Renal artery stenosis and hypertension

Whom and how to screen and treat

ROB MACGINLEY
MB BS, BMedSci, MMedSci, MClinEpi, FRACP

GEORGE MANGOS
MB BS, MD, FRACP

Patients with renal artery stenosis are at high risk of cardiovascular events. Aggressive medical therapy to lower cardiovascular risk is the first priority in these patients; endovascular treatment is required in only a few carefully selected cases.

Renovascular disease, often presenting in the patient with vascular disease and no other symptoms, has been considered a common and potentially treatable cause of secondary hypertension. However, whether medical therapy or endovascular treatment is the optimal strategy for patients with renovascular disease has been an area of contention. Recent evidence now suggests that the benefit of angioplasty of the renal arteries may be limited to selected patients.

The scope of this review is to direct clinicians to the groups of patients who may require screening, to discuss the appropriate modalities of screening and to consider the selection of patients for intervention in addition to the successful medical management that currently occurs.

Dr MacGinley is a Nephrologist at Geelong Hospital, and Senior Lecturer in Medical Education at the School of Medicine, Deakin University Medical School, Geelong, Vic.
Associate Professor Mangos is a Nephrologist and Associate Professor of Medicine at the St George Clinical School, University of New South Wales, and St George Hospital, Sydney, NSW.
Associate Professor Mangos is Convenor and Dr MacGinley a member of the Caring for Australasians with Renal Impairment (CARI) Renovascular Working Group. The group's evidence-based guidelines on the management of renovascular disease will be published early in 2010 and will be available on the CARI website (www.CARI.org.au).

IN SUMMARY

- **Renovascular disease is common and is an underlying cause in a significant proportion of patients who have refractory hypertension.**
- **The appropriate selection of patients for investigation and subsequent interventional treatment is the key. Interventional treatment for severe renal artery stenosis (RAS) is reasonable in patients with poorly controlled hypertension despite taking more than four antihypertensive agents, pulmonary oedema with normal left ventricular systolic function, a progressive decline in renal function or recent end-stage kidney disease.**
- **Although magnetic resonance angiography and spiral computed tomography angiography are more accurate than other imaging techniques in detecting RAS, the benefits of these modalities must be weighed against their potential side effects.**
- **Appropriate medical therapy with multiple medications, including antihypertensive agents, antiplatelet agents and statins, is probably as effective in the nonselected population as interventional therapies.**
- **Cardiovascular mortality is high in patients with RAS: the key aim of therapy is to target cardiovascular risk factors to prevent mortality and morbidity.**

Who develops renal artery stenosis?

The following case is typical of a patient who may present in general practice and in whom a diagnosis of renal artery stenosis (RAS; Figure 1) should be considered. Comments on the appropriate assessment and treatment of this patient are discussed later in the article.

Case study

A 75-year-old man comes to your practice with a blood pressure of 160/70 mmHg. He has been a smoker, had high lipid levels and had poorly controlled hypertension for the past 10 years despite taking four antihypertensive agents.

Clinical examination demonstrates carotid bruits, no renal bruits and a fourth heart sound. His serum creatinine level is 150 µmol/L (estimated glomerular filtration rate [eGFR] 45 mL/min) and urinalysis shows 1+ protein.

The ultrasound of his renal tract shows a discrepancy in renal size (right 10 cm; left 7.8 cm) and a suggestion of increased velocity in the renal artery of the smaller kidney; however, there is too much interference to make any significant conclusion about the presence of RAS.

