

ATHEROSCLEROTIC RENAL ARTERY STENOSIS, ACE INHIBITORS, AND AVOIDING CARDIOVASCULAR DEATH

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John Main

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Atherosclerotic renal artery stenosis (ARAS) has become topical since the development of percutaneous angioplasty and stenting. Studies defining the place for intervention have been difficult to perform and inconclusive. However, it is becoming clear that intervention makes only a modest contribution to blood pressure control. Furthermore, although ARAS is often present in elderly patients with renal impairment, the contribution of intervention to preventing progression of renal failure has been disappointing. The increasingly widespread use of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) has increased the clinical relevance of ARAS, and may be altering the indications for intervention. ARAS is more likely to end in cardiovascular death than renal failure, suggesting that it may be more rewarding to focus on the heart than the kidneys in this condition.

WHY HAVE CLINICAL TRIALS REVEALED SO LITTLE ABOUT ARAS?

There is a stark difference in our understanding of the benefits of intervention in coronary artery disease (CAD) as opposed to ARAS. There are three principal reasons for this: the non-specific nature of the clinical sequelae of ARAS, all of which have more common causes (table 1); a lack of understanding of the link between ARAS and renal damage; and the relative rarity of pathologically significant ARAS, which precludes intervention trials of the size which have informed the management of CAD.

The relation between CAD and its clinical sequelae is relatively clear cut. Coronary artery narrowing produces angina, and angina in the presence of coronary artery narrowing is almost invariably caused by that narrowing. Coronary artery narrowing increases the risk of arterial thrombosis and myocardial infarction, and myocardial infarction has no other common cause. The relation between ARAS and clinical disease is much more complex.

Renal artery narrowing may activate the renin–angiotensin–aldosterone system (RAAS) and raise blood pressure, but the vast majority of those with ARAS have pre-existing essential hypertension. ARAS and impaired renal function commonly co-exist, but many patients with severe renal impairment (loss of 70% or more of renal function) have unilateral stenosis (which at worst could cause loss of 50%). In a recent example, 21 of 35 patients with ARAS and severe renal impairment (serum creatinine > 300 $\mu\text{mol/l}$) had only a unilateral stenosis.¹ Furthermore, in cases with unilateral ARAS and renal impairment, split function studies show equally severe loss of function in both kidneys.² Although it has often been assumed that the co-existence of ARAS and renal impairment implies cause and effect, this clearly often cannot be so. It is becoming increasingly apparent that chronic progressive renal failure is common in arteriopathies whether or not they have ARAS, probably caused by a combination of hypertensive nephropathy and so called atherosclerotic nephropathy. Atherosclerotic nephropathy is not yet clearly defined but is a useful concept to explain the progressive renal damage seen in some hypertensive arteriopathies. It is probably caused by a combination of hypertensive and ischaemic damage, the latter arising from micro- and cholesterol embolisation to the kidney. The shared predispositions explain the common co-occurrence with ARAS. Almost all studies of the incidence of ARAS in patients with end stage renal failure (ESRF) have assumed that the ARAS caused the ESRF—they are therefore overestimates. Studies of the incidence of new ESRF developing in those with ARAS show that it is much rarer than cardiovascular death. For example, during follow up of 98 patients with ARAS and initially poor renal function (mean creatinine clearance 35.5 ml/min), 35 died (at least 25 of cardiovascular causes), whereas only nine progressed to ESRF.³

There is no doubt that glomerular filtration rate (GFR) can be reduced by ARAS and improve after intervention. For the most part, this is a haemodynamic effect which does not lead to nephron loss. Beyond a tight ARAS (probably at least 75%, see discussion below), GFR becomes proportional to systemic blood pressure. Successful revascularisation will restore GFR and remove the dependence on blood pressure. Much more controversial is the assumption that the nephrons beyond an ARAS are gradually dying because of ischaemia. It is worth noting that progressive

Correspondence to:
Dr John Main, Renal Unit,
James Cook University
Hospital, Marton Road,
Middlesbrough TS4 3BW, UK;
john.main@stees.nhs.uk

Table 1 Clinical presentations of ARAS and alternative causes

Clinical presentation	Alternative causes
▶ Hypertension	Essential hypertension; renal impairment
▶ Renal failure	Hypertensive or atherosclerotic nephropathy
▶ Pulmonary oedema	Left ventricular failure

Table 2 Traditional pointers to possible ARAS

- ▶ Recent significant worsening of longstanding hypertension, especially if associated with any rise in serum creatinine
- ▶ Rapid worsening of renal function (that is, over weeks). Gradual loss of renal function (over months and years) is more likely caused by atherosclerotic or hypertensive nephropathy
- ▶ Sudden onset anuric renal failure, when ARAS to a single functioning kidney progresses to acute occlusion
- ▶ Acute pulmonary oedema—especially in association with good left ventricular function

renal failure is highly unusual in cases of fibromuscular disease of the renal artery, despite very tight stenoses.

