Predictors of Improved Renal Function After Percutaneous Stent-Supported Angioplasty of Severe Atherosclerotic Ostial Renal Artery Stenosis

Thomas Zeller, MD; Ulrich Frank, MD; Christian Müller, MD; Karheinz Bürgelin, MD; Lutz Sinn, MD; Hans-Peter Bestehorn, MD; Nancy Cook-Bruns, MD; Franz-Josef Neumann, MD

Background—Percutaneous stent-supported angioplasty is a treatment option for atherosclerotic ostial renal artery stenosis. Improvement of renal function by such intervention, however, is controversial and thought to be limited to specific subsets, such as nondiabetic patients and bilateral stenoses. In this prospective study, we investigated predictors for improvement of renal function and blood pressure after renal artery stent placement.

Methods and Results—The study included 215 consecutive patients with ostial renal artery stenosis of ≥70% diameter stenosis undergoing stent-supported angioplasty. The primary end point was decrease in serum creatinine concentration at 1 year; the secondary end point, decrease in average mean arterial blood pressure assessed by 24-hour monitoring. One-year follow-up was complete in 191 surviving patients. In 52% (99/191) of the patients, serum creatinine concentration decreased during 1-year follow-up. Median serum creatinine concentration dropped significantly from 1.21 mg/dL (quartiles: 0.92, 1.60 mg/dL) at baseline to 1.10 mg/dL (quartiles: 0.88, 1.50 mg/dL) at 1 year (P=0.047). On average, mean arterial blood pressure decreased significantly, from 102±12 mm Hg (mean±SD) at baseline to 92±10 mm Hg at 1 year (P<0.001). Significant independent predictors of improved renal function were baseline serum creatinine (odds ratio [95% CI], 2.58 [1.35 to 4.94]; P=0.004) and left ventricular function (OR 1.51 [1.04 to 2.21]; P=0.032). Female sex, high baseline mean blood pressure, and normal renal parenchymal thickness were independent predictors for decreased mean blood pressure.

Conclusions—Stent-supported angioplasty for severe ostial renal artery stenosis improves renal function and blood pressure in a broader spectrum of patients than previously thought. (Circulation. 2003;108:2244-2249.)

Key Words: kidney | stenosis | stents | angioplasty | hypertension

Ostial renal artery stenosis is a common manifestation of atherosclerosis.1–3 The natural history of renal artery stenosis is characterized by relentless progression causing poorly controllable hypertension and chronic renal failure caused by hypertensive or ischemic nephropathy.4–9 Percutaneous transluminal renal angioplasty is a treatment option for renal artery stenosis that has been investigated in various studies.10–15 Recent reports addressed the adjunctive placement of stents and showed improved short-term and long-term technical success rates compared with plain balloon angioplasty.3,16–27 The effect of percutaneous renal revascularization on preservation of renal function is still a matter of debate. Earlier studies reported improvement of renal function only for patients with bilateral renal artery stenosis and a short history of deterioration of the renal function.17,18,28 Conversely, endovascular therapy was not found to be beneficial in patients with unilateral renal artery stenosis,13,16–24 severe nephrosclerosis,29 or diabetes mellitus.30 Interpretation of the earlier trials, however, is hampered by low sample sizes or the use of interventional techniques that do not comply with current standards.

The aim of this prospective study was to reassess the effect of percutaneous renal revascularization on renal function and blood pressure in a large cohort undergoing stent placement for severe ostial renal artery stenosis. Specifically, identifying characteristics were assessed, which could predict or preclude improvement of renal function during 1-year follow-up.

Methods

Patient Selection and Renal Stent Placement

This prospective study included consecutive patients undergoing stent placement for hemodynamically relevant arteriosclerotic renal lesions located within 1 cm of the ostium. Indications for renal stent–supported angioplasty were hemodynamically significant renal artery stenosis plus hypertension (World Health Organization grade 1 or higher irrespective of concomitant therapy) and/or impaired renal function (serum creatinine concentration >1.1 mg/dL in women or >1.2 mg/dL in men). In most cases, assessment of renal artery stenosis was based primarily on

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Unilateral renal artery stenosis was classified as hemodynamically relevant if the difference in intrarenal resistance index according to Pourcelot between the 2 renal arteries was >0.05. Before intervention, duplex ultrasound was always confirmed by angiography showing a percent diameter stenosis of 70% on visual estimation. The visual estimate was checked by quantitative computerized angiography (QCA-CMS, Medis Medical Imaging Systems) (Table). With bilateral renal artery stenosis, the preinterventional diagnosis of hemodynamic relevance was based on angiography and confirmed after the intervention with duplex ultrasound showing an increase of the intrarenal resistance index of >0.05. Patients who had been on a hemodialysis program for >1 year, patients with interventions in chronically occluded arteries, and those who did not provide informed consent to participate were excluded. Between October 1996 and October 2000, the study enrolled 215 consecutive patients with 277 ostial renal artery stenoses, representing 91% of all patients undergoing renal artery angioplasty during this period (Figure 1). Our institutional ethics committee approved the study.

