Effects of Converting Enzyme Inhibition on Split Renal Function in Renovascular Hypertension

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SUMMARY The effects of captopril on effective renal plasma flow and glomerular filtration rate were studied using a noninvasive radioisotopic method on individual kidneys in eight patients with renovascular hypertension and 12 patients with essential hypertension with various renin levels. Four patients with renovascular hypertension had unilateral while three had bilateral renal artery stenosis. The effective renal plasma flow and glomerular filtration rate were determined by using 131I-iodohippurate sodium and 99mTc-diethylenetriamine pentaacetic acid, respectively. Glomerular filtration rate and effective renal plasma flow were significantly reduced in the stenotic kidneys of patients with renovascular hypertension compared with values in nonstenotic kidneys (p < 0.01). Treatment with captopril, 37.5 to 75 mg/day for 1 to 48 weeks, further reduced the glomerular filtration rate only in stenotic kidneys, and effective renal plasma flow increased in both kidney types. In two of the three renal hypertensive patients with bilateral renal artery stenosis, captopril produced a reversible azotemia that was unrelated to the fall in blood pressure, as evidenced by the lack of azotemia seen after a moderate blood pressure reduction induced by other antihypertensive medications. These results indicate that endogenous angiotensin II is essential in maintaining the glomerular filtration rate in stenotic kidneys and suggest that a reduction in glomerular filtration rate during captopril administration could indicate the presence of renal artery stenosis. (Hypertension 8: 415-421, 1986)

KEY WORDS • renal failure • angiotensin II • glomerular filtration • essential hypertension

Reversible renal failure or a deterioration in renal function associated with captopril treatment is known to occur in patients with bilateral renal artery stenosis or stenosis of a solitary or transplanted kidney. The mechanisms postulated to cause renal failure in these situations include direct nephrotoxicity, renal ischemia, and inhibition of endogenous angiotensin II which is essential to the maintenance of the glomerular filtration rate (GFR) in stenotic kidneys. Sodium nitroprusside-induced systemic arterial hypotension causes a reduction in both effective renal plasma flow (ERPF) and GFR in patients with renovascular hypertension (RVH) and bilateral renal artery stenosis, which suggests that hypoperfusion of the stenotic kidney per se may contribute to the development of acute azotemia in patients with captopril-associated renal failure. Although the precise mechanism for this type of acute azotemia is still controversial, captopril is widely used as a potent antihypertensive agent in patients with RVH and unilateral stenosis. Thus, it is important to evaluate the renal function of the affected kidneys in these patients.

The renal function of individual kidneys has been studied extensively in patients with unilateral RVH using an angiotensin II analogue. The present investigation used noninvasive radioisotopic methods to clarify the effects of angiotensin II inhibition on the renal function of individual kidneys in patients with RVH undergoing long-term captopril treatment.
Materials and Methods

Eight patients with RVH (24-63 years old; 5 with unilateral renal artery stenosis and 3 with bilateral stenosis) and 12 patients with essential hypertension (EH; 26-52 years old) were included in the study. Each patient had had outpatient systolic and diastolic blood pressure measurements in excess of 160 and 90 mm Hg on at least three occasions. All patients were hospitalized in the clinical ward of the university hospital for at least 4 weeks while the diagnosis of RVH or EH was made. All patients were cautioned to abstain from smoking, and all antihypertensive medications were discontinued at least 2 weeks before the study began. During their hospitalization, patients were fed constant isocaloric diets (30 cal/kg) containing approximately 167 mEq of sodium and 60 mEq of potassium per day. Fluid intake was not restricted. The protocols were approved by the local ethics committee of our university, and patients were requested to sign an informed consent.

The RVH diagnosis was made by renal vein renin measurement, renal angiography, and examination of the contracted renal mass in the affected side using excretory urography. Patients with other secondary forms of hypertension were excluded from the study on the basis of urinalysis results, plasma renin activity (PRA), and serum creatinine, plasma aldosterone, plasma cortisol, 24-hour urine vanillylmandelic acid, and 17-hydroxycorticosteroid levels. Rapid-sequence intravenous pyelography was performed on all patients with EH included in the study. Funduscopic examination, electrocardiography, chest roentgenography, and echocardiography were used to diagnose each patient’s hypertension as either Stage I or II according to the World Health Organization classification. A split renal function test measuring the GFR and ERPF of individual kidneys was performed as described below.