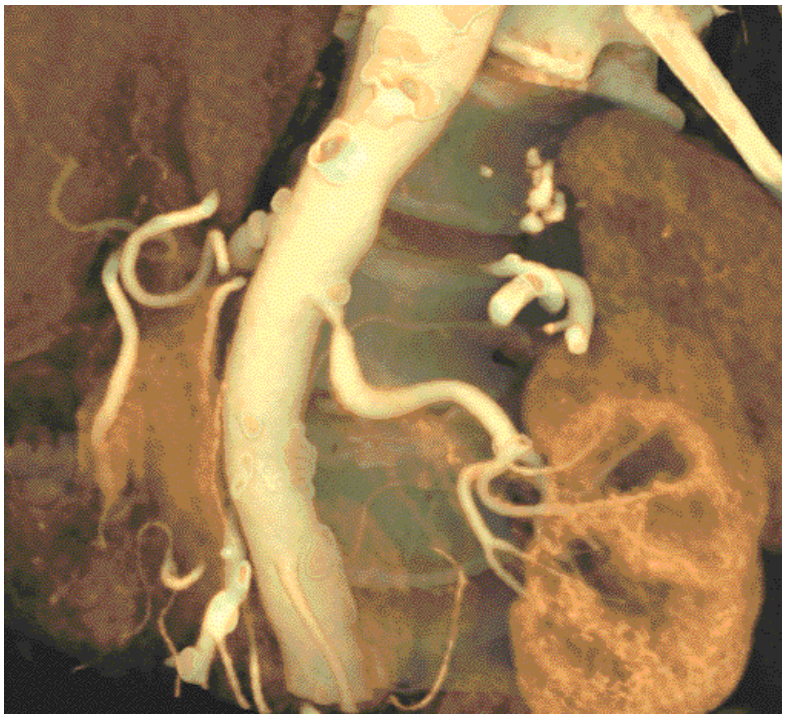
How should this patient be further evaluated and treated?

Aetiology of renal artery stenosis

With the increasing incidence of hypertension, chronic kidney disease (CKD and/or diabetes in our population, the finding of atherosclerotic disease of the cerebral and coronary vessels in patients with these conditions is expected. However, we now know that there is a high likelihood that such patients will also have renal artery atherosclerotic disease.

Studies from the 1960s and 1970s showed that 27% of patients over 50 years of age had more than 50% stenosis of their renal artery (autopsy data) and up to 6% of cohorts with hypertension undergoing arteriography had RAS. In patients with refractory hypertension, between 20 and 40% of unselected subjects have been shown to have RAS.[1]

There is evidence that RAS is progressive, with studies conducted prior to interventions or medical treatments (such as statins) estimating a 14 to 39% progression of lesions over one to six years.[2] A clearer understanding of accurate progression rates is difficult to obtain because this atherosclerotic population has a high mortality rate. In the recent Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) study, 26% of patients with atherosclerotic renovascular disease died from a cardiovascular event during the five-year study duration.[3]



PHOTOLIBRARY

Figure 1. Spiral computed tomography angiogram showing severe stenosis of the left renal artery.

Classification of renovascular disease

Renovascular hypertension is systemic hypertension due to narrowing of the renal arteries. Although large and small (that is, intrarenal) vessel disease can exist, from a haemodynamic point of view, a proximal stenosis is significant when there is a pressure gradient across the stenosis. This pressure gradient triggers intrarenal adaptive mechanisms distally, leading to renal ischaemia and hypertension. The presence of coexistent small vessel disease will render the kidney nonresponsive to revascularisation.

RAS has two main aetiologies: atherosclerosis and fibromuscular dysplasia. Atherosclerosis accounts for 70 to 90% of cases of RAS and usually involves the ostium and proximal third of the main renal artery.[4] Fibromuscular dysplasia is a collection of vascular diseases that affects the intima, media and adventitia and is responsible for 10 to 30% of cases of RAS.[5]

Despite the many studies in the literature, there is no unifying classification of the degrees of stenosis versus severity and outcome. At least a 50% narrowing is necessary to produce a pressure gradient as mentioned above, as shown by a study combining three-dimensional magnetic resonance angiography (MRA) and direct measurements

Table. Selection of patients for revascularisation of high-grade renal artery stenoses*

- Patients with refractory hypertension (blood pressure >160/100 mmHg and resistant to more than four antihypertensive agents)
- Patients who experience a greater than 30% rise in serum creatinine level after the commencement of ACE inhibitor or ARB therapy
- Patients with a progressive and rapid decline in kidney function with other causes excluded
- Patients with proven episodes of pulmonary oedema and normal baseline left ventricular function (often associated with severe hypertension)
- Patients with a high-grade stenosis (>70%) recently commenced on dialysis who have viable kidney tissue diagnosed by nuclear scanning (to attempt to recover dialysis-independent kidney function)

* Based on evidence reviewed in references 1 and 4. Includes evidence from both case studies and randomised controlled trials.

