Split Renal Function Outcome after Renal Angioplasty in Patients with Unilateral Renal Artery Stenosis

AGNÈS LA BATIDE-ALANORE,* MICHEL AZIZI,† MARC FROISSART,‡ ALAIN RAYNAUD,§ and PIERRE-FRANÇOIS PLOУIN*
*Hypertension Department, †Clinical Investigation Center (CIC 9201), Assistance Publique des Hôpitaux de Paris/INSERM, §Physiology Department and INSERM U356, and ‡Radiology Department, Hôpital Européen Georges Pompidou, Assistance Publique Hôpitaux de Paris, Paris, France.

Abstract. The general use of bilateral rather than separate renal function evaluation has led to the publication of conflicting results concerning the effect of percutaneous transluminal renal angioplasty (PTRA) on renal function, especially in patients with atherosclerotic renal artery stenosis. The aim of this study was to evaluate prospectively, in standardized conditions, split renal function (SRF) and GFR outcome after successful PTRA, by measuring single kidney GFR with synchronous inulin or $^{51}$Cr-ethylenediaminetetraacetic acid clearance and $^{99m}$Tc-diethylenetriamine pentaacetic acid scintigraphy, in a well-defined population of patients with unilateral renal artery stenosis. Thirty-two consecutive hypertensive patients (18 with atherosclerotic and 14 with dysplastic disease) with significant unilateral stenosis of the main native renal artery ($\geq 60\%$) and normal renal function were included in the study. Renal and angiographic follow-up evaluations were performed 6 mo after PTRA. PTRA alone or combined with stenting ($n = 2$) was technically successful in all patients. Repeat PTRA was necessary in two patients, evaluated 6 mo after the second PTRA. Six mo after PTRA, total GFR had increased slightly but significantly in the 29 patients with positive lateralization indices. SRF and single-kidney GFR of the stenotic kidney increased significantly, whereas concurrently the GFR and SRF of the nonstenotic kidney decreased significantly. Six mo after successful PTRA reducing renal ischemia, a reversal of both the hyperperfusion of the stenotic side and the hyperperfusion of the nonstenotic side was observed, which was accompanied by a slight increase in total GFR.

Renal revascularization by percutaneous transluminal renal angioplasty (PTRA), with or without stenting, is used to treat renovascular disease. PTRA has beneficial BP-lowering effects in patients with fibromuscular dysplasia (1) but is less effective in patients with atherosclerotic disease. In patients with atherosclerotic disease, PTRA reduces BP to an extent similar to that with standardized antihypertensive drug regimens with fewer antihypertensive drugs (2–4). Conflicting results have been published concerning the effects of PTRA on renal function, especially in patients with atherosclerotic renal artery stenosis (RAS) (4). In most studies, the use of overall, bilateral rather than separate renal function evaluation decreased the probability of detecting any significant changes after revascularization, because GFR normally equilibrates between the two kidneys to maintain normal renal function, especially in the presence of unilateral RAS.

Therefore, this study aimed to evaluate prospectively the effect of PTRA on split renal function (SRF) and GFR in a well-defined population of patients with unilateral RAS, by measuring single-kidney GFR with synchronous inulin or $^{51}$Cr-ethylenediaminetetraacetic acid ($^{51}$Cr-EDTA) clearance and $^{99m}$Tc-diethylenetriamine pentaacetic acid ($^{99m}$Tc-DTPA) scintigraphy.

Materials and Methods
Selection of Patients

Thirty-two consecutive patients, of both genders, were referred to the Hypertension Clinic and were included prospectively if they satisfied the following criteria:

1. Age 20 to 75 yr.
2. Significant unilateral RAS of a main native renal artery, diagnosed by renal intravenous digitalized subtraction angiography and confirmed by renal arteriography before PTRA. Significant unilateral RAS was defined as a reduction in renal artery diameter of $>60\%$ on the stenotic side, with $<50\%$ contralateral RAS. PTRA was considered to be indicated in the presence of hypertension if renal artery diameter was reduced by $>75\%$, irrespective of the lateralization indices or, for stenosis of between 60 and 75%, if one lateralization index was positive (either a renal vein renin ratio $>1.5$ or positive captopril scintigraphy result, see below) and after a multidisciplinary consensus was reached.
3. Hypertension (supine casual BP $>140/90$ mmHg, measured with a standard sphygmanometer after 5 min of rest).
4. Both atherosclerotic and dysplastic RAS were included in the study. Classification of the lesion was based on clinical history and on radiologic appearance of the RAS.
5. Successful PTRA with or without stenting was defined as residual stenosis of $<30\%$ immediately after PTRA.

