Effect of Renal Artery Stenting on Renal Function and Size in Patients with Atherosclerotic Renovascular Disease

Paul S. Watson, MBBS; Peter Hadjipetrou, MBBS; Stephen V. Cox, MBBS; Thomas C. Piemonte, MD; Andrew C. Eisenhauer, MD

Background—Renal artery stenting is widely performed, but little is known about its effectiveness in preserving renal function and size in patients with renovascular disease and chronic renal insufficiency. We studied the effect of renal artery stenting on renal function and size in patients with obstructive renovascular disease and chronic renal insufficiency.

Methods and Results—Stent deployment was performed in patients with chronic renal insufficiency (creatinine >1.5 mg·dL⁻¹) and global renovascular obstruction (bilateral renal artery stenosis or unilateral stenosis in the presence of a solitary or single functional kidney). The effect of renal artery stenting on renal function was assessed by comparing the slopes of the regression lines derived from the reciprocal of serum creatinine versus time plotted before and after stent deployment. Renal size was assessed by serial ultrasound of pole-to-pole kidney length. Stenting was successful in all 61 vessels in 33 patients. Twenty-five patients had complete follow-up (mean 20±11 months). Before stent deployment, all patients exhibited a negative slope, indicating progressive renal insufficiency. After stent deployment, the slopes were positive in 18 and less negative in 7 patients. Thus, the mean slope increased from −0.0079 to 0.0043 dL·mg⁻¹·mo⁻¹ (P<0.001). Ultrasonography on 41 kidneys revealed preservation of size, with the kidney length measuring 10.4±1.4 cm at baseline and 10.4±1.1 cm at last follow-up (P=NS). Patient survival at 20±11 months was 90%.

Conclusions—In patients with chronic renal insufficiency and global obstructive atherosclerotic renovascular disease, renal artery stenting improves or stabilizes renal function and preserves kidney size. (Circulation. 2000;102:1671-1677.)

Key Words: stents ■ kidney ■ atherosclerosis ■ stenosis

A high prevalence of obstructive renovascular disease in the aging has been well documented, particularly in those with hypertension and peripheral vascular disease.1–3 It is estimated that atherosclerotic renovascular disease is the cause of renal failure in 5% to 15% of adult patients who begin dialysis yearly.4–6 Also, it has been shown that kidneys supplied by stenosed arteries are at increased risk of progressive atrophy.7

Of particular clinical and economic concern is the effect that renal artery stenting may have on subsequent renal function and the need for dialysis in patients with atherosclerotic renovascular disease and renal impairment. The technical success, low complication rates, and rates of restenosis after percutaneous transluminal balloon angioplasty (PTA) and stenting for renal artery stenosis (RAS) have been widely published.8–15

Despite these favorable reports, the ability of revascularization to salvage or improve the function of the treated kidney has not been demonstrated. A major impediment to the study of the direct effect of treatment on the treated kidney has been the lack of simple methods to assess the function of each kidney in this normally paired organ system. In the setting of normal creatinine production, an elevated serum creatinine is indicative of a loss of more than half of functioning nephrons. Thus, in unilateral RAS, an abnormal serum creatinine level suggests concomitant dysfunction of the companion “nonstenosed” kidney, obscuring the direct effect of treatment of unilateral disease on the usual measurements of overall renal function. To circumvent this problem and isolate the direct effects of revascularization, we studied a series of patients with severe (>70%) stenoses of all remaining renal arteries (global renal ischemia) and evaluated the effects of stenting all the stenoses on overall renal function and individual kidney size.

Methods

Patient Selection
Between January 1994 and January 1999, all patients with RAS presenting to our service were evaluated for inclusion. Patients were considered eligible if they had mild or moderate chronic renal impairment (serum creatinine >1.5 but <4.0 mg·dL⁻¹) and atherosclerotic renovascular disease with demonstrable (>70% lu-
minal diameter) stenoses involving all renal arteries or if they had unilateral RAS in the setting of a solitary or single functional kidney. A nonfunctional kidney was defined as one being atrophic (pole-to-pole length <7.5 cm) and supplied by an occluded or small diffusely diseased renal artery. Patients with RAS involving only 1 of 2 functioning kidneys were excluded because changes in overall renal function after unilateral intervention in this group could reflect changes in the treated kidney, the contralateral “nonstenotic” kidney, or both. This could be particularly important if hypertension were ameliorated; although such an amelioration would be clinically beneficial, the direct effect of revascularization could be obscured by the effect of blood pressure control.

