Renal failure in atherosclerotic renovascular disease: pathogenesis, diagnosis, and intervention

R G Woolfson

Atherosclerotic renovascular disease (ARVD) is increasingly recognised as an important cause of both chronic and end stage renal failure. These patients tend to do badly on dialysis, which reflects their systemic atherosclerotic burden. In an effort to delay and perhaps prevent their need for renal replacement therapy, some patients are subjected to a variety of medical, radiological and surgical interventions, although evidence for each is sparse. The purpose of this review is to describe the epidemiology and pathophysiology of renal failure in ARVD, discuss the available diagnostic techniques, consider the evidence for benefit from intervention in the context of pathogenesis and finally, identify those gaps in our knowledge which impede the practice of evidence based medicine.

Epidemiology of ARVD

The prevalence of ARVD in patients with chronic renal failure is not known but dialysis registry data provide some epidemiological information about ARVD among patients who develop end stage renal failure (ESRF). Over a 20 year period in an American haemodialysis unit, Mailloux et al reported a 16% incidence of ARVD among new patients with a median age of 70 years (range 37-86 years). Similarly, in an 18 month retrospective study in a UK haemodialysis unit, Scoble et al reported a 14% incidence of ARVD among patients over the age of 50 years. ESRF patients with ARVD generally present with substantial comorbidities and have a poor prognosis on dialysis. Given their poor prospects, many patients may not be offered dialysis and therefore these figures are likely to underestimate the true incidence of the disease. These studies do identify age as a risk factor for ARVD and a cause for ESRF. Consistent with this, in a series of 133 hypertensive patients with chronic renal failure (mean (SD) creatinine clearance 51(26) ml/min) not due to glomerulonephritis or polycystic kidney disease, the incidence of atherosclerotic renal artery stenosis (ARAS) was shown to rise progressively with age (see fig 1). The prevalence of ARAS in patients who are undergoing investigation for atherosclerosis is in proportion to their burden of extrarenal disease (see fig 2). Therefore it is much higher in patients with aortoiliac disease than in patients undergoing coronary angiography, in whom cardiac pain may be the result of a relatively small burden of atherosclerosis but with a particularly critical distribution. This relationship is confirmed by studies that have reported the prevalence of extrarenal vascular disease in patients with proved high grade ARAS. Louie et al investigated the prevalence of carotid and peripheral vascular disease in 60 patients with ARAS graded as greater than or less than 60%. In the less severe group, 25% and 50% of patients were affected by carotid and peripheral vascular disease respectively increasing to 46% and 73% for those with ARAS exceeding 60%. Given that diabetes mellitus is a risk factor for systemic atherosclerosis, it is not surprising that it is also associated with an increased prevalence of ARAS.

The true incidence of ARVD may also be underestimated as a result of its varied presentation which includes the patient with recurrent “flash” pulmonary oedema. The diagnosis may be suspected in an elderly uraemic arteriopath with a normal urinary sediment and absent proteinuria, however, the presence of proteinuria, even up to nephrotic range, with or without evidence of glomerular bleeding, does not exclude the diagnosis.

Progression of ARAS

Reported rates of progression of ARAS vary between 18% and 53% over mean follow up periods which range from 24 to 52 months. The risk of progression appears to be determined by the severity of disease at the time of diagnosis. Zierler et al used serial duplex Doppler scans to show that 8% of normal arteries developed a stenosis exceeding 60% at three years whereas 48% of those with a significant but not critical (that is, <60%) stenosis at baseline progressed. The reported incidence of complete occlusion ranges from 7% to 16% and this tends to affect kidneys with baseline stenoses exceeding 60% in patients with bilateral disease.

