

Controversies in the management of the renal artery stenosis

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Abstract

Optimal management of renal artery stenosis has continued to remain elusive. The previous non randomized studies and registry data suggested a benefit of renal artery stenting. However, the recently completed randomized studies comparing renal stenting to medical management failed to show any benefit. These studies had some flaws in their design and methodology. In an appropriately selected patient population renal artery stenting may have a role. In addition, there might be some role of adjunctive therapies like antiplatelet medications and embolic protection. This review summarizes the current literature on this controversial topic. (Cardiol J 2013; 20, 1: 11–16)

Key words: kidney, renal artery stenosis, stenting

Introduction

Renal artery stenosis (RAS) affects approximately 5% of the 50 million people with hypertension in United States. In patients older than 50 years RAS may account for up to 15% of chronic renal failure and 20% with end stage renal disease. The prevalence of RAS of greater than 60% luminal narrowing is approximately 7% in patients who are 65 years of age or older [1]. Most cases of RAS result from arteriosclerosis of the renal artery. In minority, especially in younger subjects it may result from fibromuscular dysplasia. In one study of the Medicare population, the prevalence of symptomatic atherosclerotic RAS was 0.5% overall and approximately 5.5% among those with chronic kidney disease [2]. In another study of elderly population involving duplex ultrasonography, the prevalence was 7% [3]. The prevalence of the atherosclerotic RAS increases with age, particularly in patients who suffer from diabetes, hyperlipidemia, peripheral vascular disease, coronary disease and hypertension.

Caps et al. [4] found that 50% of patients with RAS greater than 60% progressed at the follow-up of 33 months. However, only 3% progressed to complete occlusion in this study. There is a close association between severity of RAS and renal atrophy leading to ischemic nephropathy [4, 5].

Fibromuscular dysplasia

Fibromuscular dysplasia accounts for less than 10% of all cases of RAS. It is usually seen in young (< 40 years) females and involves the mid or distal segments of the renal artery. Fibromuscular dysplasia can be successfully treated with angioplasty. In a study of Tegtmeier et al. [6] percutaneous transluminal renal angioplasty (PTRA) was used to treat 66 patients with 85 renal artery stenoses due to fibromuscular dysplasia. The initial success rate for the procedure was 100%. The recurrence rates were 8% of lesions and 10% of patients. Cumulative patency rate predicted for 10 years was 87.07%. The mean systolic pressure decreased by 52 mm

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Hg and the mean diastolic pressure decreased by 35 mm Hg in response to treatment. Approximately, 40% of the patients were cured, 60% were classified as improved, and only 1 (2%) did not respond to PTR. Renal function was improved in 86% of the patients and stabilized in 14% of the patients.

The optimal medical management for the atherosclerotic RAS (ARAS) continues to remain controversial. Refractory hypertension and end stage renal disease may occur in patients with advanced RAS but the incidence of these outcomes was reported to be low in patients who are treated medically [4, 7, 8]. Except for patients with renal artery occlusion there seems to be a poor correlation between severity of the stenosis and the renal function [9, 10].

Atherosclerotic renal artery stenosis and cardiovascular outcomes

Patients suffering from ARAS are at a higher risk of cardiovascular events. In one study the rate of chronic kidney disease was 25% vs. 2% in patients with and without ARAS. Similarly, the incidence of coronary artery disease was 67% vs. 25%, stroke was 37% vs. 12% and that of peripheral vascular disease was 56% vs. 13%, respectively [2]. Renal insufficiency in patients with ARAS has been associated with decreased survival [11]. The long-term cardiovascular outcomes following coronary angiographies were significantly higher in patients with concomitant ARAS than those without [12, 13]. ARAS has also been associated with left ventricular dysfunction and congestive heart failure [14, 15]. Conversely, improvement in renal function in patients with ARAS following PTR has been reported to improve survival as well as quality of life [16–18].