Captopril, 37.5 to 75 mg/day, was administered for 1 week to all patients. Four of the five patients with RVH and unilateral renal artery stenosis and six patients with EH were given captopril for 48 weeks, after which the split renal function was reevaluated. The PRA and plasma aldosterone level on Day 7 of captopril administration, were significantly reduced in both the group with RVH and the group with EH. Neither group had any significant changes in heart rates, measured 60 minutes after captopril administration, or systolic and diastolic blood pressures, measured 60 minutes after captopril administration had been given. Changes in blood pressure, heart rate, PRA, and plasma aldosterone level on Day 7 of captopril administration are shown in Table 1. Supine blood pressure and heart rate were recorded twice a day with an indirect sphygmomanometer (Model BP-203; Nippon Kohrin Co., Tokyo, Japan) at 0900 (60 minutes after captopril administration) during the hospitalization. On the day of the split renal function test, blood pressure and heart rate were recorded every 5 minutes for 60 minutes after the first dose of captopril. Blood urea nitrogen, serum creatinine, and other electrolytes were determined at 2- to 3-month intervals during the long-term captopril study.

The GFR of individual kidneys was assessed 2 to 3 minutes after a single intravenous injection of 5 mCi of 99mTc-diethylenetriamine pentaacetic acid (DTPA) using the formula described by Gates. The GFR determined in 75 patients by the isotopic method and conventional sodium thiosulfate clearance was 0.847 (Figure 1). Split ERPF was measured using 250 mCi of 131-I-iodohippurate sodium. The radioactivity was counted with the same gamma counter equipped with a high energy collimator and analyzed as described by Schlegel and Hamway with the following minor modifications:

\[
\text{Percent TRUc} = \frac{\text{RK (cpm/e R)} + \text{LK (cpm/e x 100)}}{\text{net injection (cpm)}} \times 100
\] (1)

\[
\text{Total ERPF} = \text{percent TRUc} \times 15.7 + 63.5
\] (2)

\[
\text{Split ERPF} = \frac{\text{total ERPF} \times \text{percent split renal uptake}}{\text{percent TRUc}}
\] (3)

where TRUc is the depth-corrected renal count, e is the linear attenuation coefficient of 131-I-iodohippurate sodium, and X is the kidney depth in centimeters (RK = right kidney; LK = left kidney). Formula 2 was obtained from a linear regression analysis of 41 patients in whom the ERPF was determined by both the radioisotopic method and the conventional p-aminohippurate clearance method. The correlation coefficient between the two methods was 0.947 (Figure 2). The reproducibility of the radionuclide-computed split renal function was examined by performing the test four times on eight kidneys at 1-week intervals. The coefficients of variation for the GFR and ERPF averaged 10.5% and 11% respectively. The filtration fraction (FF) was determined by dividing the GFR by the ERPF. Blood chemistries were done on the morning of the renal function test. Blood pressure was measured twice while the patients were in the supine position (the same posture used during renal function determinations).

All results are expressed as means ± SE. A one-way analysis of variance was used to compare blood pressure and heart rate between the two groups following captopril administration. The Student’s t test was used to compare within-group changes.

Results

Changes in blood pressure, heart rate, PRA, and plasma aldosterone level on Day 7 of captopril administration are shown in Table 1. Supine blood pressure during Week 2 of the control period was 184 ± 15 mm Hg for the group with RVH and 176 ± 21 mm Hg for the group with EH. Although both systolic and diastolic blood pressures, measured 60 minutes after captopril administration, were significantly reduced in both groups, the reduction was smaller in the group with EH. Neither group had any significant changes in heart rate (recorded at the same time as blood pressure).

Figure 3 shows the effects of captopril on the total and split GFR and ERPF for the patients with EH. These parameters did not change significantly after 1 week of captopril treatment. Both the split and total
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Figure 1. Clearance (C) obtained by 99mTc-diethylenetriamine pentaacetic acid (DTPA) plotted against conventional sodium thiosulfate (Thio) clearance in 75 patients. Correlation coefficient was high (r = 0.847).

ERPF increased slightly during captopril treatment (from 667 ± 74 to 725 ± 71 ml/min for total ERPF). The FF showed changes similar to those seen in ERPF.

In patients with RVH and unilateral stenosis, baseline GFR for the stenotic kidneys was 24.3 ± 4.9 ml/min and was significantly smaller than that of the nonstenotic kidneys (p < 0.01). Although the latter value did not change significantly after captopril treatment, the former value decreased further to 8.8 ± 1.2 ml/min (p < 0.05 compared with pretreatment level). Baseline ERPF also was significantly lower in the stenotic as opposed to the nonstenotic kidneys (p < 0.01). Although captopril did not change the ERPF on the stenotic side, it caused a slight but significant increase on the nonstenotic side (p < 0.05). The FF decreased on both sides (Figure 4). The data for individual patients are shown in Table 2.

In patients with RVH and bilateral stenosis, captopril caused a bilateral reduction in GFR and FF; total GFR was reduced to 70% of pretreatment level. The ERPF did not change significantly despite a profound reduction in blood pressure (see Table 1; Figure 5).

