Abstract

Introduction: Renal artery stenosis (RAS) is not rare, but is often asymptomatic. In older individuals, atherosclerosis is the most common cause of RAS. Atherosclerotic RAS is usually one manifestation of widespread atherosclerotic disease, and its presence increases the morbidity and mortality of other manifestations of atherosclerotic disease.

Review: Renal arterial disease discovered incidentally can be managed expectantly as long as blood pressure and kidney function are well maintained. Revascularization can be considered with the prospect of improving blood pressure control or impaired kidney function, but its outcomes are heterogeneous. The potential for serious deterioration in kidney function after revascularization underscores the need to select patients carefully for vascular procedures in the kidney.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are effective in treating most cases of hypertension in atherosclerotic RAS. In addition, clinical data suggest that the survival of patients with renovascular hypertension is better when ACE inhibitors are part of therapy than when they are not. This benefit may be in part due to the fact that ACE inhibitors reduce morbidity and mortality in congestive heart failure which is common co-morbidity in patients with RAS. Withdrawal of the ACE inhibitor in such patients should occur only when the rise in serum creatinine level exceeds 30% above baseline within the first two months of ACE inhibitor initiation, or if hyperkalemia develops.

Conclusion: Renovascular hypertension is best managed with ACE inhibitors or ARBs as long as blood pressure and renal function are well maintained. Revascularization should be considered if blood pressure control is not adequate or if renal function deteriorates.

Key words: renovascular disease, renal artery stenosis, renal artery occlusion

Introduction

Renal vascular disease manifesting as renal artery stenosis (RAS) is not a rare entity, but is quite often asymptomatic. Among 716 potential living kidney donors who underwent conventional arteriography in a single center, 6.6% had renovascular disease due to fibromuscular dysplasia and 1.7% had renovascular disease due to atherosclerosis [1].

Atherosclerosis is by far the most common cause of RAS in older individuals. Population based studies have shown that hemodynamically significant RAS affects up to 6.8% of individuals above 65 years of age and that its presence is significantly and independently associated with increasing age, low high-density lipoprotein cholesterol levels and increasing systolic blood pressure [2]. RAS is also reported to affect 1-5% of all patients with hypertension [3], and this percentage increases to 17% in case of coexistent diabetes mellitus [4].

Atherosclerotic RAS rarely occurs in isolation, but is usually one manifestation of widespread atherosclerotic disease. This is reflected by the fact that up to 26% of patients referred for evaluation of peripheral vascular disease [5], 10.4% of autopsy patients with stroke [6] and 4.8-15% of patients undergoing abdominal arteriography immediately following coronary angiography [7, 8] have significant RAS.

The complex interaction between atherosclerotic RAS and hypertension is further enhanced by the deleterious effect of RAS on renal perfusion and kidney function. This may explain, at least in part, the negative impact of RAS on the morbidity and mortality of other manifestations of atherosclerotic disease.

In a retrospective analysis of patients with hypertension and renovascular disease, their 5 and 10 year survival rates were found to be 83% and 67% respectively, which was greatly reduced in comparison with that of matched controls in the general population, and was also less than
that of matched hypertensive patients. Age, cigarette smoking and the presence of atheromatous disease were significantly and independently related to outcome among these patients [9].

The prospective Cardiovascular Health Study has also shown that the presence of renovascular disease conferred an increased risk of adverse coronary events, which was not dependent on the effects of associated atherosclerotic risk factors, other prevalent cardiovascular disease, or high blood pressure [10].

In another cohort of patients who underwent abdominal aortography immediately following coronary angiography, the presence of significant RAS was found to be a strong independent predictor of mortality, with an unadjusted 4-year survival rate of 57% compared to 89% in patients without RAS. In addition, bilateral disease was associated with a 4-year survival rate of 47%, compared to 59% in patients with unilateral disease [7].

Also, in a large cohort of patients who underwent intraarterial digital subtraction angiography for peripheral vascular disease (PVD) in a single center, RAS was an independent predictor of mortality. The estimated 5-year survival probability was 37% for patients with RAS as compared with 72% for patients without RAS [5].