Current evidence on the role of PTR and stenting in patients with ARAS

As has been previously alluded to, the role of renal angioplasty and stenting has remained controversial. Leertouwer et al. [19] performed meta-analysis on the studies of renal arterial stent placement (14 articles, 678 patients) and renal PTA (10 articles, 644 patients) published up to August 1998. A random-effects model was used to pool the data. The mean follow-up was approximately 17–19 months. In the PTR alone arm of this study technical success was achieved in 77% of patients. Hypertension was cured in 10% and improved in 53% of the patients. Renal insufficiency stabilized in 41% and improved in 38% patients. In the renal stent arm

of the meta-analysis technical success rate was 98%. Hypertension improved in 49% and was cured in 20%. Renal insufficiency improved in 30% and stabilized in 38% of these patients. The restenosis (> 50% at 6 months) was 26% in PTR alone group vs. 17% in the renal artery stenting group. Interestingly the cure rate for hypertension was higher and the improvement rate for renal function was lower after stent placement than after renal PTA (20% vs. 10% and 30% vs. 38%, respectively; $p < 0.001$).

Stenting vs. medical management

Three small randomized, controlled trials showed no benefit of renal stenting combined with medical management over medical management alone [20–22]. A significant improvement in blood pressure (BP) however was noted in the renal stenting arm of one of the studies including patients with bilateral stenosis [21]. However, these earlier trials was that they were small sized and thus underpowered to detect any clinically significant benefit. These trials evaluated surrogate end points like BP, creatinine and reduction in number of hypertensive medications. The medical regimens designed were inadequate and inconsistent. They enrolled patients with < 50% stenosis and the crossover between the treatment arms was allowed but analysis was done on the basis of intention to treat. There were no standardized core laboratories for the assessment of renal angiograms. The biggest flaw of these small trials was that they lacked the analysis on cardiovascular outcomes.

Recent randomized trials comparing stenting plus medical therapy with medical therapy alone

Three recently published randomized controlled trials no benefit of medical therapy with stenting when compared to medical therapy alone [23–25].

NITER trial

Nephropathy Ischemic Therapy trial [23] included the 52 elderly patients with > 70% stenosis. The diagnosis in each of these patients was obtained by Doppler and confirmed by magnetic resonance angiography (MRA). Endpoints of this study included death, initiation on dialysis, decline in estimated glomerular filtration rate (eGFR) by 20% and hospitalization. There was no benefit of preserved renal function or improved survival observed when stenting was added to medical management.

However, there were some serious limitations in the design of this study. This was a small study in which the diagnosis of RAS was primarily made with the Doppler/MRA. The medical therapy was not precisely defined. There was crossover allowed in the study and the study lacked a core laboratory adjudication.

STAR trial

Stenting in Renal Dysfunction Caused by Atherosclerotic Renal Artery (STAR) trial [24] was a multi centric, randomized clinical trial conducted at 10 European centers including, 140 patients with eGFR < 80 mL/min/1.73 m² and a renal stenosis of greater than 50%. The primary endpoint was greater than a 20% decline in eGFR. Seventy six patients were randomized to medical treatment only and 64 patients to both medical treatment and stenting. Of the 64 patients randomized to the stent only 46 patients actually received the stent. Sixteen percent of patients in medical treatment alone arm and 10% in medical treatment plus stent arm reached the end point of > 20% decline in eGFR (p = NS). The groups did not differ in BP control or the composite end point of decline in renal function and survival. There were certain inherent problems with the design of this study. The study groups were small to begin with. The follow-up was short and the study had no core laboratory adjudication. Approximately, 28% of the patients who were randomized to the stent arm did not receive the stent. Medical treatment was poorly defined. The authors of the STAR trial concluded that their results are compatible with both efficacy and harm and therefore were inconclusive.

ASTRAL trial

Angioplasty and Stenting for Renal Artery Lesions [25] was a multi centric randomized trial conducted in European centers in which 806 patients with at least one RAS > 50% and whose physicians were uncertain whether early revascularization was clinically indicated were randomized to stenting and medical therapy vs. medical therapy alone. The primary end point which was defined as a change in renal function measured by the reciprocal of the serum creatinine level, was not significantly different between the two study groups at 5 years of follow-up. The secondary outcomes, including decline in BP and rates of myocardial infarctions, cerebrovascular events, congestive heart failure or risk adjusted mortality were similar in both treatment arms. As was seen with earlier randomized studies, the ASTRAL trial also had certain important

limitations. The study included many patients without clinically significant lesions who would not benefit from renal stenting. Also, this trial was underpowered to detect the difference in cardiovascular events. Almost a quarter of patients who were randomized to stent arm underwent angioplasty only without a stent placement. Twelve percent of the patients who received a stent had a residual stenosis > 50%, and 7% of the patients in the stent arm had angioplasty only. There were high complication rates and the medical treatment was not well defined. There were 3 procedure related deaths reported in this study.

