

Review

Atherosclerotic renal artery stenosis—the challenge of patient mortality

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Date accepted for publication 10 February 2003

Abstract

In this article we review mortality and cardiovascular disease incidence and prevention—in particular focusing on the role of ACEI and angiotensin receptor blockers in reducing blood pressure and providing 'nephro' and 'cardio' protection.

Keywords: Atherosclerotic renal artery stenosis; mortality; ACE inhibitors.

Introduction

In this review article we shall be discussing the vexed issue of patient survival in atherosclerotic renal artery stenosis (ARAS). We shall not be venturing into the controversy surrounding the decision about renal arterial intervention and its effect on blood pressure and renal function. Radermacher *et al.* have championed the concept of the resistive index to predict the outcome of revascularisation^[1]. The ASTRAL trial that has already randomised 235 patients will try to solve the problem of the best course of action in ARAS.

We hope to establish the case that the treatment of ARAS should include statin-based lipid-lowering therapy, aspirin, and should be angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) based, complemented by impeccable BP control. There are problems with the use of ACEI but do they arise in absolutely all situations in ARAS? It is important to review the renal, and general, fate of patients diagnosed with ARAS.

The population

ARAS is a long-term cause of hypertension and renal failure. Although the real incidence of ARAS

is unknown, its importance is growing because of the increased mean age of the population and the greater prevalence of hypertensive and diabetic populations. Atherosclerosis in different vascular beds is common in these patients^[2].

Baboolal's study from 1998 reported the mortality rate, rate of decline in renal function and incidence of end-stage renal disease (ESRD) in 51 patients with bilateral ARAS followed-up for a median period of 52 months^[3]. None of these patients had undergone any surgical or radiological intervention. Renal function was determined by serial measurements of serum creatinine. Bilateral ARAS was associated with a high mortality rate. The crude mortality rate at 60 months was 45%. Assessment of renal function showed impaired renal function at time of angiography and a non-uniform and variable decline in renal function during the period of observation. The median glomerular filtration rate (GFR) decreased from 39 ml/min (range 15–80 ml/min) at time of angiography to 31 ml/min (range 10–70 ml/min) and 24 ml/min (range 10–40 ml/min) at 24 and 60 months, respectively ($P < 0.05$). The calculated mean rate of decline in GFR for all patients was 4 ml/min/year (range 1–16 ml/min/year). Over the 5 years, there was a progressive increase in the incidence of ESRD. Of the original 51 patients who underwent angiography, six

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patients reached ESRD. The crude incidence of ESRD was 12% in untreated ARAS.

To assess the prevalence of ARAS in the elderly population, one recent population screening exercise used participants in the Forsyth County cohort of the Cardiovascular Health Study who were invited to undergo renal duplex sonography (RDS) to define the presence or absence of ARAS (defined as a stenosis with a focal renal artery peak systolic velocity exceeding 1.8 m/s in the main renal artery and defined as occlusion when an imaged renal artery lacked a Doppler signal)^[4]. 870 CHS participants underwent RDS. Of these examinations, 834 (96%) were technically adequate to define the presence or absence of ARAS. The RDS study cohort had a mean age of 77.2 ± 4.9 years and consisted of 63% women and 37% men. The overall prevalence rate of RVD was 6.8%. Among the 57 patients with RVD, 50 (88%) had unilateral disease and 7 (12%) had bilateral disease. Seven cases were seen of renal artery occlusion (RAO), including one case with contralateral renal artery stenosis^[4].

The consequences for renal function and patient survival of ARAS have been shown to be dire, particularly if the patient eventually requires renal replacement therapy. A report has been published recently of patients with peripheral vascular disease and coincident ARAS who were followed prospectively—98 patients (71 men) with more than 50% ARAS (unilateral 64, bilateral 34) were recruited for study^[5]. Measurements of serum creatinine, blood pressure and renal size were recorded at baseline and every 6 months, for at least 2 years. Data were available for 85 patients with a minimum follow-up of 2 years. The mean age was 71 (range 51–87) years. All 52 patients with unilateral renal artery stenosis were managed conservatively; 21 of the 33 patients with bilateral disease had no intervention and the remaining 12 had angioplasty or reconstruction. The overall mortality rate was 32% at 2 years (27 patients) and this was similar in all three groups. In only 3 patients was death related directly to renovascular disease; coronary disease accounted for the majority of deaths. All 3 patients who needed dialysis died within 1 year. In survivors there was a significant increase in serum creatinine concentration at follow-up. Blood pressure did not increase significantly^[5].