ABBREVIATIONS: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

across a stenotic lesion.[6] Despite a lack of consensus, most authors use a reduction in luminal diameter of 50% as a cut-off point to define the presence of haemodynamically significant RAS.[6] In the soon to be published Caring for Australasians with Renovascular Disease (CARI) guidelines, the following classification has been devised based on the likelihood of progression:[1]

- less than 50% stenosis: insignificant
- 50 to 70% stenosis: moderate
- more than 70% stenosis: severe.

Diagnosis and assessment

Although all the imaging modalities used to investigate RAS have improved over the past decade, they do have potential side effects, which must be considered when selecting the most appropriate investigation for each patient. Additionally, in groups in whom significant harm is possible from undergoing screening diagnostic tests, there is the principal that any tests should be performed only in those who have a high pretest probability of having the disease. In the context of RAS, such patients may have impaired renal function, hypertension requiring more than four antihypertensive agents, diabetes or vasculopathy, or a renal bruit.

Case study continued

The patient has had refractory hypertension for many years, and investigations have revealed that the renal vascular bed is affected with a shrunken kidney (likely from ischaemia) and proteinuria of a level consistent with vascular disease. Although it is possible that this patient might experience side effects from imaging, he has a high pretest probability of having RAS and should therefore be further investigated.

Which imaging test to use?

The reported diagnostic accuracies of the different imaging tests used to investigate the renal arteries overlap, and the sensitivities and specificities of these tests vary according to methodological issues, specific patient groups and gold standard comparisons. The selection of the diagnostic test will depend on local resources available, cost and local expertise and experience, in addition to patient factors.

Duplex ultrasonography

The least invasive test is duplex ultrasonography, which, in the hands of teams with technical expertise, is a useful screening tool. Unfortunately, subsequent tests are often required because of the high rate of false-positive and false-negative results. Of note, the sensitivity and specificity of ultrasonography vary depending on the skill of the laboratory, and generally this investigation is of limited use in obese individuals. The calculation of the renal resistive index (RI) may predict the response to revascularisation – for example, a low RI indicates a healthy kidney distal to a stenosis.

Intra-arterial digital subtraction angiography

Intra-arterial digital subtraction angiography (IA-DSA) is regarded as the definitive tool to diagnose the presence of RAS. It is the only investigation that directly measures the lumen size of the renal artery and can measure a pressure gradient across most lesions. However, it is invasive, does not establish the functional nature of the stenotic lesion, and the degree of stenoses may be subject to substantial interobserver variations. In patients with large atherosclerotic burden, the significant complication of cholesterol embolic syndrome can result.

Renal scintigraphy

Renal scintigraphy is no longer recommended for the diagnosis of RAS based on its poor accuracy and the promised functional benefits in trials have not resulted in better outcomes in either treatment or diagnosis.

Spiral computed tomography angiography

It is reasonable to recommend spiral computed tomography angiography (spiral CTA) as an accurate, minimally invasive screening test especially suited to the diagnosis of RAS due to fibromuscular dysplasia. However, in patients who have moderate CKD (eGFR <60 mL/min) or more severe CKD, prehydration with intravenous saline (with or without n-acetyl cysteine or sodium bicarbonate) should be used to reduce the incidence of contrast nephropathy. If contrast nephropathy develops, management is expectant, and dialysis is rarely required. Usually renal function recovers fully, although it is not uncommon to observe some loss of GFR in patients with underlying CKD secondary to the contrast insult.

Gadolinium-enhanced MRA

Gadolinium-enhanced MRA is highly sensitive in detecting atherosclerotic RAS and has significantly higher accuracy than any other modality in excluding the disease. The use of gadolinium in patients with eGFR less than 30 mL/min should be avoided in view of the risk of the relatively recently described nephrogenic systemic fibrosis, which is most likely to occur with repeated doses of gadolinium in patients with end-stage kidney disease. Nephrogenic systemic fibrosis is an illness causing fibrosis of skin and other tissues (not unlike scleroderma) and may not be reversible.