Aside from baseline severity, the identification of other risk factors for progression of ARAS remains contentious and does not explain why only some stenoses progress. Some studies report no correlation with blood pressure, BMI, smoking, diabetes or cholesterol levels. This lack of consistent findings makes it difficult to target those patients who are at greatest risk of progression of ARAS. The progression of ARAS appears to be related to the severity of atherosclerosis. The risk of progression increases with age, diabetes, male gender, hypertension, hypercholesterolaemia, obesity and smoking, as well as the severity of atherosclerosis. The risk of progression appears to be determined by the severity of disease at the time of diagnosis. Zierler et al used serial duplex Doppler scans to show that 8% of normal arteries developed a stenosis exceeding 60% at three years whereas 48% of those with a significant but not critical (that is, <60%) stenosis at baseline progressed. The reported incidence of complete occlusion ranges from 7% to 16% and this tends to affect kidneys with baseline stenoses exceeding 60% in patients with bilateral disease.
pressure, smoking, diabetes mellitus, hyperlipidaemia, or the presence of coronary or peripheral vascular disease.\textsuperscript{11} 12 16 In contrast, Crowley et al reported that age, female gender, hypertension, severity of coronary disease, and ARVD at baseline were independent variables for progression of ARAS in 1214 patients with a mean follow up of 2.59 years.\textsuperscript{17} Data which suggest that the rate of stenosis progression is falling, perhaps secondary to better control of hyperlipidaemia or hypertension, are not convincing.

Development of renal atrophy
The important adverse outcome in ARAS is the development of renal atrophy and dysfunction which may result directly from the stenosis, as occurs in patients with fibromuscular dysplasia (FMD).\textsuperscript{11} In 85 patients with ARAS who underwent repeated angiography, Schreiber et al noted progression of stenoses in 44% of kidneys, although renal atrophy (reduction in renal length $\geq 1.5$ cm) affected 70%.\textsuperscript{11} When patients without progressive stenoses ($n=48$) were considered separately from those with progressive stenoses ($n=37$), renal atrophy and increased creatinine were significantly more likely in the progressive group but even so, approximately one quarter of the non-progressive group also demonstrated worse function and renal atrophy. This study provides strong evidence that progressive parenchymal injury and renal dysfunction reflects not just progress of the underlying stenosis but also another pathological process.

Two subsequent studies have confirmed the relationship between severity of ARAS and risk of renal atrophy. Guzman et al performed repeated duplex Doppler at six monthly intervals in 54 patients with ARAS over a mean follow up period of 44 months.\textsuperscript{17} Renal atrophy (exceeding 1 cm) was not observed in kidneys with baseline ARAS less than 60%, but by 12 months had affected 26% of kidneys with baseline ARAS exceeding 60%. When patients were subdivided into those with unilateral or bilateral ARAS, then the 12 month risk of atrophy was 13% and 43% respectively. Similarly, Caps et al reported a 24 month cumulative incidence of renal atrophy (exceeding 1 cm) of 5.5% in those with no baseline ARAS, 11.7% in those with stenoses less than 60% and 20.8% in those with stenoses exceeding 60%.\textsuperscript{18}

The development of renal atrophy in non-progressive ARAS could be due to vascular dysfunction in the intrarenal microcirculation distal to the stenosis rather than hypoperfusion secondary to a critical stenosis. Lerman et al used electron beam computer tomography to measure whole kidney, cortical and medullary blood flow in 42 patients with ARAS, FMD, or essential hypertension who had previously undergone renal angiography and were matched for blood pressure and baseline creatinine.\textsuperscript{19} Even when corrected for renal volume, whole kidney perfusion and cortical perfusion were significantly less in the ARAS group compared with the groups with FMD or essential hypertension ($p<0.05$), although medullary blood flow was conserved. Consistent with this evidence of abnormal cortical perfusion in ARAS, whole kidney and cortical blood flow correlated significantly with the degree of renal artery stenosis in the FMD group but not in the patients with ARAS. Similar results were reported by Tullis et al who used duplex Doppler to show bilateral abnormal renal haemodynamics in patients with unilateral ARAS exceeding 60%.\textsuperscript{20} Farmer and colleagues have explored the relationship between ARAS and renal function.\textsuperscript{21} Seventy four patients with angiographically proved ARAS underwent simultaneous estimation of isotopic glomerular filtration rate (GFR) and DMSA scintigraphy to accurately calculate individual kidney function. A significant correlation ($r=0.016$) was demonstrated between the degree of stenosis and the GFR of the affected kidney, but there was no significant difference in GFR between paired kidneys when only one was stenosed. Ostensibly, this study provides further evidence to support a relationship between renal function and degree of stenoses. However, given that renal function is similarly reduced in both stenosed and non-stenosed kidneys, it could also be concluded that there is an underlying systemic process which affects parenchymal function of both kidneys and which is also responsible for the ARAS. This conclusion is consistent with a recent report that the severity of renal dysfunction did not correlate with the severity of stenosis in 63 patients with ARAS.\textsuperscript{22}