Received July 20, 2000. Accepted October 31, 2000.
Correspondence to Dr. Michel Azizi, Clinical Investigation Center, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015 Paris, France. Phone: 33-1-56-09-29-12; Fax: 33-1-56-09-29-29; E-mail: michel.azizi@egp.ap-hop-paris.fr
1046-6673/1206-1235
Journal of the American Society of Nephrology
Copyright © 2001 by the American Society of Nephrology
6. Absence of insulin-dependent diabetes mellitus and renal insufficiency, defined as a Cockcroft and Gault creatinine clearance of <60 ml/min per 1.73m².

7. Possibility of follow-up over 1 yr.

All antihypertensive treatments that might interfere with renal function evaluation, such as diuretics, angiotensin converting enzyme (ACE) inhibitors, and nonsteroidal anti-inflammatory drugs, were withdrawn at least 2 wk before PTRA and were not reintroduced during follow-up. Patients were treated with calcium channel blockers (n = 28), centrally acting antihypertensive agents (n = 15), β-blockers (n = 7), α-blockers (n = 3), or various combinations of these drugs. All patients were advised to follow their usual sodium diet throughout the study.

PTRA Procedure

All PTRA were performed by the same physician (A.R.), as described previously (5). After angioplasty, the balloon catheter was withdrawn with the guidewire left across the lesion until a repeat aortogram was performed to confirm satisfactory angioplasty. When obstructive parietal damage or a recoil phenomenon was observed, repeated, slow, long-lasting (3 to 4 min) pressure inflations were performed, and, if necessary, a Wallstent endoprostheses was inserted. At the end of the procedure, renal angiography was repeated and the technical outcome was assessed from this immediate postprocedural angiography. No antiplatelet aggregation therapy was specifically prescribed to patients after PTRA.

Renal Vein Renin Ratio Determination

Renal vein renin release was stimulated by a single oral dose of 1 mg/kg captopril administered 1 h before renal vein sampling. Plasma active renin were measured by immunoradiometric assay, using a commercially available kit (ERIA, Diagnostics Pasteur, Marnes-la-Coquette, France). A captopril-stimulated renal vein renin ratio ≥1.5 was considered to be a positive lateralization index.

GFR Determination

Creatinine clearance was estimated from plasma creatinine concentration with the use of the Cockcroft-Gault formula (6) and was standardized to a body surface area of 1.73 m². Pre-PTRA and follow-up total GFR were determined for each patient with the use of the same technique: insulin renal clearance (n = 17) (7), 51Cr-EDTA renal clearance (n = 10) (8), and plasma 51Cr-EDTA (n = 5) (9). Tests were carried out after patients fasted overnight, and patients remained supine during the clearance periods, resuming the standing position only to void.

Renal Scintigraphy and SRF Determinations

Renal scintigraphy was performed in the supine position, with the back of the patient against a wide-field view γ camera (Helix-SPX, Elscint Corp., Haifa, Israel) that was equipped with a low-energy, high-resolution all-purpose collimator, which allowed visualization of the kidneys and the heart. The 10% window was centered on the 99mTc 140 keV photopeak. GFR measurements and pre- and postcaptopril renal scintographies were performed on the same day. For precaptopril renal scintigraphy, 200 to 300 MBq of 99mTc-DTPA was injected 30 min after oral hydration (7 ml/kg) at 8:00 a.m., i.e., during the equilibration or distribution period for clearance determinations. At 12:00 p.m., after the completion of GFR measurements, a single oral dose of 50 mg of captopril was given to the patient, and postcaptopril scintigraphy was performed 1 h later at 1:00 p.m. with the use of a single intravenous dose of 300 to 400 MBq 99mTc-DTPA. Each study included a flow study of 60 frames (64 × 64 pixels) of 1 s each and was followed by a sequence of 120 frames of 10 s each for 20 min.

