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Clinical management of atheromatous renovascular disease

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Background and definition

Renal artery stenosis (RAS) is common, being due to atheroma in over 90% of cases in developed countries with the remainder mainly due to fibromuscular disease (FMD). The latter tends to occur in younger patients, predominantly women, and usually presents with severe hypertension; a good outcome can be expected following angioplasty. Renal dysfunction is not normally a major concern with FMD. Atheromatous RAS lesions excite clinical interest because of the possibility for revascularisation that might improve the clinical presentation of hypertension, acute and chronic kidney disease (CKD) and/or heart failure. The lesions classically occur in patients with generalised macrovascular atheroma, often in combination with end-organ smaller vessel disease, notably 'intrarenal' disease. Atherosclerotic renovascular disease (ARVD) is therefore considered a systemic syndrome. Ischaemic nephropathy is the term used when reduced renal function occurs in association with renovascular disease.

Epidemiology

ARVD is associated with ageing and other risk factors for 'inflammatory' atherosclerotic disease such as hypertension, smoking, diabetes and hyperlipidaemia. The community prevalence is about 7% in the elderly,[1] whereas large epidemiologic studies have demonstrated an incidence of about four cases per 1,000 patient-years in those aged >67 years.[2] Its association with other atheromatous macrovascular disease leads to high prevalence figures for ARVD in patients with peripheral vascular disease (40%),[3] coronary artery disease (10%),[4] congestive cardiac failure (CCF) (30%),[5] aortic aneurysm (30%) and stroke (10%). ARVD is present in at least 10% of patients investigated for CKD, while 11% of US dialysis patients have a diagnosis of ARVD.[6] It is also detected in about 2% of all cases of hypertension. However, it must be emphasised that in many of these cases ARVD is often only an association and not causative. This has implications for treatment, especially outcomes after revascularisation.

Clinical features

ARVD can present with one or more of the following conditions:

Hypertension

Over 90% of all patients with ARVD are hypertensive. As mentioned above, it is often questionable whether a given RAS lesion is causative of the hypertension. Essential hypertension may be more a contributor to the development of ARVD rather than a result of its presence. The pattern is typically that of severe systolic hypertension with low diastolic pressure and widened pulse pressure, resistant to medical therapy.

Acute kidney injury

ARVD may present with acute kidney injury (AKI) for several reasons including:

- severe bilateral RAS or occlusion – an indication for revascularisation therapy
- in association with accelerated-phase hypertension
- cholesterol atheroembolisation in patients with severe aortic atheroma who undergo angiographic procedures or anticoagulation
- radiocontrast injury during intra-arterial or computed tomographic angiography, and
- classically, in association with agents that block the renin-angiotensin system.

There should be clinical suspicion of underlying severe RAS in the presence of a significant deterioration of renal function (eg >30% increase in serum creatinine) after initiation of angiotensin-converting enzyme-I (ACE-I) or angiotensin receptor blocker (ARB) therapy. Most cases will not be associated with RAS, but renal artery imaging should be considered because a minority of patients will have significant RAS that might require a revascularisation procedure to allow uncomplicated use of these beneficial drugs.

Chronic kidney disease

The most common presentation of ARVD is in asymptomatic CKD patients referred to nephrology clinics. The hypertension (rather than ischaemia resulting from the 'hydraulic' effects of the RAS lesion) may be most important in the pathogenesis of the CKD. ARVD is more often an association with, rather than the cause of, most of these cases of CKD.[7] Histopathological studies of ARVD have shown a pattern of non-specific intrarenal injury hard to distinguish from hypertensive damage.[8]

Cardiac failure

Significant RAS can be detected in patients presenting with 'flash' pulmonary oedema[9] – life-threatening acute

heart failure in patients with no evidence of significant myocardial ischaemia. There is usually severe hypertension and severe bilateral renal artery disease. This syndrome is considered a definite indication for renal revascularisation. Up to 35% of elderly patients with CCF will have ARVD,[5] but no studies have investigated whether revascularisation will improve cardiac function and patient survival in this situation.

Investigations

Diagnostic clues that may suggest the need to investigate for ARVD include the following:

- The presence of audible vascular bruits (epigastric, renal or iliofemoral) in a patient with unexplained hypertension and/or CKD.
- Random cholesterol may not be elevated.
- Urinary albumin creatinine ratio should be assessed as proteinuria is common in ARVD, often reflecting the degree of underlying renal parenchymal damage (as in CKD from other causes).
- The presence of an atrophic kidney (eg >1.5 cm disparity in bipolar renal length) at ultrasound is an additional diagnostic clue.

