Angioplasty of Atherosclerotic and Fibromuscular Renal Artery Stenosis: Time Course and Predicting Factors of the Effects on Renal Function

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The effects of percutaneous transluminal renal angioplasty (PTRA) on the renal function of stenotic kidneys are usually assessed by evaluating the changes in serum creatinine, which is quite a rough indicator of glomerular filtration rate (GFR). In 27 hypertensive patients with 19 atherosclerotic and 11 fibromuscular significant renal artery stenoses, we investigated with renal scintigraphy the short-term (5 days) and long-term (10 months) effects of a technically successful PTRA (in seven cases combined with a stent implantation) on GFR of the stenotic and contralateral kidneys; these measurements were combined with those of plasma renin activity (PRA) and of angiotensin II (AII). We found that in short-term studies after PTRA GFR rose from 29.7 ± 3.5 to 34.6 ± 3.1 mL/min and from 36.9 ± 4.0 to 45.1 ± 4.3 mL/min, respectively, in atherosclerotic and fibromuscular poststenotic kidneys. In long-term studies GFR further and significantly increased, to 37.8 ± 3.2 mL/min in the former group, whereas it stabilized in the latter group (46.0 ± 3.6 mL/min). In patients with fibromuscular stenosis these changes in GFR were associated with clear-cut reductions in blood pressure (BP), PRA, and AII; these decrements also occurred in patients with atherosclerotic stenosis but to a much lesser extent. We also found that in short- and long-term studies the percent of PTRA-induced increments of GFR in the poststenotic kidneys were inversely correlated with the baseline values of GFR. In addition, the absolute and percent increments of GFR were positively correlated with the basal levels of AII. Thus the time course of the improvement in GFR after angioplasty may differ in kidneys, depending on the etiology of the stenosis, in that in those with fibromuscular stenosis it was entirely apparent within a few days whereas in those with atherosclerotic stenosis it required several months to be fully expressed. Also, it appears that the more compromised kidneys are those that benefit most from the dilatation and that AII levels are useful indicators of the possibility that the stenotic kidney will have a favorable functional outcome in terms of restoration of renal blood flow. Am J Hypertens 2000;13:1210 –1217 © 2000 American Journal of Hypertension, Ltd.

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schematic nephropathy due to renal artery stenosis (RAS), most frequently atherosclerotic, is a major cause of progressive loss of renal function and, eventually, of end-stage renal disease. This devastating evolution could be prevented, or at least postponed, if patients with RAS were detected and treated in the early stage of their disease.

Surgical revascularization of stenotic arteries has been used extensively in the past for preserving renal function and available data indicate that about 60% of patients treated with this approach have either improved or unchanged serum creatinine levels during a prolonged follow-up. However, surgery has major limitations represented by relatively high perioperative mortality and morbidity, as well as by high costs. Nowadays percutaneous transluminal renal angioplasty (PTA), alone or in combination with stent implantation, can be offered as a valid alternative to surgery, particularly in high-risk patients, in that studies addressing the effects of these procedures on renal function have obtained results, on average, superimposable to those achieved with aortorenal bypass or endarterectomy, the frequency of improvement in renal function being, however, extremely variable.

The more recent investigations, which used stent implantation—resulting in wider lumen diameter of the renal artery and in lower rate of restenosis than angioplasty—yielded a slightly higher rate of creatinine improvement or stabilization (66% to 69%). Yet the precise effects of these dilating maneuvers on glomerular filtration rate (GFR) remain uncertain because serum creatinine is an inaccurate marker of GFR, particularly in patients in whom renal function is already impaired or in those in whom the contralateral normal kidney may compensate for the loss of function of the stenotic one.

Also, relatively little attention has been paid to the differences in the magnitude and in the time course of the changes in GFR induced by angioplasty in kidneys with atherosclerotic and with fibromuscular RAS. These may well differ considering the discrepancy in the duration of hypertension and of renal ischemia, which are usually much longer in kidneys with atherosclerotic RAS.

