Prostaglandin I$_2$/E$_2$ Ratios in Unilateral Renovascular Hypertension of Different Severities

Masahito Imanishi, Tetsu Tsuji, Satoko Nakamura, Makoto Takamiya

Abstract—Differences between prostaglandins I$_2$ and E$_2$ in their renal synthesis and pathophysiological roles were investigated in unilateral renovascular hypertension of different severities in 18 patients: 6 with mild stenosis (<75% of the diameter) of the renal artery, 7 with moderate stenosis (75% to 90%), and 5 with severe stenosis (>90%). Before and after aspirin administration (10 mg/kg), renal venous and aortic plasma was assayed for 6-ketoprostaglandin F$_{1\alpha}$ (instead of prostaglandin I$_2$), prostaglandin E$_2$, and renin activity. In mild or moderate stenosis, the mean 6-ketoprostaglandin F$_{1\alpha}$ level in renal venous plasma from the stenotic side was not different from that from the normal side or from aortic plasma. Prostaglandin E$_2$ levels and renin activity in such patients were higher on the stenotic side than on the normal side and higher in venous than in aortic plasma. Aspirin inhibited prostaglandin E$_2$ synthesis and suppressed renin release from stenotic kidneys and lowered blood pressure as the renin activity decreased in patients with mild or moderate stenosis. In severe stenosis, levels of 6-ketoprostaglandin F$_{1\alpha}$ and prostaglandin E$_2$ were higher on the stenotic side than on the normal side and higher in venous than in aortic plasma. Aspirin inhibited the synthesis of both prostaglandins and suppressed renin release from the stenotic kidney. In patients with unilateral renovascular hypertension with mild or moderate stenosis of the renal artery, prostaglandin E$_2$, rather than I$_2$, seems to contribute to further acceleration of renin release. Prostaglandin I$_2$ may increase and participate in further renin release when the stenosis is severe. (Hypertension. 2001;38:23-29.)

Key Words: prostaglandins ■ hypertension, renovascular ■ kidney

In unilateral renovascular hypertension (RVH), prostaglandin (PG) in the stenotic kidney is one factor stimulating renin release. Studies performed in vivo and in vitro have suggested that PGI$_2$ is the PG most responsible for modulating renin release when renal perfusion pressure decreases because of renal arterial stenosis. However, PGE$_2$ also can cause renin release. PGE$_2$ synthesis in the stenotic kidney increases in human unilateral RVH, but conclusions about the synthesis of PGI$_2$ have been difficult to reach because measurement in clinical laboratories of 6-keto-PGF$_{1\alpha}$ (instead of PGI$_2$, which is unstable), especially in plasma, has been difficult. Recently, however, modification of the method used in a laboratory study made possible the accurate measurement of the levels of 6-keto-PGF$_{1\alpha}$ in plasma. For the present study, we gathered patients with various degrees of renal arterial stenosis to establish a way to assess the renal synthesis of PGs. We investigated the renal synthesis and pathophysiological roles of PGI$_2$, in addition to those of PGE$_2$.

Methods

Patients

The subjects studied were 18 patients with RVH with unilateral renal arterial stenosis and 1 normotensive patient after renal arterial angioplasty (Table 1). Digital subtraction angiography (DSA) and radionuclide renograms were obtained for all patients, and the degree of stenosis of their renal arteries was assessed in terms of the inner renal arterial diameter. The arterial diameter was measured by computerized DSA, and the percent stenosis of the artery was calculated as $S=\frac{1}{\ln(1-L/5)} \times 100$, where $S$ is the percent stenosis of the renal artery, $L_n$ is the mean width of the intact renal artery measured once proximally and once distally to the stenotic lesion, and $L_s$ is the width of the stenotic section of the renal artery.

For the radionuclide renograms, which are widely used in screening to rule out unilateral RVH, we used $^{123}$Iorthoiodohippurate. The generation curve in renograms obtained with this tracer assesses split renal function, especially whether renal blood flow is lower than flow on the unaffected side. We classified the results of the renograms on a 3-point scale. A rating of + indicates that the maximum peak of the curve for the affected kidney is later by 2 minutes than the peak for the normal kidney (ie, renal blood flow in the affected kidney has decreased). A rating of ± indicates that the maximum peak is delayed 1 minute but <2 minutes: such results were considered borderline. A rating of − indicates that the blood flow of the stenotic kidney has not decreased; the delay, if any, in the peak is <1 minute.

