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When should atheromatous renal artery stenosis be considered?

A guide for the general physician

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Atheromatous renal artery stenosis (ARAS) is common – it is present in 15–30% of otherwise unselected patients with coronary, peripheral or cerebral vascular disease.[1] It is easy to find; in our unit, about 75% of cases selected only on clinical clues and basic ultrasonography have some degree of ARAS at angiography. However, it is much more difficult to identify patients in whom ARAS is contributing to morbidity because all the possible clinical manifestations of ARAS can also be caused by other complications of atheromatous disease (Table 1).

This article will discuss clinical scenarios in which ARAS should be considered with a view to revascularisation. The increasing refinement and availability of computed tomography (CT) and magnetic resonance (MR) angiography make definitive investigation simpler and safer than traditional angiography. Duplex scanning of the renal artery may have a role, but it is highly operator-dependent and can be impossible in obese subjects even in skilled hands.

The introduction of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (AIIRA) has both unearthed previously silent cases of ARAS and made the diagnosis more important. Drugs of both classes abolish AII mediated glomerular efferent arteriolar constriction which is vital to maintain glomerular filtration rate (GFR) when renal perfusion pressure is reduced. This loss of GFR is independent of the cause of reduced renal blood flow and is also seen in the presence of hypotension or hypovolaemia of any cause as well as in renal artery stenosis. The effect of these drugs is dose dependent to some extent, and their effect on renal function in ARAS may also be masked by intravascular volume overload and/or hypertension. If the

Key Points

- **Atheromatous renal artery stenosis (ARAS) is common in arteriopaths**
- **All the clinical manifestations of ARAS have more common causes in arteriopaths**
- **ARAS and chronic renal failure (CRF) often co-exist, but the CRF is not usually due to the ARAS (and therefore not improved by revascularisation)**
- **The role of intervention in preventing end-stage renal failure remains unclear**
- **The response to intervention in hypertension is usually no better than mild improvement**
- **When pulmonary oedema is due to ARAS, the response to intervention can be dramatic**
- **When acute oliguric renal failure occurs as a consequence of renal artery occlusion, excellent renal recovery can occur after intervention**

KEY WORDS: atheromatous renal artery stenosis, ischaemic nephropathy, athero-embolic nephropathy, renovascular hypertension

drug is stopped promptly, the effect on renal function is normally fully reversible.

Specific management will not be discussed in this article, but patients with ARAS are likely to benefit from healthy lifestyle modifications, blood pressure lowering and statins.

ARAS as a cause of hypertension

Theoretical background

Reduced renal blood flow stimulates renal renin release, which in turn increases production of angiotensin II and aldosterone:

- AII raises blood pressure by its potent vasoconstrictor effect
- aldosterone causes renal salt and water retention; this effect is largely nullified by the normal kidney in unilateral ARAS as a result of pressure-induced natriuresis, but causes fluid retention in bilateral ARAS (Fig 1) or in ARAS in a solitary functioning kidney (Figs 2(a) and (b)).

Confounders

ARAS is a marker of severe generalised atherosclerosis which usually develops in a setting of long-standing essential hypertension. Many patients will also have significant parenchymal renal damage that will be contributing to the hypertension. Clearly, successful intervention can at best improve blood pressure (BP) control.

Clinical clues

An obvious pointer is sudden worsening of previously well controlled BP in a patient known to have vascular disease.

Although ACEI/AIIRA will probably significantly reduce GFR in the affected kidney in unilateral ARAS, this may not be reflected in serum creatinine (SCr) if the contralateral kidney has good function. An increase in SCr of up to 30% following introduction of ACEI is common in the setting of chronic renal failure (CRF) of any cause. It simply reflects reduction of glomerular perfusion in the remaining nephrons which, in the presence of hyperperfusion, is protective against further nephron damage.[2]

Table 1. Clinical manifestations of atheromatous renal artery stenosis and more likely alternative diagnoses.

Severity	Clinical manifestation	Other causes
Unilateral or bilateral	Hypertension	Essential hypertension
Bilateral	Progressive CRF	Hypertensive and/or athero-embolic nephropathy
Bilateral	ACEI induced renal failure	Low output heart failure
Bilateral	Pulmonary oedema	Left ventricular failure

ACEI = angiotensin-converting enzyme inhibitor; CRF = chronic renal failure.

Evidence

Studies of revascularisation for ARAS show very low cure rates and relatively minor improvements in BP, in sharp contrast to the good results of revascularisation for fibromuscular dysplasia (Fig 3).[3,4] It is possible that substantial benefit in a small proportion of individuals is not revealed in trials that have to look at group outcomes.