The GFR ratios (between the stenotic and nonstenotic kidneys of the patients with RVH and the individual kidneys of the patients with EH were compared before and during captopril treatment. Before treatment, the mean ratio was 0.5 (range, 0.2–0.8) for the group with RVH and 0.9 (range, 0.7–1.0) for the group with EH. During treatment, the ratio decreased in all patients with RVH and unilateral stenosis to a mean of 0.2 (p < 0.01); the ratio for the patients with EH did not change significantly.

To evaluate the long-term effects of angiotensin II inhibition on the individual kidneys of patients with RVH, the split renal function determination was repeated after 48 weeks of daily captopril (37.5–75 mg) administration. In the absence of other drugs, the blood pressures and heart rates were not changed significantly and no adverse reactions were observed. Furthermore, there were no significant changes in
Table 1. Hemodynamic Effects of Captopril (37.5–75 mg/day for 7 days) in 12 Patients with Essential Hypertension and Eight with Renovascular Hypertension

<table>
<thead>
<tr>
<th>Patients</th>
<th>MBP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>PRA (ng ANG I/ml/hr)</th>
<th>ALDO (ng/dl)</th>
<th>Serum Na⁺ (mEq/L)</th>
<th>Serum K⁺ (mEq/L)</th>
<th>Serum Cr (mg/dl)</th>
<th>Serum BUN (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EH (n = 12)</td>
<td>126±11</td>
<td>74±12</td>
<td>1.5±1.3</td>
<td>7.3±4.5</td>
<td>141±1</td>
<td>4.5±0.3</td>
<td>1.0±0.1</td>
<td>15±3</td>
</tr>
<tr>
<td>Unilateral RVH (n = 5)</td>
<td>148±18</td>
<td>72±11</td>
<td>5.8±2.5</td>
<td>6.7±2.5</td>
<td>142±2</td>
<td>4.4±0.2</td>
<td>1.0±0.1</td>
<td>15±3</td>
</tr>
<tr>
<td>Bilateral RVH (n = 3)</td>
<td>144±16</td>
<td>69±10</td>
<td>6.8±3.2</td>
<td>9.3±3.6</td>
<td>146±1</td>
<td>4.7±0.2</td>
<td>1.3±0.2</td>
<td>24±5</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EH (n = 12)</td>
<td>113±10*</td>
<td>72±11</td>
<td>3.1±1.3*</td>
<td>4.9±3.2</td>
<td>142±1</td>
<td>4.4±0.1</td>
<td>1.1±0.2</td>
<td>16±2</td>
</tr>
<tr>
<td>Unilateral RVH (n = 5)</td>
<td>116±15†</td>
<td>69±9</td>
<td>7.5±4.0*</td>
<td>5.0±3.8</td>
<td>142±1</td>
<td>4.5±0.1</td>
<td>1.1±0.1</td>
<td>17±5</td>
</tr>
<tr>
<td>Bilateral RVH (n = 3)</td>
<td>106±18†</td>
<td>73±12</td>
<td>9.8±2.9*</td>
<td>5.6±3.7</td>
<td>140±1</td>
<td>5.6±0.7</td>
<td>2.0±0.9</td>
<td>33±10*</td>
</tr>
</tbody>
</table>

Values are means ± SE. MBP = mean blood pressure; HR = heart rate; PRA = plasma renin activity; ANG I = angiotensin I; ALDO = plasma aldosterone; Cr = creatinine; BUN = blood urea nitrogen; EH = essential hypertension; RVH = renovascular hypertension.

*p < 0.05, †p < 0.01, compared with pretreatment values.

Blood urea nitrogen or in serum creatinine, sodium, or potassium levels in the patients with RVH and unilateral stenosis or in the patients with EH. In patients with RVH, the PRA remained markedly elevated while the plasma aldosterone levels were within normal range. These levels in the patients with EH were not significantly different from those seen at the end of Week 1. In the stenotic kidneys of the patients with RVH, the ERPF and GFR were 140 ± 50 and 12 ± 2 ml/min, respectively, whereas the values for the nonstenotic kidneys were 297 ± 26 and 46 ± 5 ml/min, respectively. These results were comparable to those obtained after 1 week of treatment, which indicates that no further deterioration in the stenotic kidney function occurred (Table 3).

Discussion
The present study demonstrates that captopril reduces GFR and FF but not ERPF in the stenotic kidneys of patients with RVH and unilateral renal artery
sion. In the contralateral kidneys, however, GFR was unaltered while ERPF was slightly increased. As a consequence, there was a slight decrease in total GFR and a slight increase in total ERPF. The hemodynamic changes in the nonstenotic kidneys were similar to those seen in patients with EH.