In a recent report 50 men and 48 women were identified with ARAS^[6]. Mean age at entry was 68.7 ± 8.3 (SD) years, and baseline creatinine clearance (CrCl) was 35.5 ± 20.7 ml/min. During follow-up (27.7 \pm 18.7 months), 10 patients required dialysis therapy, 11 patients underwent revascularisation, and 35 patients (36%) died^[6]. The same group has reported on patients with unilateral RAO—of 299 patients with ARVD who had presented to a single centre over a 12 year period, 142 (47.5%) patients with RAO were identified^[7]. There was no relationship between baseline renal function and contralateral renovascular anatomy. Patients with contralateral normal, insignificant (<50%), or significant (>50%) renal artery stenoses had baseline creatinine

of 243 ± 235 , 292 ± 197 , or 210 ± 102 $\mu\text{mol/l}$, respectively, but patients with bilateral RAO (creatinine, 540 ± 304 $\mu\text{mol/l}$; $P < 0.0001$) were significantly worse. Over a mean follow-up period of 31 ± 21 (2–82) months, the overall rate of progressive renal functional decline was -4.1 ml/min/year. Nine patients required dialysis at presentation and a further 15 (10.5%) during the course of the study. There were 85 (59.9%) deaths; median survival of the whole group was 25 months, and 5-year survival was 31%. Multivariate analysis indicated that low baseline GFR was the chief variable independently associated with increased probability of death or need of dialysis but that renal vascular anatomy had no prognostic impact^[7].

A recent report using the massive resources of the USRDS focused on survival of ARAS patients on dialysis programmes^[8]. The incidence trends, clinical features, prior treatment, and survival of patients with ARAS-ESRD were determined. Primary causes of ESRD were assessed in patients starting ESRD therapy during 1991–1997. The incidence of ARAS-ESRD increased from 2.9/100 000 per year (1.4% of new ESRD cases) to 6.1/100 000 per year (2.1%). The annualised increase was 12.4% per year. Alarming, and even in the USA, the spiritual home of type II diabetes, this was a greater rate of increase than for ESRD from diabetes mellitus (DM-ESRD; 8.3% per year) and ESRD overall (5.4% per year). The risk for ARAS-ESRD vs. other-cause ESRD correlated positively with age (odds ratio (OR), 1.7 per 10-year increment; $P < 0.0001$) and male sex (OR, 1.2; $P < 0.0001$) and negatively with black (OR, 0.17; $P < 0.0001$), Asian (OR, 0.29; $P < 0.0001$), and Native American race (OR, 0.31; $P < 0.0001$). The unadjusted prevalence of coronary heart disease, cerebrovascular disease, and peripheral vascular disease was greater in patients with ARAS-ESRD vs. other-cause ESRD ($P < 0.001$). Of patients with ARAS-ESRD, 5% underwent revascularisation in the 2 years before ESRD compared with 0.5% of patients with other-cause ESRD, including DM-ESRD. Adjusted for age, race, sex, comorbidity, and laboratory values, the survival of patients with ARAS-ESRD was similar to that for patients with other-cause ESRD (risk ratio, 1.01; $P = 0.5$). These findings suggest that RVD-ESRD is increasing faster than other-cause ESRD in North America and is not independently associated with an increased mortality risk—but the type of patient who experiences ARAS-ESRD is a severe vasculopath^[8].

