dependent (BOLD) MR at 3 Tesla from the same kidneys are shown below. The right kidney has low cortical  $R2^*$  (blue) with small areas of medullary deoxygenation typical of a normal kidney. Moderate vascular stenosis such as observed with fibromuscular disease is associated with well-preserved tissue oxygenation as shown here<sup>20</sup>. The small left kidney has higher levels of cortical  $R2^*$  and a large, deep area of medullary deoxygenation (red) illustrating physiologic oxygen

deprivation as a result of extreme vascular compromise. Hence, progressive occlusive disease ultimately overrides compensatory changes within the kidney to produce ischemic injury.



**FIGURE 4.** Algorithm for evaluation and intervention in renovascular disease (from Textor, in Brenner's Textbook, with permission <sup>91</sup>)

**TABLE 1**  
**Major Causes of vascular occlusion producing Renovascular Hypertension**

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<b>Unilateral disease</b>
Unilateral atherosclerotic renal artery stenosis
Unilateral fibromuscular dysplasia (FMD)
Medial fibroplasia
Perimedial fibroplasia
Intimal fibroplasia
Medial hyperplasia
Renal artery aneurysm
Arterial embolus
Arteriovenous fistula (congenital / traumatic)
Segmental arterial occlusion (post-traumatic)
Extrinsic compression of renal artery, e.g pheochromocytoma
Renal compression, e.g. metastatic tumor
<b>Bilateral Disease or Solitary Functioning Kidney</b>
Stenosis to a solitary functioning kidney
Bilateral renal arterial stenosis
Aortic coarctation
Systemic vasculitis (e.g. Takayasu's, Polyarteritis)
Atheroembolic disease
Vascular occlusion due to endovascular aortic stent graft

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TABLE 2

Summary of Prospective, Randomized trials of medical therapy vs renal revascularization in atherosclerotic renal artery stenosis.

Author/No. Patients	Inclusion/BP measurement	Outcome	Weaknesses/Limitations
The ASTRAL Investigators—  NEJM 361;1953, 2009  ASTRAL * N=806	“Uncertainty”-- “Patient’s doctor was uncertain”. Primary endpoint. 20% change in renal function.	No difference in BP, serum creatinine, mortality, CHF at 33 months (median).  20-22% renal event  49-51% Cardiovascular event	Enrollment bias: “uncertainty” not defined  Non-standard imaging 42% “<70%” 58% ≥70%  Nonstandard medical therapy  Only 335 of 403 patients assigned to stents treated  6% Crossover
Bax, et al: STAR *  Ann Int Med 150:840, 2009	RAS>50% Clearance <80 mL/min/1.73m2 Endpoint ≥20% change in clearance	No difference in rates of developing a fall in GFR between groups.  Med failure: 4/74 (46/64 randomized to stent were actually treated)	Minor disease 28% of assigned stent group not treated, mainly due to minimal stenosis
Uzzo, et all Transplant Proc. 34:723, 2002  N=52	High-grade stenosis entire renal mass (>75% stenosis) Creatinine ≤ 4 mg/dL	Stop points BP, doubling Cr ESRD, CV event or death.  Median f/u: 74mo: No difference between groups: 67% reached stop point.	Enrollment bias?  All patients required to be surgical candidates.
Van Jaarsveld, et al NEJM 342, 2000  N=106 ASO	Resistant: 2 drugs DBP>95 mm Hg or creatinine rise with ACEI RAS>50%  Exclusion: Creat ≥2.3 Solitary kidney/total occlusion Kidney <8 cm  BP automated oscillometric	No difference in BP outcomes at 3 mos between groups: Fewer drugs: 1.9 vs 2.4 in PTR A group p<.01  Creat Clearance (3 mos) ml/min: PTR A: 70 Med Rx: 59 (p=.03)  Abnormal renograms PTR A: 36% Med Rx: 70% (p=.002)  Renal artery occlusion PTR A 0 Med Rx 8	Large crossover for BP Control (44%)  Few/no stents.  Short follow-up.  Inadequate BP control in both groups
Plouin, et al Hypertension 31:822, 1998  N=49 (unilateral ASO)	<75 years Normal contralateral kidney RAS>75% or >60%, lateralizing study  Exclusion: Malig HTN CVA, CHF, MI within 6 mos  BP: Automated Sphygomanometer, ABPM at 6 mos	No difference in BP or Creatinine clearance between groups: Fewer drugs (DDD) in PTR A: PTR A 1.0 Med Rx: 1.78, p<.01	Excluded RAAS blockade.  27% crossover in Medical group  Enrollment selection bias (exclusion).



Author/No. Patients	Inclusion/BP measurement	Outcome	Weaknesses/Limitations
Webster, et al J. Human Hypertens 12:329, 1998 N=55 (unilateral=27) N=135 eligible	DBP $\geq$ 95, 2 drugs  Exclusion: CVA, MI within 3 mos: Creat>500(mcmol/L) RAS>50%  BP: Random Zero Device No ACEI allowed	No BP Difference in Unilateral ARAS:  Lower BP in Bilateral ARAS: PTRA: 152/83 Med Rx: 171/91 p<.01	Improved BP in bilateral disease.  Limited BP control by current standards.

DDD=defined daily doses

\* ASTRAL: = Angioplasty and Stent Therapy for Renal Artery Lesions

STAR = Stent placement in patients with Atherosclerotic Renal Artery Stenosis

Overview of prospective randomized trials comparing medical therapy for renovascular hypertension to percutaneous renal artery angioplasty (PTRA) with and without stenting or surgery. These studies contained selected patient populations that excluded highest risk groups. Each was different, but all found less blood pressure or renal functional benefits in interventional groups than reported from previous observational studies alone. These data highlight advances in medical therapy and relatively modest rates of renal functional loss for patients with limited disease. Crossover rates from medical to angioplasty arms were significant in the early trials mainly related to blood pressure control, however, and emphasize the importance of restoring blood supply in selected patients, particularly those with bilateral disease.

ASTRAL <sup>1</sup>

STAR <sup>85</sup>

Surgery: Uzzo <sup>86</sup>

Webster <sup>87</sup>

Plouin <sup>88</sup>

Van Jaarsveld <sup>89</sup>