The first percutaneous transluminal renal angioplasty (PTRA) for the treatment of atherosclerotic renal artery stenosis (RAS) was performed in 1977 (1), the same year as the first coronary angioplasty (2). Whereas percutaneous coronary revascularization is now a routine practice for the treatment of coronary artery disease, the diagnostic and therapeutic strategies for appropriately treating patients with RAS have not developed. Why not? The answers to this question are controversial, and factors complicating the issue include the often-asymptomatic nature of RAS and conflicting data regarding the benefits of treatment. Patients with RAS may develop poorly controlled hypertension, progressive renal insufficiency, or renal atrophy, all of which are usually asymptomatic in the early stages. Previous studies have used the cure of hypertension, rather than an improvement in hypertension, as an end point in renal revascularization studies, and this confounds the issue, especially when both essential hypertension and renovascular hypertension are present in the same patient. Furthermore, there is inconsistency in published reports regarding the benefit of non-surgical renal revascularization for treating hypertension or preventing renal dysfunction.

ROLE OF MEDICAL THERAPY AND BALLOON ANGIOPLASTY IN THE TREATMENT OF RAS

Medical therapy is preferred over renal revascularization for patients with atherosclerotic RAS and advanced renal disease as manifested by chronic renal failure (creatinine $>$2.5 mg/dl with unilateral RAS), proteinuria (>1 g/day), diffuse intrarenal vascular disease, renal atrophy (kidney length $<$7.0 cm), or a resistive index $>$80 (3). Although PTRA is felt to be the treatment of choice for fibromuscular dysplasia leading to RAS, the data supporting this approach are primarily descriptive and from the pre-stent era (4). However, in cases of atherosclerotic RAS, which account for the vast majority of patients with hypertension and RAS, the results of PTRA have been disappointing. In the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) trial, 106 patients with atherosclerotic RAS, hypertension despite treatment with $\geq$2 antihypertensive medications, and a serum creatinine $\leq$2.3 mg/dl were randomized to PTRA versus medical therapy, and this study demonstrated that PTRA offered little benefit over medical therapy for the treatment of hypertension (5). However, limitations of this study included the enrollment of patients with insignificant RAS, a 44% cross-over from medical therapy to PTRA, and low use of stents (20%). Nevertheless, due to the scant data that previously existed on the subject, this study had a broad impact on clinical practice, and enthusiasm for percutaneous revascularization of patients with atherosclerotic RAS diminished.

ROLE OF STENTING IN THE TREATMENT OF RAS

The frequent involvement of the ostial renal artery in atherosclerotic RAS leads to high elastic recoil with PTRA, and subsequently high restenosis rates of 42% to 47% (6,7). The problem of elastic recoil is alleviated with the use of endovascular stents, which provide mechanical scaffolding. Results from observational studies have demonstrated that renal stenting is safe and effective in reducing blood pressure (8,9), whereas a randomized trial proved the superiority of renal stenting over PTRA for immediate procedural success (88% stent vs. 57% PTRA) and lowering restenosis (14% stent vs. 48% PTRA) (10). However, concerns have existed regarding the deleterious effects of renal stenting on renal function, especially for patients with chronic renal insufficiency (8). These concerns have largely been dismissed by recent studies demonstrating improvement or stabilization of renal function after unilateral or bilateral renal stenting in patients with atherosclerotic RAS and progressive renal insufficiency (11,12).

The study by Rocha-Singh et al. (13) in this issue of the Journal is the first prospective multicenter study in which patients with atherosclerotic RAS were treated with balloon-expandable stents and evaluated by independent angiographic and Duplex core laboratories to determine the success of the index procedure and demonstrate long-term efficacy at follow-up examinations. The investigators enrolled 208 hypertensive patients with de novo or restenotic lesions $\geq$70% at the aorto-ostial renal artery junction who were not successfully treated with PTRA (residual stenosis $\geq$50%, flow-limiting dissection, persistent peak-to-peak translesional pressure gradient of $\geq$20 mm Hg). Acute technical success was achieved in 94.9% of the lesions treated with reduction in diameter stenosis from 61.5% to $\pm$2.2%. The primary end point of the study was the nine-month restenosis rate as determined by duplex ultrasonography or angiography and reported to be 17.4%. Renal stenting resulted in improvement of blood pressure from 168 $\pm$ 25/82 $\pm$ 13 mm Hg to 149 $\pm$ 25/77 $\pm$ 12 mm Hg with a reduction in the number of antihypertensive medications from 2.8 $\pm$ 0.9 to 2.3 $\pm$ 1.3 between baseline and
two-year follow-up (\( p < 0.001 \) for all). Serum creatinine increased slightly from 1.36 ± 0.52 to 1.46 ± 0.81 (\( p = 0.04 \)) between baseline and two-year follow-up but did not change significantly in the subgroup of patients with baseline renal insufficiency (serum creatinine \( \geq 2.0 \) mg/dl). Major adverse event rate for the two-year period was 19.7%, with target lesion revascularization accounting for the majority of events.