SRF (%) were determined by the Patlak-Rutland method (10), with both extravascular and intravascular background corrections, with the use of subrenal and cardiac background regions of interest (ROI), respectively. The ROI of both kidneys were determined with the use of a threshold method on a summed frame (from 1 min 30 s to 2 min 30 s). The same kidney and background ROI were used for both pre-and postcaptopril studies. The same threshold values were used for follow-up studies in a given patient. Depth attenuation was corrected with the use of lateral views to determine the skin-to-kidney center distance and a linear attenuation coefficient of 0.12 cm⁻¹ for 99mTc in soft tissues.

Follow-up Evaluations

Follow-up studies, which involved BP, biologic, GFR, scintigraphic, and arteriographic evaluations for all patients, were performed within 6 mo of PTRA, with a minimum observation period of 3 mo. When significant angiographic restenosis (≥60%) that required repeat PTRA was observed, follow-up evaluation was planned for 3 to 6 mo later and was preceded by a control angiography to check the effectiveness of the revascularization. In addition, proteinuria was measured on a 24-h urine sample before and after PTRA.

The BP results of PTRA were evaluated with the use of the criteria established by the US Cooperative Study for Renovascular Surgery and modified as described by Geyskes (14). BP measurements were performed with the use of a standard sphygmomanometer, and phase V of the Korotkoff sounds was taken as diastolic BP (DBP). Patients were classified as “cured” when DBP was <90 mmHg without treatment. Improvement was defined either as a DBP ≥91 and <109 mmHg with a DBP decrease greater than 15% or as a DBP decrease of at least 10% plus one antihypertensive drug stopped. Treatment was considered to have failed to lower BP in all other cases.

Statistical Analyses

We carried out an ANOVA with one repeated factor (pre-PTRA and post-PTRA) and one grouping factor (RAS cause). The assumptions of the ANOVA (homogeneity of variance and normality) were checked for each variable, and natural logarithmic transformations were applied as appropriate. To evaluate the effect of PTRA on each variable, we calculated 95% confidence intervals (CI) for the differences between the initial and final evaluations. When the limit of the
95% CI did not cross 0, the difference between pre- and post-PTRA values was significant.

The initial clinical characteristics of the patients with atherosclerotic or fibromuscular dysplasia RAS were compared with the use of unpaired t tests. The regression coefficient was estimated by the least-squares method. Proportions were compared by the \( \chi^2 \) method. The STATVIEW 4.01 and SUPERANOVA programs were used for statistical analysis (Apple Macintosh Abacus Concepts Inc., Berkeley, CA). Data are expressed as means ± 1 SD in the tables unless otherwise specified. Probability values below 0.05 were considered to be significant.

**Results**

For all tested parameters, there was no significant treatment \( \times \) RAS cause interaction in the ANOVA. Therefore, only treatment and RAS cause effects are reported in the tables.

**Baseline Evaluation before PTRA**

**Initial Characteristics.** Eighteen of the 32 patients in the study had atherosclerotic unilateral RAS, and 14 had dysplastic unilateral RAS (Table 1). All patients had severe hypertension at their first outpatient visit (179 ± 27/107 ± 15 mmHg) independent of the RAS cause. As expected, all patients with fibrodysplastic RAS were women (14 of 14). These patients were significantly younger and had a significantly shorter duration of hypertension, lower plasma creatinine, and higher creatinine clearance values than those with atherosclerotic RAS (Table 1). Mild proteinuria (0.5 ± 0.4 g/24 h) was observed in 8 of 29 patients. The frequencies of positive results for both renal vein renin ratio and captopril renal scintigraphy were similar between the patients with atherosclerotic and dysplastic RAS (Table 1). Both lateralization indices were negative in three patients with atherosclerotic RAS. Atherosclerotic RAS were ostial in 6 of 18 patients and truncal in the remaining. All dysplastic stenoses were truncal.

