Differential Renal Function During Angiotensin Converting Enzyme Inhibition in Renovascular Hypertension

BRUCE JACKSON, BARRY P. McGrath, P. GEOFFREY MATTHEWS, CLEM WONG, and COLIN I. JOHNSTON

SUMMARY Renal function was measured sequentially in 32 patients with proven renovascular hypertension who were treated with the oral angiotensin converting enzyme inhibitor captopril. Renal function was assessed by serial measurement of serum creatinine. Six patients showed acute rises in serum creatinine concentration compatible with acute renal failure. Acute renal failure was confined to those patients with stenosis to a solitary kidney (transplant or native, occurring in 3 of 8 patients) or bilateral renal artery stenosis (occurring in 3 of 13 patients). No rise in serum creatinine concentration was observed in 11 patients with unilateral renal artery stenosis during long-term angiotensin converting enzyme inhibitor therapy. Acute renal failure during angiotensin converting enzyme inhibitor therapy was not related to the degree of blood pressure fall or the plasma angiotensin II level. Eleven patients with renovascular hypertension were followed prospectively with estimation of renal function by $^{99m}$Tc-diylenetriaminopentaacetic acid (DTPA) clearance (determined by computer analysis of scintillation camera renography). In six patients with unilateral renal artery stenosis, total $^{99m}$Tc-DTPA clearance and serum creatinine level remained constant following angiotensin converting enzyme inhibitor therapy, while in five patients with bilateral renal artery stenosis $^{99m}$Tc-DTPA clearance fell from 40 ± 9 to 27 ± 5 mℓ/min (p < 0.05). Split renal function studies revealed that $^{99m}$Tc-DTPA clearance fell in most kidneys with stenosed arteries during angiotensin converting enzyme inhibition, including the stenosed kidney from patients with unilateral renal artery stenosis (16 stenosed kidneys studied; change in Tc-DTPA clearance, −7.5 ± 2.7 mℓ/min). With unilateral disease total clearance was unchanged as function increased in the nonstenosed kidney (6 nonstenosed kidneys; change in Tc-DTPA clearance, +8.2 ± 4.6 mℓ/min). Serum creatinine concentration returned to pretreatment levels following withdrawal of angiotensin converting enzyme inhibitor therapy in all patients with acute renal failure, and $^{99m}$Tc-DTPA clearance of stenosed kidney also returned to pretreatment levels in two patients studied following angiotensin converting enzyme inhibitor withdrawal after 2 and 4 months of therapy. These results indicate that orally administered angiotensin converting enzyme inhibitors reduce renal function in kidneys with marked renal artery stenosis. Although the functional impairment was reversible following angiotensin converting enzyme inhibitor withdrawal, the long-term consequences to kidneys that develop functional impairment during such therapy are unknown. (Hypertension 8: 650–654, 1986)

Key Words • renovascular hypertension • renin angiotensin system • scintillation camera renography • acute renal failure • captopril • enalapril

MEDICAL therapy with angiotensin converting enzyme (ACE) inhibitors offers considerable promise as an alternative to renovascular surgery in patients with generalized atheromatous disease, particularly when the risks of operation are high.1–3 Such patients are often difficult to treat with conventional agents, and so the use of ACE inhibitors in these patients is an important issue. However, the use of orally administered ACE inhibitors in renovascular hypertension has been associated with acute deterioration of renal function, suggesting that these drugs are contraindicated in such patients.4–9 The present study recorded the number of acute rises in plasma creatinine in a series of patients with renovascular hypertension treated with ACE inhibitors. A prospective study measuring split renal function by computed radioisotope renography in patients with renovascular hypertension was also undertaken.
Patients and Methods

The diagnosis of renovascular hypertension was made in patients with hypertension that was difficult to control and in whom a renal arteriogram had demonstrated marked renal artery stenosis. The functional significance of the stenosis was assessed by renal vein sampling for renin estimation, the renin response to 12.5 mg of captopril p.o. (which produces an exaggerated reactive hyperreninemia in patients with marked stenosis), the chronic effects of ACE inhibition on blood pressure, and when performed, the response to operation.