ARAS as a facet of organ damage

Since in most people ARAS is part of a diffuse atherosclerotic disease, it is not known whether these complications are due to ARAS itself or to the systemic vascular disease. Support for the latter concept also comes from a cross-sectional analysis of end-organ damage from raised BP comparing essential

hypertensives with patients with ARAS using a case control study of 92 patients divided into two groups (46 in each), one with renovascular hypertension (RVH) and the other with essential hypertension (EH) and abdominal aortic aneurysm, with a comparable degree of diffuse atherosclerotic vascular disease^[9]. The vascular state of the extracranial carotid arteries and abdominal and inferior limb districts was investigated with angiography and sonography. The prevalence of left ventricular hypertrophy (LVH) and ischaemic heart disease (IHD) was assessed by electrocardiography. Serum creatinine and urinary protein excretion were employed in the renal evaluation. While the analysis of the results confirmed an even diffusion of atherosclerotic vascular disease between the two groups, a significant difference was found in the prevalence of heart and renal damage. LVH was present in 32.6% of atherosclerotic nephropathy (AN) patients vs. 10.8% in EH ($P = 0.02$). Serum creatinine > 135 mmol/l was found in 50% of RVH and in 23.9% of EH ($P = 0.01$). The prevalence of proteinuria in RVH was also higher although not reaching statistical significance. The results suggest that, in patients with comparable degrees of atherosclerotic vascular disease, AN is responsible for the higher prevalence of target organ damage in this condition compared to those with EH^[9].

From these reports we have to conclude that the 'best' medical therapy is likely to be targeted at the diffuse abnormality of vessel structure and function. There is increasing evidence for activation of the renin-angiotensin and the sympathetic nervous systems in these patients. For methodological reasons, the findings in humans regarding whether elevated sympathetic nerve activity contributes to RVH have been less consistent compared with the results obtained in experimental models of RVH. There are several lines of evidence to support the view that sympathetic nerve activity is elevated in patients with RVH. It is uncertain whether this adrenergic over-activity is specific for RVH or is the cause of severe hypertension with target organ damage. Central or peripheral stimulation of sympathetic nerve activity by angiotensin II, or stimulation of central sympathetic outflow via afferent renal nerves of ischaemic kidneys, are possible mechanisms to explain the elevated sympathetic nerve activity in RVH^[10].

In a recent study, a total of 14 patients with hypertension were studied before angioplasty of angiographically identified RAS^[11]. Nine out of 14 patients had RVH proven at the 1-year follow-up visit. A total of 19 healthy subjects served as a control group. Right heart catheterisation, including the positioning of a coronary sinus thermodilution catheter was performed for haemodynamic recordings and blood sampling. Using a radiotracer dilution technique with infusion of tritiated noradrenaline and adrenaline, fractional extraction and clearance were calculated. Total body and cardiac noradrenaline spillovers were used as indices

of systemic and cardiac sympathetic nervous activity. The study group had normal left ventricular ejection fraction and cardiac pressures. Cardiac noradrenaline spillover was increased by 127% in the hypertensive patients compared with healthy subjects (200 ± 53 vs. 88 ± 10 pmol/min in controls, $P < 0.05$). Total body noradrenaline spillover was similar in both groups. 26 and 47% decreased cardiac fractional extraction of noradrenaline and adrenaline, respectively, compared with normotensive subjects ($P < 0.01$ for both). Patients with ARAS and hypertension had altered cardiac sympathetic function with increased sympathetic drive and impaired catecholamine extraction. The increased cardiac sympathetic drive may have adverse long-term effects on prognosis (LVH, arrhythmias) in this patient group with high cardiovascular mortality^[11].

Clues that alleviating ARAS may be beneficial

A general comment must be made about the landmark HOPE study reported in 2000^[12]. Here, over 9000 subjects at increased vascular risk were randomised to receive either Ramipril 10 mg, or vitamins, with placebo for each active arm. There was an impressive reduction in mortality in the Ramipril group, compared with the non-ACEI/ARB group, despite a similar BP. ARAS patients are at even higher risk than HOPE subjects from adverse vascular events^[12].

