European Heart Journal (2011) **32**, 1590–1598
doi:10.1093/eurheartj/ehq510

REVIEW

Controversies in cardiovascular medicine

Renovascular hypertension: screening and modern management

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Received 30 September 2010; revised 9 November 2010; accepted 16 December 2010; online publish-ahead-of-print 27 January 2011

The diagnosis and management of patients with renovascular disease and hypertension continue to elude healthcare providers. The advent of novel imaging and interventional techniques, and increased understanding of the pathways leading to irreversible renal injury and renovascular hypertension, have ushered in commendable attempts to optimize and finetune strategies to preserve or restore renal function and control blood pressure. Large randomized clinical trials that compare different forms of therapy, and smaller trials that test novel experimental treatments, will hopefully help formulate innovative concepts and tools to manage the patient population with atherosclerotic renovascular disease.

Keywords Atherosclerosis • Renovascular disease • Renovascular hypertension • Percutaneous transluminal renal angioplasty

Introduction

Major improvements in imaging, medical therapy, and techniques of renal revascularization have changed the landscape of renovascular disease during the past decade. This has been particularly true for renal artery stenosis (RAS) secondary to atherosclerosis, which remains one of the most common conditions that accelerate hypertension and might be incidentally detected. Despite, or perhaps because of, these developments, few clinical questions provoke more controversy and debate than the optimal management of patients with main RAS.

Prevalence

Recent studies have detected significant atherosclerotic RAS (ARAS), defined as a decrease of at least 60% in luminal diameter, in over 6% of persons aged over 65 years.[1] Its prevalence increases with age and in patients with known cardiovascular risk factors or atherosclerosis, and ranges from 30% among patients with coronary artery disease to 50% among elderly or those with diffuse atherosclerotic vascular diseases. Buller *et al.*[2] found RAS in 39% of 851 patients undergoing cardiac catheterization with resistant hypertension, renal impairment, flash pulmonary oedema, and/or atherosclerosis in other vascular territories, with ARAS $\geq$ 50 in 14.3 and $\geq$70 in 7.3% of patients. In the USA, 12–14% of new patients entering dialysis programs have ARAS, although its contribution to end-stage renal disease is unclear.[3]

Rationale for treatment

Stenosis of the renal artery (STAR) leads to hypertension and potentially to chronic renal failure. Despite successful reduction in deaths from cardiovascular disease, chronic kidney disease continues to increase, and the incidence of ARAS as underlying cause increases faster than any other cause.[4] Even when silent,[5] ARAS constitutes an independent risk factor for aggravation of cardiovascular disease,[6,7] which in turn is the leading cause for a rate of death of about 16%/year associated with ARAS. Increased risk of cardiovascular disease in ARAS patients may result from activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous systems, decreased glomerular filtration rate (GFR), or concomitant atherosclerosis in other vascular beds.[8]

Damage to intra-renal structures is a foremost contributor to renal impairment in ARAS patients, and the severity of histopathological damage is an important determinant and predictor of renal functional outcome.[9] Renovascular hypertension secondary to ARAS leads to higher rates of target organ injury compared with similar levels of essential hypertension[10] and to a greater decrease in

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renal function.[11] Therefore, there is a clear healthcare need to prevent deterioration of kidney function in the population. Indeed, an American Heart Association (AHA) Science Advisory[12] asserts that the poor prognosis associated with ARAS requires increased awareness of the disease and a need for early diagnosis, although to date no study has shown a benefit to early treatment for ARAS.

Aetiology and characteristics

The two most common primary diseases of the renal arteries are ARAS and fibromuscular dysplasia (FMD). Atherosclerosis accounts for ~90% of cases (*Table 1*) and usually involves the ostium and proximal third of the main renal artery and the perirenal aorta. Data on progression of ARAS are inconsistent, with progressive stenosis reported in 51% 5 years after diagnosis and annual occlusion rate of 5%/year in the 1990s.[13,14] In the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study, 8/50 lesions (16%) in the drug cohort progressed to occlusion within 1 year.[15] In contrast, in 1189 patients undergoing cardiac catheterization, disease progression occurred in 133 (11.1%) patients, but only 4 (0.3%) progressed to total occlusion.[16] In 119 elderly participants in the Cardiovascular Health Study, ARAS progressed at 1.3%/year at 8-year follow-up, but none occluded.[17]

Increased awareness for blood pressure control and number of patients taking statins might decrease the rate of progression nowadays.

Fibromuscular dysplasia is a heterogeneous group of idiopathic, segmental, non-atherosclerotic vascular diseases that affect the intima, media, and adventitia. Such lesions can be incidentally detectable in 5% of normotensive and 16% of resistant hypertensive individuals.[18] When haemodynamically significant, FMD most commonly affects women 15–50 years of age with normal kidney function.[19] Medial fibroplasia, characterized by its classic 'string of beads' appearance, represents the most common dysplastic lesion. The natural history of renal FMD is poorly defined. Progression was described in over 35% of patients, but larger size follow-up series are missing.

Rare aetiologies associated with the occurrence of RAS are large artery vasculitides, antiphospholipid syndrome, and mid-aortic syndrome. Takayasu's arteritis mainly affects the aorta and its major branches, and RAS is present in 26%.[20] Antiphospholipid antibodies affect all vascular districts, and 26% of patients with uncontrolled hypertension have RAS.[21] Mid-aortic syndrome, a rare congenital disease of the aorta and its branches, is associated with > 60% chance of RAS.