In this study we took advantage of dynamic renal scintigraphy with $^{99m}$Tc-DTPA, a technique that may be particularly convenient for clinical and follow-up studies, to compare the short-term and long-term effects of successful PTRA on GFR of kidneys with atherosclerotic and fibromuscular RAS and of their contralateral normal companions. In addition, because AII plays a pivotal role in maintaining GFR in stenotic kidneys, we also evaluated the effects of angioplasty on plasma renin activity (PRA) and angiotensin II (AII) to assess whether the functional outcome of the procedure was related to the degree of activation of the renin-angiotensin system.

**METHODS**

**Patients and Protocol** The study was conducted in 27 hospitalized patients (16 men, 11 women; mean age, 52 years; range, 18–74 years) who, in the course of the diagnostic work-up for moderate to severe hypertension, underwent a conventional angiography because of a strong suspicion of renovascular hypertension. Indeed, these radiologic studies revealed 19 significant atherosclerotic RAS (15 unilateral, two in a solitary kidney, and one bilateral) and 11 fibromuscular dysplasias (seven unilateral and two bilateral). Patients with atherosclerotic RAS were significantly older (58 ± 3 vs 40 ± 5 years, $P < .05$) and at admission all but three patients were receiving treatment with antihypertensive agents, including calcium antagonists ($n = 18$), $\beta$-blockers ($n = 8$), $\alpha$-blockers ($n = 6$), and diuretics ($n = 4$), alone or in combination. Patients who were receiving treatment with angiotensin-converting enzyme (ACE) inhibitors were excluded, on purpose, from the study because of the known effects of these compounds on GFR and PRA and AII levels.

Serum creatinine was, on average, 1.5 ± 0.1 mg/dL (range, 0.9–4.1) and 0.9 ± 0.1 mg/dL (range, 0.8–1.3), respectively, in patients with atherosclerotic and fibromuscular RAS. Throughout the study patients received a standard hospital diet containing approximately 150 mEq sodium/day and had blood pressure checked daily between 8 and 10 AM in the supine position.

Within 2 to 3 days before the diagnostic angiography and PTRA, which were carried out in the same session, blood was collected for measurement of creatinine, PRA, and AII, and baseline renal scintigraphy was performed. In preparation for this latter evaluation, hydration was ensured by not restricting fluid intake and by administering 300 mL of water by mouth at least half an hour before the study. All studies were done with patients kept in the supine position and using a large field of view $\gamma$ camera (Helix Elscint, Haifa, Israel) and a low-energy, high-resolution collimator positioned under the camera’s couch. As radiopharmaceutical, a fixed dose of 111 MBq of diethylene triamine penta-acetic acid ($^{99m}$Tc-DTPA) was administered intravenously in an antecubital vein. Images were then acquired with a time frame of 1 s for 60 frames, followed by 76 images of 15 s. Computer processing of scintigraphic data was performed to produce a time-activity curve, after selection of a region of interest (ROI) around each kidney and a semilunar background ROI positioned around the inferolateral edge of each kidney. Glomerular filtration rate ($\text{mL/min/1.73 m}^2$) of the two kid-
neys were then calculated from background-corrected renograms according to the Gates method. The mean longitudinal diameter of the ischemic kidneys was 10.3 cm (range, 6.8–11.9). Because of these divergent trends in the poststenotic changes, the risk of arterial spasm and embolism. In all cases no major complications were observed.

**Humoral Measurements** Measurements of PRA (ng/mL/h) and of AII (pg/mL) were performed in samples collected from a peripheral vein in 23 patients (16 with atherosclerotic and seven with fibromuscular stenosis) who were kept in the supine position for at least half an hour. Plasma renin activity was measured with the enzymatic method using a radioimmunoassay, quantifying the amount of angiotensin I generated during 1 to 3 h of incubation of plasma at 37°C, pH 5.7. The sensitivity of the entire assay is 0.25 ng/mL/h and its interassay reproducibility 11%. Angiotensin II was measured by radioimmunoassay after extraction of the peptide from plasma, as described in detail elsewhere; the sensitivity of the method is 1.25 pg/mL and its interassay reproducibility 16%.