On the basis of the results of the DSA and renograms, we divided the 18 patients with unilateral stenosis of the renal artery into 3 groups: 6 patients with mild stenosis (<75% of the diameter) of the renal artery, 7 patients with moderate stenosis (75% to 90%), and 5 patients with severe stenosis (>90%). Three images of DSA from a patient from each group (patients 3, 12, and 16) are shown in Figure 1 (panels A, B, and C, respectively). Figure 1D and 1E shows DSA (arterial and nephrographic phases) for patient 15. The left main renal artery was almost obstructed, but blood was supplied to the left kidney by small bypasses.
All patients with mild or moderate stenosis and also patients 14 and 18 underwent renal angioplasty (by percutaneous transluminal renal arterial angioplasty or aortorenal arterial bypass), and their renal arterial stenoses were found after treatment to be reduced to 45% of the estimated original diameter of the artery. By angioplasty, systemic blood pressure in patients 1 to 13, 14, and 18 became normal or was somewhat decreased to some extent. The diagnosis for these patients was RVH. Patients 15 to 17 could not undergo angioplasty, but RVH was diagnosed by the captopril test and by measurement of plasma renin activity (PRA) in renal veins.

Patient 19 had unilateral RVH and had undergone percutaneous transluminal renal arterial angioplasty before the present study. This patient was studied as the normotensive subject mentioned above. The values of PRA in Table 1 are the results of the assay of peripheral venous blood sampled early in the morning soon after the patient had been admitted.

The present study was approved by the Ethical Review Committee of the National Cardiovascular Center. Informed consent was obtained from all patients.

**Study Protocol**

All medication was stopped for at least 2 weeks before the study, except for patients 9, 11, and 17, who continued taking 40 mg of slow-release nifedipine daily because their blood pressure was ≥180/110 mm Hg without medication. The dosage of the drug was not changed during the study. The blood pressure of the other patients was <180/110 mm Hg without medication after admission. The study was performed in the cardiovascular laboratories of the Division of Radiology before the renal arterial angioplasty. The design of the protocol has been described previously. In brief, blood pressure in the left upper arm was measured every 2 minutes with an automatic ultrasound sphygmomanometer (BP-103, Nippon Colin Co, Ltd), and the heart rate was monitored. Thirty minutes after catheterization of the right femoral artery and vein by the Seldinger technique, abdominal aortic and bilateral renal venous blood samples were drawn almost simultaneously for measurement of PRA and plasma concentrations of PGE2 and 6-keto-PGF1α. After this control sampling, aspirin DL-lysine (Venopirin, Green Cross Corp) was injected intravenously at a dose of 18 mg/kg (10 mg/kg as aspirin). In 30 minutes, a blood sample was taken again at the same sites. We compared the means of blood pressure and heart rate from 26 to 36 minutes after the aspirin injection (n=6) with those from 10 to 0 minutes before the injection (n=6).

At least 3 weeks after the renal arterial angioplasty for patients 5, 9, 11, 13, and 19 (who became normotensive), we repeated the study without the administration of aspirin.

### TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Gender</th>
<th>Stenotic Side, % of Stenosis</th>
<th>Origin</th>
<th>Renogram</th>
<th>PRA, ng·mL⁻¹·h⁻¹</th>
<th>BUN, mg/dL</th>
<th>Creatinine, mg/dL</th>
<th>BP on Admission, mm Hg</th>
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<tr>
<td>RVH with mild stenosis (&lt;75%)</td>
<td></td>
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<td></td>
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<tr>
<td>1</td>
<td>18</td>
<td>M</td>
<td>L, 68</td>
<td>FMD</td>
<td>–</td>
<td>9.8</td>
<td>18</td>
<td>1.1</td>
<td>170/92</td>
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<td>2</td>
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<td>L, 73</td>
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</tr>
<tr>
<td>3</td>
<td>23</td>
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<td>R, 70</td>
<td>FMD</td>
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<td>4.0</td>
<td>11</td>
<td>0.8</td>
<td>158/92</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>M</td>
<td>R, 67</td>
<td>FMD</td>
<td>–</td>
<td>3.0</td>
<td>16</td>
<td>0.9</td>
<td>154/92</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>F</td>
<td>R, 70</td>
<td>FMD</td>
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<td>15</td>
<td>0.7</td>
<td>168/90</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
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<td>R, 69</td>
<td>FMD</td>
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<td>3.6</td>
<td>13</td>
<td>0.6</td>
<td>150/100</td>
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<td>Mean±SD</td>
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<tr>
<td>RVH with moderate stenosis (75%–90%)</td>
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<tr>
<td>7</td>
<td>19</td>
<td>M</td>
<td>R, 90</td>
<td>FMD</td>
<td>±</td>
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<td>13</td>
<td>0.8</td>
<td>180/118</td>
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<tr>
<td>8</td>
<td>28</td>
<td>F</td>
<td>L, 78</td>
<td>FMD</td>
<td>±</td>
<td>8.2</td>
<td>12</td>
<td>0.7</td>
<td>164/108</td>
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<tr>
<td>9</td>
<td>32</td>
<td>F</td>
<td>R, 76</td>
<td>FMD</td>
<td>±</td>
<td>12.4</td>
<td>18</td>
<td>0.8</td>
<td>190/120</td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>M</td>
<td>R, 75</td>
<td>AS</td>
<td>±</td>
<td>8.5</td>
<td>17</td>
<td>0.9</td>
<td>174/106</td>
</tr>
<tr>
<td>11</td>
<td>64</td>
<td>M</td>
<td>L, 83</td>
<td>AS</td>
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<td>9.6</td>
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<td>1.1</td>
<td>198/100</td>
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<tr>
<td>12</td>
<td>65</td>
<td>M</td>
<td>L, 80</td>
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<td>+</td>
<td>7.1</td>
<td>17</td>
<td>1.1</td>
<td>176/100</td>
</tr>
<tr>
<td>13</td>
<td>66</td>
<td>M</td>
<td>L, 90</td>
<td>AS</td>
<td>+</td>
<td>4.5</td>
<td>20</td>
<td>1.2</td>
<td>192/104</td>
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<td>Mean±SD</td>
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<tr>
<td>RVH with severe stenosis (&gt;90%)</td>
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<tr>
<td>14</td>
<td>48</td>
<td>F</td>
<td>L, &gt;90</td>
<td>FMD</td>
<td>+</td>
<td>19.8</td>
<td>19</td>
<td>1.2</td>
<td>158/114</td>
</tr>
<tr>
<td>15</td>
<td>58</td>
<td>F</td>
<td>L, &gt;99</td>
<td>AS</td>
<td>+</td>
<td>10.6</td>
<td>17</td>
<td>0.9</td>
<td>170/96</td>
</tr>
<tr>
<td>16</td>
<td>61</td>
<td>M</td>
<td>R, &gt;90</td>
<td>AS</td>
<td>+</td>
<td>7.5</td>
<td>18</td>
<td>1.3</td>
<td>160/98</td>
</tr>
<tr>
<td>17</td>
<td>67</td>
<td>F</td>
<td>L, &gt;99</td>
<td>AS</td>
<td>+</td>
<td>30.3</td>
<td>19</td>
<td>1.0</td>
<td>186/98</td>
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<tr>
<td>18</td>
<td>77</td>
<td>F</td>
<td>R, &gt;90</td>
<td>AS</td>
<td>+</td>
<td>7.3</td>
<td>15</td>
<td>0.6</td>
<td>194/100</td>
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<td>62±11</td>
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<td>Patient after renal arterial angioplasty</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19*</td>
<td>48</td>
<td>M</td>
<td>L, &lt;20</td>
<td>FMD</td>
<td>–</td>
<td>1.7</td>
<td>18</td>
<td>0.8</td>
<td>126/80</td>
</tr>
</tbody>
</table>

BUN indicates blood urea nitrogen; creatinine, serum level of creatinine; BP, blood pressure; M, male; F, female; R, right; L, left; FMD, fibromuscular dysplasia; and AS, atherosclerosis.