RECOMMENDATION: investigation is recommended in (a) long-standing hypertensives with recent worsening of BP control and evidence of atheromatous vascular disease in any organ, and (b) hypertensives whose SCr rises by more than 30% after introduction of an ACEI/AIIRA.

ARAS as a cause of renal impairment

1 Progressive chronic renal failure

Theoretical background

This is an area in which there is controversy. Indisputably, ARAS can progress to renal artery occlusion (RAO). The chance of developing RAO is proportional to the

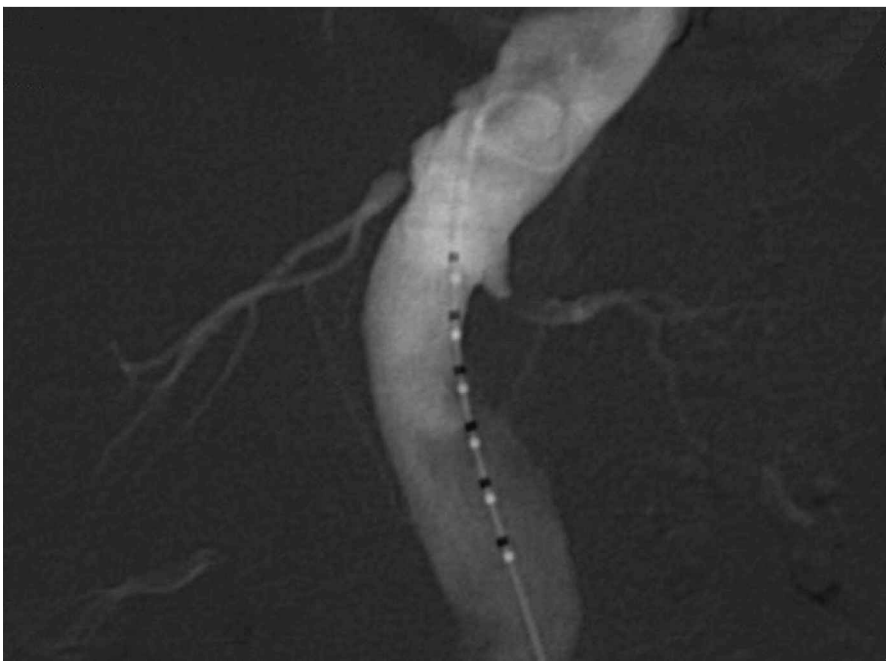

Fig 1. Intra-arterial digital subtraction angiography showing bilateral renal artery stenosis and extensive nonrenal arterial disease (by kind permission of Dr Bill Leen, Consultant Radiologist, James Cook University Hospital).