Therefore, 3 of these trials had serious flaws in their design. None of the studies were designed to have an adequate power to evaluate a composite end point of cardiovascular outcomes. All only evaluated the surrogate endpoints. The major issue with these trials was that the patients with clinically significant lesions who would benefit from renal stenting were not included in the studies. The medical management was either imprecisely defined or inadequate in each of the trials. Thus, the best treatment option for the treatment of RAS continues to remain elusive [26].

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) [27] study is a large multi centric, randomized trial which is expected to be completed in 2012. The study includes the patients, with greater than 60% stenosis and receiving at least two anti-hypertensive medications, and with creatinine < 3 mg/dL. This trial is comparing renal stenting vs. optimal medical management, and is expected to help us understand whether renal stenting improves renal function, patient survival, cardiovascular outcomes and quality of life. There are separate core laboratories which will analyze all angiograms, allocation of medical treatment, laboratory work up and other imaging tests. Pending the results of the CORAL study, the best option for the treatment of RAS remains unclear. Another ongoing trial is looking at the effect of stenting with optimal medical management vs. medical management alone on the renal function at 12 months following stenting. Another study RADAR is currently going on and is looking at the effect of renal artery stenting when compared to medical therapy alone [28].

Current practice and guidelines

According to the current guidelines on peripheral artery disease [29], revascularization in patients suffering from RAS and recurrent episodes of congestive heart failure have received a class I

indication. They have recommended renal revascularization as a class IIa indication in patients with (i) global renal ischemia, (ii) progressive chronic kidney disease, (iii) unstable angina (worsening, or resistant), (iv) hypertension that is worsening, resistant, malignant or associated with an unexplained unilateral small kidney or in patients who cannot tolerate antihypertensive medications.

Future direction

Clinical significance of a hemodynamically significant stenosis

RAS causes a drop in BP distal to the site of occlusion. In a unilateral stenosis this drop in pressure may act as a stimulus for the activation of renin-angiotensin-aldosterone axis. The contra lateral kidney responds by pressure natriuresis in order to lower BP. This fall in BP further decreases the BP and perfusion distal to the stenotic lesion in the affected kidney [30]. This drop in BP is important for the development and perpetuation of renovascular hypertension. Thus what constitutes a hemodynamically significant lesion is important for an interventionalist to know because these hemodynamically significant lesions are more likely to respond to the renal angioplasty and stenting. De Bruyne et al. [30] obtained trans-stenotic pressure gradient before and after unilateral stenting in 15 patients. Stenosis severity was expressed as the ratio of distal pressure (P_D) to the aortic pressure (P_A). Balloon inflation was adjusted so as to create 60% of stenosis with a controlled pressure gradient of 1 to 0.5 between the aorta (P_A) and the distal part of the renal artery (P_D) with each step lasting 10 min. The plasma renin concentrations were measured at the end of each step in the aorta and both renal veins. In this study they found that when the P_D/P_A ratio is greater than 0.9 there was no significant change in the levels of renin concentrations observed. Thus, a lesion with a P_D/P_A ratio of greater than 0.9 is unlikely to give rise to renovascular hypertension. However, a P_D/P_A ratio of less than 0.9 resulted in a significant increase in the renin levels as measured from the renal vein sampling of the stenotic kidney. The renin levels returned to baseline when the stenosis was relieved. Interestingly plasma renin concentrations also increased in the contralateral non stenotic kidneys. Evaluations for hemodynamically significant lesions in patients with renal stenosis may help improve proper patient selection for the angioplasty and stenting. In a recent study Lessar et al. [31] the role of renal translesional pressure gradient and intravascular ultra-

sound in predicting the improvement in hypertension following renal artery stenting in patients with RAS was evaluated. In this study 62 patients had translesional pressure gradient, resting and hyperemic systolic gradient (HSG), fractional flow reserve, and mean gradient measured by a guidewire and angiographic parameters including minimum lumen area and diameter, area stenosis, and diameter stenosis measured quantitatively by intravascular ultrasound. $HSG \geq 21$ mm Hg was found to be an independent predictor of improvement in hypertension following renal stenting, with decrease in the number of anti hypertensive medication in the group with $HSG \geq 21$ mm Hg.

