Dilemmas in the management of renal artery stenosis

Ching M. Cheung, Janet Hegarty and Philip A. Kalra*

Department of Renal Medicine, Hope Hospital, Stott Lane, Salford M6 8HD, UK

Atherosclerotic renovascular disease (ARVD) accounts for >90% of renal artery stenosis (RAS) in Western populations; the remainder are due to fibromuscular disease (FMD). The epidemiology is quite different in the Indian subcontinent and the Far East where Takayasu’s arteritis may be responsible for up to 60% of RAS cases. ARVD is very commonly associated with hypertension and renal dysfunction; it is a disease of ageing and is frequently observed in association with other vascular diseases. There is increasing evidence that in patients with ARVD and chronic renal dysfunction the aetiology of the latter is more often due to long-standing intra-renal vascular disease and parenchymal injury than to reversible ischaemia. This is reflected in the variability in renal functional outcome following revascularization, with an improvement in renal function being observed in only a minority of patients; the majority show no apparent change or even a decline in renal function. A major current challenge concerns the identification of patients who are likely to benefit from renal revascularization procedures, but technological advances in imaging offer potential in aiding this selection. Large-scale randomized controlled trials are required to determine the overall effects of renal artery intervention and, more specifically, to help identify which subgroups of patients will benefit from revascularization.

Introduction

Renal artery stenosis (RAS) is very commonly associated with hypertension and renal failure but, although the condition should be considered when either is present, care must be taken before attributing causation. This is especially true of atherosclerotic RAS, which accounts for >90% of all patients with RAS in Western populations, and the greater part of this review will concentrate on our current knowledge of the associations and management of this condition. Fibromuscular disease (FMD) is the pathology seen in most of the remaining Caucasian patients with RAS and, as its management is far less controversial, this will be briefly discussed first, together with a description of Takayasu’s arteritis which is responsible for up to 60% of all RAS cases in the Indian subcontinent.
Takayasu’s arteritis

Takayasu’s arteritis is a chronic inflammatory condition with a predilection for the aorta and its major branches. It is common in Southeast Asia, South America and the Mediterranean basin, but is rare in Caucasian populations (incidence of 2.6 per million).\(^1\) The pathogenesis of the vasculitis is uncertain, but some evidence exists for an autoimmune aetiology or a genetic predisposition. In Japan, there is an association with tuberculosis. The pathology involves a granulomatous inflammation that leads to fibrosis and destruction of the vascular media; eventually the vessel wall manifests segmental thickening with alternating stenotic and dilated areas interspersed with normal areas of vessel. Type 1 (cranial vessels) and type 2 (aortic arch) disease are more common in Japanese populations, whereas types 3 (abdominal aorta) and 4 (diffuse vessel involvement) are most common in the Indian subcontinent.

Clinically, there are two phases of Takayasu’s arteritis. The first is associated with inflammation and is marked by a syndrome of systemic ill health with fever and malaise, coupled with raised inflammatory markers. The second ‘pulseless’ phase is marked by ischaemic complications secondary to the vascular stenoses, which include hypertension and angina. In the Indian subcontinent, renal involvement is highly prevalent because of the large preponderance of type 3 and 4 Takayasu involvement, and so almost all patients are hypertensive. Indeed, in these populations Takayasu’s arteritis may account for up to 60% of all cases of RAS.\(^2\)

The mainstay of treatment is steroid therapy which is continued until the inflammatory markers settle. Surgical intervention may be necessary to prevent major complications such as aneurysmal rupture or vascular occlusion. Percutaneous renal angioplasty (PTRA) can successfully restore renal artery patency in 90% of patients.\(^3\) Overall prognosis is related to major vascular complications; death can be due to cerebrovascular accident, congestive cardiac failure or ruptured aneurysm, but with timely treatment annual mortality can be limited to 3%.

Fibromuscular disease of the renal arteries

FMD is now believed to be a relatively common condition, accounting for ∼10% of all cases of RAS.\(^4\) Autopsy studies have demonstrated a prevalence of 1–2% in the general population in the West,\(^5\) but it is uncommon in Africans and Asians. The renal arteries are affected in 60–75% of all cases of FMD, with the right renal artery being more commonly involved than the left. However, other major arteries can be involved, notably the carotids (in 15% of cases) and the vertebral,
mesenteric, coeliac axis, hepatic, iliac and coronary vessels. The pathogenesis of FMD is uncertain. An effect of female hormones has been postulated in view of the large female preponderance, but a few cases have occurred in a familial autosomal dominant pattern, and others in association with $\alpha_1$ antitrypsin deficiency. Mural ischaemia induced by vasoconstriction of the vasa vasorum has also been suggested, and smoking is certainly linked to some of the more severe cases.