Again, although there is no doubt that bilateral ARAS can cause recurrent pulmonary oedema,⁴ in the group of patients with pulmonary oedema and generalised arterial disease, hypertensive or ischaemic left ventricular failure are more likely causes. This very high level of confounding pathologies producing similar clinical problems makes it very difficult to design and interpret trials of intervention in ARAS. Such trials are further hampered by the number of possible combinations of pathological and clinical abnormalities. Even if the severity of stenosis is only stratified into three levels (say, > 50%, > 90%, and occlusion), there are two kidneys to consider, and multiple clinical scenarios—for example, level of renal function, rate of change of renal function, degree of hypertension, and presence or absence of pulmonary oedema. Should patients with a 50% unilateral ARAS and a serum creatinine concentration of 500 µmol/l be in the same trial of intervention as those with a 95% stenosis to a solitary functioning kidney and a serum creatinine of 180 µmol/l? Obviously not, unless recruitment is so vast as to allow adequate stratification, but the logistical problems of mounting separate trials for each possible combination seem insurmountable.

New technology in imaging, angioplasty, and stenting and increasing familiarity of operators with intervention are also reducing risk and restenosis rates. This further reduces the usefulness of trials—firstly, the risk of intervention is not that of the trial, it is that of the local unit; and secondly, in the time any trial takes to complete, technology improves, casting doubt on the current relevance of the results.

The level at which a stenosis starts to produce clinical effects remains unclear. As with all new medical or surgical treatments, the invention of angioplasty encouraged case finding erring on the side of over-diagnosis. Many reports opt for a diagnostic cut off of > 50% two dimensional luminal narrowing. It is likely that many stenoses at this level are not haemodynamically significant (that is, result in activation of the RAAS).⁵ A cut off of 75% is more likely to identify a group suffering adverse consequences of ARAS.⁶ This discrepancy partly explains the disparity between the apparently alarming frequency with which ARAS is found on screening patients with vascular disease elsewhere (for example, 34% of elderly heart failure patients)⁷ and the remarkable rarity of ACE inhibitor or ARB induced renal impairment in huge cardiological trials of these drugs in patients with multiple risk factors for ARAS (for example, 2% in a trial of over 65 year olds with heart failure).⁸

WHEN TO LOOK FOR ARAS

This area was covered in the last review of ARAS for *Heart*.⁹ The four clinical settings traditionally thought to make it worth considering ARAS are shown in table 2.

It is increasingly easy to safely visualise the renal arteries, particularly with magnetic resonance angiography (MRA) which avoids the risks of x ray exposure, arterial puncture, and contrast nephropathy (fig 1). It seems likely that the problem for clinicians in the future will not be who to investigate but deciding when a demonstrated lesion is likely to be clinically relevant, and whether the risks of intervention are exceeded by the potential benefits. It should be noted that we already know that incidental ARAS can for the most part be safely ignored, at least as a cause of renal failure. One hundred and twenty six patients were incidentally found to have an ARAS > 50% during angiography for peripheral vascular disease. None had renal revascularisation, and after 8–10 years follow up, none had developed ESRF.¹⁰

ARAS IN THE ERA OF ACE INHIBITORS AND ARBS: EVERYTHING IS DIFFERENT

The introduction of ACE inhibitors and ARBs has had profound effects on the diagnosis, investigation, and treatment of ARAS. It is probable that the renal effects of ACE inhibitors and ARBs in the presence of ARAS are close enough to allow them to be considered identical—and henceforth in this article reference to ACE inhibitors implies ARBs as well.

ACE inhibitor induced acute renal failure (ARF) occurs in settings where glomerular afferent arteriolar blood flow is reduced, and GFR is therefore dependent on AII mediated efferent arteriolar vasoconstriction. It should be stressed that ACE inhibitor induced ARF is not dependent on a drop in blood pressure or renal blood flow after the introduction of



Figure 1 Magnetic resonance angiogram showing right renal artery stenosis, left renal artery occlusion, and aneurysmal dilation of the abdominal aorta.

an ACE inhibitor. Indeed, in the presence of a significant stenosis, renal blood flow and GFR are blood pressure dependent—so any intensification of antihypertensive treatment can cause reduced GFR. A sudden rise in serum creatinine after introduction of an ACE inhibitor is particularly likely to reflect ARAS if there has been no drop in blood pressure.

ACE inhibitor induced ARF is not a specific indicator of ARAS. It occurs whenever GFR is AII dependent. In the patient population at risk of ARAS likely to be prescribed ACE inhibitor treatment, the two most common other causes are low output heart failure and longstanding hypertension. In patients with longstanding hypertension, functional or anatomical vasoconstriction of intrarenal arteries and arterioles is the cause of reduced glomerular blood flow.