CONCLUSION
The presence of progressive ARAS is an important risk factor for the development of renal atrophy and dysfunction. However, evidence that renal atrophy and dysfunction can develop in the absence of progressive stenosis is also compelling. It is essential that diagnostic techniques and therapeutic strategies should recognise both these processes.
Investigation of the patient with ARAS

A variety of techniques are available to diagnose ARAS. These include renal arteriography, ultrasound with duplex Doppler, magnetic resonance angiography, and captopril scintigraphy.

Renal arteriography has long been considered the gold standard investigation despite the risks of radiocontrast nephropathy and the precipitation of cholesterol emboli syndrome. Significant morbidity and mortality make this investigation a relatively unattractive screening test, especially in an aging patient group with increasing comorbidities and a high prevalence of non-insulin dependent diabetes mellitus.

Ultrasound can measure renal length to provide evidence of renal asymmetry or aortic atherosclerosis, which may suggest the possibility of ARAS. Some departments routinely undertake duplex Doppler, although the technique is difficult and time consuming. Reproducibility varies significantly from centre to centre and even in expert hands, may be unsuccessful in up to 20% of patients. Common pitfalls include obscuration of vessels by overlying bowel gas and shadows, poor control of angle of beam, insensitivity to stenoses less than 50%, inability to differentiate between severe stenosis and occlusion, and failure to detect accessory vessels. The development of intravascular ultrasound may usefully characterise atherosclerotic plaques, but the technique is likely to be associated with the same complications as any other intervention.

Magnetic resonance angiography is fast becoming the new gold standard investigation, especially with dynamic non-nephrotoxic contrast medium infusion (gadolinium) which has reduced signal loss due to saturation and turbulence. Recent technical developments have significantly improved the speed of data acquisition, quality of images and diagnostic sensitivity, but examinations remain lengthy and claustrophobic for patients. In contrast to angiography, radiographers can complete the investigation, although the computer reconstruction is highly skilled.

Captopril scintigraphy is commonly used in non-uraemic patients with renovascular hypertension and is of proved efficacy in both diagnosis and also prediction of blood pressure lowering outcome after intervention. However, careful patient preparation is critical: angiotensin converting enzyme (ACE) inhibitors, angiotensin II blockers, and diuretics should be discontinued (which may be dangerous in a patient with heart failure), and the patient should be fasted but adequately hydrated. The safety of administration of a single dose of captopril (25 mg or 50 mg) in patients with high grade ARAS is unclear, although the risk of acute renal failure from therapeutic ACE inhibition is well recognised. A variety of isotopic tracers are available of which the technetium labels, and in particular Tc-MAG3, give the best images in patients with renal impairment. A variety of diagnostic criteria are used and include changes in divided function, the time activity curve, and residual cortical activity. In general, the inclusion of more criteria (and performance of scans before and after captopril) increases diagnostic sensitivity but there is still marked observer variability. False negatives may occur in patients with single kidneys, segmental stenoses, or bilateral disease.

Although widely reported in non-uraemic patients with renovascular hypertension, there are few data regarding the use of captopril scintigraphy to diagnose ARAS in uraemia. Datseris et al undertook captopril MAG3 renography in 41 patients with a GFR less than 41 ml/min/1.73m². Seven patients were categorised as being at high risk of significant ARAS and this was confirmed in five of these patients who subsequently underwent angiography. The authors noted that scintigraphy findings tended to be non-specific when the GFR was less than 10 ml/min/1.73m² or if the divided function was less than 10%.