Options for renal artery imaging

Magnetic resonance angiography. A non-invasive and sensitive option is magnetic resonance angiography (MRA) (Fig 1). Its safety has been questioned as over 250 cases of nephrogenic systemic fibrosis have accompanied the use of certain prepara-tions of the contrast agent gadolinium.[10] However, most of these have occurred in dialysis patients or in those with AKI. MRA is generally considered safe in patients with glomerular filtration rate (GFR) >15 ml/min.

Computed CT angiography or multislice CT. These procedures are sensitive for the detection of RAS (Fig 2). The main limitation is the risk of contrast nephropathy in patients with advanced CKD, who receive contrast, but this can be prevented by simple precautions and prophylaxis.

Duplex ultrasonography. Although time-consuming and operator-dependent, this technique is non-invasive and very accurate for the detection of significant RAS.

Intra-arterial angiography (IA) (usually IA-digital subtraction angiography). Conventional angiography is usually reserved to confirm the presence of RAS at the time of a revascularisation procedure or in diagnosis of more complicated/uncertain cases. It is invasive and associated with a risk of contrast nephropathy.

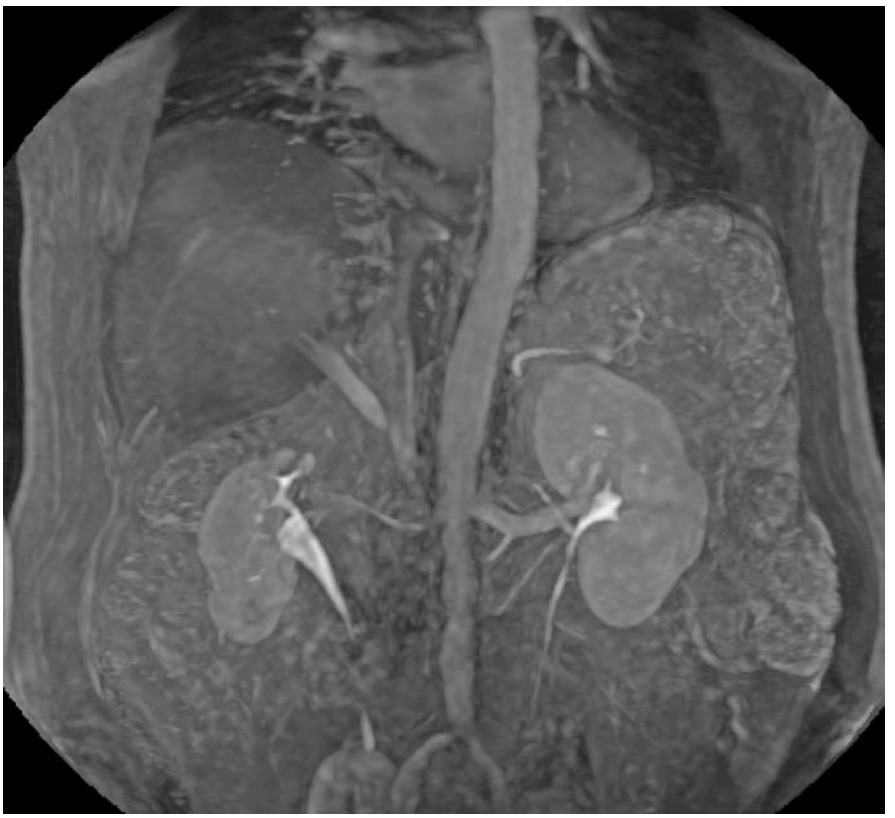

Fig 1. Contrast-enhanced magnetic resonance angiography showing small right kidney supplied with small calibre vessel. A significant renal artery stenosis is visible at the right renal artery ostium.