An ACE inhibitor induced rise in serum creatinine is also usual in the presence of chronic renal failure of any cause. The normal compensatory increase in filtration rate in surviving nephrons is AII dependent and therefore abolished by ACE inhibition. This results in an increase in creatinine (of no more than 30%) followed by stability, and actually indicates likely long term renal benefit from continued ACE inhibitor treatment.^{11 12}

Sudden loss of renal function in someone on long established ACE inhibitor treatment is not particularly likely to represent new onset ARAS. Causes of decreased cardiac output or hypovolaemia should be sought first. Sometimes, an apparently stable dose of ACE inhibitor is the culprit. Most ACE inhibitors are renally excreted. In the face of even mild pre-existing renal impairment, ACE inhibitor can start to accumulate. GFR in an ACE inhibitor treated kidney is blood pressure dependent, so a small drop in blood pressure reduces GFR, causing further accumulation of ACE inhibitor and so on.

EFFECTS OF ACE INHIBITOR TREATMENT ON RENAL FUNCTION IN ARAS

To understand further the diagnostic clues given by changes in renal function after ACE inhibitor introduction in patients with ARAS, it helps to consider a few different clinicopathological scenarios. In cases of bilateral ARAS (most commonly ARAS to a solitary functioning kidney with a contralateral longstanding renal artery occlusion (RAO)) and reasonable baseline renal function (serum creatinine < 200 $\mu\text{mol/l}$), the introduction of ACE inhibitor treatment is highly likely to switch off most of GFR. Creatinine will rise significantly, usually within a few days. ACE inhibitor induced renal impairment is a highly sensitive test for the presence of bilateral ARAS. In 52 patients with bilateral ARAS, after ACE inhibitor treatment, creatinine rose by at least 20%, median 38%, maximum 101%.¹³ It should be noted that ACE inhibition is not an absolute—even in the face of bilateral ARAS, the phenomenon of ACE inhibitor induced ARF is partially dependent on ACE inhibitor dose, blood pressure, and volume state. Also, the observed changes in renal function are entirely reversible after discontinuation of ACE inhibitor treatment.

In cases of unilateral ARAS and background parenchymal damage in both kidneys, switching off GFR in one kidney will approximately halve GFR. If baseline GFR is 50–60 ml/min or less, a halving of GFR will approximately double serum creatinine. This degree of change should spark consideration of ARAS. Whether intervention in this setting delays the onset of ESRF is controversial. Although in cardiology it may

Abbreviations

- ▶ **ACE:** angiotensin converting enzyme
- ▶ **ARAS:** atherosclerotic renal artery stenosis
- ▶ **ARB:** angiotensin II receptor blocker
- ▶ **ARF:** acute renal failure
- ▶ **CAD:** coronary artery disease
- ▶ **ESRF:** end stage renal failure
- ▶ **GFR:** glomerular filtration rate
- ▶ **MRA:** magnetic resonance angiography
- ▶ **RAAS:** renin–angiotensin–aldosterone system
- ▶ **RAO:** renal artery occlusion

be true that an open artery is better than a closed one,¹⁴ the rate of progression of most nephropathies is proportional to blood pressure. Restoring patency to a renal artery and exposing the remaining glomeruli to the full force of the systemic blood pressure could hasten the onset of ESRF.

In the presence of unilateral ARAS and good underlying renal function in both kidneys, the use of ACE inhibitor treatment will switch off GFR in one kidney but creatinine will probably remain normal. Whether ACE inhibition alters the outcome in such kidneys is not known. We know that the severity of stenosis predicts risk of occlusion, and occlusion is usually (not necessarily immediately) followed by irreversible loss of function. There is neither compelling reason nor evidence to suppose that ACE inhibitor induced switching off of GFR accelerates nephron death. On the contrary, it is conceivable that good blood pressure control and pharmacologic suppression of the RAAS might delay the progression of ARAS and reduce the risk of occlusion.

Arguably therefore, although full dose ACE inhibitor introduction without a significant rise in creatinine does not exclude the presence of unilateral ARAS, in the absence of poor blood pressure control it allows us to ignore the possibility.

ACE INHIBITION AS TREATMENT FOR RENOVASCULAR HYPERTENSION

ACE inhibition is of course the logical treatment for any renin dependent component of high blood pressure. In the not uncommon setting of a unilateral RAO with a small irreversibly damaged kidney providing < 10% of renal function, ACE inhibition is the treatment of choice (these kidneys have sufficient collateral blood supply to allow them to release significant quantities of renin). This situation is often suspected in a typical patient with one small kidney on ultrasound scanning. Whether it is necessary to exclude contralateral ARAS before commencing ACE inhibitor treatment, or reasonable to simply monitor renal function carefully immediately after introduction, is not clear. In theory one could worry about the progression of a silent non-haemodynamically significant ARAS to the good kidney after introduction of ACE inhibitor treatment. One could equally argue that the use of ACE inhibitor treatment would act as an early warning system, as creatinine will rise before the (probably reversible) ARAS progresses to (possibly irreversible) RAO and therefore ESRF.