**Baseline GFR and SRF.** Before PTRA, total GFR was significantly lower in patients with atherosclerotic RAS than in patients with dysplastic RAS, mainly because of the nonstenotic kidney’s having a significantly lower split GFR (Table 2). The GFR of the nonstenotic kidney accounted for 66 ± 15% of total GFR (atherosclerotic, 63 ± 16%; dysplastic, 71 ± 12%; not significant). At baseline, SRF (%) was lower in patients with dysplastic RAS than in patients with atherosclerotic RAS, but the difference between the two groups was not statistically significant. This indicates that the ischemic consequences of RAS were more severe in patients with dysplastic RAS than in patients with atherosclerotic RAS. Total RBF/CO (sum of RBF/CO for both the stenotic and nonstenotic kidneys) was significantly lower in patients with atherosclerotic RAS than in patients with dysplastic RAS, because the RBF/CO of the nonstenotic kidney was significantly lower in patients with atherosclerotic RAS (Table 3).

**Immediate and Long-Term Angiographic Results after PTRA**

PTRA alone or combined with stenting of the RAS was technically successful in all patients. Immediate post-PTRA angiography showed either no residual stenosis or a residual stenosis of <30%. In two patients with atherosclerotic RAS, we observed a recoil phenomenon that led to the insertion of a Wallstent endoprosthesis. The immediate postprocedural angiography showed no residual stenosis for these two patients. At the first angiographic control, two patients with atherosclerotic RAS displayed signs of severe restenosis (>75%), which required repeat PTRA. Three to 6 mo after the repeat

**Table 1.** Baseline characteristics of the patients with an atherosclerotic or a dysplastic unilateral renal artery stenosis (mean ± SD)\(^a\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 32)</th>
<th>Atheroma (n = 18)</th>
<th>Dysplasia (n = 14)</th>
<th>Atheroma Versus Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49 ± 16</td>
<td>59 ± 11</td>
<td>37 ± 12</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>15/17</td>
<td>15/3</td>
<td>0/14</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Duration of hypertension (yr)</td>
<td>9 ± 9</td>
<td>13 ± 10</td>
<td>5 ± 5</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Current smokers (n/%)</td>
<td>10/31</td>
<td>4/22</td>
<td>6/43</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)(^b)</td>
<td>179 ± 27</td>
<td>177 ± 28</td>
<td>182 ± 26</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)(^b)</td>
<td>101 ± 15</td>
<td>104 ± 14</td>
<td>112 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>24 ± 3</td>
<td>26 ± 3</td>
<td>23 ± 3</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Antihypertensive treatment [median (range)](^b)</td>
<td>1 (0–5)</td>
<td>1 (0–5)</td>
<td>1.5 (0–5)</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma creatinine (µmol/L)</td>
<td>86 ± 22</td>
<td>96 ± 20</td>
<td>75 ± 19</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min per 1.73 m(^2))</td>
<td>82 ± 23</td>
<td>72 ± 19</td>
<td>95 ± 22</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Proteinuria &gt;0.10 g/24 h (n/n)</td>
<td>8/29</td>
<td>13/18</td>
<td>7/12</td>
<td>NS</td>
</tr>
<tr>
<td>Renal vein renin ratio(^c)</td>
<td>20/30</td>
<td>13/18</td>
<td>7/12</td>
<td>NS</td>
</tr>
<tr>
<td>Captopril renography(^c)</td>
<td>22/32</td>
<td>8/18</td>
<td>14/14</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>One positive test(^c)</td>
<td>29/32</td>
<td>15/18</td>
<td>14/14</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\) SBP, systolic BP; DBP, diastolic BP; BMI, body mass index.

\(^b\) At the initial outpatient visit.