A recent investigation determined whether the insertion/deletion (I/D) polymorphism of the ACE gene is associated with the high prevalence of target organ damage reported in ARAS^[13]. A total of 65 atherosclerotic patients (age 68.2 ± 5.2 years) with ARAS and 49 atherosclerotic patients (age 68.0 ± 6.3 years) with EH were sequentially enrolled when attending the outpatient clinic for specialist assessment of their vascular disorder. Cardiac, renal, and vascular involvement were assessed in both groups and blood was taken for genetic analysis. Patients with ARAS had a higher prevalence of LVH, carotid artery disease, and albuminuria than those with EH. In ARAS, but not in EH, the DD genotype was significantly associated with severe arterial disease. In ARAS, carotid disease (lumen narrowing $> 60\%$) was present in 62% of DD patients vs. 25% of the other genotypes (OR = 4.90, 95% confidence interval (CI): 1.70–14.13). Such an association was also present in peripheral vascular disease; 72.4% in DD patients vs. 41.6% in the other genotypes (OR = 3.67, 95% CI = 1.29–10.36). Logistic regression analysis showed that the DD genotype was the strongest predictor of risk of severe carotid disease. Thus, there was an association of the severity of vascular disease with the DD genotype of the ACE gene^[13].

The same group also investigated whether DD genotype was a risk factor for mortality in RVD by performing

a follow-up study of 61 ARAS patients (age 68.0 ± 6.5 years) enrolled after angiographic demonstration of a renal artery stenosis^[14]. The average follow-up was 48.1 ± 14.9 months. Genotype was I/D in 30 patients, DD in 27 patients, and II in 4 patients. At enrolment, a complete assessment of heart, blood vessels, and renal function was performed. During the follow-up period, 13 patients died (9 DD, 4 ID) and 7 patients evolved into end-stage renal failure. The cumulative survival rate at 5 years was $45.4 \pm 13.4\%$. Factors associated with mortality were analysed with Cox proportional hazard regression. The multivariate analysis showed that DD genotype, severe carotid disease, and smoking were independent predictors of mortality. The multivariate analysis of predictors of renal failure showed that the only significant association was found with a baseline serum creatinine level of $265 \mu\text{mol/l}$ or greater. The DD genotype of the ACE gene was a marker for mortality in RVD^[14].

The practical employment of ACEI/ARB in ARAS patients has been reported recently by Tullis *et al.*^[15]. A cross-sectional analysis was performed on 139 patients with ARAS. All patients had at least one diseased renal artery by duplex ultrasound. Renal arteries were classified as normal, less than 60% stenosis, or 60% or greater (high-grade) stenosis. Data regarding blood pressure, coexisting risk factors, and medications were collected. The extent of ARAS was significantly associated with progressive elevation of the systolic blood pressure, whereas the diastolic component was elevated in the case of unilateral high-grade stenosis: no high-grade stenoses, $153 \pm 22/81 \pm 10$ mmHg; unilateral high-grade stenosis, $162 \pm 22/86 \pm 9$ mmHg; and bilateral high-grade stenoses, $174 \pm 27/82 \pm 9$ mmHg ($P = 0.002$ systolic; $P = 0.02$ diastolic). 82% of the patients were taking known antihypertensive medications. ACEI usage vs. non-usage was associated with a significantly lower systolic (157 ± 27 vs. 169 ± 22 mmHg; $P = 0.03$) and diastolic (79 ± 9 vs. 85 ± 9 mmHg; $P = 0.001$) blood pressure. The effect of ACEI usage was observed in patients with high-grade ARAS. None of the other classes of antihypertensive medications were associated with significantly lower blood pressure. In patients with ARAS, blood pressure levels were correlated with the severity of renal artery disease. Patients taking ACEIs had significantly lower blood pressures, and the effect of ACEI usage was strongest among patients with unilateral ARAS.

It would be redundant here to review the large amount of evidence that places ACEI/ARB at the forefront of measures known collectively as 'nephro-protection'^[16,17]. Of course, as more and more patients receive ACEI/ARB-based therapies as the number of indications increases, these patients are at risk of acute renal failure, for example in the context of dehydration, or serious intercurrent illnesses. Patient education about the actions of these powerful drugs is mandatory, as it is for statins.

What shall we use if we won't use ACEI/ARB?