Textor et al.9 using the angiotensin II analogue [Sar1, Thr8] angiotensin II, have reported a striking heterogeneity in the renal hemodynamic responses of patients with RVH depending on baseline PRA. The variability in the response was partly attributable to the agonistic action of the analogue. Textor et al.6 also studied the renal hemodynamics in 12 patients with RVH using captopril and reported a reduction in GFR but not ERPF in the stenotic kidneys. This finding suggests the importance of angiotensin II in the region-
al renal function. The present study confirms their findings. In addition, our findings suggest that endogenous angiotensin II exerts a tonic effect on the stenotic kidneys and thereby contributes to the maintenance of the GFR. We failed to demonstrate contralateral kidney hypertrophy,13 which is reported to occur in experimental models of RVH and invariably in human RVH.

A relatively well-preserved total GFR and a slightly improved total ERPF justify the therapeutic use of angiotensin converting enzyme inhibitors in patients with RVH and unilateral stenosis. However, the long-term consequences of captopril treatment on the renal function of stenotic kidneys should be studied closely. In four of our patients with unilateral RVH in whom split renal function was reevaluated at Week 48 of captopril treatment, the results were found to be nearly identical to those observed after 1 week of treatment. However, in patients with RVH and bilateral renal artery stenosis, hemodynamic changes characteristic of stenotic kidneys were seen on both sides during captopril treatment and led to a marked reduction in total GFR and FF as well as a slight to moderate azotemia. This finding is also in agreement with previous observations.2,14 In two patients, the azotemia worsened when captopril was administered with diuretics, which suggests that the activation of the renin-angiotensin axis accentuated the effects of captopril.

A systemic arterial hypotension caused by other antihypertensive drugs possibly could produce the same effects as captopril. Since we did not examine split renal function in the same patients using other antihypertensive drugs, we cannot determine whether the GFR reduction following captopril treatment is a result of a specific inhibition of endogenous angiotensin II formation or of the reduced renal perfusion pressure caused by the captopril-induced systemic hypotension.7 In two of our patients with RVH and bilateral renal artery stenosis, CV3317 (Takeda Pharmaceuticals Co., Osaka, Japan), which is more potent than captopril for angiotensin converting enzyme inhibition, was also found to cause acute, reversible azotemia. When these patients were treated with a combination of diuretics and /3-blockers, or /-methyldopa, azotemia was not produced despite a nearly equal reduction in the arterial pressure. Similar results have been reported in rats made hypertensive by bilateral renal artery constriction.15 This evidence supports the notion that endogenous angiotensin II, formed either in the circulation16 or intrarenally, or both, may contribute to the maintenance of the GFR through efferent arteriolar constriction, which subsequently increases the filtration pressure. Hall et al.,17 using aortic constriction techniques, have already suggested the im-

### Table 3. Effect of 1 Week of Captopril (37.5–75 mg/day) Treatment on Split Renal Function in Three Patients with Renovascular Hypertension and Bilateral Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient no.</th>
<th>Pretreatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Total</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>1</td>
<td>28.3</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>18.9</td>
<td>25.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>24.6</td>
<td>20.8</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>23.9 ± 2.7</td>
<td>20.3 ± 3.1</td>
<td>44.3 ± 0.7</td>
</tr>
<tr>
<td>Effective renal plasma flow (ml/min)</td>
<td>1</td>
<td>83</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>131</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>113</td>
<td>138</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>109 ± 14</td>
<td>128 ± 17</td>
<td>237 ± 31</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>1</td>
<td>0.343</td>
<td>0.155</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.144</td>
<td>0.168</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.218</td>
<td>0.151</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>0.235 ± 0.047</td>
<td>0.158 ± 0.004</td>
<td>0.193 ± 0.021</td>
</tr>
</tbody>
</table>
portance of endogenous angiotensin II in the control of the GFR and FF in sodium-depleted dogs. They demonstrated that captopril-induced inhibition of angiotensin II production was responsible for a marked reduction in the GFR, which could be restored by an intravenous infusion of angiotensin II but not norepinephrine. Since captopril reduced GFR but not ERPF in the stenotic kidneys in our patients, our results support the evidence that the major site of action of angiotensin II is in the postglomerular arterioles. 18

In the patients with EH, captopril did not affect GFR but slightly increased ERPF in both kidneys. Previous evidence indicated that the renal vasculature is sensitive to angiotensin II19 and that the arterial resistance is increased in patients with EH. 20 Hence, it is conceivable that captopril decreases vascular resistance in patients with EH by inhibiting angiotensin II formation.

In conclusion, our results demonstrate that split renal function is clinically useful for the functional evaluation of individual kidneys in patients with RVH treated with captopril or other antihypertensive drugs. Total renal function may mask the reduction in the GFR of the affected kidney in captopril-treated patients with RVH and unilateral arterial stenosis. As indicated previously, this drug should be used with caution in patients with RVH and bilateral renal artery stenosis. Noninvasive split renal function tests during captopril administration allow kidney function to be expressed as a GFR ratio between each kidney, which is a potentially useful new index in the differential diagnosis of unilateral RVH.

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