Table 1 Aetiology of renal artery stenosis and occlusion

Disease	Prevalence
Atherosclerotic renal artery disease	85–90%
Fibromuscular disease	~10%
Acute renal artery occlusion (thrombosis, embolism, trauma)	<2%
Aortic dissection with renal artery involvement	<1%
Takayasu/giant cell arteritis	<1%
Mid-aortic syndrome	Rare
Antiphospholipid syndrome	Rare

Diagnosis

Anatomic and haemodynamic

Major advances in vascular imaging allow easier non-invasive identification of vascular lesions than ever before. The threshold for performing imaging procedures depends primarily on the importance of excluding high-grade stenosis before proceeding to long-term medical therapy, and on the commitment to proceed with revascularization if needed. Magnetic resonance (MR) and computed tomography (CT) angiography provide detailed images of the aorta and renal arteries, often allowing identification of multiple vessels, estimation of renal size, and anatomy. The main limitation of all forms of angiography is lack of information on renal flow or pressure distal to RAS; e.g. a morphologically severe stenosis might not induce a pressure gradient if flow is slow due to renal parenchymal impairment. Doppler ultrasound (DUS) is operator-dependent but highly specific in competent laboratories, and while it provides minimal information about kidney function, it can provide reliable haemodynamic assessment of arterial lesions and identify structural abnormalities in the kidney size.

Definition of a functionally significant RAS that justifies revascularization remains unsettled. To cause hypertension, RAS should produce a severe enough pressure gradient between the aorta and afferent arterioles to upregulate renin production; a peak systolic pressure gradient >20 mmHg has been proposed.[22] The gradient is commonly measured simultaneously in the aorta and by a 4-F catheter distal to the lesion.[23] Because the catheter might obstruct flow, a more accurate, but costly alternative is a 0.014 in pressure wire. A 0.9 aorta to renal artery pressure gradient ratio corresponds to a systolic gradient ≈25 mmHg and defines functionally significant RAS documented by renin release in humans.[24]

Conventional catheter angiography

Intra-arterial digital subtraction angiography aims to confirm the diagnosis of RAS, evaluate the extent of intra-renal vascular disease, and identify associated aneurysmal or occlusive aortic disease. It offers the highest spatial and temporal resolution for anatomically visualizing main and branch arterial disease. A major advantage of invasive imaging is that haemodynamic significance can be directly measured and treated immediately. Guidelines for renal artery revascularization suggested that a significant ARAS is defined as a ≥ 50% diameter stenosis by visual estimation, associated with a peak translesional gradient ≥20 mmHg, or a mean gradient ≥ 10 mmHg.[22] Being invasive, however, conventional catheter angiography (CCA) has the highest risk including ionizing radiation and complications related to iodinated contrast and intervention. Conventional catheter angiography is also the most expensive in terms of financial cost and time, effort, and inconvenience for the patient.[25]

Recently, an AHA Science Advisory advocated screening CCA as part of cardiac catheterization on patients at high risk for ARAS who are potential candidates for revascularization.[12] Although non-selective 'drive-by angiography' is relatively safe and convenient, its usefulness remains questionable. Once diagnosed, many patients undergo revascularization, although it remains difficult to predict who would benefit from intervention.[26]

Discordance between high technical success of percutaneous transluminal renal angioplasty (PTRA) with or without stenting in patients with ARAS and moderate clinical response rates is partly explained by the limitations of angiography for the assessment of haemodynamic and functional significance of RAS. Using current criteria, a diameter stenosis > 50% by renal angiography falsely identifies RAS as significant in ~38% of cases compared with trans-stenotic pressure gradient measurements, where haemodynamic significance is defined as distal renal to aortic pressure ratio <0.9 (*Table 2*).[24]

Computed tomography

Advances in CT technology allow spiral multi-detector acquisitions that provide accurate anatomic images of small renal arteries. The median sensitivity and specificity of CT angiography (CTA) compared with CCA are 94 and 93%, respectively,[25] but it is less invasive, and offers faster acquisition, better soft tissue visualization, and multiplanar renal artery imaging. Its accuracy is comparable with MR angiography (MRA), but CTA has added risks of ionizing radiation and nephrotoxicity from iodinated contrast agents. Furthermore, severe renal artery calcification may obscure luminal narrowing, and the technique does not provide physiologic assessment of the stenosis.

Magnetic resonance imaging

Compared with CCA, MRA has median sensitivity and specificity of 92 and 93.5% without and 96 and 93% with gadolinium,[25] respectively. It provides high-quality noninvasive anatomic images of the renal arteries, and has become a common screening procedure (*Figure 1*). The variety of available pulse sequences offer comprehensive evaluation of the kidneys without markedly increasing scanning time or cost, but MRA is limited by frequent overestimation of the degree of stenosis, especially with less-advanced machines. A recent concern regarding the use of gadolinium-enhanced MRI is nephrogenic systemic fibrosis, with incidence of 1–6% for dialysis patients, and GFR < 30 mL/min was designated as a relative contraindication.

Table 2 Diagnostic performance of quantitative angiography and Doppler-derived parameters for identifying significant RAS (distal renal to aortic pressure ratio <0.90; adapted from ref.[24])

	Optimal cut-off value	Confidence intervals
Quantitative angiography		
Diameter stenosis	>61%	58–69
Minimal luminal diameter	<1.74 mm	1.58–2.52
Duplex sonography		
Peak systolic velocity	>320 cm/s	238–373
Renal aortic ratio	3.80	2.98–4.10

Optimal cut-off values and 95% confidence intervals (bootstrap procedure).