Here we enter the realm of realism. We are proposing ACEI/ARB-based antihypertensive therapy, not ACEI/ARB monotherapy, as monotherapy cannot hope to control BP adequately. If we eschew ACEI/ARB will we then have greater recourse to calcium-channel blockers? We have mounting concerns about these drugs in the context of scarred failing kidneys with significant proteinuria. Two large important trials have cast significant doubt on (dihydropyridine) calcium-channel blocker use. The first, in hypertensive African Americans with chronic renal failure, compared the effects of an ACEI (Ramipril), a dihydropyridine calcium-channel blocker (amlodipine), and a beta-blocker (metoprolol) on hypertensive renal disease progression. The trial used 1094 African Americans aged 18–70 years with hypertensive renal disease (GFR of 20–65 ml/min per 1.73 m^2) enrolled between February 1995 and September 1998^[18]. Participants were randomly assigned to receive amlodipine, 5–10 mg/day ($n = 217$), Ramipril, 2.5–10 mg/day ($n = 436$), or metoprolol, 50–200 mg/day ($n = 441$), with other agents added to achieve one of two blood pressure goals. Among participants with a urinary protein to creatinine ratio of >0.22 (corresponding approximately to proteinuria of more than 300 mg/day), the Ramipril group had a 36% (2.02 (SE, 0.74) ml/min per $1.73 \text{ m}^2/\text{year}$) slower mean decline in GFR over 3 years ($P = 0.006$) and a 48% reduced risk of the clinical end points vs. the amlodipine group (95% CI, 20–66%). In the entire cohort, there was no significant difference in mean GFR decline from baseline to 3 years between treatment groups ($P = 0.38$). However, compared with the amlodipine group, after adjustment for baseline covariates the Ramipril group had a 38% reduced risk of clinical end points (95% CI, 13–56%), a 36% slower mean decline in GFR after 3 months ($P = 0.002$), and less proteinuria ($P < 0.001$). Ramipril, compared with amlodipine, retarded renal disease progression in patients with hypertensive renal disease and proteinuria and may offer benefit to patients without proteinuria.

The second study concerned type II diabetes^[19]. In this study Lewis and co-investigators randomly assigned 1715 hypertensive patients with nephropathy due to type II diabetes to treatment with irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo. The target blood pressure was 135/85 mmHg or less in all groups. The groups were compared with regard to the time to the primary composite end point of a doubling of the baseline serum creatinine concentration, the development of end-stage renal disease, or death from any cause. The mean duration of follow-up was 2.6 years. Treatment with irbesartan was associated with a risk of the primary composite end point that was 20% lower than that in the placebo group ($P = 0.02$) and 23% lower than that

in the amlodipine group ($P = 0.006$). The risk of a doubling of the serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group ($P = 0.003$) and 37% lower in the irbesartan group than in the amlodipine group ($P < 0.001$). Treatment with irbesartan was associated with a relative risk of end-stage renal disease that was 23% lower than that in both other groups ($P = 0.07$ for both comparisons). These differences were not explained by differences in the blood pressures that were achieved. The serum creatinine concentration increased 24% more slowly in the irbesartan group than in the placebo group ($P = 0.008$) and 21% more slowly than in the amlodipine group ($P = 0.02$).

Doxazosin was dropped prematurely from the ALL-HAT study because of an increased incidence of hospitalised diuretic requiring heart failure episodes in hypertensive patients. While beta-blockers are both logical and effective antihypertensives in the ARAS context as they blunt the sympathetic system activation, they significantly reduce renin synthesis. We all know that many patients are intolerant through tiredness, erectile dysfunction, and worsening of peripheral vascular disease symptoms, of doses sufficient to lower BP adequately.

Conclusions about BP therapy

If we are faced with refractory hypertension in patients where renal arterial intervention alone will not significantly impact BP control, do we have a choice? Can we leave these patients dangerously hypertensive or use ACEI/ARB very cautiously as part of an antihypertensive strategy? Now, the idea of using ACEI/ARB in the context of a small shrivelled renal nubbin, with no worthwhile function we are sure is reasonable (particularly if the other kidney, on which renal function depends predominantly, has normal arterial patency), but there is more to discuss in situations of mild-moderate bilateral ARAS; even more so if the patient originally was diagnosed through ACEI/ARB acute renal failure and has had renal arterial intervention.