The pathology of FMD includes three main subtypes.

- Intimal fibroplasia accounts for 5–10% of FMD, and affects children and young adults but without female preponderance. Collagen is circumferentially deposited in the intima, resulting in smooth tubular stenoses.

- Medial fibroplasia is the most common pathological form of FMD (75–80%), typically affecting women in their fourth decade. Areas of intima and media thinning with loss of the elastic lamina occur in the vessel wall, leading to the formation of aneurysms. These areas alternate with localized regions of media fibrosis, resulting in the classical ‘string of beads’ appearance at angiography (Fig. 1). The proximal one-third of the artery is usually spared, and this form is bilateral in 40% of cases.

- Perimedial fibroplasia accounts for 10% of FMD. Fibrous tissue replaces the outer portion of the medial muscle layer leading to severe stenoses but no aneurysm formation.

Medial hyperplasia is a rarer form of FMD in which the pathology is true muscle hyperplasia.

The typical presentation is with hypertension but usually well-preserved renal function in young adults, but there have been recent reports of

![Fig. 1 Renal angiogram showing the typical ‘string of beads’ appearance of fibromuscular dysplasia.](image-url)
FMD having remained undetected until older age. However, FMD should always be considered in young patients (<35 years) who present with severe or accelerated-phase hypertension. Clinical examination may reveal an abdominal bruit. Carotid arterial involvement leading to dissection or Berry aneurysm formation can be associated with a range of neurological features, whereas mesenteric angina or claudication may be manifestations of extra-renal FMD at other sites. Although progressive narrowing of the renal arteries may occur in about a third of patients, progression to occlusion is rare.

In contrast with the management of patients with atherosclerotic RAS, the treatment of renal FMD is far more certain. PTRA is the intervention of choice, but RAS lesions in the distal renal arteries, and complicated or lengthy lesions, may not be amenable to PTRA and may require surgery. Otherwise the results of PTRA are good, with a re-stenosis rate of only ~20%; 36% of patients can be cured of hypertension and most of the remainder have a reduced drug burden and improved blood pressure control at 1 year.7

Atherosclerotic renovascular disease

Atheromatous narrowing of the renal arteries is very common and accounts for most cases of renovascular disease. More than 90% of lesions are ‘ostial’, occurring within 1 cm of the origin of the renal artery (Fig. 3) and the disease may be unilateral or bilateral. Although RAS lesions excite greatest interest because of the potential for revascularization and improved patient outcome, the fact that up to 50% of patients have occlusion of the renal artery (RAO) should not be overlooked. Hence we prefer the term ‘atherosclerotic renovascular disease’ (ARVD) as a more accurate general description of this condition. Risk factors for the development of ARVD are the same as for other atheromatous vascular pathologies, and include age, hypertension, smoking, hyperlipidaemia, diabetes and renal failure.

What constitutes a significant RAS lesion?

The definition of what degree of narrowing constitutes a ‘significant’ RAS lesion is somewhat controversial. Some interventional radiologists will only attempt angioplasty in ‘critical’ (>90% RAS) stenoses, whereas others have no reservations with intervening for RAS >60% of the arterial luminal diameter. However, it should be borne in mind that quantification of the degree of an RAS lesion by radiological means is not a precise science and is subject to intra-observer variability. The crucial
Dilemmas in the management of RAS

physiological point concerns whether a stenosis is ‘functionally significant’—whether or not it is responsible for stimulating a response from the kidney by inducing a degree of renal ischaemia. Such a response could be hypertension and/or retention of salt and water, reversible renal failure or structural damage leading to irreversible renal failure. Unfortunately, the pathophysiological relationships between RAS and these complications have not previously been clarified, and this partly explains why there is so much uncertainty regarding when to intervene in patients with RAS.

Some investigators have focused on the trans-stenotic pressure gradient as a key parameter of functional significance. Experiments in dogs have demonstrated significant pressure gradients across RAS lesions of 60%, and in humans even RAS lesions of <50% can be associated with gradients of 15 mm Hg. These data only add to the uncertainty, and hence a pragmatic approach would be to consider revascularization in RAS >60%, dependent upon the clinical presentation. This will be discussed in a later section.