A few studies have compared these different investigations in patients with ARAS and mild renal failure. Kaplan-Pavlovic and Nadja compared duplex Doppler with captopril scintigraphy in 28 patients with a mean blood pressure of 175/106 mm Hg of whom 36% had a creatinine greater than 120 µmol/l. Using angiography as gold standard, they reported no difference in sensitivity, specificity, positive predictive value or negative predictive value between these tests. In another study of 89 patients (mean blood pressure 169/96 mm Hg, creatinine range 60–800 µmol/l) with angiographically proved ARAS exceeding 60%, the sensitivity and negative predictive value of magnetic resonance angiography (97% and 98%, respectively) exceeded that of duplex Doppler (81% and 88%, respectively).

CONCLUSION

The lack of comparative data regarding these different diagnostic techniques in patients with renal failure is disappointing. But it seems likely that, although currently limited by availability, magnetic resonance angiography is destined to replace both contrast angiography and captopril scintigraphy as the investigation of choice in the patient with ARVD. What nuclear medicine might be best positioned to offer is a scan which can discriminate renal dysfunction secondary to critical stenosis from dysfunction due to oblitative microvascular disease, perhaps similar to those developed for hibernating myocardium. Until then, measurement of renal size, individual kidney GFR, and renal biopsy are the only ways to ascertain that renal tissue is viable and that the consideration of revascularisation is worthwhile.

Revascularisation in patients with ARAS

Current aims of revascularisation include recovery or preservation of renal function and the treatment of resistant hypertension. But given the expanding indications for and benefits from ACE inhibition (and angiotensin II receptor blockade) in cardiovascular disease, the demand for interventions which reverse angiotensin II dependent renal dysfunction is set to increase. Interventions commonly undertaken to treat patients with ARAS include a variety of surgical procedures, angioplasty...
(PTRA) and PTRA with stent deployment (PTRAS). There are few randomised prospective data comparing any of these interventions with one another or even with “best” medical management; the history of intervention in this disease has largely been driven by technical development.

Current criteria for intervention in a stenosed kidney include renal size, with bipolar length less than 8 cm frequently used as a cut-off for revascularisation. In some centres, renal biopsy is used to differentiate ischaemic but recoverable renal parenchyma from irreparably damaged tissue. Measurement of the single kidney GFR allows the clinician to quantify the functional contribution from a stenosed kidney and by comparison with the contralateral kidney may help differentiate between dysfunction due to the ARAS as opposed to more generalised microvascular obliteration. Anecdotal reports of the rescue of patients with progressive ARAS from dialysis by revascularisation suggest that these criteria are best used in combination.

SURGERY
A full discussion of surgical procedures is beyond the scope of this review but anecdotal reports suggest that surgery which bypasses the grossly diseased aorta may offer better results, perhaps by reduction of atheroembolic events. Renal outcomes after surgical revascularisation have been reported by several groups over the last 20 years.29 These show improved renal function in 50% (range 22%–77%) of patients, stable function in 30% (range 12%–53%), worse function in 20% (11%–44%), and an overall surgical mortality up to 17%. Patient selection is critical with analyses indicating much greater risk for elderly patients, with different determinants of survival at 30 days (ischaemic heart disease, congestive cardiac failure, and cerebral vascular disease) compared with 90 days (preoperative renal function, age, and presence of an abdominal aortic aneurysm).30

ANGIOPLASTY (PTRA)
After PTRA, studies report that about 40% of patients have improved renal function with the remainder split equally between stable or worse function.31 One very informative study reported that renal function outcome at three and 12 months after PTRA depended on the mean creatinine before intervention.32 As with surgery, results were not at all encouraging in those patients with poor baseline function (mean creatinine 461 µmol/l) of whom over 50% had either worse function or required dialysis at 12 months (see fig 3).