For renal stent placement, the guiding catheter technique and implantation of various types of approved stents were used, as described previously. In 50 patients (23%) with bilateral stenoses, we treated both stenoses simultaneously. Antiplatelet therapy was started at least the day before intervention and routinely consisted of 75 mg of clopidogrel daily for 4 weeks and 100 mg of aspirin indefinitely. Immediately before the intervention, we administered a bolus dose of 5000 IU of heparin.

### Study Protocol

The preinterventional workup and all follow-up visits included duplex ultrasound, measurement of serum creatinine, ambulatory 24-hour blood pressure monitoring (BSI, SpaceLab Medical Inc), and documentation of the number and dose of antihypertensive drugs. Follow-up examinations were scheduled before discharge and 6 months and 12 months after the intervention.

### Study End Points and Definitions

The primary end point was the proportion of patients with decreased serum creatinine within 1 year of study entry (serum creatinine at 1 year less than baseline serum creatinine). Analysis was by intention to treat. In patients who were included in or withdrawn from a hemodialysis program during the study period, the last creatinine measurement before entering the hemodialysis program was taken as baseline.

### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients* (n=215)</th>
<th>Improvement in Renal Function After 1 y (n=99)</th>
<th>No Improvement in Renal Function After 1 y (n=92)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±9</td>
<td>67±8</td>
<td>66±8</td>
<td>0.25</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>80 (37)</td>
<td>39 (39)</td>
<td>34 (37)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>212 (99)</td>
<td>98 (98)</td>
<td>89 (96)</td>
<td>0.36</td>
</tr>
<tr>
<td>Renal insufficiency, n (%)</td>
<td>111 (52)</td>
<td>61 (62)</td>
<td>32 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diameter stenosis at baseline, † (%)</td>
<td>79±12</td>
<td>79±12</td>
<td>78±11</td>
<td>0.14</td>
</tr>
<tr>
<td>Diameter stenosis after stent, † (%)</td>
<td>8±10</td>
<td>9±11</td>
<td>8±10</td>
<td>0.18</td>
</tr>
<tr>
<td>Concomitant atherosclerosis, ‡ (%)</td>
<td>196 (91)</td>
<td>92 (92)</td>
<td>84 (90)</td>
<td>0.68</td>
</tr>
<tr>
<td>Reduced left ventricular function, n (%)</td>
<td>124 (58)</td>
<td>60 (61)</td>
<td>45 (49)</td>
<td>0.06</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>135 (63)</td>
<td>58 (58)</td>
<td>64 (69)</td>
<td>0.12</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>191 (89)</td>
<td>85 (85)</td>
<td>84 (90)</td>
<td>0.27</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>88 (41)</td>
<td>40 (40)</td>
<td>36 (39)</td>
<td>0.86</td>
</tr>
<tr>
<td>Active and former smokers, n (%)</td>
<td>132 (61)</td>
<td>57 (57)</td>
<td>58 (62)</td>
<td>0.45</td>
</tr>
<tr>
<td>Resistance index &gt;0.8, n (%)</td>
<td>62 (22)</td>
<td>18 (18)</td>
<td>14 (15)</td>
<td>0.59</td>
</tr>
<tr>
<td>Bilateral intervention, n (%)</td>
<td>50 (23)</td>
<td>25 (25)</td>
<td>20 (20)</td>
<td>0.45</td>
</tr>
<tr>
<td>Functional single kidney, n (%)</td>
<td>12 (6)</td>
<td>9 (8)</td>
<td>3 (3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean serum creatinine, mg%</td>
<td>1.51±1.04</td>
<td>1.62±1.04</td>
<td>1.19±0.69</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>145±19</td>
<td>143±18</td>
<td>147±18</td>
<td>0.19</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79±11</td>
<td>79±10</td>
<td>79±12</td>
<td>0.95</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>102±12</td>
<td>102±12</td>
<td>103±12</td>
<td>0.64</td>
</tr>
<tr>
<td>No. of antihypertensive drugs, n</td>
<td>3.0±1.1</td>
<td>3.1±1.2</td>
<td>2.9±1.1</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Including 16 patients who died during follow-up and 8 patients lost to follow-up.
†By quantitative computerized angiography, ‡concomitant coronary artery, or cerebrovascular or peripheral occlusive disease. P value for the comparison of patients with improvement of renal function with patients without improvement of renal function at 1 y.
baseline or follow-up creatinine concentration, respectively. In addition to serum creatinine concentration, the creatinine clearance calculated by the Cockcroft and Gault formula was analyzed.