**Epidemiology of ARVD**

ARVD is a disease of ageing. A post-mortem study from as far back as the 1960s found that incidental RAS >50% occurred in >40% of
patients aged >75 years,\textsuperscript{10} irrespective of their cause of death. Such a high prevalence should not be surprising, as a similar proportion of elderly patients will have significant coronary, cerebrovascular and/or peripheral vascular disease. ARVD is frequently associated with these conditions, as will be discussed below. Therefore many patients have ‘clinically silent’ ARVD, and so it is not possible to estimate the true prevalence of the condition in the general population. However, Hansen \textit{et al.}\textsuperscript{11} used Doppler ultrasound screening to show that 6.8\% of elderly ‘free-living’ people had incidental RAS >60\%. A more recent study of the US Medicare population demonstrated that ARVD was diagnosed with an incidence of 3.9 cases per 1000 years in patients aged >65 years.\textsuperscript{12}

RVD can present in association with hypertension, acute or chronic renal failure, cardiac failure or one or more of the extra-renal vascular pathologies alluded to above, and each of these will be considered below.

\section*{ARVD and its association with heart and other vascular diseases}

\subsection*{Coronary artery disease}

Several studies, especially those performed by the group at Duke University Medical Center, have shown a high prevalence of ARVD in patients with symptomatic coronary artery disease. When abdominal aortography is performed at the same time as coronary angiography, up to 15\% of patients can be expected to have significant RAS (>50\% stenosis) with a similar proportion having insignificant RAS.\textsuperscript{13} The presence of RAS is associated with more severe and extensive coronary artery disease, and follow-up studies have shown that it has a negative impact on survival in this patient group.\textsuperscript{14}

\subsection*{Cardiac dysfunction including ‘flash’ pulmonary oedema}

ARVD is also known to be associated with cardiac dysfunction. ‘Flash’ pulmonary oedema (sudden onset left ventricular failure in patients who have no previous cardiac history and well-preserved cardiac function at echocardiography) may be the presenting clinical syndrome in up to 10\% of patients with ARVD.\textsuperscript{15} Patients with bilateral disease are at increased risk of this condition, which is currently one of the few widely accepted indications for renal artery revascularization.\textsuperscript{16} There is also a high prevalence of ARVD in patients with congestive cardiac failure, with over a third of elderly patients likely to have RAS.\textsuperscript{17} These associations
should not be surprising; in a recent cross-sectional study of 79 patients with ARVD only four (5.1%) were found to have normal hearts. Compared with a control group of patients with chronic kidney disease (CKD) from other causes, but with similar degree of renal impairment and blood pressure, ARVD patients were found to have significantly higher prevalence of left ventricular hypertrophy (78.5% compared with 46.0%) and left ventricular diastolic dysfunction (40.5% compared with 12.0%), and greater left ventricular mass index (183 ± 74 g/m² compared with 116 ± 33 g/m²).18

Aortic aneurysm and peripheral vascular disease

Several investigators have defined the prevalence of ARVD in patients undergoing aortography for intermittent claudication. Missouris et al.19 showed that 57 (44.9%) of 127 patients referred for investigation of peripheral vascular disease had ARVD, and the presence of the latter correlated with the severity of peripheral vascular disease. Olin et al.20 reported a cohort of patients who underwent aortic or peripheral angiography and found significant RAS in 41 (38%) patients with abdominal aortic aneurysm, 7 (33%) patients with aorto-occlusive disease and 74 (39%) patients with peripheral vascular disease.

Cerebrovascular disease

The coexistence of ARVD in patients who have stroke and/or carotid stenoses is also well established. In an autopsy series of 346 cases of brain infarcts, >75% RAS was found in 10.4% of subjects and carotid artery stenosis in 33.6%. Patients with carotid stenosis were more likely to have ARVD than those without carotid disease.21 Conversely, ARVD patients are more likely to have carotid disease; in a prospective study of 60 patients, the prevalence of carotid disease was 46% in patients with RAS but only 12% in non-RAS patients.22

ARVD and hypertension

ARVD is found in 2–5% of all cases of hypertension and ~90% of patients with ARVD are hypertensive. However, as will be discussed later, it is likely that the hypertension precedes ARVD development in many cases. Hence, essential hypertension more often contributes to the development of ARVD, rather than the latter being important in the pathophysiology of the hypertension. The definition of true ‘renovascular
hypertension’ is specific, and the Cooperative Study of Renovascular Hypertension was established in order to define the clinical characteristics differentiating the former from essential hypertension.23 The clinical findings most significantly associated with a renovascular aetiology are shown in Table 1.