RENAL REVASCULARISATION TO ALLOW ACE INHIBITOR USE

The interlinked problems of renal revascularisation to permit ACE inhibitor use, and the high cardiovascular morbidity of ARAS patients, are perhaps currently the most interesting

Atherosclerotic renal artery stenosis: key points

- ▶ Cardiovascular death is much more likely than end stage renal failure in atherosclerotic renal artery stenosis. This should influence investigation and management strategies
- ▶ The high cardiovascular death rate in this group may be related to activation of the renin-angiotensin-aldosterone system (RAAS).
- ▶ Revascularisation may be indicated to directly reduce the stimulus to increased RAAS, and also to allow further pharmacological blockade of the system
- ▶ The difficulties in clearly attributing possible clinical sequelae to renal artery stenosis are a major obstacle to conducting meaningful trials of intervention

aspects of this topic. As the evidence base for the benefits of ACE inhibitor treatment accumulates, it is becoming clear that nearly all patients with ARAS will have some indication for ACE inhibitor use, because of CAD, impaired left ventricular function, cerebrovascular disease, or renal impairment with proteinuria.^{15–16} In patients with bilateral ARAS it is usually impossible to use ACE inhibitor treatment without unacceptable loss of renal function. It is, however, usually possible to re-introduce ACE inhibitor treatment after successful renal revascularisation. Until now, the major reason for intervention in bilateral ARAS with stable renal function, acceptable blood pressure control, and no pulmonary oedema has been to prevent RAO. It has not been shown that the benefits of such a strategy outweigh the risks, although some nephrologists already consider this so likely as to preclude randomised controlled trials. The added theoretical benefits of revascularisation to permit ACE inhibitor introduction make it more likely that intervention will become the norm in this setting.

The benefits of ACE inhibitors and also aldosterone antagonists^{17–18} in cardiovascular disease have drawn attention to the multiple adverse effects of an activated RAAS.^{19–20} High renin hypertension has long been known to predict an adverse outcome.²¹ The severity of ARAS is a predictor of non-renal mortality after adjustment for other risk factors.⁶ Although this could be simply because ARAS is a marker of advanced generalised arterial disease, it is likely that an activated RAAS, independently of any effects on blood pressure or volume status, accelerates the progression of atherosclerosis and contributes to left ventricular dysfunction. This suggests that we should intervene not simply to improve blood pressure control or prevent progression of renal disease, but to switch off overactivity in the RAAS and thereby reduce cardio- and cerebrovascular morbidity and mortality. This probably requires not only revascularisation but thereafter introduction of ACE inhibitors and also aldosterone antagonists. The RAAS will probably remain overactive after revascularisation because of almost inevitable co-existent intrarenal vascular and parenchymal damage, and the extra benefit seen with aldosterone antagonism on top of ACE inhibition in trials may be due to suppressing the phenomenon of aldosterone escape.²²

ARAS: THE NEAR FUTURE

Perhaps the two certainties about ARAS in the next few years are: firstly, that it will be increasingly diagnosed (because of the ready availability of MRA); and secondly, in deciding what to do about these lesions, big trials are unlikely to provide unequivocal guidance. However, we already know

that the underlying disease process in ARAS and CAD is the same. Furthermore, the outcome for ARAS patients is broadly similar to those with CAD, and the treatments should also be similar—aggressive risk factor management and the use of ACE inhibitors or ARBs and aldosterone antagonists. Introduction of ACE inhibitors which does not result in a significant rise in serum creatinine may well be increasingly used as a convenient surrogate for the absence of clinically relevant ARAS. If these drugs do produce an unacceptable loss of renal function and there is no other obvious cause for ACE inhibitor induced ARF, the safety of MRA makes it an attractive tool to confirm or exclude ARAS. Amenable lesions will be stented to allow re-introduction of ACE inhibitor treatment.

We know that ARAS is common in patients with CAD, and we also know that CAD is more common in arteriopathies when they also have ARAS.²³ Whether screening for prognostically significant but clinically silent CAD in ARAS is worthwhile is unknown. Unlike many questions surrounding ARAS, it is perhaps answerable.

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F T Leong

Department of Cardiology, Addenbrooke's Hospital, Cambridge, UK

L O Hughes

Department of Cardiology, Norfolk and Norwich University Hospital, Norwich, UK

Correspondence to: Dr Fong Leong, F.T.Leong@leeds.ac.uk