Duplex ultrasound

Doppler ultrasound is an ideal screening modality for ARAS, as it is noninvasive, radiation-free, low cost, and involves no contraindications due to renal failure or contrast allergy. It can be applied serially to monitor disease progression and allows direct measurement of physiologic patterns, like flow velocities and vascular resistance. However, commonly used criteria describing a stenosis > 60% may falsely identify significant RAS compared with trans-stenotic pressure gradients (*Table 2*).[24]

The major drawbacks of DUS are operator-dependence and lack of uniformity in diagnosis. Common pitfalls are failure to visualize the entire renal artery, accessory renal arteries, and missing the highest peak systolic velocity during spectral Doppler tracing.[27]

Peak systolic velocity > 200–320 cm/s[22,24] in the main renal artery associated with post-stenotic turbulence is most frequently used to determine relevant RAS and correlates with ≥60% angiographic RAS (*Figure 1*) with sensitivity and specificity of 71–98 and 62–98%, respectively. Another approach is to image the intra-renal interlobar or segmental arteries. A side to side difference of >0.05 of the resistive index is the most frequently used indirect duplex parameter (*Figure 2*), with specificity of 99% for the detection of at least 70% RAS and a sensitivity of 77%.[28] Other indirect parameters include missing early systolic peak, retarded acceleration, and increased acceleration time, which are less specific and ideally should be used to support the diagnosis based on peak systolic velocity.[29]

Radermacher *et al.*[30] reported that the resistance index by DUS provides a measure of parenchymal disease that can predict improved kidney function or blood pressure control after stenting, but others could not replicate these findings.[31]

Functional

Activation of the renin–angiotensin system

The link between activation of the RAAS and hypertension has evoked development of agents capable of blocking this system, such as angiotensin receptor blockers (ARB) or converting enzyme (ACE) inhibitors. Systemic RAAS activation appears to be transient in untreated individuals, and blood pressure subsequently sustained by alternative pressor pathways, such as oxidative stress and endothelial dysfunction.[32] Renin release results from a decline of kidney perfusion pressure associated with a trans-lesion gradient of 10–20%,[23] in turn resulting from a 70–80% decrease in luminal cross-sectional area.[33,34] Lateralization of plasma renin activity to the stenotic kidney suggests a haemodynamically significant stenosis.

Methods of measuring the RAAS response include renin sodium profiling, assessment of plasma renin activity before and after captopril, effect of ACE-inhibitors on blood pressure and renal

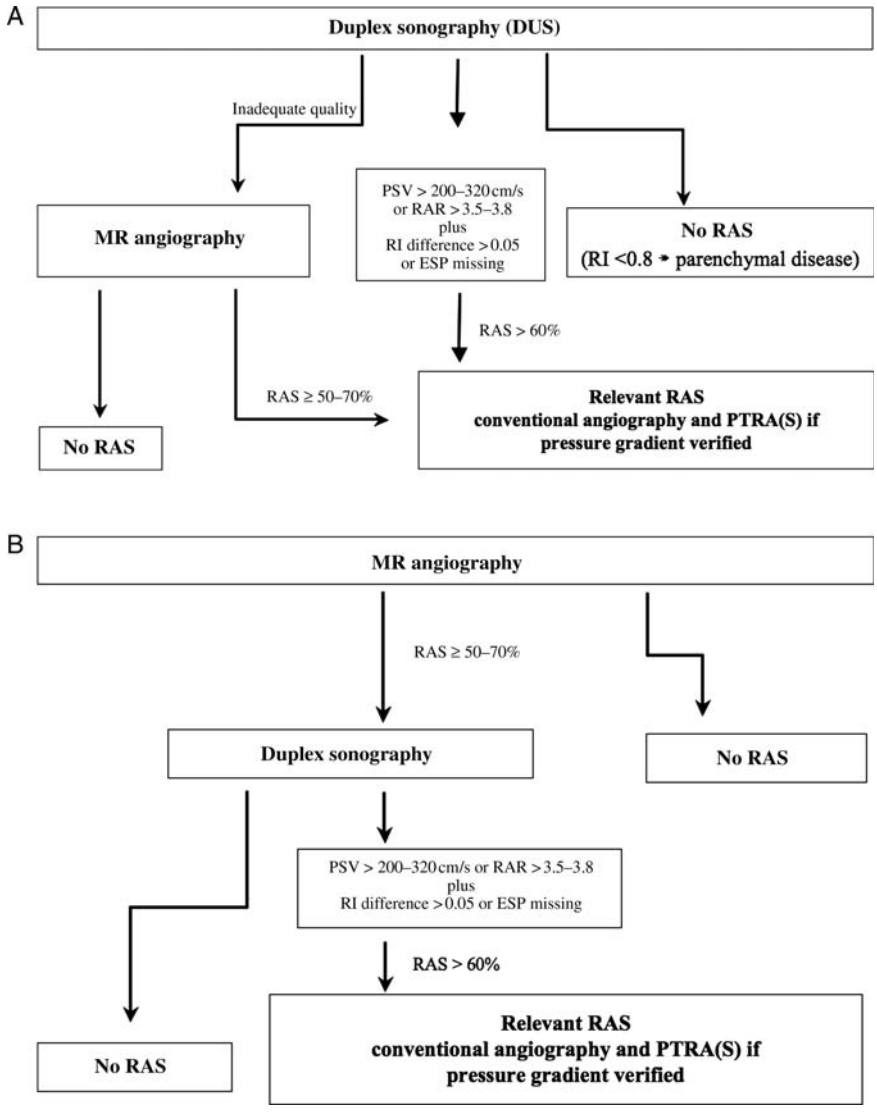

Figure 1 Flow chart of primary renal artery assessment using duplex sonography (*A*) or magnetic resonance (MR) angiography (*B*). RAS, renal artery stenosis; PSV, peak systolic velocity; ESP, early systolic peak; RAR, renal aortic ratio; RI, resistance index; RI difference, side to side; PTRA(S), percutaneous transluminal renal angioplasty (with stenting).

function, and captopril renography for differential renal perfusion. Captopril renography has lost popularity, as it has little predictive value and provides no direct visualization the renal vessels. However, it can assess the relative function of the kidneys in the presence of a unilateral high-grade stenosis.[34]

These RAAS tests are not recommended in most elderly patients with ARAS, in whom hypertension is often not renin-dependent and imaging techniques are preferable, but are more useful for identifying patients with FMD.