Although many investigators incorrectly attribute the coexistence of hypertension and ARVD to a diagnosis of renovascular hypertension, the most rigorous definition of the latter requires the demonstration of a cure or major improvement in hypertension following a revascularization procedure for RAS. That the RAS is often pathophysiologically insignificant in ARVD is reflected by the disappointing effects of technically successful renal revascularization upon blood pressure control.

**ARVD and acute renal failure**

Patients with ARVD can present with acute renal failure, for which there are several possible causes:

- bilateral renal arterial occlusion (RAO)
- intra-renal cholesterol atheroembolization
- damage from radiocontrast agents during intra-arterial angiography
- hypovolaemia, often with concurrent diuretic use
- concurrent use of angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (AII-RBs).

### Table 1 Clinical features suggestive of renovascular disease

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Renal abnormalities</th>
<th>Other</th>
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<tbody>
<tr>
<td>Abrupt onset of hypertension in patients aged &lt;30 years (suggestive of FMD)</td>
<td>Unexplained renal failure in patients aged &gt;50 years</td>
<td>Unexplained acute pulmonary oedema or congestive cardiac failure</td>
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<tr>
<td>or &gt;50 years (suggestive of ARVD)</td>
<td>Elevation in plasma creatinine level after the initiation of ACE-I or AII-RB therapy</td>
<td>Femoral, renal, aortic or carotid bruits</td>
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<tr>
<td>Absent family history of hypertension</td>
<td>Asymmetrical kidneys on imaging</td>
<td>History of extra-renal vascular disease</td>
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<tr>
<td>Accelerated or malignant hypertension</td>
<td></td>
<td>Hypokalaemia</td>
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<tr>
<td>Resistance to therapy (≥3 drugs)</td>
<td></td>
<td>Neurofibromatosis</td>
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The prevention of RAO development underpins the rationale of some investigators for performing revascularization in patients with tight RAS lesions (this will be discussed below). Cholesterol embolization is probably more common than currently recognized, but it should be suspected when acute renal failure is seen in patients with aortic atheromatous disease who undergo aortic surgical or angiographic procedures, thrombolysis or anticoagulation. Associated clinical features include purpuric rash or livedo reticularis, focal digital ischemia, proteinuria and eosinophilia. The demonstration of characteristic clefs left by cholesterol crystals in tissue biopsy specimens is a pathognomonic finding (Fig. 3). Cholesterol embolization may be responsible for a spectrum of renal impairment: some patients manifest only a moderate loss of renal function with subsequent improvement, whereas in others progressive renal failure occurs. Eventual return of kidney function can occur even after a prolonged period of renal insufficiency. Studies have shown that atheroembolic showers are nearly universal after instrumentation in renal and other atherosclerotic vessels, and it is for this reason that some radiologists now use protection devices in order to prevent distal renal embolization whilst performing renal interventional procedures.

The use of ACE-I or AII-RB therapy is frequently associated with minor renal functional deterioration, especially in elderly patients and those with comorbidity, but in the majority of cases the agents can be continued without risk of progressive decline. However, there should be a high index of clinical suspicion for underlying ARVD in all patients in whom renal function deteriorates significantly (>30% increase in serum creatinine) with the use of these drugs. Cases of ACE-I-related uraemia have been reported since the introduction of these agents in the early 1980s, and they are responsible for at least 3% of all acute uraemic admissions. Acute renal failure occurs when such agents are given to patients with RAS in whom glomerular perfusion is critically dependent upon the action of angiotensin II on efferent arteriolar tone. However, it is not only patients with ARVD who are at risk; two-thirds of those with ACE-I-related uraemia will have normal renal vasculature but low cardiac output states such that further renal haemodynamic stress supervenes during intercurrent illness. Examples of this include sudden volume depletion (e.g. from haemorrhage, major surgery, severe intestinal fluid loss or diuretic therapy); the concomitant use of non-steroidal anti-inflammatory agents is often an additional exacerbating factor. Although reversal of renal dysfunction should be anticipated if the agents are withdrawn in a timely fashion, renal angiographic imaging should be considered so as to identify those patients with significant RAS in whom revascularization procedures may allow uncomplicated re-introduction of these
beneficial drugs. It is likely that their use will be indicated in many patients with ARVD (see below).