Case study continued

If the resources were available, the specialist would most likely consider spiral CTA for this patient or move directly to IA-DSA because he has poorly controlled hypertension.

What to do when renal artery stenosis is diagnosed?

Patients with renovascular disease have a markedly increased risk of coronary events, stroke, heart failure and death. Indeed, the risk of these events is significantly greater than the risk of progression to end-stage kidney disease. Although the immediate concern in patients with RAS is the control of blood pressure, overall cardiovascular mortality needs to be reduced. Aggressive medical therapy to reduce this risk is the first priority and supported by the evidence.[1,3] Referral to a renal specialist (or a similar hypertension specialist) for consideration of the involvement of interventional vascular clinicians is required in only a few selected cases (see the Table). There is no indication for recurrent imaging to follow renal size or the degree of stenosis. Knowledge of any progression of a stenosis does not dictate the required intervention. However, vascular physicians may organise follow-up imaging for patients with stented arteries at six months then yearly.

Diet and lifestyle

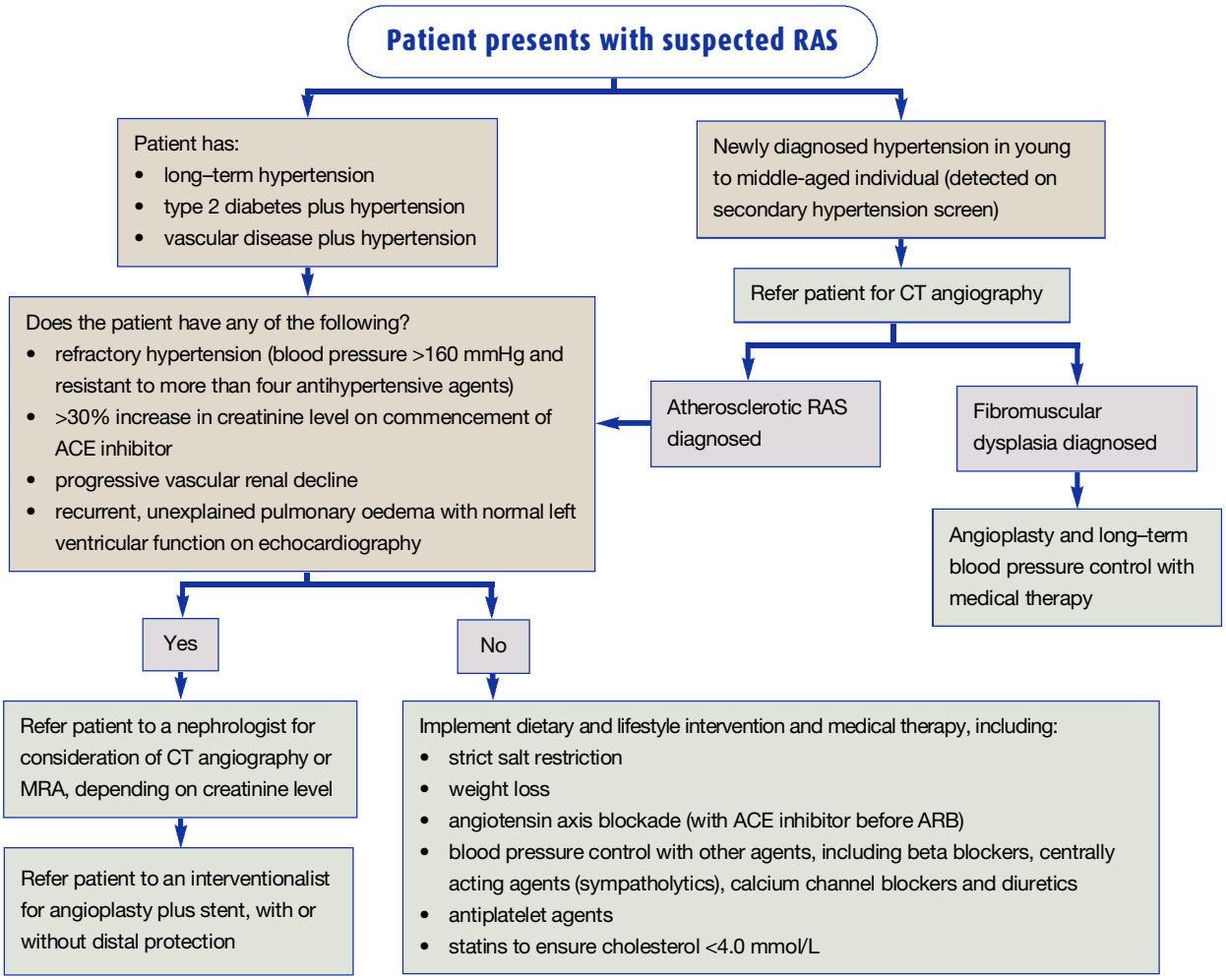
As in patients with other vascular diseases, salt restriction, weight loss, physical activity and cigarette cessation are likely to benefit patients with RAS by reducing their overall cardiovascular risk. In the recent ASTRAL study, patients with any degree of RAS (vascular burden) had a high mortality, probably secondary to uncontrolled hypertension or the existence of vascular disease in other beds.[3]