As secondary end point, we assessed the proportion of patients with a decrease in average mean blood pressure during 1-year follow-up (average mean arterial blood pressure at 1 year less than baseline average mean arterial blood pressure). Average mean arterial blood pressure was calculated from all arterial blood pressure readouts during the 24-hour recording period.

Primary success of the procedure was defined as residual percent diameter stenosis <30% by quantitative computerized angiography (Table). Restenosis was assessed as described previously. Briefly, restenosis was defined by the same criteria as those for the definition of relevant stenosis at study entry. All patients with suspected restenosis on duplex ultrasonography underwent angiographic reexamination. Left ventricular function was assessed by left ventricular angiography or echocardiography if angiography was not available. Global left ventricular ejection fraction was determined by the area-length method and coded as reduced left ventricular function if ≤45%.

Statistical Analysis
Discrete variables were expressed as counts, and comparison was done by x² test. Unless stated otherwise, we show continuous variables as mean±SD and tested comparisons by ANOVA for independent samples. The Kolmogorov-Smirnov test showed that creatinine concentrations and changes in creatinine concentrations were not distributed normally. Hence, we show creatinine concentrations as median (quartiles) and tested differences between baseline and 1 year by the Wilcoxon rank sum test. To identify independent predictors for the primary and secondary end points, we performed logistic regression analysis (SPSS computer software, version 10.0). Baseline serum creatinine; baseline mean blood pressure; age; sex; diameter stenosis ≥90%; resistance index >0.80 after intervention; parenchymal/pelvic ratio >1 of the affected kidney; left ventricular function; concomitant atherosclerotic disease, such as coronary disease, peripheral occlusive disease, and cerebral occlusive disease; bilateral stenosis; dyslipidemia; obesity; smoking; and diabetes mellitus were entered into the model. All hypothesis testing was two tailed. Probability values of P<0.05 were considered significant.

Results
Study Population and Technical Outcome
The study profile and demographic characteristics of the study population are shown in Figure 1 and the Table, respectively. In all 215 patients with 277 lesions, the renal artery stenosis could be reduced to <30% diameter stenosis. Six patients (2.8%) suffered severe procedure-related adverse events, including renal artery rupture requiring surgery in 1 patient, progression from preterminal renal failure to terminal renal failure caused by renal embolism or dye-induced nephropathy in 4 patients, and occlusion of the common femoral artery after sheath removal in 1 patient. The latter was treated successfully by surgery. In addition, there were 5 clinically unapparent complications (2.3%): 1 dissection of the descending aorta in which the false lumen subsequently thrombosed, 1 wire-induced renal artery dissection with a persistent occlusion of a side branch, 2 stent displacements needing the placement of a second stent, and 1 wire-induced perforation of a segment artery with spontaneous sealing of the leakage. In addition, 4 false aneurysms (1.8%) had to be treated by duplex-guided compression therapy. There were no procedure-related deaths or subacute stent thromboses.

Sixteen patients died during the first year after intervention, accounting for a 1-year mortality rate of 7.4%. Causes of death were congestive heart failure or myocardial infarction in 12 patients (73%), stroke in 2 (13.5%), and malignancy in 2 (13.5%). An additional 8 patients were lost to follow-up. Thus, a total of 191 patients with 249 treated lesions were available for 1-year follow-up. At 1 year after study entry, 28 restenoses in 249 renal arteries available for follow-up (11.2%) were detected; 24 of these had been present at 6-month follow-up.

Improvement of Renal Function
In the entire study cohort, serum creatinine concentrations decreased significantly during the study period (Figure 2). The primary end point, reduction in serum creatinine concentration during 1-year follow-up, was reached in 99 of 191 patients (52%). Among those, 7 patients hospitalized with flash pulmonary edema and/or acute renal failure requiring acute hemodialysis could be withdrawn from the chronic hemodialysis program. At 1-year follow-up, the median decrease in serum creatinine concentration was 0.02 mg/dL (quartiles: −0.11 mg/dL, 0.23 mg/dL, P=0.011). Likewise, we found a significant increase in creatinine clearance in the entire cohort, by 2.3±15.1 mL/min (P=0.028).