Regarding end stage renal disease (ESRD) patients, renovascular disease was characterized clinically in 83 of 683 dialysis patients in a single center. Their 2-year, 5-year and 10-year survival rates were 56%, 18%, and 5% respectively, which was significantly worse than other diagnostic groups [11].

**Review**

Atherosclerotic RAS is progressive in nature. However, the rate of progression is quite variable, and this can have a great impact on management decisions.

In a prospective study among a group of hypertensive patients that used duplex scanning to document the natural history of atherosclerotic RAS, the 2-year cumulative incidence of renal atrophy (a reduction in kidney length of greater than 1 cm) was 5.5%, 11.7%, and 20.8% in kidneys with a baseline renal artery disease classification of normal, less than 60% stenosis, and 60% or more stenosis respectively. Also, there was a significant risk of renal atrophy among kidneys exposed to elevated systolic blood pressure and among those with low renal cortical blood flow velocity as assessed by renal duplex scanning. The occurrence of renal atrophy was well correlated with changes in the serum creatinine concentration [12].

Also, in the DRASTIC trial, 9% of patients who were randomized to receive medical treatment experienced total occlusion of the affected renal artery by 12 months [13].

However, in a prospective population-based study that estimated the incidence of new RAS and the progression of established RAS among elderly Americans with a low rate of clinical hypertension who were followed up for 8 years, progression to significant RAS was observed in only 4% of kidneys, and no case of RAS diagnosed at baseline progressed to occlusion [14].

This demonstrates that renal arterial disease discovered incidentally can pose no problem for either kidney function or blood pressure for several years, and as long as blood pressure and kidney function are well maintained, expectant management appears to be entirely appropriate.

Nevertheless, revascularization of RAS is often considered with the prospect of improving blood pressure control or impaired kidney function. The potential of revascularization to prevent or delay further decline in kidney function in some patients with RAS was documented by a number of observational studies. Impressive early results in this respect were reported by Morris and colleagues, who noted that renal function recovered in eight patients who underwent surgical revascularization at a time before the general availability of dialysis, six of whom returned to essentially normal renal function [15].

Surprisingly, randomized controlled trials comparing percutaneous transluminal renal angioplasty (PTRA) with medical therapy in the treatment of RAS failed to demonstrate any long term benefit on the preservation of renal function in the PTRA group, even though angioplasty was slightly more effective in improving blood pressure control in some studies. Overall, the evidence from these studies was not sufficiently robust to determine the comparative effectiveness of angioplasty and medical treatment in the management of RAS [16, 17].

The failure of these studies to detect a meaningful overall improvement in serum creatinine level may be explained by the heterogeneous outcomes of revascularization. Overall, among RAS patients who underwent PTRA with stenting, 26% had an improvement in glomerular filtration rate (GFR), 48% had a stable GFR, whereas 26% had a decline in GFR [18].

The rapid deterioration in renal function that occurs in some patients after revascularization may be due to the relatively high risk of complications of revascularization. Apart from contrast nephropathy, possible complications of PTRA include hemorrhage, injury to the femoral, iliac or renal arteries, stent thrombosis, distal renal embolism,
septicemia, and cholesterol embolism to the lower limbs [18].

As expected, the risk is even higher for surgical revascularization. In a retrospective analysis that compared surgical revascularization and PTRA in the management of RAS, both procedures had similar efficacy; however, surgical revascularization had a higher complication rate and higher thirty-day mortality than PTRA (9% versus 2%) [19].

The potential for serious deterioration in kidney function after revascularization, percutaneous or surgical, and the possibility of serious complications underscore the need to select patients carefully for vascular procedures in the kidney.

Several factors were explored for the potential of predicting which patient is most likely to benefit from revascularization. A shrunken kidney, a kidney with cortical necrosis or a kidney proven by biopsy to have irreversible damage is not likely to benefit from revascularization. In addition, a duplex ultrasound scan revealing renal resistance index greater than 80 indicates small vessel and large vessel disease. Such findings predict poor response to either percutaneous or surgical revascularization with respect to improvement in hypertension, renal function, or kidney survival [20].