Tomographic imaging

Tomographic imaging techniques (MR, CT, and positron emission tomography) have several potential advantages for the assessment of ARAS beyond visualization of the renal artery. First, their cross-sectional capability allows assessment of both kidneys individually and simultaneously. Second, they can provide same session quantitative assessments of the haemodynamics and function of the post-stenotic kidney.

Both CT and MR have been validated for the assessments of renal blood flow and GFR. Computed tomography was used to assess renal functional reserve, tubular function, and endothelial function.[35,36] Positron emission tomography can quantify renal cortical perfusion[37] and metabolic activity; further studies are needed to realize its full potential.

An emerging MR technique to investigate the functional effects of ARAS on the kidney, Blood Oxygen Level Dependent (BOLD) MRI, assesses renal levels of deoxyhaemoglobin, and thereby indirectly renal oxygen content. Textor *et al.*[38] have shown that furosemide, which inhibits medullary tubular transport and oxygen consumption, decreases medullary deoxyhaemoglobin

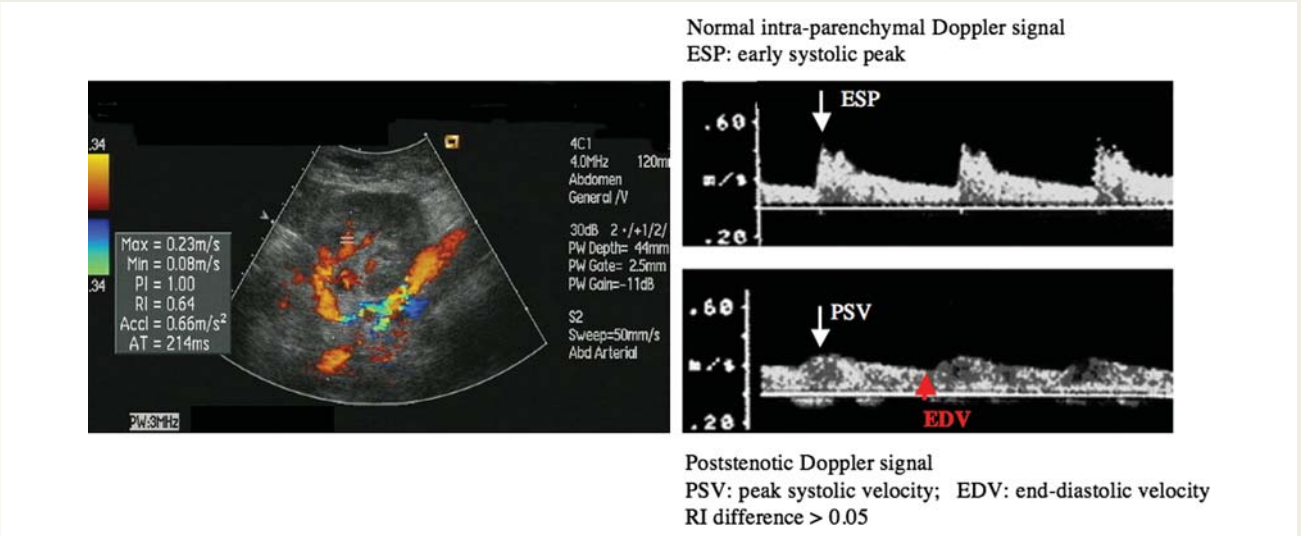

Figure 2 Relevant indirect Doppler criteria to diagnose renal artery stenosis (RAS). (Left) Intra-parenchymal colour Doppler spectrum. (Top right) Normal right intra-parenchymal Doppler spectrum. The early systolic peak (arrow) and normal acceleration time (time span between end-diastolic and systolic peak) indicate normal renal blood flow. Normal resistance index (RI; ratio of end-diastolic and systolic peak velocities) argues against parenchymal disease compromising blood flow. (Bottom right) Left-sided intra-parenchymal Doppler spectrum lacking early systolic peak, with increased acceleration time and a flattened Doppler spectrum. Side to side difference of the intrarenal RI > 0.05 indicates haemodynamically significant (>70%) RAS.

in normal nephrogram human kidneys, while atrophic kidneys distal to total occlusion did not respond (*Figure 3*), suggesting low viability. This technique offers much promise, as it involves no radiation or contrast agents.

The sophistication and wealth of information that tomographic imaging tools provide also underlie their high cost and limited availability, and their use is currently mostly experimental and confined to large medical centres.