\(^c\) Positive/performed.
Table 2. Effects of PTRA on GFR and SRF in patients with atherosclerotic or dysplastic unilateral RAS (mean ± SD)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before PTRA</th>
<th>After PTRA</th>
<th>Mean Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GFR (ml/min per 1.73 m\textsuperscript{2})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall (n = 32)</td>
<td>89 ± 20</td>
<td>94 ± 22</td>
<td>5 (−2, 10)</td>
</tr>
<tr>
<td>atheroma (n = 18)</td>
<td>83 ± 20\textsuperscript{b}</td>
<td>86 ± 27</td>
<td>3 (−5, 11)</td>
</tr>
<tr>
<td>fibromuscular dysplasia (n = 14)</td>
<td>98 ± 17</td>
<td>104 ± 10</td>
<td>6 (−4, 16)</td>
</tr>
<tr>
<td>SRF of the stenotic kidney (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall (n = 32)</td>
<td>34 ± 15</td>
<td>43 ± 11</td>
<td>9 (6, 13)\textsuperscript{c}</td>
</tr>
<tr>
<td>atheroma (n = 18)</td>
<td>37 ± 16</td>
<td>44 ± 12</td>
<td>7 (2, 11)</td>
</tr>
<tr>
<td>fibromuscular dysplasia (n = 14)</td>
<td>29 ± 12</td>
<td>42 ± 9</td>
<td>13 (7, 19)</td>
</tr>
<tr>
<td>GFR of the stenotic kidney (ml/min per 1.73 m\textsuperscript{2})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall (n = 32)</td>
<td>31 ± 16</td>
<td>41 ± 14</td>
<td>10 (5, 14)</td>
</tr>
<tr>
<td>atheroma (n = 18)</td>
<td>32 ± 16</td>
<td>38 ± 16</td>
<td>6 (0, 12)</td>
</tr>
<tr>
<td>fibromuscular dysplasia (n = 14)</td>
<td>29 ± 15</td>
<td>44 ± 11</td>
<td>15 (8, 22)</td>
</tr>
<tr>
<td>GFR of the nonstenotic kidney (ml/min per 1.73 m\textsuperscript{2})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall (n = 32)</td>
<td>59 ± 17</td>
<td>53 ± 15</td>
<td>−6 (−9, −2)\textsuperscript{c}</td>
</tr>
<tr>
<td>atheroma (n = 18)</td>
<td>51 ± 16\textsuperscript{b}</td>
<td>47 ± 16</td>
<td>−4 (−8, 1)</td>
</tr>
<tr>
<td>fibromuscular dysplasia (n = 14)</td>
<td>69 ± 14</td>
<td>60 ± 9</td>
<td>−8 (−15, −2)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}For all tested parameters there was no significant treatment × RAS cause interaction in the ANOVA. Therefore, only treatment and RAS cause effects are reported in the table. The magnitude of the difference between pre-PTRA and post-PTRA values for both patients with atherosclerotic RAS and those with dysplastic RAS was expressed as mean (95% CI). When the limit of the 95% CI did not cross, the difference between pre- and post-PTRA value was significant. PTRA, percutaneous transluminal renal angioplasty; SRF, split renal function; RAS, renal artery stenosis; CI, confidence interval.

\textsuperscript{b}P < 0.01, atheroma versus fibromuscular dysplasia, by ANOVA.

\textsuperscript{c}p < 0.001, before versus after PTRA, by ANOVA.

PTRA, control angiograms showed no significant restenosis. Only eight of the remaining patients (six patients with atherosclerotic RAS and two patients with dysplastic RAS) had moderate restenosis (≤50%) that did not require repeat PTRA. The median follow-up was 6 mo (range, 3 to 12 mo) after PTRA.

Long-Term Evaluation after PTRA

BP Outcome. PTRA had a major effect on both clinic systolic BP (SBP) and DBP in all patients. SBP and DBP decreased from their pre-PTRA levels by 33 mmHg (95% CI, 22 to 44 mmHg; \( P < 0.001 \)) and 17 mmHg (95% CI, 11 to 23 mmHg; \( P < 0.001 \)), respectively. The decrease in BP after PTRA was significantly larger in patients with dysplastic RAS than in patients with atherosclerotic RAS (SBP, 47 mmHg [95% CI, 33 to 60 mmHg] \( P < 0.05 \)) and DBP, 26 mmHg [95% CI, 18 to 44 mmHg] \( P < 0.001 \)). According to US Cooperative Study criteria, 11 of 18 patients (56%) with atherosclerotic RAS and 12 of 14 patients (86%) with dysplastic RAS had their hypertension cured or improved after PTRA (\( \chi^2 = 4.97, \text{df} = 2, \ P = 0.08 \)). The fall in BP was obtained with significantly fewer antihypertensive treatments than immediately before PTRA (before, \( n = 2 \) [range, 0 to 3]; after, \( n = 1 \) [range, 0 to 3]; \( P < 0.05 \)).