PTRA PLUS STENT DEPLOYMENT (PTRAS)
The development of the stent has allowed interventional radiologists to attempt treatment of more severe atherosclerotic lesions, particularly those extending from the renal ostia. Perhaps as a result of this different case selection, results appear less satisfactory and only 27% (range 15%–36%) of patients have improved renal function, 52% (range 29%–91%) stable function, and the remaining 21% (range 0%–45%) worse function.33 34 PTRAS is associated with a vigorous inflammatory reaction and average restenosis rates of 13% (range 9%–25%) have been reported during follow up (range 12–24 months).33 34

CONCLUSION
These studies do not provide overwhelming encouragement to intervene in ARAS but ostensibly indicate that surgical reconstruction is the best option; however, this is likely to reflect case selection and the use of stents in patients with ostial stenoses which are usually a marker of more advanced atherosclerotic disease. A recently published comparison between PTRA and PTRAS has shown improved patency rates in stented arteries, although this was not associated with functional benefit.35 This mismatch between technical success and functional outcome has previously been reported,36 37 and provides evidence of on-going parenchymal injury, presumably due to continuing uncontrolled atheroembolic disease from proximal unstable atherosclerotic plaques; such reports question the contribution of the stenosis per se to renal dysfunction in ARAS. Even if function is improved, there is only very limited evidence to suggest that renal atrophy which is due to a proximal stenosis can be reversed by intervention.38 Most studies report improved blood pressure and reduced dosage of antihypertensive medication after intervention, however, the need for medication is rarely abolished and any benefit is not usually sustained.39 40

Medical interventions
A recent retrospective study from the Mayo Clinic has suggested that long term effective management of hypertension and renal function can be achieved in patients with unilateral ARAS.41 In contrast, overall mortality and kidney function were worse in medically managed patients with bilateral ARAS or ARAS in a single kidney,42 which is consistent with a previous report of 38% two year mortality in patients with bilateral ARAS managed medically.43 Although specific evidence of benefit is absent, medical interventions routinely applied to patients with ARAS include the prescription of aspirin and active management of conventional risk factors such as hypertension, dyslipidaemia, diabetes mellitus, and cessation of
smoking. There are also no data regarding specific risk factors in uraemia, such as hyperhomocysteinaemia, increased oxidative stress, or endogenous inhibitors of nitric oxide synthase. In short, “best medical treatment” in patients with ARAS remains unknown.

HYPERTENSION

Although excessive blood pressure lowering in patients with bilateral ARAS can lead to progressive elevation of plasma creatinine, data regarding optimal blood pressure levels may be inferred from large studies. Tight blood pressure control was associated with improved outcomes in both the Modification of Diet in Renal Disease study and UK Prospective Diabetes Study Group studies, both of which likely included a significant proportion of patients with ARAS. Two other studies have shown specific renoprotection from ACE inhibition in uraemic patients of whom a proportion will have had ARAS. With regard to their safe use in patients, clinicians should be reassured that no excess of adverse renal events has been reported in large multicentre studies which have investigated ACE inhibition in the treatment of patients with heart failure, a significant proportion of whom will have had underlying ARAS. Furthermore, two recent studies have shown that control of hypertension by ACE inhibition is safe and effective in patients with ARAS and is not associated with an increased risk of renal atrophy. Nevertheless, these drugs should be introduced at the lowest dose with renal function checked after three to five days.

DYSLIPIDAEMIA

Dyslipidaemia is a risk factor for atherosclerosis, although curiously several studies demonstrated no relationship between cholesterol concentrations and progression of ARAS. However, subtle lipid abnormalities may be characteristic. There are no data that report benefit from cholesterol lowering in ARVD.

PLAQUE INSTABILITY

Recent data reports increased cardiovascular morbidity and mortality in patients with irregular as opposed to smooth carotid plaques. The increased risk, which must reflect a systemic predisposition to unstable atherosclerotic plaques, did not correlate with conventional risk factors and this suggests additional as yet unrecognised factor(s) for plaque progression. Similarly, the very high incidence of recurrent disease after coronary angioplasty in haemodialysis patients suggests that plaques behave differently in uraemia. Unstable atherosclerotic plaques may embolise cholesterol crystals and other debris that lodge in the dependent circulation, even down to the capillary level. In the kidney, cholesterol embolisation can lead to progressive microvascular obliteration, chronic inflammation and worsening renal failure, with the diagnosis clinched by the characteristic appearance of intravascular cholesterol clefts on renal biopsy (see fig 4).