Pathology, natural history and prognosis

About 90% of atherosclerotic RAS lesions occur at the renal ostia (within 1 cm of the aortorenal junction) and calcification is common in the plaques. Lesions are bilateral in around 30% of patients, and 25% present with at least one completely occluded renal artery (RAO). Historically, there was evidence that medically-managed severe RAS lesions (eg RAS >70%) had a 10% annual risk of progression to RAO.[11] This underpinned an increased use of revascularisation procedures to reduce the loss of functioning renal mass. In the modern therapeutic era it is likely that statins beneficially influence the likelihood of RAS progression.[12]

Patients with ARVD are at high risk of mortality, largely due to the influence of their macrovascular comorbidities and heart disease. Factors associated with reduced survival are greater extrarenal macrovascular disease burden and poor renal function at ARVD diagnosis. The risk of death in patients with ARVD is six times greater than their risk of developing end-stage renal disease (ESRD),[2] but the annual mortality rate approaches 33% in those with ESRD.[6]

Treatment

Medical

ARVD is part of a systemic macrovascular disease syndrome. Reducing its progression and any ischaemic complications are the major aims of treatment. General lifestyle modification should include increased exercise and smoking cessation. Statins are indicated because of the generalised vascular disease. Most patients will also receive antiplatelet therapy. Combinations of several antihypertensive drugs may be necessary for effective blood pressure control (target <130/80 mmHg). As many ARVD patients have heart disease, proteinuria and/or a tendency to progressive renal parenchymal damage, both ACE-I and ARBs are actually optimal antihypertensive choices for these patients.

Renal revascularisation

Renal revascularisation is performed in about 16% of newly presenting ARVD cases,[1] endovascular procedures accounting for at least 95% of these interventions. Angioplasty with stent placement, or primary stenting, are preferable to angioplasty alone due to better arterial patency and lower restenosis rates.[13] In two clinical situations there is almost unanimous agreement about the value of revascularisation: patients presenting with AKI who have severe RAS and those with 'flash' pulmonary oedema. In most other clinical scenarios there is uncertainty regarding the evidence of benefit from revascularisation,[14] for example in:

- patients with severe anatomical RAS to slow or halt progressive CKD
- severe hypertension
- clinically stable patients with high-grade RAS (eg >70%).

The Angioplasty and STenting for Renal Artery Lesions trial

The ASTRAL trial,[15] designed in the UK with the aim of determining the benefit of revascularisation in some of the above clinical situations, has recently presented its initial results.[16] Two groups, each comprising 403 patients (63% men), average age 70 years at baseline, with atherosclerotic RAS, were randomised to either endovascular revascularisation with medical therapy or to medical therapy alone. Mean creatinine was 179 μmol/l and mean estimated GFR 40 ml/min. The average degree of RAS