**ARVD and chronic kidney disease**

Many patients have CKD in association with ARVD, and hypertension is usually present. The prevalence of ARVD in patients with end-stage renal disease (ESRD) in the Western world is also high (at least 15%, reaching >25% in the elderly), and so the condition is increasingly recognized in patients joining renal replacement therapy programmes. We believe that, in the majority of these patients, the hypertension (rather than the ARVD) is most important in the pathogenesis of the CKD. Hence, the ARVD is more often an association, rather than the cause, of the majority of these cases of CKD and ESRD, which has important implications for treatment and will be discussed later.

**Pathogenesis of chronic renal dysfunction in ARVD**

*Natural history of RAS lesions*

Previous invasive and non-invasive studies have demonstrated a rapid rate of progression of high-grade stenoses to RAO with consequent loss of functioning renal mass. For example, in the early 1980s Schreiber *et al.* used serial arteriography and found that 16% of 85 patients with RAS developed RAO over a follow-up period of 12–60 months. Similar rates of progression to RAO were found a decade later by Zierler *et al.* who used serial duplex ultrasound in 80 patients with RAS. Data from Duke University have shown that significant RAS progression occurred in 11.1% of patients during a mean interval of 2.6 years between angiographic studies. Understandably, these observations have underpinned the rationale for revascularization in patients with moderate-severe RAS (RAS >60%). However, we now practice in an era of vascular protection, and it is likely that statin therapy may slow or halt the rate of progression of some RAS lesions; unfortunately, this possibility has never been investigated. There is also a major assumption that increasingly severe RAS lesions are responsible for the renal dysfunction seen in many patients with ARVD, but this is not supported by renal functional outcomes after revascularization as the majority of patients with severe RAS lesions manifest no improvement in renal function, and some show a progressive renal functional decline despite restoration of renal artery patency.
Lack of a relationship between RAS severity and renal dysfunction

There is no doubt that in some patients who have a tight stenosis in the main renal artery a drop in renal perfusion will result in impaired renal function simply via a hydraulic effect, but this appears to be the case in the minority of patients and does not explain why patients with unilateral RAS also develop renal failure. The lack of relationship between the severity of ARVD lesions and the degree of renal dysfunction has been documented in several recent studies, both epidemiological and involving isotopic measurement of single-kidney glomerular filtration rate (SK-GFR). Using the latter approach, Farmer et al. found no correlation between RAS severity and the degree of dysfunction for individual kidneys, except for kidneys with RAO. In addition, patients with unilateral severe RAS often had similar or even worse SK-GFR in the contralateral kidney supplied by a normal renal artery. These findings emphasize the pathophysiological importance of intra-renal (parenchymal) disease in the aetiology of renal impairment in most ARVD patients.

The importance of hypertensive intra-renal injury in ARVD

There is now compelling evidence that intra-renal injury, probably most often caused by long-standing hypertension and predating RAS development, is the major factor responsible for renal dysfunction in the majority of patients who have CKD with ARVD. In an ultrasound study examining the incidence of and risk factors for renal atrophy (reduction in renal length of >1 cm) in 122 patients with ARVD, although renal atrophy was seen at 2 years in 20.8% of kidneys supplied by high-grade RAS, the rate of atrophy was still 5.5% in kidneys supplied by a normal vessel. In this study, systolic hypertension was independently associated with a high risk for renal atrophy, and as the latter was linked with deteriorating renal function it is clear that hypertensive renal damage is a major contributor to renal dysfunction in these patients.

Proteinuria appears to be a key marker of this intra-renal injury in ARVD patients, and it is strongly linked to baseline renal function as well as long-term outcome. In a group of 94 patients with angiographically proven ARVD, 48% had proteinuria >0.5 g/24 h and a clear relationship was observed between lower baseline glomerular filtration rate (GFR) and increased degree of proteinuria. A prospective study found that increased proteinuria at ARVD diagnosis was the chief predictor of future deteriorating function, just as it is in a variety of other diseases of the renal parenchyma (e.g. chronic glomerulonephritis). Although such proteinuria might be associated with an alternative renal pathology, in the majority of ARVD patients it is likely to represent non-specific tubulo-interstitial and glomerular injury due to a combination of insults.
The term ‘ischaemic nephropathy’ has been used to describe the intra-renal damage in ARVD, but as histological changes include a constellation of hypertensive damage, cholesterol atheroembolism, intra-renal vascular disease and focal segmental or global sclerosing glomerular lesions, the term ‘atherosclerotic nephropathy’ has also been applied. In a few specialist centres in the USA, biopsy of a RAS kidney is sometimes used to evaluate suitability for renal revascularization, which from the foregoing appears logical if rather invasive. Although small-scale investigations have shown a relationship between the severity of histopathological damage and renal functional outcome in atherosclerotic nephropathy, this needs more systematic study.