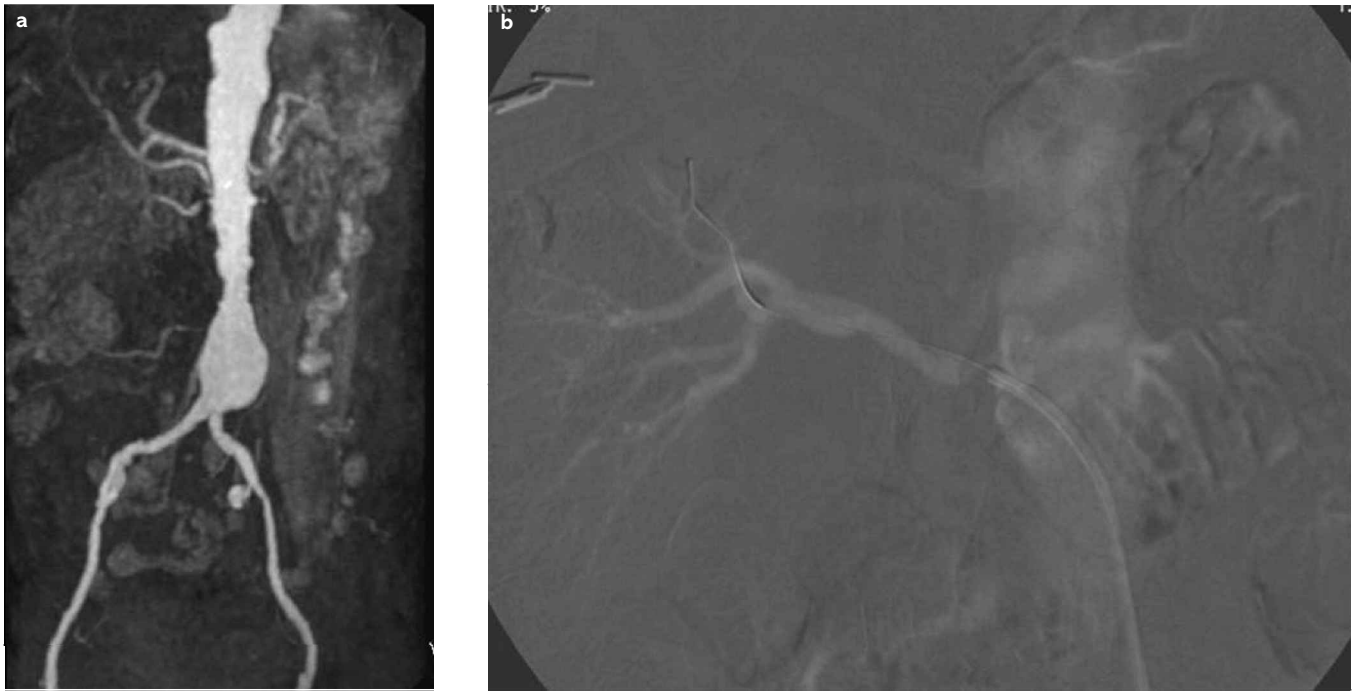

Fig 2. (a) Magnetic resonance angiogram (MRA) showing right renal artery stenosis and left renal artery occlusion (note extensive non-renal arterial disease); **(b)** intra-arterial digital subtraction angiogram of the same patient confirming MRA findings, with guide wire crossing stenosis. Dilute appearance of contrast is due to gadolinium as contrast agent to prevent nephrotoxicity (by kind permission of Dr Bill Leen, Consultant Radiologist, James Cook University Hospital).

degree of stenosis. A kidney beyond an RAO usually atrophies if renal blood flow is not restored, although collateral circulation often prevents immediate infarction.

Hypothetically, ARAS (not RAO) can cause 'ischaemic nephropathy' (gradual nephron loss due to poor blood supply), but this theory is increasingly discredited. Gradual nephron loss is not usually seen despite very tight stenoses in fibromuscular diseases of the renal artery, so poor blood supply in itself seems an inadequate explanation for the CRF often seen in ARAS. CRF progressing over months to years is not likely to be due to ARAS.

ARAS can cause end-stage renal failure (ESRF) if both renal arteries become occluded. The problem for the clinician is that those most at risk (one artery occluded, the other stenosed) are likely to have stable renal function until late in the evolution of the stenosis. Renal function beyond a very tight stenosis becomes inversely proportional to blood pressure; these patients may also develop recurrent pulmonary oedema or ACEI-induced acute renal failure (ARF) (see below).

Although it is highly likely that revascularisation might reduce the risk of RAO in some patients with severe ARAS, even without intervention these patients are much more likely to die of nonrenal vascular disease than reach ESRF.[5,6]

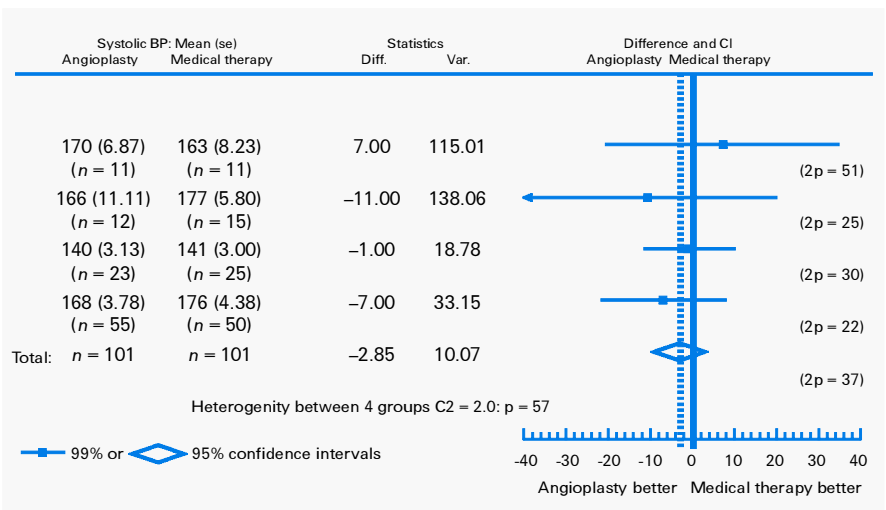

Fig 3. Meta-analysis of randomised controlled trials of effects of renal artery revascularisation on blood pressure (BP blood pressure; CI = confidence interval) (reproduced, with permission, from Ref 3).