**Statistical Analysis** Values of all parameters observed before PTRA were compared to those observed after it using a Student t test for paired data. The same test for unpaired data was used for comparisons between patients with atherosclerotic and fibromuscular stenosis. A P value < .05 was considered statistically significant. The least-squares analysis was used to determine the correlation coefficient between two variables.

**RESULTS**

**Effects of PTRA in Patients With Atherosclerotic RAS** Alone or in combination with stent implantation, PTRA caused, in the short term, a significant reduction of systolic blood pressure (SBP), which, however, returned toward baseline values during long-term follow-up (Table 1). Blood pressure was normalized without medications in one patient only. After PTRA the GFR was either unchanged or improved in 16 of the 19 kidneys both in short- and long-term studies (Fig. 1). As a result, GFR rose, on average, from 29.7 ± 3.5 mL/min to 34.6 ± 3.1 mL/min and further to 37.8 ± 3.2 mL/min in long-term studies (P < .05 with respect to short-term) (Fig. 2, upper left panel). At variance with the findings in the poststenotic kidneys the GFR decreased, although not significantly, in the contralateral ones (from 45.2 ± 5.7 mL/min to 42.8 ± 5.1 mL/min and 41.7 ± 4.3 mL/min, respectively, in short- and long-term studies) (Fig. 2, upper right panel).

Because of these divergent trends in the poststenotic and contralateral kidneys the increments in total GFR, as well as the decrements in serum creatinine, failed to reach statistical significance with respect to baseline values (Table 1). However, in a subset of 10 patients whose creatinine at baseline was ≥ 1.5 mg/dL (mean, 1.8 ± 0.1 mg/dL) PTRA caused a progressive reduction to 1.6 ± 0.2 and 1.4 ± 0.1 mg/dL, respectively, in
short- and long-term follow-up studies \((P < .01)\), whereas total GFR increased correspondingly, from 50.7 ± 6.4 mL/min to 52.9 ± 6.1 and 57.8 ± 5.9 mL/min.

After PTRA both PRA and AII tended to decrease but only the changes in AII during the long-term follow-up reached statistical significance with respect to baseline (Table 1).

### Effects of PTRA in Patients With Fibromuscular RAS

In this group of patients PTRA induced significant and rapid reduction in both SBP and diastolic blood pressure (DBP), which stabilized during long-term follow-up (Table 1). In two patients hypertension was cured by the procedure. After PTRA the GFR was either unchanged or improved in nine of the 11 poststenotic kidneys, causing the GFR to rise from 36.9 ± 4.0 mL/min to 45.1 ± 4.3 mL/min and 46.0 ± 3.6 mL/min, respectively, in short- and long-term studies \((P < .05\) or more for both with respect to baseline) (Fig. 2, lower left panel). Also, in kidneys contralateral to fibromuscular RAS GFR tended to decrease after PTRA (from 54.9 ± 7.2 mL/min to 52.8 ± 5.2 mL/min.