As will be described below, measurement of the ultrasonographic resistive index (RI) within the kidneys of patients with ARVD has proved to be of value in predicting renal functional outcome after revascularization. This is logical as an increased RI is likely to be a surrogate marker of worse degrees of the intra-renal damage described above.

### Diagnosis of ARVD

**Clinical pointers to ARVD diagnosis**

ARVD should always be suspected in patients presenting with renal dysfunction and hypertension who have evidence of atheromatous disease. Specific clinical features include significant deterioration of renal function (>30% increase in serum creatinine) with accompanying use of ACE-I or AII-RBs, or unexplained pulmonary oedema, but the presence of femoral, renal or aortic bruits and the coexistence of severe extra-renal vascular disease are the main clinical pointers to ARVD diagnosis (Table 1). Hypertension may be absent, particularly in patients with chronic cardiac dysfunction. In those hypertensive patients without renal insufficiency, a high index of suspicion for RAS diagnosis is advised in cases with severe (often systolic) hypertension, especially when they are unresponsive to three or more antihypertensive agents and show evidence of widespread vascular disease.

**Investigation of ARVD**

Patients with clinical findings suggestive of ARVD should undergo further investigation. This should involve a combination of anatomical and functional assessments, and ideally consideration of the degree of intra-renal parenchymal damage, usually by surrogate markers (RI and proteinuria). Although intra-arterial angiography was previously the chief investigation for visualizing the proximal renal vessels, this is now being superseded by less invasive angiographic techniques.
Duplex ultrasonography
This technique can be used to identify and assess the severity of RAS from alterations in flow velocity and flow characteristics in the stenotic segment of the renal artery. Its sensitivity ranges from 92% to 98%. Intra-renal RI can also be measured by this technique, and several studies have confirmed the usefulness of RI as a determinant of renal functional outcome after revascularization. In ARVD patients, a high RI (measured in the kidney contralateral to the RAS) predicts a poor blood pressure and renal functional response to angioplasty, presumably as this is a marker of severe and irreversible intra-renal disease. However, measurement of RI is known to be operator dependent, and there is uncertainty as to whether the technique can be sufficiently reproducible to have broad applicability outside research centres.

Magnetic resonance imaging
Contrast-enhanced magnetic resonance angiography (MRA) is useful for evaluating the proximal renal vasculature and the aorta, and is becoming the favoured imaging method for the proximal renal vasculature (Fig. 3). The sensitivity for detection of RAS ranges from 83% to 100% and specificity ranges from 92% to 97%. Gadolinium is non-nephrotoxic at low doses and therefore avoids the risk of contrast nephropathy, a particular issue in those patients with renal insufficiency. Noteworthy advances in MRI include the possibility of measuring individual renal

Fig. 3 Cholesterol crystal embolization following renal angioplasty. The arteries are thickened and occluded with numerous cholesterol clefts within the arterial lumens. The clefts are empty because of the dissolution of cholesterol by lipid solvents during histological preparation.
function, with the potential of providing a comprehensive functional and anatomical scan in a single visit.\textsuperscript{48}

**Computed tomography angiography**

CT angiography has a similar sensitivity and specificity to MRA for detection of RAS.\textsuperscript{49} Limitations on its use include risk of contrast nephropathy and poor visualization of the distal main renal artery and segmental branches.

**Renal scintigraphy and measurement of individual kidney function**

In many circumstances the assessment of individual renal function with isotopic SK-GFR can be helpful in deciding the optimal management of the patient with ARVD. For example, in patients with unilateral or bilateral significant RAS it may be considered inappropriate to revascularize a kidney with a very low GFR. The determination of SK-GFR involves both an isotope study to assess global GFR coupled with a dimercaptosuccinic acid (DMSA) scan to demonstrate the split of renal function.\textsuperscript{50} This investigation may not be available in some centres, and a simpler alternative is renal scintigraphy which can at least demonstrate the non-functioning or very poorly functioning RAS kidney.

**Treatment options in ARVD**

**Medical treatment**

ARVD should be considered as part of a diffuse vascular disease process, rather than as a solitary disease affecting the renal circulation. Extra-renal vascular comorbidities should not be overlooked, as they may be the major contributor to the poor outcome of ARVD patients. However, it is the combination of ARVD with renal failure which has excited greatest interest.