Renal Function Outcome. In contrast to its effect on BP, PTRA had no effect on plasma creatinine concentration or creatinine clearance (data not shown). However, the mild proteinuria present at baseline in patients with atherosclerotic RAS decreased significantly from 0.6 ± 0.7 g/24 h to 0.2 ± 0.3 g/24 h (\( P < 0.05 \)) and disappeared in all four patients who had dysplastic RAS and who had proteinuria at baseline.

GFR, SRF, and SRF Outcome. Six mo after PTRA, total GFR increased slightly but not significantly in both patients with atherosclerotic and with dysplastic RAS (mean change [95% CI], 3 [−5,11] versus 6 [−6,16] ml/min per 1.73 m\textsuperscript{2}, respectively; not significant). If we excluded the three patients for whom both scintigraphic and renal vein renin lateralization indices were negative from the analysis, the change in total GFR was statistically significant (\( F_{1, 27}, \ P = 0.04 \)).

In contrast, we observed major changes in the functions of each of the kidneys assessed separately: SRF and GFR of the stenotic kidney increased significantly after PTRA, regardless of RAS cause, whereas the GFR of the nonstenotic kidney decreased significantly from pre-PTRA values (Table 2). Changes in GFR were correlated significantly and positively with changes in the SRF of the stenotic kidney (\( r = 0.48, \ n = 32, \ P = 0.02 \)). Total RBF/CO did not change significantly after PTRA, although a significant increase in RBF/CO of the stenotic kidney was observed (Table 3).

Discussion

Renovascular disease is a recognized cause of end-stage renal failure, especially in elderly patients with atherosclerotic disease. It has been estimated that atheromatous renovascular...
Table 3. Effects of PTRA on the RBF/CO in patients with atherosclerotic or dysplastic unilateral RAS (mean ± SD)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before PTRA</th>
<th>After PTRA</th>
<th>Mean Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total RBF/CO ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall ((n = 32))</td>
<td>17.0 ± 3.4</td>
<td>17.9 ± 3.7</td>
<td>0.9 (−0.5, 2.1)</td>
</tr>
<tr>
<td>atheroma ((n = 18))</td>
<td>15.3 ± 2.4\textsuperscript{b}</td>
<td>17.0 ± 4.0</td>
<td>1.7 (0.3, 3.3)</td>
</tr>
<tr>
<td>fibromuscular dysplasia ((n = 14))</td>
<td>19.4 ± 3.3</td>
<td>19.2 ± 2.9</td>
<td>−0.2 (−2.4, 2.0)</td>
</tr>
<tr>
<td>RBF/CO ratio of the stenotic kidney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall ((n = 32))</td>
<td>6.6 ± 2.2</td>
<td>7.7 ± 2.0</td>
<td>1.1 (0.4, 1.8)\textsuperscript{c}</td>
</tr>
<tr>
<td>atheroma ((n = 18))</td>
<td>6.4 ± 2.1</td>
<td>7.6 ± 2.0</td>
<td>1.2 (0.4, 2.0)</td>
</tr>
<tr>
<td>fibromuscular dysplasia ((n = 14))</td>
<td>6.8 ± 2.4</td>
<td>7.8 ± 1.9</td>
<td>1.0 (−0.5, 2.4)</td>
</tr>
<tr>
<td>RBF/CO ratio of the nonstenotic kidney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall ((n = 32))</td>
<td>10.5 ± 2.7</td>
<td>10.2 ± 3.0</td>
<td>−0.3 (−1.1, 0.5)</td>
</tr>
<tr>
<td>atheroma ((n = 18))</td>
<td>8.9 ± 2.0\textsuperscript{b}</td>
<td>9.4 ± 3.3</td>
<td>0.5 (−0.7, 1.6)</td>
</tr>
<tr>
<td>fibromuscular dysplasia ((n = 14))</td>
<td>12.5 ± 2.2</td>
<td>11.3 ± 2.4</td>
<td>−1.2 (−2.0, −0.4)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} For all tested parameters, there was no significant treatment × RAS cause interaction in the ANOVA. Therefore, only treatment and RAS cause effects are reported in the table. The magnitude of the difference between pre-PTRA and post-PTRA values for both patients with atherosclerotic RAS and those with dysplastic RAS was expressed as mean (95% CI). When the limit of the 95% CI did not cross 0, the difference between pre- and post-PTRA value was significant. RBF/CO, renal blood flow/cardiac output ratio.