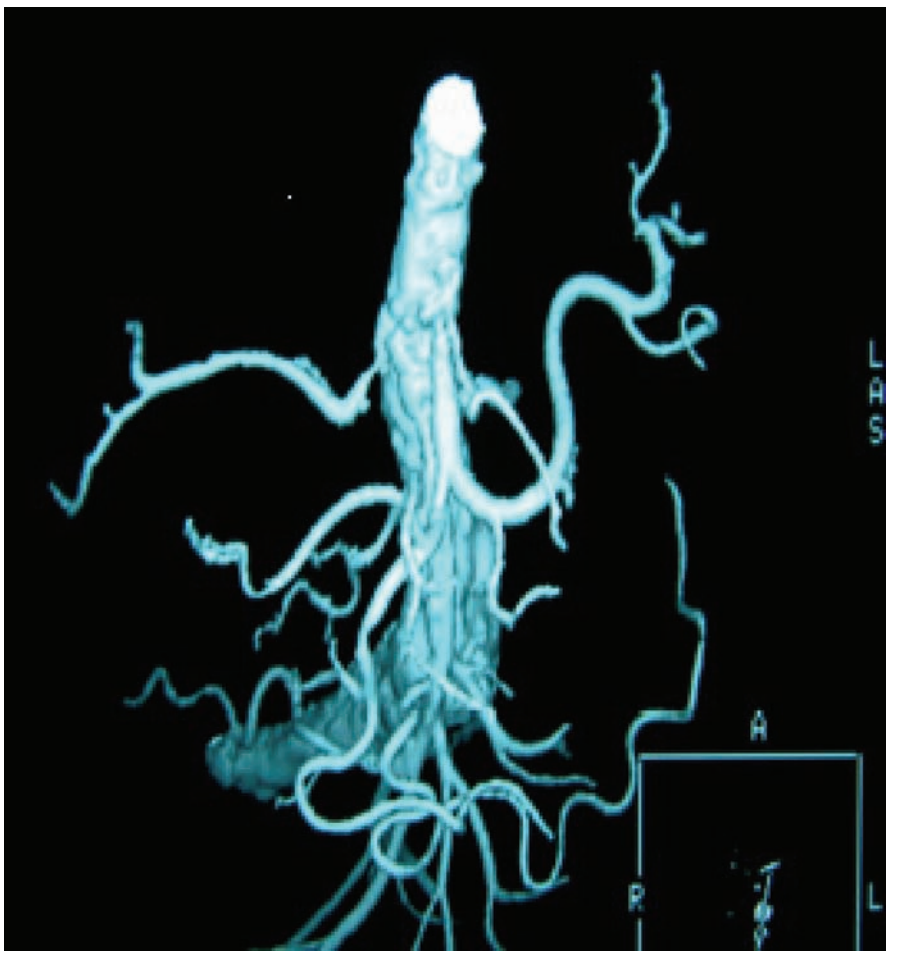

Fig 2. Reconstructed computed tomography image showing significant right renal artery stenosis (reproduced courtesy of Dr Alistair Cowie, Radiology Department, Salford Royal Hospital).

Key Points

Atheromatous renovascular disease (ARVD) is usually associated with systemic atherosclerosis manifested by peripheral and cerebrovascular disease, coronary artery disease and heart failure

Renal artery stenosis (RAS) lesions are often functionally insignificant, and hence incidental in many cases

The Angioplasty and STenting for Renal Artery Lesions trial showed no benefit of renal revascularisation for renal function, blood pressure control and mortality in the largest randomised trial of ARVD management

Standard medication for vascular disease is as effective as revascularisation so there may be little indication to screen for ARVD in asymptomatic chronic kidney disease and hypertension

There is clinical consensus, but no clear evidence, that patients with severe RAS and dialysis-requiring acute kidney injury or pulmonary oedema should receive revascularisation therapy

KEY WORDS: Angioplasty and STenting for Renal Artery Lesions (ASTRAL) trial, atherosclerotic renovascular disease, endovascular revascularisation, ischaemic nephropathy, renal artery stenosis

was 76% in the most affected vessel, mean blood pressure 150/76 mmHg, with patients receiving an average of 2.8 different antihypertensive medications. After a mean follow-up of 33.6 months the results showed that endovascular revascularisation did not improve renal functional outcome, (the primary outcome measure (Fig 3)) or the secondary outcomes of blood pressure control, renal or cardiovascular events (about 12% per year) or mortality (around 8% per year (Fig 4) compared with medical therapy alone. This lack of overall benefit has to be considered in light of the complications associated with revascularisation:[17] 3% of patients had a major arterial complication and 10–20% less serious complications of groin haematoma or reversible AKI.

Conclusions

The findings of ASTRAL coupled with a synopsis of the current ARVD literature can help guide the approach to managing patients with ARVD:

1 There is no worthwhile clinical benefit associated with renal revascularisation in patients with clinically asymptomatic ARVD: that is, patients found to have RAS when referred with stable CKD and/or moderate to severe hypertension. Indeed, it could be argued that such patients should no longer undergo angiographic screening for the condition.

2 The current medical therapy regimen used for these high-risk atherosclerotic patients appears to be effective. The overall annual mortality of 8% for ASTRAL patients compares favourably with the 16.3% noted in US Medicare patients with ARVD who presented in 2000–2001.[2]