Suspected renovascular disease was initially evaluated by duplex ultrasonography, MRI angiography, and/or radionuclide imaging and subsequently confirmed by aortography and/or selective renal angiography. Patients already on dialysis or in whom renal impairment was secondary to parenchymal proteinuria (nephrotic range proteinuria), obstructive nephropathy, or in whom renal impairment was secondary to parenchymal pathology were excluded.

Procedures

Patients were pretreated with oral aspirin (325 mg) and ticlopidine (Ticlid, 500 mg) or clopidogrel (Plavix, 300 mg). Angiography, PTA, and stenting were performed transfemorally. Heparin was administered (3000 to 8000 U) to maintain an activated clotting time (PTA, and stenting were performed transfemorally. Heparin was administered (3000 to 8000 U) to maintain an activated clotting time

Postintervention slopes were constructed from plots by using the reciprocal of serum creatinine versus time were created retrospectively (before stent deployment) and prospectively (after stent deployment) for each patient. Only patients with adequate prior documentation (at least 5 serum creatinine measurements) of the course of renal function were included. The time course of change in renal function was assessed by comparing baseline with final follow-up kidney length. Atrophy was defined as a >1-cm reduction in kidney length at follow-up. The 1-cm threshold was based on published between-observer variability.7

After the initial review, the patients’ referring physicians were asked and encouraged to measure serum creatinine regularly. Plots of the reciprocal of serum creatinine versus time were created retrospectively (before stent deployment) and prospectively (after stent deployment) for each patient. Only patients with adequate prior documentation (at least 5 serum creatinine measurements) of the course of renal function were included. The time course of change in renal function was assessed by comparing the slopes (dL/mg/mo) of the regression lines constructed from the coordinates of the reciprocal of serum creatinine and time.

Follow-Up Protocol

Patients were evaluated at 1, 3, and 6 months and every 6 months thereafter. Review involved clinical examination, recording of blood pressure and current medical therapy, measurement of serum creatinine, and urinalysis. Blood pressure was based on the mean of 3 determinations after 15 minutes of rest at 3 separate intervals.

Restenosis surveillance incorporated renal artery duplex sonography at baseline, at 6 months, and then yearly. All studies were performed in one accredited vascular laboratory. After an overnight fast, patients were examined while supine, with the measurement of aortic peak systolic velocity (PSV) in the proximal, middle, and distal segments of each artery achieved while maintaining the angle of the duplex ultrasound beam and the vessel at <60°. Restenosis was suggested by an increase in in-stent velocity >100 cm·s⁻¹ above baseline associated with a renal artery PSV/aortic PSV ratio >3.5. Angiography was performed if restenosis was suggested by sonography, by the recurrence uncontrollable hypertension, or by the deterioration of renal function. Renal size was assessed every 6 months by B-mode ultrasonographic measurement of pole-to-pole length. The effect of stenting on renal atrophy was assessed by comparing baseline with final follow-up kidney length. Atrophy was defined as a >1-cm reduction in kidney length at follow-up. The 1-cm threshold was based on published between-observer variability.7

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Postintervention slopes were constructed from plots by using the final “presten” serum creatinine level as the starting reference and subsequently serially measuring serum creatinine after a 3- to 4-week period, which allowed the postintervention serum creatinine to stabilize. This scheme was chosen to avoid creating an artificial improvement in the slope that could occur in the event of postprocedural, transient, contrast-mediated renal insufficiency. Transient
high values of serum creatinine after the procedure would favorably skew the follow-up reciprocal plots. This problem is avoided by using the immediate preprocedure creatinine as the initial postprocedural value and rejecting transient postprocedural fluctuations of serum creatinine. Follow-up was considered adequate only when at least 5 serum creatinine measurements were available over a period of ≥8 months.

**Statistical Analysis**

Demographic and procedural data are expressed as counts, percentages, or mean±SD. For each patient, lines of best fit were constructed from the data obtained before and after stent deployment by use of a computer least squares linear regression analysis (Excel, Microsoft Inc). The mean number of coordinates used to calculate present and poststent slopes was 13±6 and 9±3, respectively. The degree of correlation between reciprocal serum creatinine and time before and after stent deployment was assessed by calculation of the Pearson correlation coefficient (r). Comparison of the rate of change in renal function before and after stenting was assessed by using a 2-tailed paired Student t test comparing the slope before and after stent deployment for each patient. In addition, pole-to-pole kidney size (cm), measured by ultrasound, and blood pressure (mm Hg) before and after stent deployment were compared by using a 2-tailed paired Student t test.