Although it is highly likely that revascularisation might reduce the risk of RAO in some patients with severe ARAS, even without intervention these patients are much more likely to die of nonrenal vascular disease than reach ESRF.[5,6]

Confounders

Recent studies have shown that progressive CRF and ARAS often coexist even with unilateral ARAS. Individual kidney GFR estimations show function to be:

- as bad in nonstenosed kidneys
- unrelated to the degree of stenosis, and
- unchanged after revascularisation (Fig 4).[7–9]

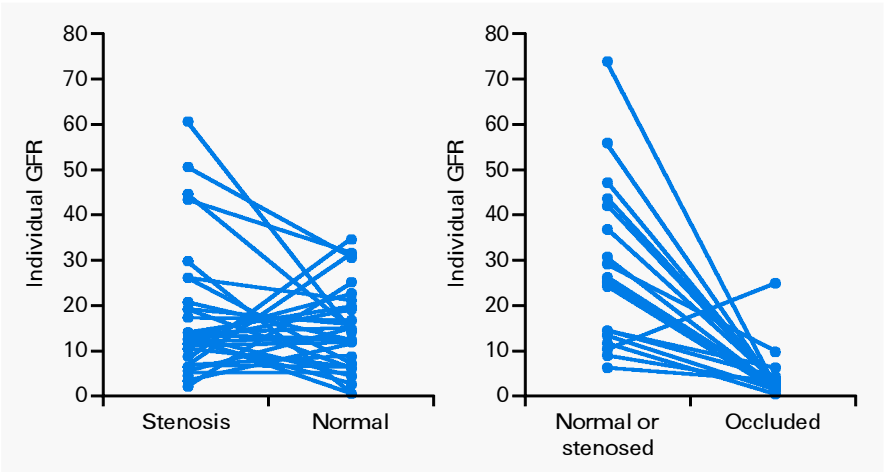

Fig 4. Individual kidney function is reduced in kidneys with occluded renal arteries but not stenosed renal arteries in comparison with contralateral kidneys with nonstenosed arteries (GFR = glomerular filtration rate) (reproduced, with permission, from Ref 7).

CRF appears to result not from the stenosis but from a combination of hypertensive nephropathy and so-called 'athero-embolic nephropathy' in which the renal damage is due to cholesterol and athero-emboli arising from the diseased aorta.

Clinical clues

ACEI/AIIRA in bilateral ARAS (most commonly occlusion on one side and a stenosis on the other) normally produces a rapid large rise in SCr from a normal or slightly elevated baseline. In bilateral ARAS, GFR becomes proportional to systemic BP, and any drug which produces a significant drop in BP will also elevate SCr. Lack of progression of CRF does not rule out significant bilateral ARAS – or indeed progression of the stenosis.

Ultrasonography may show renal asymmetry as a pointer to unilateral RAO. Gradually progressive CRF is more likely to point to athero-embolic nephropathy than to worsening ARAS.

Evidence

There are numerous claims of renal functional improvement or stabilisation after intervention in CRF, but these are variously flawed.[10] Good BP control and attending a nephrology clinic have both been shown to stabilise CRF, so the contribution of intervention to apparent improvement is often unclear. On theoretical grounds, those most likely to benefit will have a tight stenosis to a solitary but well functioning kidney. As the stenosed kidney still has good function, successful intervention will have little impact on baseline SCr. The benefit (reduced risk of RAO, and therefore of ESRF) is not discernible in individuals. Proof that intervention is worthwhile would require a randomised controlled comparison of intervention versus medical treatment, with follow-up to death or ESRF. ASTRAL, the largest ever randomised trial of intervention in ARAS is currently underway in the UK.[11] This may shed light on the relative risks and benefits of intervention in the various settings described here.

A common finding in most studies is that the likelihood of stabilisation of renal function diminishes with the degree of renal impairment. This supports the theory that ARAS is seldom the cause of CRF even when both problems coexist.

The future

The pressure to intervene has recently increased as the benefits of ACEI become clear. Many patients with ARAS fulfil criteria for treatment with ACEI to reduce their risk of cardiovascular events.[12] In the presence of bilateral ARAS, however, an adequate dose of ACEI normally causes ARF. Successful revascularisation often allows safe institution of ACEI therapy, although there is unlikely ever to be a randomised controlled trial to prove that revascularisation to allow the introduction of ACEI is beneficial.

RECOMMENDATION: investigation is indicated in patients with an ACEI or AIIRA induced rise in SCr of more than 30%, especially if not associated with hypotension.

2 Sudden onset oligo-anuric renal failure

Theoretical background

When the stenosis to a solitary functioning kidney progresses to occlusion, renal blood flow becomes insufficient to maintain GFR. The occlusion occurs after prolonged ARAS, so renal collaterals are sufficiently developed to prevent immediate renal infarction; revascularisation within a few days can restore renal function.