Although there is no evidence base to guide best medical ‘vascular protective’ management, attention should be focused on limiting the progression of atheromatous disease by vigorous control of hypertension and hyperlipidemia, use of antiplatelet agents, cessation of smoking and lifestyle modification including reduced dietary intake of salt and increased exercise. Specific considerations include statins and antihypertensive therapy.

**Statins**

As yet there are no randomized control trial data to support the need for statin therapy in all CKD patients. However, by inference from outcomes in statin trials in non-renal patients there is a strong case to treat all ARVD patients with statins, irrespective of their serum cholesterol,
because of the marked association between ARVD and extra-renal vascular disease. As well as having the ability to stabilize atherosclerotic plaque and to slow progression, or even induce regression, of atherosclerotic renal artery lesions, statins may also have beneficial effects independent of lipid-lowering, such as reduction of proteinuria.

**Antihypertensive therapy**

Patients may require combinations of several antihypertensive drugs for effective blood pressure control (target <140/80 mm Hg, or 125/75 mm Hg in those with significant proteinuria). β-blockers can reduce renin release from the injured kidney but may be poorly tolerated because of concurrent peripheral vascular disease or congestive cardiac failure. β-blockers are a beneficial class as patients tend to suffer with mainly systolic hypertension. Although seemingly counter-intuitive, both ACE-I and AII-RBs are actually optimal antihypertensive choices for patients with ARVD, especially for those with proteinuric chronic parenchymal disease, and those with coexisting coronary artery disease and cardiac dysfunction. Successful normalization of blood pressure should now be possible in >90% of ARVD patients, but careful monitoring of renal function is required, particularly in patients with significant bilateral RAS, or RAS affecting a solitary kidney. It should be remembered that serum creatinine may still lie within the reference range, even after ACE-I-related shutdown (‘autonephrectomy’) of one kidney, and hence optimal monitoring should involve scrutinization of serial creatinine values or estimated GFRs (eGFRs). However, even when significant deterioration of renal function is seen to accompany ACE-I or AII-RB therapy the benefits of continuation of these drugs may outweigh the detriment to renal function, particularly in patients with marked cardiovascular comorbidity (e.g. congestive cardiac failure).

**Renal revascularization**

Revascularization procedures have been utilized for the treatment of RAS for over three decades, and the chief rationale for revascularization in ARVD would now include the following:

- maintainence of functioning renal mass by preventing RAO and/or renal atrophy in patients with high-grade RAS
- preventing progression of CKD, and especially the development of ESRD requiring dialysis
- control of severe hypertension
- improvement in serious comorbid cardiac disease.
During the last 20 years surgical reconstruction has largely been replaced by percutaneous interventional techniques—angioplasty with or without stent placement. Recent data indicate that the latter approach now accounts for 95% of all revascularization procedures. However, interventional radiological procedures should not be performed without careful patient evaluation as complications occur in ~10% of cases, although the majority of these are minor (e.g., groin hematoma). Contrast nephropathy and cholesterol embolization may occur in a large proportion of patients, but they appear to be only clinically significant in the minority; fortunately, arterial rupture or thrombosis are uncommon.

**Current evidence for renal revascularization**

To date there have been four published clinical trials which have sought to investigate the benefits of interventional procedures in patients with ARVD. Van de Ven *et al.* primarily investigated whether angioplasty with stenting was more successful than angioplasty alone for ostial RAS, and this proved to be the case in terms of arterial patency but not renal function. In the other three studies there was at best a modest improvement in blood pressure control in the revascularized patients, but again no improvement in renal function. Although it should be borne in mind that even modest blood pressure reduction might translate into improved cardiovascular outcomes over an extended time period, the evidence for this is seriously lacking. In all these randomized control trials patient numbers were small (~100 or less) and the studies were not adequately powered to detect significant changes in renal function or, even less, in major cardiovascular outcomes. Nevertheless, many retrospective studies of renal revascularization have been reported from individual centres. In most studies, irrespective of the revascularization technique, a definite improvement in renal function is generally reported in a minority (~25%) of patients, although the overall effect upon renal functional outcome in the whole ARVD group may be minimal. Such retrospective studies lack the scientific rigour on which to build a reliable evidence base, as they can be subject to conscious and unconscious bias in selection, reporting and publication, and hence the available literature can be seen as increasing the dilemma of how best to manage ARVD. Further large-scale randomized control trials are essential in order to determine the overall effects of intervention and, more specifically, to help identify which subgroups of patients will benefit from revascularization. Two European trials (ASTRAL and STAR) are currently well advanced, and an American trial (CORAL) is due to commence recruitment shortly.