### Table 1. Effects of PTRA on Blood Pressure, Renal Function, and the Renin Angiotensin System

<table>
<thead>
<tr>
<th>Patients With Atherosclerotic Stenosis ((n = 18))</th>
<th>Patients With Fibromuscular Stenosis ((n = 9))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP (mm Hg)</strong></td>
<td><strong>SBP (mm Hg)</strong></td>
</tr>
<tr>
<td>Before PTRA 154 ± 4</td>
<td>Before PTRA 160 ± 5</td>
</tr>
<tr>
<td>Short-Term 146 ± 3*</td>
<td>Long-Term 138 ± 5*</td>
</tr>
<tr>
<td>Long-Term 150 ± 5</td>
<td>Long-Term 138 ± 4*</td>
</tr>
<tr>
<td><strong>DBP (mm Hg)</strong></td>
<td><strong>DBP (mm Hg)</strong></td>
</tr>
<tr>
<td>Before PTRA 82 ± 2</td>
<td>Before PTRA 102 ± 3†</td>
</tr>
<tr>
<td>Short-Term 84 ± 2</td>
<td>Long-Term 90 ± 2*</td>
</tr>
<tr>
<td>Long-Term 88 ± 1</td>
<td>Long-Term 92 ± 3*</td>
</tr>
<tr>
<td><strong>GFR (mL/min/1.73 m²)</strong></td>
<td><strong>GFR (mL/min/1.73 m²)</strong></td>
</tr>
<tr>
<td>Before PTRA 66.6 ± 7.6</td>
<td>Before PTRA 87.9 ± 7.7</td>
</tr>
<tr>
<td>Short-Term 69.8 ± 7.7</td>
<td>Short-Term 96.2 ± 5.6</td>
</tr>
<tr>
<td>Long-Term 72.5 ± 7.5</td>
<td>Long-Term 95.6 ± 4.5</td>
</tr>
<tr>
<td><strong>Creat (mg/dL)</strong></td>
<td><strong>Creat (mg/dL)</strong></td>
</tr>
<tr>
<td>Before PTRA 1.5 ± 0.1</td>
<td>Before PTRA 0.9 ± 0.05</td>
</tr>
<tr>
<td>Short-Term 1.4 ± 0.1</td>
<td>Short-Term 5.7 ± 2.7†</td>
</tr>
<tr>
<td>Long-Term 1.3 ± 0.1</td>
<td>Long-Term 0.5 ± 0.09*</td>
</tr>
<tr>
<td><strong>PRA (ng/mL/h)</strong></td>
<td><strong>PRA (ng/mL/h)</strong></td>
</tr>
<tr>
<td>Before PTRA 1.6 ± 0.5</td>
<td>Before PTRA 0.5 ± 0.09*</td>
</tr>
<tr>
<td>Short-Term 0.6 ± 0.1</td>
<td>Short-Term 10.0 ± 3.6</td>
</tr>
<tr>
<td>Long-Term 0.6 ± 0.1</td>
<td>Long-Term 0.6 ± 1.2*</td>
</tr>
<tr>
<td><strong>A II (pg/mL)</strong></td>
<td><strong>A II (pg/mL)</strong></td>
</tr>
<tr>
<td>Before PTRA 12 ± 3</td>
<td>Before PTRA 18 ± 5</td>
</tr>
<tr>
<td>Short-Term 8 ± 1</td>
<td>Short-Term 7 ± 2*</td>
</tr>
<tr>
<td>Long-Term 7 ± 1*</td>
<td>Long-Term 2 ± 1*</td>
</tr>
</tbody>
</table>

*PTRA = percutaneous transluminal renal angioplasty; SBP and DBP = systolic and diastolic blood pressure; GFR = total glomerular filtration rate; Creat = serum creatinine; PRA = plasma renin activity; AII = angiotensin II.

During hospitalization values of blood pressure refer to the mean of those measured within 3 days before PTRA and within the 5 days after it (short-term), whereas long-term values refer to those measured at the follow-up visit. Short-term creatinine refer to the last value before discharge. Statistical significance of the *difference between values observed after PTRA and those before it, and †between patients with atherosclerotic and fibromuscular RAS \((P < .05\) at least).

**FIG. 1.** Individual values of GFR before PTRA, on the horizontal axis, and after PTRA, on the vertical axis, in short-term (left panel) and long-term (right panel) studies in kidneys with atherosclerotic (filled square, \(n = 19\)) and fibromuscular (empty square, \(n = 11\)) stenosis. In 25 kidneys values of GFR were either unchanged or improved after PTRA, whereas in the remaining five kidneys GFR worsened; four of these cases were the same in short- and long-term studies. GFR = glomerular filtration rate; PTRA = percutaneous transluminal renal angioplasty.
and 51.7 ± 3.1 mL/min) (Figure 2, lower right panel); thus, as in the group of patients with atherosclerotic RAS, the increments in total GFR did not reach statistical significance (Table 1).