Medical therapy

In patients with unilateral RAS, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are useful for their ability to improve blood pressure and their overall cardiovascular benefit. A small initial rise in serum creatinine (less than 30%) is usually transient (i.e. occurring for less than three months) and acceptable.[5]

Bilateral RAS is considered a contraindication to the use of

Diagnosing and managing renal artery stenosis (RAS)[1,4]



ABBREVIATIONS: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CT = computed tomography; MRA = magnetic resonance angiography.

ACE inhibitors and ARBs. Acute renal failure occurs in about 30% of patients with bilateral RAS but is usually reversible. Initiation of ACE inhibitor or ARB therapy in such patients would usually be undertaken in hospital and in patients in whom the benefit would be very high (for example, in those with congestive heart failure).[7] It is essential that renal function is monitored if ACE inhibitors or ARBs are used in patients with bilateral RAS (greater than 60%) or in patients with RAS (greater than 60%) to a solitary functioning kidney. This includes initial testing at five and seven days and then two weeks after the initiation of a low dose of the medication.

Generally, ACE inhibitors should be used before ARBs in view of the large body of evidence for ACE inhibitors in many vascular disease states, and their lower cost. However, evidence for the use of ARBs in reducing mortality from cardiovascular disease is accumulating.

No other agents have been shown specifically to be as beneficial as ACE inhibitors or ARBs in this vascular population, but beta blockers, calcium channel blockers, diuretics and centrally acting agents are often used in combination due to the refractory hypertension that occurs in these patients.[5]

Although not formally studied in any comparative studies versus placebo, it would be standard practice for all patients with renovascular disease to be taking aspirin and/or another antiplatelet agent and a statin, both to delay renal disease progression and to reduce their high risk of cardiovascular mortality.

Endovascular treatment – definitely not for all

The effect of endovascular treatment of RAS on blood pressure reduction has been studied in more than 60 uncontrolled studies. Controlled studies have now involved more than 1000 unselected patients with renovascular disease randomised to medical treatment or renal angioplasty, with or without stenting (the largest of these studies being the ASTRAL study).[3] There has been no difference in either blood pressure reduction or renal decline after 12 months when medical therapy has been compared with revascularisation overall. Disappointingly, the adverse event rate in those undergoing angioplasty has ranged from 10 to 25% in the controlled studies, indicating that angioplasty is not without serious complications.