*Patient 19 could be studied only after renal arterial angioplasty. Patients 5, 9, 11, and 13 (with values given above) were studied again after renal arterial angioplasty.
Measurements of Renin Activity and PGs in Plasma

PRA was measured by radioimmunoassay. The method for measurement of 6-keto-PGF$_{1\alpha}$ and PGE$_2$ in plasma has been published previously. In brief, PGs were extracted from 5 mL of plasma in a Bond-Elut C18 cartridge (500 mg, Analytichem International Inc) with ethyl acetate. After the extraction, the sample was purified by high-pressure liquid chromatography. By chromatography, we separated the fractions containing 6-keto-PGF$_{1\alpha}$ and PGE$_2$ from each other. 6-Keto-PGF$_{1\alpha}$ and PGE$_2$ were measured with radioimmunoassay kits for 6-keto-PGF$_{1\alpha}$ and PGE$_2$ ($^{125}$I labeling, New England Nuclear Corp). The mean recovery of authentic PGs was 70%, and intra-assay and interassay variation in the measurement of the 2 PGs in the present study was <8% and <15%, respectively. The levels we found for 6-keto-PGF$_{1\alpha}$ in aortic plasma were consistent with those previously reported.

Statistical Methods

Results for renin activity, PGE$_2$, and 6-keto-PGF$_{1\alpha}$ in plasma from renal veins and aorta were compared by 2-way ANOVA followed by the Friedman test for matched samples. Levels of PRA and PGs in each site sampled after the aspirin injection were compared with those sampled before the injection by the Wilcoxon signed rank test, as were data for systolic and diastolic blood pressure before and after the aspirin injection. These results are given as mean±SD. The basal levels of PRA and PGs at the 3 sites in patients with mild and moderate stenosis were compared by the Mann-Whitney $U$ test.

Correlation between the ratio of the stenotic side to the normal side for PGE$_2$ and for PRA was evaluated by the least squares method, as was that between these ratios for 6-keto-PGF$_{1\alpha}$ and for PRA. A difference with a value of $P<0.05$ was regarded as having statistical significance.

Results

Renin Activity and PGs in Plasma From 3 Sites

Figure 2 shows the PRA and levels of PGE$_2$ and 6-keto-PGF$_{1\alpha}$ in aortic and renal venous plasma before and after the administration of aspirin in RVH patients with mild stenosis (<75% of the diameter of the renal artery). Before aspirin administration, PRA and PGE$_2$ levels in the renal venous plasma of the stenotic kidney were higher than those at the 2 other sites. However, the 6-keto-PGF$_{1\alpha}$ level on the stenotic side was not different from that at the other sites. Aspirin lowered the levels of PRA and PGs in all sites, with the greatest decreases in the PRA and the PGE$_2$ level on the stenotic side.

In patients with moderate stenosis (75% to 90%), the patterns of PRA and PGs at the 3 sites and their changes after aspirin administration (Figure 3) were the same as those in the patients with mild stenosis. However, the basal PRA at the 3 sites (aorta, stenotic side, and normal side) was higher than the values in patients with mild stenosis ($P=0.0043, 0.0027, \text{and } 0.0027$, respectively).

In patients with severe stenosis (>90%), PRA and the PGE$_2$ levels at the 3 sites (Table 2) showed the same patterns as in the 2 other groups. The level of 6-keto-PGF$_{1\alpha}$ on the stenotic side was higher than that at the other sites, unlike results for the 2 other groups. Aspirin suppressed renin release from the stenotic kidney and also inhibited synthesis of both PGs there. In patient 17, the PRA on the stenotic side before the administration of aspirin was above the limit for measurement by the assay kit (>200 ng of angiotensin I/mL per hour). We took the value to be 200 ng/mL per hour when results were analyzed statistically.

Results for PRA and PGs after renal arterial angioplasty for patients 5, 9, 11, 13, and 19 are given in Figure 4. The systemic blood pressure in these patients was normal after angioplasty. PGE$_2$ levels in renal venous plasma were not different on the stenotic and normal sides but were higher than those in the aortic plasma.
Stenotic and Normal Side Ratios of Renin Activity and PG Levels

The relationships of the stenotic and normal side (S/N ratio) of PRA to the S/N ratio of PGE\(_2\) and that of 6-keto-PGF\(_{1\alpha}\) are shown in Figure 5. Figure 5A and 5B shows the 6 patients with mild stenosis and 7 patients with moderate stenosis before renal angioplasty and also the 5 patients who were normotensive after angioplasty. The S/N ratio of PRA was correlated significantly with the ratio of PGE\(_2\) but not with the ratio of 6-keto-PGF\(_{1\alpha}\). With results for the 5 patients with severe stenosis included, the S/N ratio of PRA was not correlated with that of PGE\(_2\) (Figure 5C), but the S/N ratio of PRA was significantly correlated with that of 6-keto-PGF\(_{1\alpha}\) (Figure 5D).