In these patients in basal condition the renin-angiotensin system was significantly more activated than in atherosclerotic patients and both PRA and AII were markedly and significantly reduced in short- and long-term studies after PTRA (Table 1).

Correlations  A highly significant inverse relationship was found between the baseline values of GFR and the percent increments observed after PTRA (r = −0.58 and −0.65, respectively, for short- and long-term studies, P < .001 for both) (Fig. 3). The absolute and percent increments in GFR in the stenotic kidneys after PTRA were also positively correlated with baseline values of AII (r = 0.73 and 0.76, short-term; r = 0.60 and 0.46, long-term; P < .02 or more for all) (Fig. 4). A similar relationship, but with a lower level of statistical significance, was found with baseline values of PRA (r = 0.36 and 0.45, short-term; 0.39 and 0.42, long-term; P < .09 or more). In contrast, no relationship was found in the stenotic kidneys between baseline GFR and the degree of arterial narrowing and SBP and DBP, nor between their changes after PTRA.

DISCUSSION

Time Course of the Functional Outcome of PTRA: Atherosclerotic Versus Fibromuscular Stenosis  Renal scintigraphy has been used extensively for diagnosing renovascular hypertension and for anticipating the effects of dilating procedures on BP,6,21–23 but to a much lesser extent to evaluate the functional effects of PTRA. Actually, to our knowledge, the only paper that has used renal scintigraphy to evaluate comparatively the short- and long-time effects of renal angioplasty on the function of kidneys with atherosclerotic and fibromuscular stenosis, as we have done in this study, is that by Jensen et al.24 These authors have found that, 10 days after PTRA, GFR was increased by 4.3 mL/min and 8.7 mL/min, respectively, in kidneys with atherosclerotic and fibromuscular stenosis; at 1 year follow-up they noted a further, slight increase, respectively, of 6.1 mL/min and 10.7 mL/min. In our study, within 5 days after the dilatation the increments were similar (on average, 4.8 mL/min and 8.7 mL/min, respectively, in kidneys with atherosclerotic and fibromuscular stenosis); at 1 year follow-up they noted a further, slight increase, respectively, of 6.1 mL/min and 10.7 mL/min. In our study, within 5 days after the dilatation the increments were similar (on average, 4.8 mL/min and 8.7 mL/min, respectively, in kidneys with atherosclerotic and fibromuscular stenosis). However, at variance with Jensen et al’s study, in long-term studies we found a further significant increase in GFR only in atherosclerotic kidneys (8.1 mL/min), whereas the increments in fibromuscular kidneys were similar to those observed in
short-term studies (9.1 mL/min). This delayed amelioration of GFR was also found in kidneys with atherosclerotic stenosis by other investigators. In our study it cannot be attributed to a better control of BP in the long term in that, if anything, BP tended to return toward baseline values in patients of this group. Rather, it is possible that in the poststenotic atherosclerotic kidney the recovery of GFR may result not only from the acute restoration of renal blood flow, as occurs in kidneys with fibromuscular stenosis, but also from the slow wearing off of other ischemia-related mechanisms of renal damage. Indeed, animal

FIG. 3. Relationship between GFR values before PTRA and the percent changes in GFR observed in short-term (left panel) and long-term (right panel) studies in kidneys with atherosclerotic (filled square) and fibromuscular (empty square) stenosis. Abbreviations as in Fig. 1.