Treatment

Various treatment regimens are effective for lowering blood pressure in ARAS patients, although kidney function may worsen over time.[39] Antihypertensive therapy was found to be effective at reducing blood pressure, but data on clinical outcome event rates were sparse or inconsistent across studies.[40,41]

Medical

Most patients with haemodynamically significant ARAS tolerate RAAS blockade without difficulty. However, ACE-inhibitors or ARB can reduce glomerular capillary hydrostatic pressure enough to cause a transient decrease in GFR and raise serum creatinine, warranting caution and close follow-up. Acute deterioration in renal function secondary to RAAS blockade might be observed mainly during renovascular obstruction of the entire renal mass, particularly in the presence of severe congestive heart failure, use of high-dose loop diuretics, volume contraction, and poor baseline renal function.[42] A significant (≥30%) fall in GFR (or >0.5 mg/dL rise in creatinine) may be an indication to consider renal revascularization.

Because ARAS is frequently accompanied by cardiovascular risk factors, it is imperative to manage them aggressively. Lowering lipid levels, smoking cessation, and maintaining acceptable glucose levels all require consideration.

Importantly, experimental and clinical evidence shows that damage to the kidney tissue and microcirculation by mechanisms, such as oxidative stress, microvascular loss, or enhance fibrogenic cascades, is a major determinant of renal outcomes, supporting the notion that interventions targeting renal injury pathways might constitute an adjunct or even alternative strategy to ensure adequate recovery. Interestingly, recent experimental studies have suggested that novel experimental approaches to treat the renal parenchyma directly, such as antioxidants,[36] statins,[43] and endothelial progenitor cells[35,44] (*Figure 4*), may decrease renal injury even without correcting the obstructive RAS lesion. Hence, revascularization of the stenotic renal artery may be less crucial that previously thought. Moreover, a recent pilot study showed that adding to the standard antihypertensive treatment after revascularization nebivolol, a new generation beta-blocker that releases nitric oxide, improved GFR, and proteinuria.[45]

Revascularization

Overall, both invasive and medical therapy may decrease blood pressure, but evidence weakly supports a conclusion that revascularization may result in better blood pressure control, particularly in subjects with bilateral disease. Evidence supporting benefit of aggressive diagnosis and timing of renal revascularization remains unclear. Patients treated with medical therapy alone risk deterioration of kidney function with worsening morbidity and mortality. Revascularization can provide immediate improvement in kidney function and blood pressure in selected patients, but carries a

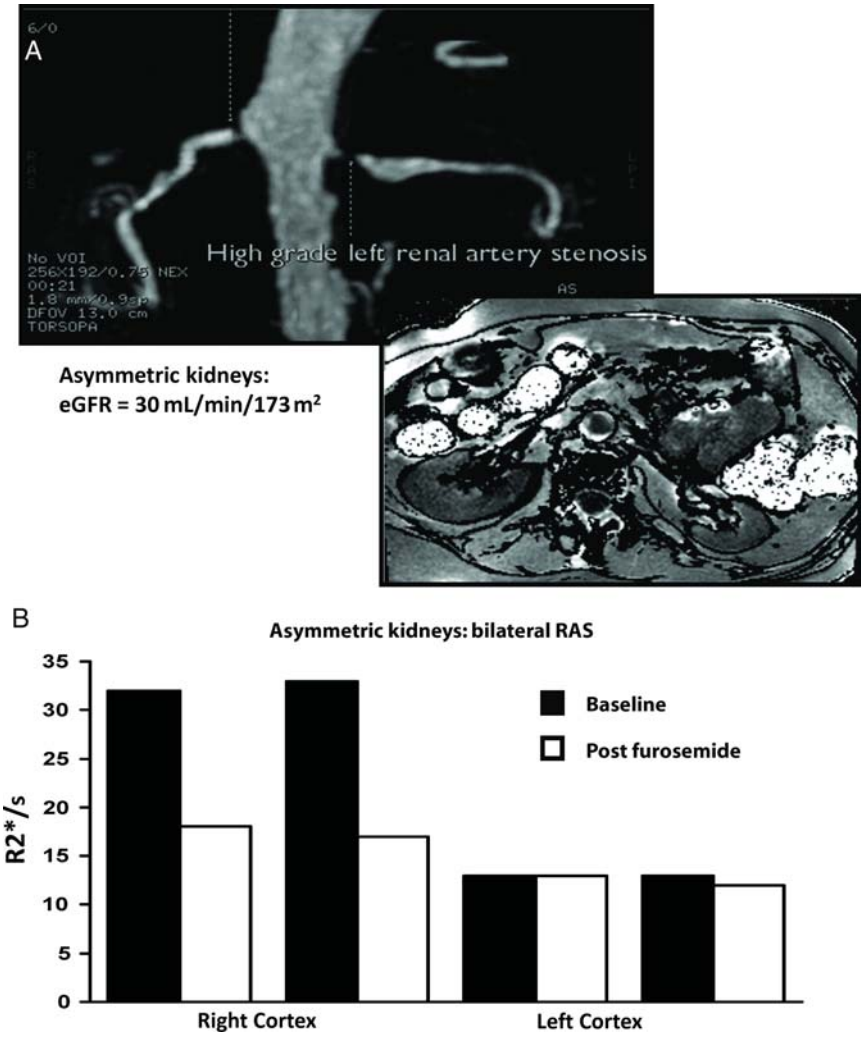

Figure 3 Magnetic resonance angiogram in a patient with bilateral RAS (*A*), more severe on the left. BOLD-MRI demonstrated low signal both before and after furosemide (*B*). The normal size right kidney had higher baseline signal that fell in response to furosemide, suggesting sustained oxygen consumption and tubular function. From ref.[38], with permission.

small risk for mortality or substantial morbidity.[46] In practice, costs and risks of both endovascular and surgical procedures limit their universal application, especially for renovascular lesions that pose no immediate hazard or risk of progression. A hyperaemic systolic gradient $\geq$21 mmHg seems to be the strongest predictor of hypertension improvement after stenting in hypertensive patients with unilateral RAS,[27,47] while diameter stenosis $>$ 50% by angiography and renal fractional flow reserve are not.