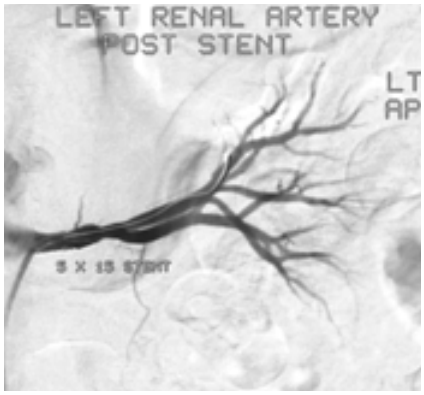


Figure 2. Stent placed in the left renal artery of an elderly woman with atherosclerotic renal artery stenosis.

Since there is no level 1 evidence (that is, evidence from systematic review of randomised controlled trials) supporting the use of revascularisation for unselected patients, it seems reasonable to restrict revascularisation to those patients with high-grade lesions (that is, greater than 70% stenosis) associated with specific clinical problems (see the Table) in specialised centres (demonstrating low complication rates). In making a decision regarding endovascular intervention in renovascular disease, clinicians must also consider the age of the patient and relative prognosis regarding other comorbidities – for example, a conservative approach is probably appropriate for older patients.

When the clinical decision to revascularise has been reached, the procedure of choice in patients with atherosclerotic RAS is renal artery stenting (Figure 2), with or without a distal protection device (a device that prevents intraluminal cholesterol from seeding and damaging the kidney downstream from the angioplasty). This is because angioplasty alone has been associated with significant rates of restenosis, and surgical revascularisation is very expensive and has no proven benefit over medical or endoluminal therapy.[4]

There have been no studies of revascularisation in patients with mild or moderate renal stenosis. It seems prudent to offer medical therapy early in these individuals, given the natural history of progressive stenosis in atherosclerotic renal disease.

Fibromuscular dysplasia should be treated by balloon angioplasty alone, based on currently available uncontrolled data.[4]

The flowchart on page 28 summarises the steps in the diagnosis and management of RAS based on the evidence reviewed in both the CARI guidelines and a recent *New England Journal of Medicine* review.[1,4]

Case study continued

Based on this patient's poorly controlled hypertension and the evidence of renal damage with a shrunken kidney, proteinuria, reduced eGFR and probable high RI (not clear due to a poorly performed ultrasound), a renal specialist became involved.

Angiography, with the use of very little contrast and prior nephroprotective strategies, was undertaken and demonstrated a near occluded RAS on the side of the shrunken kidney but only a 50% stenosis on the 10 cm kidney side. Because of this patient's age and these findings, angioplasty was not carried out. The renal specialist became involved in the aggressive medical control of this man's refractory hypertension and his high, long-term cardiovascular risk.

Conclusion

The number of patients diagnosed with renovascular disease is likely to increase with the rising incidence of hypertension and diabetes in our population. Although the imaging modalities for renal artery disease have improved, their side effects need to be balanced against their improved sensitivity when considering their use.

Medical therapy with multiple medications is probably as effective in the nonselected population of patients with renovascular disease as interventional therapies. Only in carefully selected patients and under specific circumstances should angioplasty, with or without stenting (depending on the RAS aetiology), be considered and its benefits carefully balanced against its risks. MT

References

1. CARI. Renovascular disease. Nephrology Suppl. In press 2010.
2. Schreiber MJ, Pohl MA, Novick AC. The natural history of atherosclerotic and fibrous renal artery disease. Urol Clin North Am 1984; 11: 383-392.
3. Astral Investigators. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med 2009; 361: 1953-1962.
4. Dworkin LD, Cooper CJ. Renal-artery stenosis. N Engl J Med 2009; 361: 1972-1978.
5. Hackam DG, Spence JD, Garg AX, Textor SC. Role of renin-angiotensin system blockade in atherosclerotic renal artery stenosis and renovascular hypertension. Hypertension 2007; 50: 998-1003.
6. Vasbinder GB, Nelemans PJ, Kessels AGH, et al. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: meta-analysis. Ann Intern Med 2001; 135: 401-411.
7. Tullis MJ, Caps MT, Zierler RE, et al. Blood pressure, antihypertensive medication, and atherosclerotic renal artery stenosis. Am J Kidney Dis 1999; 33: 675-681.

COMPETING INTERESTS: None.