Although this is not a randomized clinical trial, it is an important study that demonstrates renal stenting significantly reduces blood pressure and the number of antihypertensive medications required by patients with renovascular hypertension. This study also confirms that bilateral renal stenting (performed in 21% of study patients) and renal stenting in patients with chronic renal insufficiency is safe. It is of concern that only 47% of the study cohort had any lowering of their blood pressure in response to renal stenting. Therefore, at least one-half of the patients in this study had insignificant RAS, parenchymal renal disease, or essential hypertension, and the 20 mm Hg systolic blood pressure lowering in the overall cohort likely underestimates the degree of beneficial effect in the patients who actually respond to renal stenting. Efforts need to be directed toward identifying physiological and biological markers that may predict response to renal stenting for blood pressure lowering and renal function preservation. Recently, Silva et al. (14) reported that 77% of patients with RAS who had a brain natriuretic peptide level >80 pg/ml had an improvement in their blood pressure after renal stenting, whereas no response was noted in patients with a level <80 pg/ml. If this is confirmed in a larger patient cohort, then this could be one marker that could help identify patients likely to benefit from the procedure, rather than exposing patients with essential hypertension to the risks of renal stenting.

Hypertension affects more than 25% of the worldwide adult population (15). Although the vast majority have essential hypertension, it is important to identify patients with secondary treatable causes of hypertension, especially atherosclerotic RAS, the most common cause of renovascular hypertension (16). Clinical clues to the presence of RAS include: onset of hypertension after age 55 years, exacerbation of well-controlled hypertension, malignant hypertension, progressive renal insufficiency, azotemia with initiation of angiotensin-converting enzyme inhibitor therapy, renal atrophy, or cardiac dysfunction (3). Noninvasive tools for detecting RAS have sensitivities ranging from 70% to 100%, whereas their specificity varies greatly between 50% to 90% (3). Therefore, in the context of high clinical suspicion, a renal artery angiogram in multiple views is desirable. Importantly, among patients undergoing cardiac catheterization not previously suspected of having atherosclerotic RAS who have any of the following criteria: 1) severe hypertension; 2) unexplained renal dysfunction; 3) acute pulmonary edema with hypertension; or 4) severe atherosclerosis, 39% were found to have renal atherosclerosis, with 14.3% having \( \geq 50\% \) RAS (17).

The currently reported study demonstrates that the improvement in blood pressure control after renal stenting is maintained at the two-year interval. However, these results are obtained at the expense of a 17.4% restenosis rate with renal stenting, and a well-tested option for the treatment of renal stent restenosis is not available. Brachytherapy and cutting balloon atherotomy have been used for renal artery in-stent restenosis (18,19), but long-term outcomes are unknown. Although surgical revascularization is effective for the treatment of RAS, its role will remain limited and likely not be subjected to a randomized clinical trial against renal stenting due to the higher morbidity and mortality of the surgical approach.

Drug-eluting stents and distal protection devices have been used for the treatment of atherosclerotic RAS (20,21), but their roles require further elucidation. Long-term outcomes with stroke, myocardial infarction, left ventricular hypertrophy, congestive heart failure, renal failure, and death as end points after renal stenting need to be obtained, and some of these data are being gathered in the ongoing Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study (22). This National Heart, Lung, and Blood Institute-sponsored study is testing the hypothesis of whether renal ischemia with its consequent neuroendocrine activation contributes to adverse cardiovascular and renal events, independently of the blood pressure achieved. The results of this trial are years away, but based on the currently available data and reported study, it appears that in selected patients, renal artery stenting is indeed ready for primetime! Patients with atherosclerotic RAS who are hypertensive (blood pressure \( \geq 140/90 \) mm Hg) despite treatment with \( \geq 2 \) antihypertensive medications, with a serum creatinine <3.0 mg/dl and a kidney >8 cm in length should be considered for renal artery stenting. In such patients, good procedural outcomes and the long-term benefit of improved blood pressure control and renal function preservation can be expected.

Reprint requests and correspondence: Dr. Ehtisham Mahmud, Cardiac Catheterization Laboratory, University of California, San Diego, 200 West Arbor Drive, San Diego, California 92103-8784. E-mail: emahmud@ucsd.edu.

REFERENCES