There is general consensus, but no robust evidence, that renal revascularization should be indicated in patients with anatomically significant RAS who present with clinical scenarios like sudden onset, 'flash' pulmonary oedema unrelated to acute coronary syndrome, congestive heart failure with preserved left ventricular function, and acute oligoanuric renal failure with global kidney ischaemia. Others feel that ARAS patients with multi-drug-resistant renovascular hypertension, advanced CKD (stages 4–5),[48] or steadily deteriorating renal function should undergo revascularization (*Table 3*, *Figure 5*). However, there is incomplete evidence to support its use in these situations, which is also true for the vast majority of ARAS patients who present with asymptomatic chronic kidney disease or hypertension and severe RAS.

Interventional

Interventional treatment involves conventional PTRA without or with stenting. Guiding catheter techniques are commonly employed, which involve the use of coronary or peripheral guide wires, balloon catheters, and pre-mounted stents. Treatment with aspirin before the procedure, and using low osmolar contrast media and heparin during the procedure, are recommended.[19] Dual 28-day antiplatelet therapy is standard of care in most institutions, translated from coronary interventions.

Conventional PTRA is considered the treatment of choice for patients with uncontrolled hypertension and FMD. The procedure is successful in 82–100% of patients, and stenosis recurs in

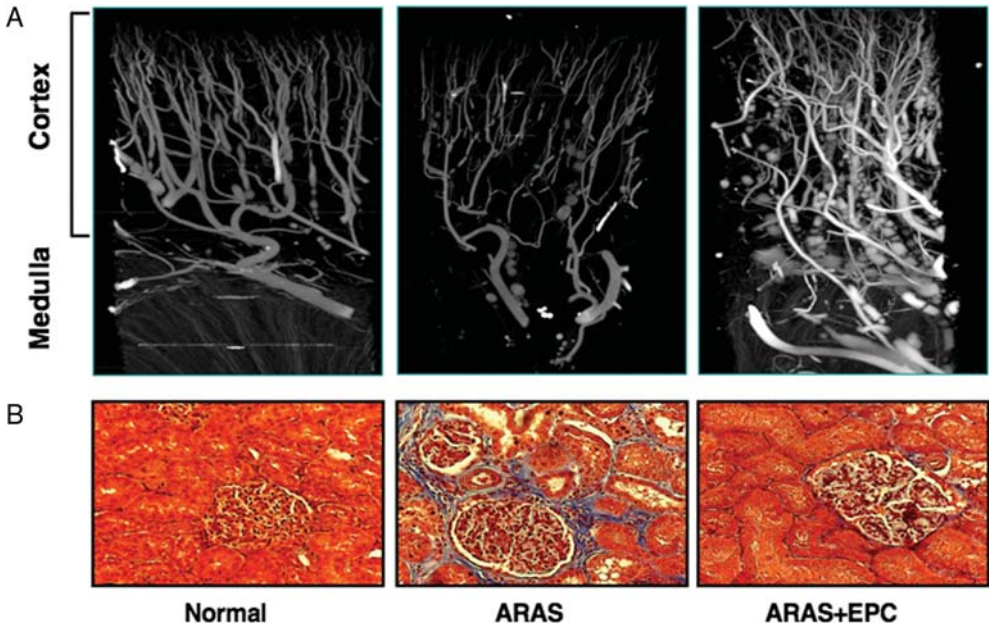

Figure 4 Representative micro-CT images of the swine kidney microcirculation (*A*) and fibrosis (*B*, trichrome staining, ×20) in normal, atherosclerotic RAS (ARAS), and ARAS pigs treated with intrarenal endothelial progenitor cells (EPC) 4 weeks earlier. EPC delivery increased microvascular density in the stenotic kidney without the need for revascularization. From ref.[35], with permission.

10–11%.[49,50] It is less effective for ARAS, because of the potential for dissection and elastic recoil in ostial lesions, with restenosis incidence of 10–47%.[51] Introduction of stents has extended the efficacy of endovascular techniques to technical success of 94–100%, residual diameter stenoses <10%, and restenosis rates of 11–23% at 1 year.[52] The timing of revascularization remains controversial. With poor evidence from randomized trials, some do not advocate its use unless there is bilateral RAS and creatinine elevation, but preceding serum creatinine concentration elevation might be a better approach.[19] The risk of death rises two—threefold for each 88 μmol/L increment in the baseline creatinine level, a major determinant of postoperative renal failure.[53] Baseline creatinine concentration >130 μmol/L is the strongest independent predictor of death within 4 years after renal stenting.[54]

Comparison of angioplasty with medical treatment of atherosclerotic renal artery stenosis

Two randomized controlled trials (RCT, level II evidence) compared PTRA to medical treatment with ≥ 6 months of follow-up,[15,55] but were underpowered for clinical outcomes including mortality, cardiovascular, and kidney events. Stents were used rarely and medical therapies varied both between and within studies. The EMMA trial investigators concluded that PTRA in unilateral ARAS has some drug sparing potential, but that its potential for lowering blood pressure was overestimated.[15,55] DRASTIC showed no significant differences between the angioplasty and drug therapy. Twenty-one cohort studies (uncontrolled, level IV evidence) of PTRA plus stenting (PTRAS) published before 2007 showed no unifying pattern regarding mortality rates. Several found that patients remained at increased risk of cardiovascular disease after PTRAS.[49] In contrast to medically treated patients, some patients showed improved kidney function. Cure, improvement, or worsening of arterial hypertension ranged 4–18, 35–79, and 0–13%, respectively. Some studies reported reduction in the New York Heart Association Functional Class after stent placement in patients with either bilateral disease or stenosis to a solitary functioning kidney.[56] Individual patient categories, such as those with congestive heart failure and pulmonary oedema, showed benefit from renal revascularization.[50] An updated comparative effectiveness analysis of studies was published in 2007.[46]