**Results**

Treatment of stenosed renal arteries with stent deployment was performed on 106 vessels in 76 patients. This report includes data for 33 of these patients (16 men and 17 women, mean age 72±7 years) who had chronic mild to moderate renal impairment and global obstructive atherosclerotic renovascular disease. These patients underwent bilateral renal artery stenting (26 patients) or unilateral stenting in the presence of a solitary or single functioning kidney (7 patients). The remaining 43 excluded patients underwent unilateral renal artery stent deployment in the setting of a nondiseased contralateral vessel and impaired or normal renal function. No patients were excluded because of proteinuria or known underlying parenchymal renal disease, ongoing dialysis, or obstructive uropathy.

The mean creatinine levels of the study patients immediately preceding intervention was 2.1±0.7 mg·dL⁻¹. All patients were hypertensive. Mean systolic and diastolic blood pressure preceding intervention measured 172±24 and 84±12 mm Hg, respectively. Patient demographic, clinical, and procedural data are shown in the Table.

<table>
<thead>
<tr>
<th>Baseline Patient Demographics and Procedural Data</th>
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<tr>
<td>Study patient population, n</td>
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<tr>
<td>Sex (M/F), n/n</td>
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<td>Age, y</td>
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<td>Baseline creatinine, mg/dL</td>
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<td>Prior coronary bypass surgery, n</td>
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<td>No. of antihypertensive drugs/patient</td>
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<td>Preintervention length, cm</td>
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<td>Predilatation balloon size, mm</td>
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<td>Postdilatation balloon size, mm</td>
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<td>No. of stents/vessel</td>
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Values are mean±SD or number of patients. BP indicates blood pressure.

All interventions were successful (adequate stent deployment with <15% residual diameter stenosis). Mean radiographic contrast dose was 247±133 mL per case or 137±59 mL per vessel. There was only one procedure-related complication, which involved a patient requiring a transfusion after a femoral arterial puncture-site hemorrhage.

All patients had (by reciprocal creatinine plots) deteriorating renal function before intervention. Twenty-five of the 33 patients had completed >8 months of follow-up with ≥5 serial serum creatinine measurements, allowing for the construction of postintervention linear regression lines. Of the remaining 8 patients, 3 died within 6 months from the time of intervention from cardiac disease (1 from myocardial infarction and 2 from congestive heart failure). The remaining 5 patients have not completed ≥6 months of follow-up.

Examples typical of the change in renal function as illustrated by the slopes of the linear regression lines of reciprocal serum creatinine plots for 3 patients are shown in Figure 2. The mean duration of follow-up of renal function for all patients was 20±11 months. Before stenting was performed, the calculated slopes of the regression lines for all patients were negative. After the stenting procedure, these slopes became positive in 18 patients (72%), indicating improvement in renal function, and became less negative in the remaining 7 patients (28%), signifying stabilization of renal function (Figure 3). The mean value increased significantly, from −0.0079 to 0.0043 dL·mg⁻¹·mo⁻¹, a mean of 20±11 months after stenting (P<0.001, paired t test). The difference between the mean of these slopes of 0.0122 dL·mg⁻¹·mo⁻¹ represents a change from progressive renal deterioration to one of progressive improvement over the follow-up period. During follow-up, one patient required hemodialysis. This individual had stenosis of a single remaining renal artery and a serum creatinine >3.5 mg·dL⁻¹ before the procedure, which was performed in the hope of delaying dialysis. Despite eventual progression to dialysis, the slope of reciprocal serum creatinine plot became less negative after treatment.

Before stenting was performed, a strong inverse correlation between reciprocal serum creatinine and time, as measured by the Pearson correlation coefficient (r), was verified (r<−0.65 in 22 [88%] of 25 patients). After the stenting procedure, this inverse relationship between reciprocal serum creatinine and time was lost, with the r value remaining negative in only 7 patients; in those 7, the r value was >−0.65 in all but one.