FIG. 4. Relationship between values of AII before PTRA on the horizontal axis and the absolute (upper panels) and percent (lower panels) changes observed in short-term (left panels) and long-term (right panels) studies after PTRA in kidneys with atherosclerotic (n = 16, filled square) and fibromuscular (n = 7, empty square) stenosis. AII = angiotensin II; other abbreviations as in Fig. 1.
studies have shown that prolonged renal ischemia, such as is likely to occur in kidneys with atheromatous stenosis, can cause alterations of the antigenic profile of the tubular epithelium, resulting in tubular atrophy and interstitial fibrosis. Chronic ischemia may also favor the release of oxidant substances and proteases, which may potentially contribute to aggravate the renal damage. In addition, autopsy studies have clearly illustrated that atherosclerotic kidneys have various degrees of vascular sclerosis, tubular atrophy, and interstitial fibrosis, which are rarely seen in kidneys with pure ischemia due to fibromuscular lesions. Animal studies have shown that these lesions are reversible after relief of the ischemia. Thus it is plausible that also in humans the reversal of these alterations requires time to occur. Therefore, at least in kidneys with atherosclerotic stenosis, several months of follow-up are required to properly evaluate the functional effects of revascularization.

**Functional Effects of PTRA in the Contralateral Normal Kidney** The improvement in total GFR observed in patients undergoing revascularization is usually attributed to the amelioration in the function of the dilated kidney, even if, to a lesser extent, it appears that also the contralateral normal kidneys may be influenced by dilatation. Indeed, in this study, both in kidneys contralateral to atherosclerotic and to fibromuscular stenosis, GFR tended to decrease. The incomplete control of BP observed in atherosclerotic patients cannot be responsible for this trend because the reduction in GFR was observed also in kidneys contralateral to the fibromuscular stenosis, ie, in patients in whom BP was essentially normalized after PTRA. Rather, this slight decrease in GFR may be mediated by the abatement of the compensatory hemodynamic changes known to occur in the contralateral kidney; a major contribution to this is probably given by the decrease in circulating AII with the attendant decrease of the selective vasoconstriction exerted by this peptide on the efferent arteriole. Preliminary results of ours have shown a reduction in filtration fraction both in the stenotic and contralateral kidneys after renal angioplasty. Whatever the mechanism, the slight reduction in GFR in the contralateral kidneys may counterbalance, in part, the increments in the dilated kidneys, thus explaining why in our studies the improvement in total GFR failed to reach statistical significance.

**Prediction of the Functional Outcome of PTRA** Renal angioplasty and stent implantation are much less invasive procedures than surgery but are not devoid of potentially serious side effects. Thus, it would be helpful to have reliable criteria to select patients whose renal function may actually benefit from dilating procedures. The degree of renal impairment at which such benefit outweighs the risks is still unsettled, but the position commonly held is that in severely deteriorated kidneys PTRA is ineffective for salvaging GFR. At variance, we found an inverse relationship between the percent increments in GFR in stenotic kidneys and their baseline values; this finding indicates that the more compromised kidneys are those that may gain most from dilatation. Obviously this conclusion applies to kidneys with moderate functional alterations, in the range of those examined in this study, and may well be invalid for kidneys whose function is more severely deteriorated.

Finally, we found a direct relationship between the absolute and percent increments in GFR and the baseline levels of AII. The degree of activation of the renin angiotensin system has been proposed as a useful indicator for predicting the BP response to dilating procedures and even the rationale for using renal scintigraphy as a test for renovascular hypertension stems from the assumption of the key role played by this system in determining the effects of dilatation on BP. Much less attention has been paid to the renin angiotensin system for predicting the functional outcome of PTRA. Our results indicate that the levels of angiotensin II are reliable markers of the susceptibility of the ischemic kidney to the functional recovery in response to restoration of renal blood flow. Indeed, if the release of renin and the production of AII are stimulated in proportion to the reduction in renal blood flow to counterbalance the fall in GFR, it is plausible that kidneys exposed to the highest concentrations of AII are those in which GFR is more likely to improve after the reversal of renal hypoperfusion. This may be particularly true in the long term, in view of the action exerted by AII in fostering the sequence of humoral events that leads to the development of interstitial fibrosis.

**REFERENCES**