Changes in Blood Pressure With Aspirin

Table 3 shows systemic blood pressure of the RVH patients before and after the administration of aspirin. Aspirin lowered blood pressure in all 3 groups.

### Table 3

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Before Aspirin</th>
<th>Aorta</th>
<th>Stenotic Side</th>
<th>Normal Side</th>
<th>Aorta</th>
<th>Stenotic Side</th>
<th>Normal Side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PRA, ng/mL · h(^{-1})</td>
<td>PGE(_2), pg/mL</td>
<td>6-Keto-PGF(_{1\alpha}), pg/mL</td>
<td>PRA, ng/mL · h(^{-1})</td>
<td>PGE(_2), pg/mL</td>
<td>6-Keto-PGF(_{1\alpha}), pg/mL</td>
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<tr>
<td>14</td>
<td>14.8</td>
<td>48.6</td>
<td>19.3</td>
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<td>12.9</td>
<td>23.7</td>
<td>14.6</td>
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<tr>
<td>15</td>
<td>9.5</td>
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<td>16</td>
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<td>3.6</td>
<td>5.6</td>
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</tr>
<tr>
<td>17</td>
<td>27.6</td>
<td>&gt;200</td>
<td>27.5</td>
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<td>17.5</td>
<td>48.3</td>
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<td>2.8</td>
<td>4.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>12.3±9.5</td>
<td>59.7±80.2*</td>
<td>12.8±10.2</td>
<td></td>
<td>8.8±6.3§</td>
<td>20.5±17.8†§</td>
<td>9.5±7.4§</td>
</tr>
</tbody>
</table>

Aorta, stenotic side, and normal side refer to plasma in the aorta or in the renal vein of the stenotic or normal kidney.

*P<0.015, †P<0.0067, and ‡P<0.022 compared with the other 2 sites by Friedman test; §P<0.05 compared with values before aspirin by Wilcoxon signed rank test.
Discussion

In patients with unilateral RVH but without severe stenosis of the renal artery, the 6-keto-PGF$_{1\alpha}$ level in the renal venous plasma from the stenotic kidney was not high, but the PGE$_2$ level was, and the S/N ratio of PGE$_2$ was correlated with that of PRA.

In experimental studies in which renal perfusion pressure is decreased by renal arterial constriction, the PG mainly responsible for stimulating renin release is generally considered to be PGI$_2$ rather than PGE$_2$. The reasons are as follows: In experiments with isolated glomerular preparations with the afferent arteriole and macula densa attached, PGE$_2$ stimulates renin release. The macula densa is involved in renin release stimulated by PGE$_2$. In a model of RVH that uses 2-kidney 1-clip hypertensive rats, the production of PGE$_2$ (but not that of PGI$_2$ or PGF$_{2\alpha}$) is greater in glomeruli of the clipped kidney than in those of the other kidney.

However, PGE$_2$ stimulates renin release in vivo but not by a direct effect on juxtaglomerular cells. In isolated glomerular preparations with the afferent arteriole and macula densa attached, PGE$_2$ stimulates renin release. Therefore, the macula densa is involved in renin release stimulated by PGE$_2$. In a model of RVH that uses 2-kidney 1-clip hypertensive rats, the production of PGE$_2$ (but not that of PGI$_2$ or PGF$_{2\alpha}$) is greater in glomeruli of the clipped kidney than in those of the other kidney.

In addition, PGE$_2$ rather than PGI$_2$ is the primary prostanooid produced by cultured endothelial cells from isolated preglomerular renal microvessels, although freshly isolated renal microvessels with muscle cells still attached produce more PGI$_2$ than PGE$_2$. In in vitro experiments, results may differ depending on the experimental conditions; still, renal preglomerular vessels may be able to synthesize PGE$_2$, as tubules and interstitial cells can. In human RVH, the kind of cells in the stenotic kidney with increased PGE$_2$ synthesis have not been identified, but it is clear that increased PGE$_2$ stimulates renin release.