3 About 10–20% of patients derive an improvement in renal function after

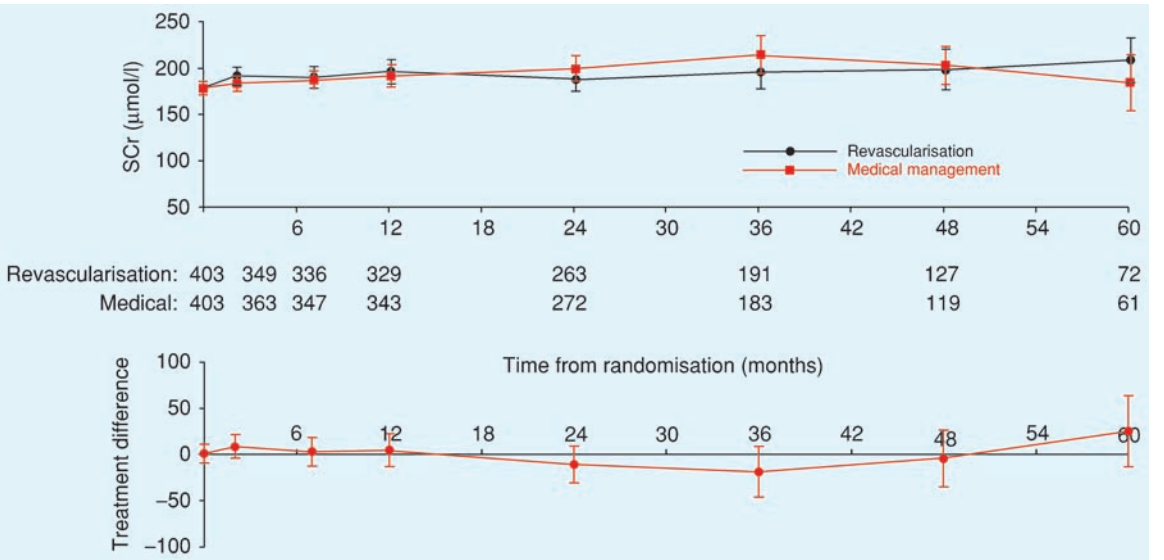

Fig 3. Angioplasty and STenting for Renal Artery Lesions trial: serum creatinine (SCr) at follow-up. Lower panel: difference between the treatment arms at each point. A negative result favours revascularisation.

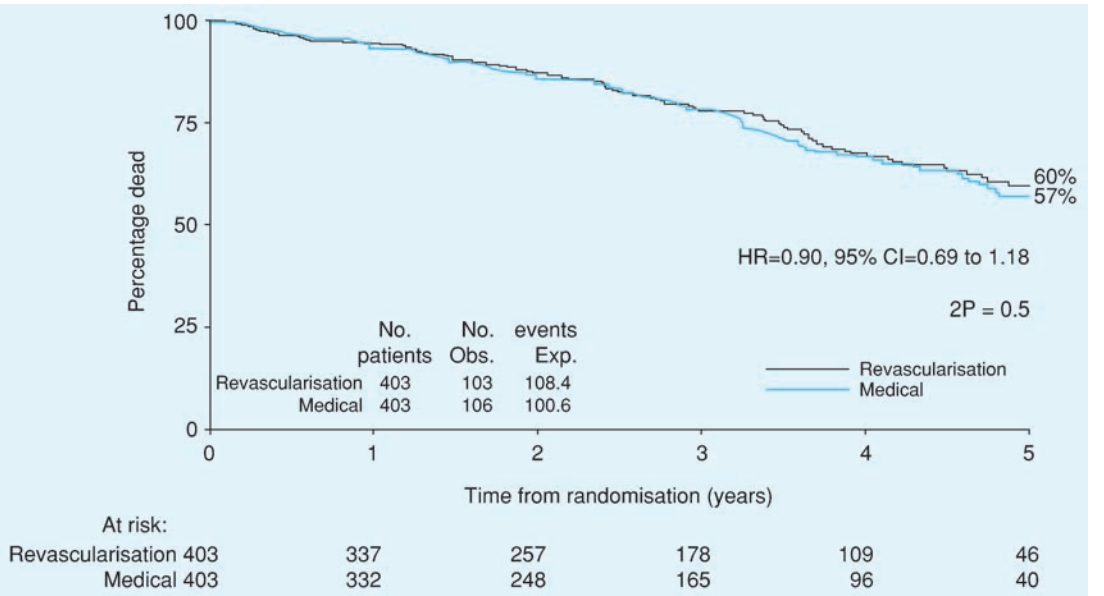

Fig 4. Angioplasty and STenting for Renal Artery Lesions trial: Kaplan-Meier plot of survival during follow-up. 2p = 2 tailed p value; CI = confidence interval; exp. = expected; HR = hazard ratio; obs. = observed.

revascularisation. Future investigations that can identify this minority group in advance of the procedure would be invaluable and prevent a large group of ARVD patients being exposed to unnecessary interventional therapy.

4 Questions still remain as to whether renal revascularisation is of clinical value in patients who present with ARVD and progressively deteriorating renal function, intolerance to ACE-I or ARBs or those with very severe hypertension. A further large trial, the US-led Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study,18 may provide some answers either alone or in a meta-analysis incorporating data from ASTRAL.

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