\textsuperscript{b} \(P < 0.01\), atheroma versus fibromuscular dysplasia, by ANOVA.

\textsuperscript{c} \(P < 0.001\), before versus after PTRA, by ANOVA.

disease is responsible for 1 to 25% of new cases of end-stage renal failure (15).

In patients with unilateral RAS, renal failure may result from both ischemia of the stenotic kidney, resulting in progressive renal fibrosis and atrophy (16), and contralateral nephroangio-
sclerosis or focal segmental glomerulosclerosis caused by a high filtration rate and uncontrolled BP (17). Although renal revascularization should slow this process, it is unclear whether PTRA is likely to improve renal function and ulti-
mately to prevent end-stage renal failure in patients with renal disease. Most studies (randomized or otherwise) that evaluated renal outcome after PTRA with or without stenting (2–4,18), especially in patients with unilateral RAS, reported no benefit in terms of renal function. The progressive nature of the consequences of ischemia in both kidneys, espe-
cially in patients with atherosclerotic disease, results in irre-
versible damage to the renal parenchyma. However, the lack of
detection of a significant renal effect of PTRA also results from met-
methodologic problems. The use of markers of total GFR, such
as plasma creatinine concentration and creatinine clearance,
and of markers that do not evaluate separate kidney function
and the absence of a standardized evaluation procedure reduce
the probability of detecting a significant change in renal
function.

The main objective of this study was to evaluate prospectively,
in standardized conditions, SRF outcome after PTRA in a welldefined population of patients with unilateral RAS, with the use of
sensitive markers of total and separate renal function. Patients
with renal failure (creatinine clearance <60 ml/min per 1.73 m\(^2\))
were excluded, to increase the probability of detecting significant
changes in SRF after renal revascularization. Renal insufficiency
in patients with unilateral RAS is indicative of damage to both the
stenotic and the nonstenotic kidney, and this damage is less likely
to be reversed by revascularization (19). To increase the proba-
bility of detecting significant changes, we evaluated post-PTRA
BP and renal function outcomes after demonstrating the successful
revascularization of the stenotic kidney by performing a con-
tral renal angiogram in all patients. Significant restenosis that
required repeat PTRA was detected in two patients. At the final
evaluation, none of the patients had more than 50% restenosis,
and mild restenosis (30 to 50%) was observed in only four
patients.

With the use of sensitive indices of global and separate renal
function, our results show that PTRA, besides its beneficial
effects on BP, consistent with previous reports (1–4), had
detectable beneficial effects on total renal function and SRF 3
to 6 mo after successful revascularization. Renal revascular-
ization induced a significant increase in the split GFR of the
stenotic kidney and a significant decrease in the split GFR of
the nonstenotic kidney, accompanied by a nonsignificant in-
crease in total GFR. The lack of a significant increase in total
GFR may be due to (1) the small size of our sample of patients,
which reduced the power to detect a significant increase in
GFR after PTRA; (2) the normality of baseline GFR measure-
ments; and (3) the inclusion of patients with negative lateral-
ization indices, which increased variability in the response to
angioplasty. Indeed, if the three patients with negative lateral-
ization indices were excluded from the analysis, total GFR
increased significantly after PTRA.