In a secondary analysis of the DRASTIC study, only patients with bilateral RAS had a substantial benefit on creatinine clearance, and they also seemed to benefit most with regard to blood pressure control [21].

In a study of 105 patients with hemodynamically significant atherosclerotic RAS who underwent PTRA with stenting, it was found that the subgroup of patients which initially had a moderately or severely impaired GFR had a significant increase in the calculated GFR one year after the procedure despite no significant change in blood pressure. In contrast, the subgroup which had normal or mildly impaired GFR, had significant reductions in systolic and diastolic blood pressure, but no significant change in the calculated GFR [22].

Among 59 chronic renal failure patients who underwent PTRA for hemodynamically significant RAS, it was found that a rapidly progressive decline in renal function prior to the procedure was associated with a more favorable response to PTRA regarding renal failure progression [23].

Timing of revascularization is also of paramount importance. In a cohort of 241 patients who were treated with PTRA and stent implantation for significant RAS, the long term survival was found to depend largely on renal function and left ventricular function at the time of the procedure; the 5-year survival rates for patients with baseline serum creatinine of more than 2.5 mg/dl, 1.2-2.5 mg/dl and less than 1.2 mg/dl were 29.6%, 89.1%, and 95.4% respectively [24]. Hence, revascularization should not be delayed for a suitable candidate in order to spare him/her the development of advanced ischemic nephropathy or congestive heart failure.

The American College of Cardiology and the American Heart Association have recently published guidelines for the management of patients with peripheral arterial disease, including RAS [25]. According to these guidelines, percutaneous revascularization is indicated for patients with hemodynamically significant unilateral or bilateral RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, hypertension with intolerance to medication, recurrent unexplained congestive heart failure or sudden unexplained pulmonary edema, or unstable angina. It is also indicated for patients with bilateral RAS or RAS to a solitary functioning kidney and progressive chronic kidney disease, and may be considered for patients with unilateral RAS and chronic renal insufficiency. Vascular surgical reconstruction is indicated for patients with RAS who have a clinical indication for revascularization when percutaneous revascularization is not feasible or has been unsuccessful [25].

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are effective in treating 86 – 92% of cases of hypertension and atherosclerotic RAS [26]. As a result of the wider use of these agents for the treatment of hypertension, it is likely that many individuals with renovascular hypertension are never detected but are simply treated.

In addition, clinical data suggest that the survival of patients with renovascular hypertension is better when ACE inhibitors are part of therapy than when they are not [27]. This benefit may be in part due to the fact that ACE inhibitors reduce morbidity and mortality in congestive heart failure [28], which is common co-morbidity in patients with RAS.

However, a major concern regarding the use of ACE inhibitors for renovascular hypertension is their potential to cause functional acute renal failure. A rise in serum creatinine of up to 30% above baseline following the initiation of ACE inhibitors in patients with heart failure is a normal hemodynamic response, and a strong association exists between this acute increase in serum creatinine and long term preservation of renal function; withdrawal of the ACE inhibitor in such patients should occur only when the rise in serum creatinine level exceeds
30% above baseline within the first 2 months of ACE inhibitor initiation, or hyperkalemia develops [29].

The benefits of revascularization for such patient are not limited to restoration of kidney function and improved blood pressure control, but extend to an improvement in heart failure symptoms [40]. Renal revascularization also has the potential to ameliorate the increased risk of adverse coronary events which is associated with renovascular disease [9]. This issue will be addressed by a prospective trial, Cardiovascular Outcomes in Renal Artery Lesions (CORAL), which will examine the effect of intensive medical management versus revascularization with or without stenting on cardiovascular events in patients with RAS [41].

Conclusion

Renal arterial disease discovered incidentally can be managed expectantly as long as blood pressure and kidney function are well maintained. Renovascular hypertension is best managed with ACE inhibitors or ARBs. Revascularization can be considered for a select group of patients with the prospect of improving blood pressure control or impaired kidney function.

References