Mean systolic and diastolic blood pressures were significantly lower after stent implantation, measuring 170±21 versus 148±15 mm Hg and 84±10 versus 72±8 mm Hg, respectively (P<0.001, P<0.001). The number of antihypertensive medications with which patients were treated was unchanged. Surveillance duplex sonography identified possi-
ble restenosis in 5 renal arteries in 5 patients. All of these patients underwent restudy renal angiography identifying true angiographic restenosis (>50% reduction in lumen diameter stenosis) in only one stented vessel, which was treated successfully with repeat balloon angioplasty. Routine angiography restenosis surveillance was not performed.

Preintervention and serial follow-up renal sonograms were completed in 22 patients (41 kidneys). Baseline preintervention pole-to-pole renal length measured 10.4±1.4 cm. Follow-up kidney length, measured at a mean of 19±10 months after stent deployment, was unchanged at 10.4±1.1 cm (P=NS). Progressive renal atrophy, as defined by a reduction in renal length in excess of 1.0 cm, was seen in only 3 of the 41 kidneys (7.3%).

Discussion

Percutaneous treatment of renovascular disease has been widely practiced since its inception >20 years ago. However, enthusiasm for “simple” balloon angioplasty of renal arteries was tempered by high rates of restenosis, particularly for aorto-ostial lesions, which were vulnerable to the effects of vessel wall recoil and the persisting encroachment of aortic atheroma.15–18 Although surgery has long been considered the standard for renal artery revascularization, longitudinal studies have reported significant perioperative morbidity and operative mortality rates of up to 6%.19–22 Over recent years, endovascular stenting has tended to supersede simple balloon angioplasty or surgical revascularization as the procedure of choice in the treatment of RAS. Numerous studies have reported excellent technical success, low complication rates, and low rates of restenosis after PTA and stenting of atherosclerotic renal arteries. Successful stenting of aorto-ostial lesions previously recalcitrant to balloon dilatation is now common practice.8–14

Proposed indications for renal artery revascularization have included poorly controlled hypertension and/or the

Figure 2. Renal function was assessed by construction of linear regression plots of reciprocal of serum creatinine versus time before and after stent deployment. Slope of line represents rate of change of renal function. Plots of 3 patients depicted above are examples of improvement (top), stabilization (middle), and slowing of the deterioration (bottom) of renal function after stent deployment.
The present study isolated the effects of renal artery stent deployment on renal size and function in a patient group with mild to moderate renal impairment and obstructive renovascular atherosclerosis. The study of patients in whom all renal arteries were obstructed ensured the presence of “global” renal ischemia and isolated the potential effects of such intervention. In addition, to homogenize our patient cohort further, no patients with renal failure requiring imminent dialysis were included. In fact, the majority of our patients27 had baseline preintervention serum creatinine levels ranging from 1.6 to 2.4 mg · dL⁻¹, and only 3 patients had a preintervention creatinine level >3.0 mg · dL⁻¹.

Virtually all previous studies that have assessed the effect of surgical or endovascular revascularization of stenosed renal arteries on renal function have used isolated serum creatinine measures and compared the percentage change before and after stent deployment. This crude “static” method introduces substantial variation into the measure of renal impairment that depends on many factors, including the particular value chosen for comparison, the time of choosing this value, the nutritional and hydration status of the patient at the time of phlebotomy, and the inherent error of the assay. These limitations can be improved by dynamically assessing renal function on the basis of the slope of the regression line created from the plot of the reciprocal of serum creatinine versus time. This methodology is dependent on the assumption that although it is widely variable between patients, the reciprocal of serum creatinine falls linearly with time in individual patients with chronic renal failure.31–34

Using this technique, Harden et al.35 were also able to suggest a slowing of renal impairment after stent deployment. However, their study included patients with both bilateral and unilateral RAS and excluded a significant number of patients with insufficient data. Improvement or stabilization of renal function was not universal in that study, perhaps reflecting the contribution of some patients with advanced irreversible disease and/or those with unilateral disease and an additional renal pathology. In addition, the inclusion of patients with severe renal impairment was reflected by poor long-term survival (<50%).

In the present study, with a mean clinical follow-up period of 20 months, we have documented stabilization or improvement in renal function in all surviving patients. When the mean slope before intervention is compared with that afterward, there is a statistically significant net improvement in renal function. Also encouraging is the 90% survival rate in this group at 20±11 months despite the fact that they were elderly and had high rates of coexistent peripheral vascular and coronary artery disease.