Seemingly paradoxically, we think it is easiest to use ACEI/ARB after renal artery stenting where one hopes that restenosis is less likely^[20]. To our knowledge there are no reports of the use of drug-eluting stents in ARAS but this has caused much excitement in many cardiologist circles^[21]. Typically we employ an angiotensin-receptor blocker, low-dose beta-blocker and Indapamide as our first-line agents, and add a calcium-channel blocker to these if needed^[22]. How low a BP to aim for is of course not yet clear but 140/80 mmHg is a vast improvement over 220/120 mmHg, obviously, and at this level on current evidence we feel that BP therapy is optimised. We follow renal function using individualised GFR^[23]. With this approach what we hope is that the patients will get protection through BP reduction and the somewhat mysterious non-BP related effector pathways. These may include endothelial

vasomotor function, preferential reduction of aortic rather than peripheral artery BP by reducing arterial stiffness, anti-atherosclerotic effects, antioxidant effects and other effector pathways at present unknown^[24].

Other indications for ACEI/ARB

These include severe LV dysfunction which is not encompassed by flash pulmonary oedema. In this situation, angioplasty and/or stenting would preserve renal function and also be permissive of ACEI usage, and seems a sensible manoeuvre in this very high-risk population (though of course as elsewhere no randomised controlled trial exists).

Other medical therapies

Statins

The importance of statin-based lipid-lowering therapies in high-risk vascular patients cannot be over-emphasised. The recent Heart Protection Study shows there is substantial survival benefit for the use of a statin for either gender, all ages, diabetic-status, prior overt CVD or just risk factors regardless of starting lipid levels^[25]. It must be appreciated that there are benefits from the use of statins that happen faster than the current accepted mechanisms of their action can easily explain which will include improvement in endothelial vasomotor function, reduction in arterial stiffness, suppression of inflammation, and alteration in plaque morphology favouring a more fibrous, stable lesion^[26]. Case reports of the benefit to individual patients of acute statin therapy also support their more widespread use^[27,28].

Aspirin

The Hypertension Optimal Study provided good evidence of additional benefit of anti-platelet/anti-thrombosis treatment over and above BP reduction in MI (but not stroke) prevention^[29].

The ability of ACEI to lower blood pressure may in part be due to the formation of vasodilatory prostaglandins. Inhibition of prostaglandin synthesis with aspirin may therefore theoretically attenuate the antihypertensive effect of ACEI (as it seems to with conventional doses of typical non-steroidal anti-inflammatories). A small but careful study however gives reassurance that in practice, in doses between 81 and 325 mg aspirin, there is no such interaction with Enalapril and Losartan^[30].

Future therapies

We hope there is some evidence given that the renal community has been terribly slow in introducing

cholesterol-lowering therapy. We fear that we will be just as mean-spirited about other more novel interventions. It will still take years before all renal patients, from diagnosis to death, are given statins (we do not dispute the urgent need for more trials like ALERT, CHORUS and HARP) but the null position surely cannot be no prescriptions?

In this category of 'orphan' risk factor we have homocysteine elevation, seen in the context of minor reductions in GFR, and long associated with significantly greater athero-thrombotic disease in the general population, as well as in renal failure. Homocysteine levels are two to five times higher in dialysis patients than the upper limit of the normal range, and although we lack a 'statin' to reduce them to normal, vitamin supplementation can reduce levels by 50–70%—very worthwhile^[31]. It also seems that folate may, like statins, ACEI and aspirin, have multiple effects^[32].

Yet how many of us bother to think about vitamin supplementation, which seems to have been swept aside in the brave new world of 'evidence-based medicine'? Even with some evidence slowly accruing we can see it is going to be many years before we act^[33].

Final thoughts

This group of patients with ARAS have a terribly high risk of sudden death. Once they have presented themselves with overt atherosclerosis in one or more vascular beds we are expected to undo decades of problems. We may only have months to achieve this. Instinctively we feel that in the current absence of randomised controlled trials we should err on the side of treatment of as many measurable or manipulable vascular risk factors as we can to eliminate the scourge that is atherosclerosis.

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