Table 3 Indications for renal revascularization

Resistant hypertension
Failure of medical therapy despite full dose of ≥3 drugs, including diuretics
Compelling need for ACE-inhibition/ARB with angiotensin-dependent GFR
Progressive renal insufficiency
Salvageable kidneys
Recent rise in serum creatinine
Loss of GFR during antihypertensive therapy, e.g. ACE-inhibition/ARB
Circulatory congestion, recurrent 'flash' pulmonary oedema unrelated to acute coronary syndrome
Refractory congestive heart failure with bilateral renal artery stenosis

GFR, glomerular filtration rate; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockade (adapted from ref.[67]).

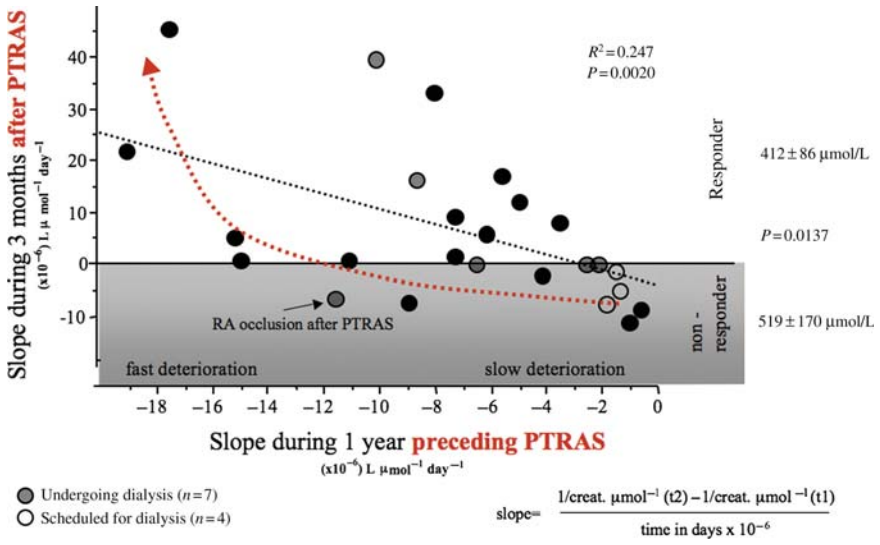

Figure 5 Relationship between changes in slope values of reciprocal serum creatinine plot vs. time before (1 year) and after (3 months) percutaneous renal artery (RA) angioplasty with (PTRAS) or without stenting. Three patients who died within 30 days after PTRAS were excluded. Adapted from ref.[68]

Major randomized controlled trials

The angioplasty and stenting for renal artery lesions (ASTRAL) trial is so far the largest published RCT to compare PTRAS combined with medical therapy to medical therapy alone for improvement in renal function.[57] In 806 patients with ARAS, differences in renal function, blood pressure, kidney, and cardiovascular events, and mortality were all unimpressive. The decline in renal function over time was slightly slower in the revascularization group, but not statistically significantly. The medical management group required a slightly higher number of antihypertensive drugs, reaching statistical, but not clinical significance.

There are several caveats associated with the ASTRAL trial, the most significant among which is selection bias. Patients were enrolled if they had substantial anatomical atherosclerotic stenosis in at least one renal artery that was considered potentially suitable for endovascular revascularization, and if the patient's doctor was uncertain that the patient would definitely have a worthwhile clinical benefit from revascularization. Both the method of revascularization and medical therapy regimen were left to local investigators and consequently were varied and poorly defined. Moreover, despite poor reliability of visual estimation of stenosis severity, there was no central core laboratory to review angiographic studies.

The stent placement and blood pressure and lipid lowering for the prevention of progression of renal dysfunction caused by atherosclerotic ostial STAR study is a European multicentre trial, aimed to detect a $\geq$20% decrease in creatinine clearance. At 2 years, the primary endpoint had been reached in 16% of the patients in the stent group and 22% in the medication group, a non-statistically significant and inconclusive difference, given the wide confidence intervals. No difference was observed in secondary endpoints (blood pressure control, cardiovascular morbidity, and death).[58] This largely underpowered trial showed that renal function deterioration might progress despite successful revascularization, underscoring the complex cause of ischaemic nephropathy with an important parenchymal component affected by atherosclerosis risk factors. However, STAR enrolled a third of patients with RAS $<$70%, and a quarter did not receive the assigned treatment but were analysed as treated due to the intention to treat study design. Moreover, it showed that if technical skill is insufficient, a considerable number of stent-related complications can occur and may cause more harm than benefit in a community setting. Whether revascularization is indicated in patients presenting with acute renal injury, severe RAS and sudden onset pulmonary oedema unrelated to acute coronary syndrome, rapidly deteriorating renal function, renal function deterioration with the RAAS blockade, or unilateral RAS and contralateral occlusion of the renal artery,[59] was answered by neither trial.