Clinical clues

The patient is typically oliguric, hypertensive and increasingly oedematous (pulmonary and/or peripheral). SCr rises by about 200–300 μmol/l per day. Loin pain is rare, but when it occurs may indicate infarction and therefore predict a poor response to revascularisation. Occlusion can be precipitated by relatively minor hypotensive episodes, and the diagnosis should be considered when ARF follows apparently straightforward surgery. A new onset oligo-anuric renal failure is an absolute indication for urgent nephrological referral, but this rare cause is unlikely to be missed by a general physician.

Evidence

There are several anecdotal reports of good sustained recovery of renal function.[13] The enthusiasm for reporting reflects the gratifying response to intervention rather than the incidence.

RECOMMENDATION: consider renal artery imaging in anyone with vascular disease and sudden onset of unexplained oligo-anuric renal failure (Table 2).

Pulmonary oedema

Theoretical background

In bilateral ARAS (or unilateral ARAS plus a nonfunctioning contralateral kidney), excess AII and aldosterone production and failure of pressure-natriuresis cause severe hypertension, fluid retention and often dramatic onset pulmonary oedema – frequently aggravated by left ventricular (LV) impairment secondary to hypertension and/or coronary artery disease.

Clinical clues

Pulmonary oedema in a hypertensive arteriopath is not unreasonably usually assumed to be caused by LV failure. With the widespread introduction of ACEI for LV failure, most cases of pulmonary oedema due to bilateral ARAS should be unmasked by a big rise in SCr within a few days of starting ACEI. Other nonspecific clues include well preserved LV function on echocardiography and high BP.

Confounders

Low output heart failure causes poor renal perfusion. ACEI commonly raises SCr in this setting.

Evidence

The frequency of anecdotal reports again reflects spectacular benefit rather than incidence.[14]

RECOMMENDATION: renal artery imaging should be performed when SCr rises more than 30% after starting ACEI/AIIRA treatment for pulmonary oedema in the absence of hypotension due to low output heart failure (Table 2).

Table 2. Indications for renal artery imaging.

- A rise in serum creatinine >30% after starting ACEI/AIIRA
- Sudden loss of BP control in long-standing essential hypertension
- Recurrent pulmonary oedema associated with hypertension and well preserved LV function
- Unexplained acute oligo-anuric renal failure

The presence of risk factors for, or clinical evidence of, atheromatous disease always increases the likelihood of ARAS

ACEI = angiotensin-converting enzyme inhibitor; AIIRA = angiotensin II receptor antagonist; ARAS = atheromatous renal artery stenosis; BP = blood pressure; LV = left ventricular.

Incidental findings

There are two common ways in which ARAS is incidentally unmasked:

1 *Abdominal ultrasonography* for any indication may demonstrate one small kidney, which in a hypertensive arteriopath could well be due to RAO. The question is not what to do about the apparently affected kidney but whether the *better* kidney has a silent ARAS, particularly if ACEI is considered for either BP control or cardiac reasons. ACEI effects are reversible, so ACEI can be introduced with careful early SCr monitoring. However, because of the increasing availability of CT and MR angiography, in the future most such patients will probably have renal artery imaging prior to ACEI treatment.

2 ARAS may also be discovered at the time of *nonrenal arteriography*. When the indication for arteriography is peripheral vascular disease, the risk of ESRF over long-term follow-up is low.[18] It would seem reasonable to refer cases of bilateral ARAS to a nephrologist as there are good reasons to consider intervention (see above).

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5 Please shade circles like this: ● Not like this: ✔
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7 Please do not mark any of the black squares on the corners of each page
8 Please fill in your full name and address on the back of the answer sheet in the space provided; this will be used to mail the form back to you after marking.

1 A 35-year-old woman, who is known to have autosomal dominant polycystic kidney disease (ADPKD) and mild hypertension, comes to the clinic with her eight-year-old daughter. She is aware of the possibility that she has passed ADPKD on to her daughter. The daughter is asymptomatic, but the mother wonders if she needs to be screened. The mother has two other children, aged five and three years. Which of the following statements are true and which are false?

(a) A DNA sample (venous blood or buccal scraping) should be obtained from the daughter and sent for mutational analysis

(b) The daughter should be thoroughly examined, including blood pressure (BP) and urinalysis; if no abnormalities are found and the kidneys cannot be palpated, the mother can be reassured that her child is not affected

(c) An ultrasound scan should be arranged; the diagnosis of ADPKD is confirmed even if this shows only one cyst in one kidney