Patients were considered in two groups. An initial retrospective analysis identified 32 patients treated with captopril for 3 or more days. Subsequently, 11 additional patients were studied prospectively. In these patients, renal function was estimated before and 1 to 6 weeks after the introduction of an orally administered ACE inhibitor (captopril in 6; enalapril in 5). Total and split renal function was determined by computer analysis of 99mTc-diethylenetriaminepentaacetic acid (DTPA) scintillation camera renograms. All studies were performed with the patient sitting upright with elevation of the blood pressure, and when performed, the response to captopril for 3 or more days (range, 3 days to 56 months). Six patients experienced acute deterioration of renal function (a twofold or greater rise in serum creatinine) that was reversible on cessation of captopril therapy (Table 1). No significant increase in serum creatinine concentration was noted in the other 26 patients. The 32 patients were grouped according to the nature of their renovascular disease: 13 patients had unilateral renal artery stenosis; 11 patients had bilateral renal artery stenosis; and 8 patients had a single kidney (transplant or native) with renal artery stenosis.

Serum creatinine estimation was by autoanalyzer (Technicon SMA1260) method using a modified Jaffe reaction. Plasma renin concentration and angiotensin II were measured by radioimmunoassay as previously described. Blood pressure measurements were made with a Dynamap (Critikon, Johnston and Johnston) automatic blood pressure recorder. Statistical comparisons were by Student's t-test, either paired or unpaired; a p level less than 0.05 was required for significance. Group results are expressed as mean ± SEM.

### Results

In the retrospective study, 32 patients with established renovascular hypertension were treated with captopril for 3 or more days (range, 3 days to 56 months). Six patients experienced acute deterioration of renal function (a twofold or greater rise in serum creatinine) that was reversible on cessation of captopril therapy (Table 1). No significant increase in serum creatinine concentration was noted in the other 26 patients.

The 32 patients were grouped according to the nature of their renovascular disease: 13 patients had unilateral renal artery stenosis; 11 patients had bilateral renal artery stenosis; and 8 patients had a single kidney (transplant or native) with renal artery stenosis.

Acute renal failure (ARF) developed in three patients with bilateral renal artery stenosis and in three with a single kidney with renal artery stenosis. Serum creatinine level remained stable in all patients with unilateral renal artery stenosis patients. Patients who experienced ARF had higher pretreatment serum creatinine levels (251 ± 45 µmol/L) than did those whose creatinine did not rise (153 ± 21 µmol/L; p < 0.05). After the introduction of ACE inhibitor therapy, blood pressure fell to a similar degree whether or not ARF subsequently developed (in 24 patients without ARF mean blood pressure fell from 133 ± 4 to 114 ± 4 mm Hg and in 6 patients with ARF, from 134 ± 6 to 116 ± 8 mm Hg; p > 0.05). No significant difference was detectable between plasma angiotensin II changes in 18 patients without ARF (from 20.1 ± 9.6 to

### Table 1. Acute Renal Failure in Captopril-Treated Patients with Renal Artery Stenosis: Recovery of Renal Function Following Withdrawal of Captopril

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Captopril (mg/day)</th>
<th>Treatment (day)</th>
<th>Pretreatment Serum creatinine (µmol/L)</th>
<th>Peak during treatment</th>
<th>Posttreatment Serum creatinine (µmol/L)</th>
<th>Recovery (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>450</td>
<td>20</td>
<td>152</td>
<td>404</td>
<td>150</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>37.5</td>
<td>4</td>
<td>250</td>
<td>650</td>
<td>130</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>150</td>
<td>12</td>
<td>122</td>
<td>277</td>
<td>147</td>
<td>5</td>
</tr>
<tr>
<td>4*</td>
<td>73</td>
<td>150</td>
<td>9</td>
<td>322</td>
<td>579</td>
<td>239</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>37.5</td>
<td>14</td>
<td>239</td>
<td>654</td>
<td>236</td>
<td>&lt;10</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>25</td>
<td>3</td>
<td>290</td>
<td>999</td>
<td>252</td>
<td>17</td>
</tr>
</tbody>
</table>

In all six patients in whom acute renal failure developed, serum creatinine fell rapidly to pretreatment levels following withdrawal of captopril.

*Rechallenge with captopril at successively lower dosages.

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9.2 ± 2.9 pg/ml) and 4 patients with ARF (from 24.6 ± 6.4 to 11.8 ± 3.1 pg/ml; p > 0.05).

Two patients illustrate aspects of ARF associated with ACE inhibition. In one (Patient 4 in Table 1), rechallenge with captopril on two successive occasions (each at a lower dosage) was associated with recurrent rises in plasma creatinine. Following withdrawal of captopril, serum creatinine fell to pretreatment levels each time. Figure 1 illustrates the course of a 29-year-old woman with fibromuscular renal artery disease. Initially, a marked stenosis was present on the left side and blood pressure control was achieved with captopril and chlorothiazide without a change in serum creatinine concentration. Following operation, hypertension was resolved, only to recur with graft thrombosis. Captopril and chlorothiazide controlled blood pressure again without a rise in serum creatinine concentration. Subsequent nephrectomy cured her hypertension. Nine months later, she was seen with severe hypertension because marked fibromuscular disease had developed in the remaining renal artery. On this occasion, captopril produced an acute rise in serum creatinine concentration. Following withdrawal of captopril, serum creatinine concentration returned to pretreatment levels. Subsequent reconstructive renovascular surgery cured her hypertension.