The vascular community now awaits results from the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, which tests the hypothesis that stenting ARAS $>$60% (pressure gradient $>$ 20 mmHg) in patients with systolic hypertension reduces the incidence of cardiovascular and renal events.[60] To date, no major differences in patient survival were evident between patients subjected to surgical vs. endovascular procedures, although few randomized trials have addressed this issue directly. Resolution of this issue with current patient demographics and optimized medical therapy is a major objective of the CORAL study. Unlike ASTRAL and STAR, CORAL is studying patients with difficult to control hypertension and systolic blood pressure $\geq$155 mmHg on two or more drugs. Chronic kidney disease is not an exclusion criterion unless serum creatinine concentration is $>$ 3.0 mg/dL.

RADAR is another ongoing, prospective, multi-centre trial to evaluate the clinical impact of PTRAS on impaired renal function in patients with $\geq$70% ARAS.[61] Three hundred patients will be

randomized to best medical treatment vs. best medical treatment plus PTRAS. Hopefully, CORAL and RADAR will help answer remaining questions. Indeed, unless the CORAL trial reveals clear benefit of intervention, the future of PTRAS is in doubt, although most clinicians believe a subgroup of patients do benefit from revascularization.

Drug-eluting stents and distal embolic protection devices

Currently, the only completed study on drug-eluting stents (DES) in ostial ARAS is the GREAT trial,[62] which compared sirolimus DES to bare metal stents in 102 patients. Relative risk reduction in angiographic binary renal artery in-stent restenosis was 50%, which was statistically insignificant (7 vs. 14%, $P = \text{ns}$), because the study was underpowered. In-stent stenosis, binary restenosis rates, late lumen loss, and repeat revascularization were all lower in the DES group. At present, DES are manufactured solely for use in coronary vessels, and the sirolimus DES is not commercially available. Given the lack of outcome data, considerable expenses, and cost associated with post-procedure need for long-term antiplatelet therapy with aspirin and clopidogrel, widespread use of DES is not recommended.

The contribution of distal embolization to worsening renal function after stenting has grown interest in using embolic protection devices (EPD). RESIST, a randomized phase II trial in 100 patients plus a glycoprotein IIb/IIIa inhibitor in a 2×2 factorial design,[63] demonstrated no overall improvement in GFR with the use of a filter-based EPD, perhaps because of increased platelet aggregation or escaped renal atheroemboli associated with the device. The rate of platelet-rich emboli was 50% with neither abciximab nor a thienopyridine, 36% with thienopyridine only, 15% abciximab only, and 0% in patients who received both. The aim of the study, small sample size, and non-randomization of thienopyridine use limit more general conclusions regarding antplatelet therapy.[64]

Surgical revascularization

Renal artery surgery offers major benefits for patients undergoing surgical repair of the aorta or nephrectomy, and for patients with complex disease of the renal arteries, e.g. aneurysms or failed endovascular procedures. Surgical procedures may include renal artery bypass grafting, endarterectomy, or occasionally extra anatomic repair using anastomosis to the hepatic or splenic arteries. Thirty-day mortality rates range between 3.7 and 9.4%[46] and is increased by the need for aortic reconstruction or bilateral renal bypass, severe preoperative azotemia, and the use of an aortic graft for aortorenal bypass. Early graft failure that occurs in 1.4–10%[65] is the strongest independent predictor of perioperative death. The major arguments against surgical revascularization include a higher mortality linked to surgery in patients with co-morbidities and the similar outcome benefits of endovascular repair.

Revascularization in fibromuscular dysplasia

Fibromuscular dysplasia predominantly affects young women with normal kidney function, so that renal artery revascularization is expected to be relatively successful. No RCTs or comprehensive systematic reviews assessed blood pressure outcomes in patients with FMD. However, a recent meta analysis on the effect of revascularization in patients with FMD included 50 studies concerning PTRA and 25 concerning surgery.[66] Hypertension was cured after PTRA or surgery in 46 and 55% of patients, respectively, with large variations across studies. The probability of cure was negatively associated with age, hypertension duration, medial-type FMD, time of publication, and more stringent definitions of cure. Cure rates after PTRA or surgery based on current definition (blood pressure $<$140/90 mmHg without treatment) were only 36 and 54%, respectively. The risk of periprocedural complications was substantial, and tended to be lower after PTRA, but selection criteria may have differed between study populations. Advances in vascular imaging and more liberal advice to undergo PTRA in patients with renal FMD and hypertension may explain the disappointing blood pressure control in more recent publications.

Conclusions

The indications for revascularization of the renal arteries are the subject of continuing controversy. Based on the results of the STAR and ASTRAL trials, the practice of indiscriminately revascularizing ARAS is no longer tenable. The challenge is to identify those selected patients who would respond, and to intervene early enough to reverse kidney damage. Intervention is not recommended if renal function has remained stable over the past 6–12 months and if hypertension can be controlled with an acceptable medical regimen. Anatomically relevant RAS $>$70% should be verified by functional measurements as systolic pressure gradient $\geq$21 mmHg or Pd/Pa pressure ratio $<$0.9. The best evidence supporting intervention seems to be for bilateral stenosis with 'flash' pulmonary oedema unrelated to acute coronary syndrome, but the evidence is from retrospective studies. Indeed, in patients with ARAS, control of hypertension may be facilitated by revascularization, but cure of hypertension is unusual, and preservation of renal function may be a more realistic goal. The choice of revascularization technique depends on the presence of associated aortoiliac diseases. For complicated cases, surgical revascularization and renal bypass are both acceptable. Novel approaches to attenuate kidney tissue injury and increase its viability regardless of revascularization may prove vital and are under investigation.

Funding

Partly supported by NIH grant numbers HL085307, DK77013, HL77131, and DK73608.

Conflict of interest: none declared.

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