When we included the last available serum creatinine concentration determination for patients who died or were lost to follow-up, we obtained essentially the same outcome, with a median decrease in serum creatinine concentration of 0.02 mg/dL (quartiles: −0.10 mg/dL, 0.25 mg/dL, P=0.001). Exclusion of patients with functional single kidney or hemodialysis requirement <1 year also did not alter the principal results of our study (median decrease in serum creatinine concentration, 0.03 mg/dL [quartiles: −0.10 mg/dL, 0.23 mg/dL], P=0.001).

In general, the decrease in serum creatinine concentration tended to be larger the higher the baseline serum creatinine (Figure 3). Patients with a serum creatinine concentration at study entry >1.5 mg/dL (n=48) had a median decrease in serum creatinine concentration by 0.33 mg/dL (quartiles: −0.01 mg/dL, 0.67 mg/dL, P=0.025), whereas those with serum creatinine concentration at study entry ≤1.5 mg/dL (n=143) had no significant change in serum creatinine concentration (median −0.01 mg/dL [quartiles: −0.11 mg/dL, 0.14 mg/dL], P=0.80). This difference between the 2 strata
defined by the 1.5-mg/dL cutoff for serum creatinine was statistically significant at \( P < 0.001 \).

In patients with improvement of renal function, the median decrease in serum creatinine concentration was 0.22 mg/dL (quartiles: 0.12, 0.39 mg/dL), whereas in those who did not improve, we found a median increase by 0.11 mg/dL (quartiles: 0.05, 0.23 mg/dL). Comparing patients with and without improvement of renal function, no significant differences in baseline characteristics except baseline serum creatinine (Table) were found. The decreases in serum creatinine concentration with diabetes mellitus (0.05 mg/dL [−0.11, 0.30 mg/dL], \( P = 0.063 \)), severe nephrosclerosis (0.09 mg/dL [−0.09, 0.21 mg/dL], \( P = 0.11 \)), and unilateral involvement (0.01 mg/dL [−0.11, 0.21 mg/dL], \( P = 0.047 \)) were similar to the decrease in the entire population. Multivariate analysis identified baseline serum creatinine (\( P = 0.004 \)) and left ventricular function (\( P = 0.032 \)) as significant independent predictors for the decrease of serum creatinine at 1 year (Figure 4). We obtained the same independent predictors when we analyzed increase in creatinine clearance as dependent variable in the model instead of decrease in serum creatinine (\( P < 0.001 \) for baseline serum creatinine; \( P = 0.011 \) for left ventricular function).

**Discussion**

In this large study on percutaneous stent-supported angioplasty of severe atherosclerotic ostial renal artery stenosis, we found substantial improvement of renal function and blood pressure control at 1 year after the intervention. According to recent American Heart Association guidelines, a slowed decline in renal function suffices to claim a benefit from renal artery angioplasty. In the entire study cohort, blood pressure decreased significantly immediately after the intervention and essentially remained unchanged during follow-up (Figure 5). Concomitantly, the need for antihypertensive medication decreased significantly (Figure 5). During 1-year follow-up, mean arterial blood pressure decreased in 133 of 175 patients (76%) with evaluable 24-hour blood pressure recordings. Female sex (\( P = 0.032 \)), parenchymal/pelvic ratio >1 (\( P = 0.036 \)), and mean arterial blood pressure at baseline (\( P < 0.001 \)) were significant predictors for a decrease in mean arterial blood pressure (Figure 4). Diabetes mellitus and severe nephrosclerosis did not preclude a postinterventional improvement of blood pressure control.

![Figure 3](image-url)  
**Figure 3.** Change in serum creatinine concentration as function of quintiles of baseline serum creatinine concentration. Boxes show median and interquartile range; whiskers, 10th and 90th percentiles.

![Figure 4](image-url)  
**Figure 4.** Predictors of improved serum creatinine concentration (left) or improved mean arterial blood pressure (right) by multivariate logistic regression analysis. Graphs show odds ratios and their 95% CIs. BPm indicates mean arterial blood pressure; crea, creatinine; PTRA, percutaneous transluminal renal angioplasty; LV, left ventricle function; and PPR, parenchymal/pelvic ratio.

![Figure 5](image-url)  
**Figure 5.** Time course of systolic (BP_s), mean (BP_m), and diastolic blood pressure (BP_d) and number of drugs during 1 year. Graph shows mean and SD. \( P < 0.0001 \) for each comparison between preinterventional and postinterventional; n, number of patients.
angioplasty. Elevated serum creatinine and impaired left ventricular function were independent predictors of improved renal function, whereas female sex, preserved parenchymal thickness, and baseline mean arterial blood pressure predicted improved blood pressure control. Diabetes mellitus and nephrosclerosis were not associated with an inferior outcome with respect to renal function or blood pressure control. Moreover, improvement of renal function was not linked to treatment of bilateral involvement.