The small size of the increase in total GFR after angioplasty
was due mainly to the increase in GFR of the stenotic kidney
and is consistent with previous studies (4,20) but not all (21).
In fact, a significant correlation was observed between changes
in GFR after PTRA and changes in SRF of the stenotic side.
The increase in renal function on the stenotic side probably was due to the increase in RBF, as shown by the significant increase in the fraction of the cardiac output delivered to the stenotic kidney after PTRA.

**Effects of PTRA on the Nonstenotic Side**

This study provides new information concerning changes in the GFR and SRF of the contralateral, nonstenotic kidney after PTRA of the stenotic RAS. Before PTRA, total GFR was maintained at a normal level, despite hypoperfusion in the stenotic kidney because of a compensating hyperfiltration in the contralateral, nonstenotic kidney. Using split intrarenal hemodynamics in the stenotic and contralateral kidneys of patients with unilateral RAS, Kimura et al. (22) showed that both GFR and hydrostatic pressure were significantly higher in the contralateral kidney than in the stenotic kidney. Their results indicate that in the contralateral kidney, afferent arteriolar vasconstriction does not occur as to compensate for the impaired renal function in the stenotic kidney and to keep renal function normal. This results in the transmission of high systemic BP to the glomerular capillaries, resulting in glomerular hypertension (23,24). Glomerular hypertension and hyperfiltration in the contralateral kidney may result in further long-term renal damage, as observed in experimental rat models (25).

Renal revascularization by PTRA reversed both the hyperfiltration of the nonstenotic kidney and the hypoperfusion of the stenotic kidney, facilitating the establishment of a new equilibrium in the distribution of renal function between the two kidneys. The decrease in split GFR of the contralateral kidney after PTRA may also have long-term beneficial effects by reversing hyperfiltration and glomerular hypertension within that kidney. In the 2K-1C rat model, unclipping the renal artery equilibrates glomerular hemodynamics between the two kidneys by inducing a decrease in the GFR and the RBF of the nonstenotic kidney and an increase in the GFR and the RBF of the stenotic kidney, whereas the administration of an ACE inhibitor increases the difference between the two kidneys despite having similar BP-lowering effects (26). In the same experimental model, ACE inhibitors also have been shown to protect the contralateral kidney from histologic damage while aggravating ischemic lesions in the ipsilateral kidney (27).

In this study, the reversal of hyperfiltration on the nonstenotic side and hypoperfusion on the stenotic side by PTRA was accompanied by a significant decrease in proteinuria in patients with this condition, probably indicating a partial reversal of the glomerular damage. Halimi et al. (28) showed that in patients with atherosclerotic renovascular disease, albuminuria may be used as a marker of preexisting intrarenal vascular and glomerular damage. The persistence of mild proteinuria in some of our patients with atherosclerotic RAS after PTRA may be due to autonomous glomerular lesions (29).

Finally, as expected, patients with fibromuscular dysplasia displayed greater improvements in renal function than did patients with atheroma, as both age and the duration of hypertension, which are determinants of contralateral kidney damage, were significantly higher in patients with atherosclerotic RAS. The significantly lower pre-PTRA GFR values in patients with atherosclerotic RAS than in patients with fibromuscular dysplasia is consistent with this hypothesis. Patients with atherosclerotic RAS also are more likely to have histologic lesions within both kidneys as a result of mechanisms other than renovascular hypertension (19,29,30).

In conclusion, after 6 mo, successful renal revascularization to relieve renal ischemia in patients with unilateral RAS is accompanied not only by improvements in BP control but also by improvements in split and possibly global renal function. Our study was prospective and carefully designed, but individual patients served as their own controls. It is likely—yet not documented—that giving control patients medication alone would have maintained a functional imbalance between the stenotic and nonstenotic kidneys with harmful renal consequences in the long-term. Our findings suggest that the renal benefits of PTRA have been underestimated in patients with unilateral stenosis. Randomized prospective studies are required to confirm that the establishment of a new equilibrium in renal function between the two kidneys after PTRA has long-term beneficial renal effects and prevents further changes in renal function, thereby reducing the incidence of end-stage renal failure in patients with renovascular disease.

**References**


Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/