The recent association between raised acute phase proteins, unstable atherosclerotic plaques and increased risk of myocardial infarction suggests that systemic inflammation predisposes to plaque instability. The importance of this observation is supported by recent data which show that reduction in C reactive protein is associated with reduction in coronary risk. A similar association between raised acute phase proteins and atherosclerosis has also been shown in dialysis and renal failure patients, although there are no data from intervention studies.

Statins can cause atherosclerotic plaque regression and may also have a specific role in the management of the unstable plaque. As well as inhibition of hepatocyte synthesis of cholesterol, statins decrease macrophage cholesterol synthesis; increase macrophage low density lipoprotein degradation; inhibit platelet derived growth factor induced proliferation of vascular smooth muscle cells and fibroblasts; inhibit thrombosis; improve endothelial function; and suppress inflammation. These properties may promote plaque stability and explain the reduction in levels of acute phase proteins observed in patients treated with a statin in the Cholesterol and Recurrent Events study. Consistent with this role, we recently reported the successful treatment of a patient with spontaneous cholesterol emboli syndrome

Figure 4 (A) Characteristic histological appearance on light microscopy of a cholesterol cleft in a small artery with evidence of intimal thickening, concentric hypertrophy, and interstitial inflammation. Embolised cholesterol crystals dissolve during the fixation process. (B) Electron micrograph demonstrating a cholesterol cleft in an afferent glomerular arteriole. The destination vessel depends on crystal size and this variability may determine the clinical presentation.
Renal failure in atherosclerotic renovascular disease

Box 1: Risk factors for development of ARVD
- Age
- Female gender
- Extrarenal atherosclerosis
- Diabetes mellitus
- Hypertension
- Smoking
- Hypercholesterolaemia

Box 2: Clinical presentations of ARVD
- Hypertension
- Deterioration in renal function or acute renal failure after introduction of ACE inhibition or angiotensin II receptor blockade
- Chronic renal failure
- Variable proteinuria, ranging to nephrotic syndrome
- Recurrent “flash pulmonary oedema”

Box 3: Pathogenesis of renal injury in ARVD
- Hypertensive nephrosclerosis
- Hyperperfusion due to critical stenosis
- Atheroembolic renal disease

affecting the renal and pedal circulations. Treatment with simvastatin lead to resolution of ischaemic symptoms, recovery of renal function, and normalisation of acute phase proteins. Of course anecdotes are inadequate and a definitive prospective trial of statin therapy in patients with ARVD is long overdue.

Conclusion
Epidemiological studies clearly indicate those patient groups at increased risk of developing ARVD, although its varied presentation means the clinician must remain vigilant. Recent studies have emphasised that renal dysfunction and atrophy result from both the stenosis and downstream vascular disease. Although the contribution of each process to an individual patient’s ARVD varies, it is tempting to consider both as different manifestations of a primary disease against which treatment should be directed.

Developments in magnetic resonance technology and its increased availability means that there is now a useful diagnostic technique for ARAS on the horizon for all. However, the ideal diagnostic test would differentiate renal injury secondary to proximal stenosis from irreversible microvascular disease. But as yet, only renal biopsy can define the reason for dysfunction and the potential for recovery with certainty. Improved diagnostic sensitivity will hopefully inform the debate over management of ARAS. Given the dual pathology, treatment of the stenosis alone is not likely to be adequate and the development of novel aggressive anti-atherogenic therapy will probably make these invasive interventions redundant in the future. At present, optimum medical treatment remains undefined and it is not known whether the treatment of conventional cardiovascular risk factors (blood pressure lowering, cholesterol lowering, and aspirin) matches the benefit from intervention. These continuing uncertainties highlight the problem which can arise when clinical management is driven by technological development rather than clinical benefit. The need for randomised prospective studies of available interventions has never been greater.

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21 References for figure 2


2 References for figure 1

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