**Definite indications for renal revascularization**

Most would agree that renal revascularization is indicated in patients presenting with recurrent ‘flash’ pulmonary oedema in association with
a high grade RAS lesion, as the procedure can be life-saving.\textsuperscript{15} There is also reasonable consensus that revascularization should be considered in patients with high-grade RAS and the following clinical scenarios.

- Severe hypertension resistant to all medical therapy.
- When a patient who requires ACE-I or AII-RB therapy (e.g. for cardiac failure) presents with significant ACE-I-related uraemia.
- When a patient has dialysis-dependent renal failure (in such patients there is probably little to be lost and, potentially, much to be gained by intervention). Some of these patients may have recent-onset RAO (see below).
- When there is evidence of recent-onset RAO in a reasonably sized kidney. Such patients present with anuria (if the RAO affects a solitary kidney), rapidly deteriorating renal function and/or accelerated-phase hypertension. Angioplasty (possibly with prior thrombolytic therapy) can dramatically rescue the functioning renal mass in this situation\textsuperscript{60}.

Although many clinicians would justify revascularization in patients who have deteriorating renal function in association with either bilateral severe RAS or RAS in a solitary kidney, there is still great uncertainty regarding its usefulness in the majority of patients who present with ARVD and chronic renal failure. As stated previously, many of the latter patients will have developed ARVD against the background of hypertensive renal impairment, and hence any RAS will often be incidental to the aetiology of the CKD.

**Prognosis of patients with ARVD**

Although many ARVD patients have CKD, only a minority progress to need dialysis; the remainder usually die from cardiovascular complications. This has been illustrated in a recent study of a random sample of the US Medicare population, in which 7434 elderly patients were noted to have incident ARVD during the period 2000–2001; during follow-up the risk of death was almost six times that of developing ESRD.\textsuperscript{12} The survival of patients with ARVD is generally poor, partly because of patient age but also because of the effects of comorbid cardiovascular disease and renal failure. Isles \textit{et al.}\textsuperscript{61} found an 83\% 5-year survival in patients with ARVD and predominating hypertension rather than renal failure. In a subgroup of 148 ARVD patients with RAO we found an overall 5-year survival of 52\%, but we observed a very strong relationship between renal dysfunction and mortality, as patients with ESRD had a relative risk of mortality almost 30 times that of patients with well-preserved function.\textsuperscript{37} This relationship has been documented previously by Mailloux \textit{et al.}\textsuperscript{62} who showed that patients with ARVD receiving dialysis had a median survival of 27 months and an average 5-year
survival of only 18%. The extent of extra-renal vascular disease is another major factor determining survival. In an epidemiological study from our department, ARVD patients with both coronary artery disease and peripheral vascular disease had the highest mortality, whereas those with coronary artery disease had significantly higher mortality than patients with isolated ARVD.

Summary of the dilemmas in the management of renal artery stenosis

ARVD accounts for the vast majority of RAS cases in Western populations; however, up to 10% are due to FMD, which can present in older age. Little controversy surrounds the management of FMD, and PTRA will often lead to cure or improvement in blood pressure and can benefit renal function. The epidemiology is quite different in the Indian subcontinent and the Far East where Takayasu’s arteritis may be responsible for up to 60% of all RAS.

ARVD is frequently associated with other cardiovascular diseases, but most particularly with CKD and hypertension. However, the latter associations are more often incidental rather than causal, and this helps to explain why revascularization is not regularly followed by an improvement in blood pressure control or renal function. Despite our increased understanding of the epidemiology and management of ARVD in recent years, uncertainty still exists in relation to the following questions.

- What is the best method for screening and/or diagnosis of ARVD?
- What degree of stenosis constitutes a functionally significant RAS lesion?
- What influence do statins have on the natural history of progressive RAS lesions?
- Which subgroups of patients should be selected for renal revascularization procedures?
- Can renal revascularization lead to improvements in survival in selected patient groups?
- What are the appropriate follow-up investigations for ARVD patients treated either conservatively or with revascularization?

As ARVD is so commonly detected in many different areas of medicine it is now of great importance to find the answers to these questions. It is hoped that with further developments in investigational techniques, careful epidemiological studies and, most of all, the results of the several ongoing randomized control trials, these will soon be forthcoming.
References