Several previous trials failed to show significant improvement of renal function after angioplasty of the renal artery stenosis. The only randomized trial (DRASTIC) comparing plain balloon angioplasty of atherosclerotic renal artery stenosis with medical treatment did not find any advantage of angioplasty with respect to renal function. Yet, interpretation of DRASTIC is hampered by a high proportion of crossovers (48%) and an outdated intervention technique. Currently, stent-supported angioplasty has widely replaced plain balloon angioplasty of renal artery stenosis because of superior acute and long-term angiographic results of stenting.24 With the use of stent-supported angioplasty, however, Blum et al16 and White et al30 did not find any significant change of serum creatinine. These discrepant results with those of the present study may be a consequence of small sample size. Moreover, earlier studies included patients with moderate diameter stenoses (50% to 70%) that are unlikely to cause hemodynamic compromise.14–19,21–24,28,29,35

With an adequate sample size, improvement of renal function was found that was similar to that reported by van de Ven et al,19 Iannone et al,20 and Dorros et al.21,22 The choice of stent-supported angioplasty as treatment modality may have contributed to the beneficial outcome in the study. We were able to reduce the renin-angiotensin system to <30% in all cases. This was achieved at the expense of an early complication rate that was comparable to or lower than that in previous reports.16–22 Likewise, the 1-year restenosis rate was as low as 11.2% and compares well with the rates reported in the literature.16,18–27 Nevertheless, 4 patients (2%) required chronic hemodialysis because of acute complications. Conversely, inclusion into a chronic hemodialysis program could be prevented in 7 patients.

As a major novel finding, we demonstrated that a broader spectrum of patients can benefit from stent-supported renal angioplasty than previously thought. In particular, diabetes mellitus and nephrosclerosis do not define subsets of patients in whom we cannot expect improvement of renal function. Contrary to the present study, Radermacher et al29 did not find a benefit from renal artery revascularization in patients with severe nephrosclerosis. This discrepancy may be explained by differences in treatment modalities between the 2 studies. We treated all patients with stent placement, which gives the largest lumen gain and the lowest restenosis rate compared with other percutaneous treatment modalities.16–27 Radermacher et al, however, performed plain balloon angioplasty in the majority of their patients. In the present study, the benefit from intervention was not linked to bilateral stenoses, as suggested by most earlier studies.19–24,29 These findings are consistent with a study on split kidney function in patients treated for unilateral renal artery stenosis.35 This study showed an increase in total glomerular filtration rate that could be attributed to a large increase in glomerular filtration rate of the affected kidney but only a marginal decrease in the contralateral kidney. As suggested by the multivariate regression models, patients with renal insufficiency and congestive heart failure were most likely to show improvement of renal function. It is conceivable that reversal of renal artery stenosis is most effective if hemodynamic compromise is severe enough to have caused renal dysfunction or if there is a coexisting systemic prerenal component.

In most reports on endovascular therapy of renal artery stenosis, stent-supported angioplasty improved blood pressure control.1,14–29 In the present study, unilateral involvement did not preclude improvement of blood pressure control. Moreover, improvement of blood pressure was independent of nephrosclerosis or diabetes mellitus. Apart from female sex, high blood pressure and the absence of extensive renal damage predicted improvement of blood pressure control after stent-supported angioplasty. This was revealed by the logistic regression model.

As a limitation of this study, we have to consider that we did not include a control group. Previous studies have shown that the natural history of severe renal artery stenosis is characterized by progressive renal failure.4–11 Whereas this study clearly demonstrates that this detrimental course can be averted by stent-supported angioplasty, the extent of the benefit from endovascular repair of renal artery stenosis compared with conservative treatment remains to be delineated by a randomized trial. This study might have underestimated the benefit in patients with normal renal function. In these patients, angioplasty may serve to prevent deterioration in renal function, an advantage that does not become apparent without a control group.

In summary, stent-supported angioplasty of severe ostial renal artery stenosis improves renal function and blood pressure control in a broader spectrum of patients than previously assumed. Diabetes mellitus, nephrosclerosis, and unilateral involvement do not justify withholding renal stent-supported angioplasty in severe renal artery stenosis. The largest benefit with respect to renal function is found in patients whose renal function is already impaired or who have concomitant left ventricular dysfunction.

References

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