To assess the severity of the renal arterial stenosis and the increment in renal PG synthesis, we needed to measure blood flow separately for the stenotic and normal kidneys with measurement of the levels of PGs in the renal venous and aortic plasma. We could not measure the blood flow of each kidney, but we could estimate the flow from radioisotope renograms and from the relationship between renal blood flow and the degree of renal arterial stenosis reported previously. There was no difference in blood flow on the radionuclide renograms between the stenotic and normal kidneys in patients 1 to 6 with the mild stenosis, as reported for similar patients previously. In our previous experimental study, the critical degree at which renal arterial stenosis starts to decrease renal blood flow is 75%, and the degree at which the stenosis decreases the flow to 50% is 90% stenosis of the diameter. In addition, as shown in Figure 1, the renal artery shows poststenotic dilatation as an adaptation that maintains the renal blood flow in patients with moderate stenosis (75% to 90%) of the artery. However, in patients with severe stenosis (>90%), the adaptation seems to work (and works less the greater the severity). We concluded that there is no decrease in blood flow of the stenotic kidney in patients with mild stenosis, only a small decrease in the flow in patients with moderate stenosis, and a large decrease in the flow (causing ischemia) in patients with severe stenosis. Together with the results from the
levels of PGs in renal venous and aortic plasma, in patients with mild or moderate stenosis, PGE₂ production in the stenotic kidney may be increased, but PGI₂ production probably is not.

In conscious dogs, renal arterial constriction increases the secretion of 6-keto-PGF₁α from the stenotic kidney. However, measurements were made only 10 minutes after constriction, and neither PRA levels in the aorta nor systemic blood pressure had increased by this time. In addition, the constriction caused a mean 38% decrease in renal blood flow. In humans with RVH, perhaps months or years after the renal arterial stenosis develops, renal venous plasma levels of PGE₂ from the stenotic kidney are elevated, but the levels of 6-keto-PGF₁α are not. The levels of 6-keto-PGF₁α are increased only when stenosis of the renal artery is severe (>90%); the renal blood flow is probably decreased to <50%. The findings may be discrepant because the effects of short-term (10-minute) stenosis or long-term (months or years) stenosis are different; alternatively, findings may depend on the severity of the renal arterial stenosis.

We cannot explain why renal PGE₂ increases in response to mild or moderate stenosis of the renal artery but PGI₂ does not. The mechanism of their increase may be different: the synthesis of PGE₂ may respond to change in hemodynamics (renal perfusion pressure), but that of PGI₂ may respond to decreases in blood flow (probable ischemia). Our earlier study of anesthetized dogs gave findings consistent with this discrepancy between PGE₂ and PGI₂: Ang II does not increase the synthesis of PGs in the stenotic kidney because of renal arterial constriction. If the finding had been the reverse, both PGE₂ and PGI₂ might increase in response to mild or moderate stenosis.

The present study showed that in patients with RVH, renin release depends on the severity of renal arterial stenosis; in particular, the results in Figure 5 and the changes in renin release and blood pressure in response to aspirin confirmed that there are both PG-dependent and PG-independent mechanisms of renin release in RVH. However, the response of blood pressure to aspirin administration shows that an absolute decrease in PRA decreases blood pressure in RVH; ie, high blood pressure in typical unilateral RVH depends on PRA. In contrast, in patients with essential hypertension with high PRA, aspirin decreases the PRA but does not affect blood pressure.

We investigated the levels of the 2 PGs in renal venous and aortic plasma in 5 patients who became normotensive with normal PRA after renal arterial angioplasty as a control study. The results from the patients suggest the significance of an increase in PGE₂ or PGI₂ in the stenotic kidney in RVH.

In conclusion, in unilateral RVH patients without severe stenosis, PGE₂ rather than PGI₂ seems to increase in the stenotic kidney and to be involved in increased renin release as 1 factor. PGI₂ in the stenotic kidney seems to increase and to be involved in renin release when renal arterial stenosis is severe. However, to prove either possibility, studies with specific synthesis inhibitors or receptor antagonists for each PG are needed, but there are no such compounds available at present for clinical use.

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**References**


Prostaglandin I$_2$/E$_2$ Ratios in Unilateral Renovascular Hypertension of Different Severities
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