Ultrasound data demonstrated the preservation of renal size over time after stenting. This contrasts with the longitudinal “natural history” study of renal atrophy in the presence of renovascular disease in which Caps et al.26 documented a cumulative 2-year incidence of renal atrophy (>1-cm reduction in renal length) of 20.8% for kidneys having >60% stenosis identified by baseline duplex scanning. In the setting of renal impairment, significant systolic hypertension and angiographically proven severe renal artery stenoses, we documented a 7.3% incidence of a >1-cm reduction in renal

preservation of renal function. Reports on the effect of revascularization on blood pressure control have generally been favorable. Although complete resolution of hypertension after stenting is uncommon, improved blood pressure control has been reported in 60% to 75% of patients and is often associated with a reduction in the number of antihypertensive medications.13,14,23–25 However, these studies are limited by small patient numbers, lack of control subjects, and the nonstandardization of antihypertensive therapy and methods of blood pressure measurement. In addition, these study patients tend to be elderly and are likely to have coexistent essential or multifactorial hypertension on which renin-independent hypertension is superimposed.

Recently, it has been appreciated that severe occlusive disease of the extraparenchymal renal artery results in chronic renal ischemia and can lead to the development of an “ischemic atrophic nephropathy” and chronic renal insufficiency.26,27 Caps et al.7 have also documented progressive renal atrophy based on 6-month serial duplex scans in patients with atherosclerotic RAS. This deterioration is of major clinical and economic significance. The average life expectancy of elderly patients (>65 years) with end-stage renal failure barely approaches 3 years.28,29 Survival is even worse for those in whom renovascular disease is the cause of renal failure, with only 56% of these patients being alive at 2 years.30 With this in mind and in the face of increasing recognition of this disease entity, it is attractive to speculate that revascularization by stent deployment in such patients slows renal atrophy and progression to end-stage renal failure.
length in 41 kidneys examined over the study period. Furthermore, the mean kidney length before and after stenting was unchanged, measuring 10.4±1.4 and 10.4±1.1 cm (P=NS), respectively.

Study Limitations
The present prospective but nonrandomized study has within it the limitations inherent in such a design. Although the series does not include a separate control group of untreated patients, each patient’s course before treatment serves as an individual internal control. Although it has been previously established that the reciprocal of serum creatinine declines linearly with time for a variety of chronic renal diseases, this has not been specifically proven in atherosclerotic renovascular disease. We have made the assumption that a negative linear relation exists for the reciprocal of serum creatinine plotted against time for this form of chronic renal disease, and the use of this methodology provides a more meaningful assessment of renal function compared with arbitrary isolated creatinine values. Serum creatinine level is not a precise measure of the loss of renal function because of variation in renal creatinine secretion, creatinine degradation by extrarenal mechanisms, and variability in the rate of creatinine production. The use of other methods of serial assessment, such as multiple measurements of creatinine clearance, is limited by potentially incomplete urine collection, inconvenience, expense, and the retrospective identification of chronic renal impairment.

To minimize errors in the quantification of renal function over time, patients in the present study were included for final analysis only if serial creatinine plots after stenting had been performed for >8 months with at least ≥5 separate creatinine measurements. In fact, for most (18 of 25) patients, follow-up creatinine measurements had been charted well past 12 months. Although 3 deceased patients were excluded from final analysis because of failure to complete the adequate follow-up period, these censored patients had no bias effect on the final outcome because all deaths were known to be secondary to cardiac events and not due to renal failure or deterioration.

Although not a study end point, the incidence of restenosis may have been underestimated because all patients were not routinely restudied angiographically. However, angiography was performed on those with significant increases in duplex renal artery velocities and/or a suggestion of restenosis. This indicator of restenosis identified only 1 restenosed stent in 5 patients (10 vessels) restudied. Although this very low restenosis rate raises questions about the appropriate criteria for ultrasonographic restenosis or its predictive value, we believe it likely that restenosis is reduced by minimizing the stent length, maximizing the lumen diameter, and carefully positioning the stents with 2 mm of protrusion into the aorta.12

Conclusions
The treatment of stenosed renal arteries with endovascular stenting can be accomplished safely with favorable medium-term survival in patients with chronic mild to moderate renal impairment and global obstructive atherosclerotic renovascular disease. Revascularization stabilizes renal function and preserves kidney size. The present study should encourage larger clinical trials and add to the growing weight of evidence advocating a more aggressive identification of this disease process and subsequent endovascular intervention in an attempt to prevent or delay progression to end-stage renal failure.

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References
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