Role of distal embolization and embolic protection devices during renal stenting and angioplasty

Renal stenting has been reported to result in the peri-procedural loss of renal function in some patients [32–37]. There are multiple factors that might be responsible for this reported periprocedural loss of renal function but the most likely being distal embolization. Distal embolization is very common during renal stenting and angioplasty and as such the interest in the protected renal stenting has evolved. Earlier studies on the use of distal protection during renal stenting reported better outcomes. However, the only prospective randomized controlled trial evaluating role of distal protection with and without abciximab in patient undergoing renal stenting (RESIST) [35] failed to show any benefit of an embolic protection alone. There could have been multiple reasons for the failure of embolic protection device in preserving renal function including incomplete protection, incomplete apposition of the device to the vessel wall, embolization prior to deployment of the device and smaller size of the embolized material. Most importantly, RESIST study was underpowered due to its small size to detect any benefit of embolic protection.

Role of antiplatelet therapy during renal artery stenting and angioplasty

In the RESIST [35] trial, Cooper et al. [35] reports the effects of renal stenting with and without distal protection device as well as with and without abciximab on the percent change in MDRD GFR at 1 month when compared to the baseline. In this 2X2 factorial designed study almost 100 patients were randomized to either stenting alone, stenting with embolic protection, stenting with abciximab and stenting with both abciximab and embolic protection. The angiographic analysis, the analysis of fil-

ter contents and the analysis of renal function were performed at 3 separate core laboratories respectively, with analyzers blinded to both the treatment and clinical outcomes. Stenting alone, stenting with embolic protection and stenting with abciximab were associated with decline in renal function at 1 month. However, an unanticipated interaction was observed between abciximab and embolic protection device with improvement in renal function observed in the group randomized to renal stenting with both abciximab and embolic protection.

Further subgroup analysis of the RESIST trial demonstrated that the embolized material captured was predominantly platelet rich suggesting platelet activation is common during renal stenting [38, 39].

In an another subgroup analysis on the use of thienopyridines in the RESIST trial it was shown that the thienopyridines significantly reduced embolization of platelet rich emboli [39]. Use of thienopyridines in subgroup of patients who were randomized to both embolic protection and abciximab was associated with no distal embolization. Thus, the use of thienopyridines may be additive or even synergistic when combined with use of abciximab [39]. However thienopyridine use was not associated with improvement in renal function at 1 month despite reducing distal embolization. This might have been possibly because the use of thienopyridine antiplatelet was not randomly allocated rather was clinically prescribed. Further, the study was not powered enough to detect the thienopyridine effect [39].

Controversies in the diagnosis of renal artery stenosis

The diagnosis of RAS has been as controversial as has been the optimal management of the RAS. Renal angiography is the gold standard for diagnosis of the renal stenosis. However, this procedure is invasive with risks of adverse events including vessel injury and contrast nephropathy. It is crucial for an interventionalist to know the anatomy and status of the renal artery before the patient is taken for angioplasty. The pretest probability of RAS plays an important role in deciding about the choice of diagnostic modality. Although the prevalence of renal stenosis in general hypertensive population is 1–5%, in patients who have a high pretest probability of having RAS, the prevalence may be as high as 40% in some patients [40, 41]. Besides renal angiography, the other diagnostic tests available for the diagnosis of the RAS include, duplex ultrasonography, computed tomographic angiography (CTA), MRA, captopril scintigraphy and

captopril test. In a meta-analysis by Boudewijn et al. [41] it was found that both CTA and MRA were equally good in the diagnosis of the RAS (both had a area under ROC curve of 0.99). Both, were found to be superior to duplex ultrasound and the captopril scintigraphy ($p = 0.02$). Duplex ultrasonography and captopril scintigraphy were both superior to the captopril test ($p = 0.01$). Renal angiography was used as a gold standard for the diagnosis of RAS in each of the studies included in the meta-analysis. The diagnosis of the RAS can be made with the use of duplex ultrasonography but if the results of the ultrasonography are inconclusive or technically limited, MRA or CTA should be used [28].

Conclusions

The diagnosis as well as the optimal medical management of the patient suffering from RAS continues to be controversial. In future we expect CORAL and RADAR trials might help answer many questions which earlier trials failed to do.

Conflict of interest: none declared

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