In the prospective study, patients were grouped according to renal arteriogram results as having either unilateral or bilateral renal artery stenosis. Six patients had unilateral renal artery stenosis. Serum creatinine concentration and total 99mTc-DTPA clearance were unchanged following the introduction of ACE inhibitor therapy (Table 2). Split renal function results are shown in Figure 2. The 99mTc-DTPA clearance in the kidneys with stenosis fell from 25 ± 12 to 14 ± 6 ml/min. The stenosed kidney was virtually nonfunctioning in three patients, and no change in clearance was detectable during ACE inhibitor therapy. In the three patients with functioning stenosed kidneys, however, significant falls in clearance occurred. In contrast, 99mTc-DTPA clearance in the normal kidneys tended to rise: 99mTc-DTPA clearance increased from 41 ± 7 to 48 ± 7 ml/min, with the most marked rises occurring in patients in whom clearance in the stenosed kidney decreased. The net effect was to maintain total renal function, with the normal kidney compensating for the functional impairment of the stenosed kidney.

Five patients had bilateral renal artery stenosis. Serum creatinine concentration rose and total 99mTc-DTPA clearance fell during ACE inhibitor therapy in this group of patients (see Table 2). Split renal function studies revealed a fall in 99mTc-DTPA clearance in eight of the 10 kidneys studied; average left kidney clearance fell from 18 ± 6 to 15 ± 5 ml/min, and right kidney clearance fell from 22 ± 5 to 16 ± 4 ml/min (Figure 3).

Combining split renal function clearance results from both patient groups showed a fall in 99mTc-DTPA clearance in 13 of 16 stenosed kidneys after the introduction of ACE inhibitor therapy (change in 99mTc-DTPA clearance, −7.5 ± 2.7 ml/min; n = 16; p < 0.01). In comparison, there was a rise in clearance in five of the six nonstenosed kidneys from the unilateral renal artery stenosis group (change in 99mTc-DTPA clearance, +8.2 ± 4.6 ml/min; n = 6; 0.1 > p > 0.05).

Cessation of ACE inhibitor therapy was followed by rapid return of serum creatinine concentration to pretreatment levels in all patients in whom renal failure developed (see Table 1). Two patients studied prospectively with 99mTc-DTPA clearance had ACE inhibitor therapy discontinued after 8 and 16 weeks of treatment, respectively. In both patients, function of the stenosed kidneys returned to pretreatment levels (Table 3).

**Discussion**

This study shows that renal function deteriorated in a substantial number of patients when ACE inhibitor therapy was used to treat hypertension associated with renal artery stenosis. Six patients experienced ARF, and in all of these patients the only functional renal

**Table 2. Effects of Angiotensin Converting Enzyme Inhibition on Renal Function in Six Patients with Unilateral Renal Artery Stenosis and Five with Bilateral Renal Artery Stenosis**

<table>
<thead>
<tr>
<th>Group</th>
<th>Before ACE inhibition</th>
<th>During ACE inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral RAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>134 ± 22</td>
<td>144 ± 32</td>
</tr>
<tr>
<td>99mTc-DTPA clearance (ml/min)</td>
<td>64 ± 16</td>
<td>64 ± 13</td>
</tr>
<tr>
<td>Bilateral RAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>150 ± 23</td>
<td>181 ± 57*</td>
</tr>
<tr>
<td>99mTc-DTPA clearance (ml/min)</td>
<td>40 ± 9</td>
<td>27 ± 5*</td>
</tr>
</tbody>
</table>

Values are means ± SEM. ACE = angiotensin converting enzyme; RAS = renal artery stenosis; DTPA = diethylenetriaminepentaacetic acid.

*p < 0.05, compared with pretreatment values.
tissue was perfused through a stenosed renal artery. In contrast, patients with unilateral renal artery stenosis did not show a rise in plasma creatinine concentration.

The pathogenesis of functional renal impairment during ACE inhibition remains unclear. Our findings do not support acute hypotension as a major contributing factor, as there was no difference in the blood pressure fall between groups with or without ARF. Interference with glomerular dynamics caused by reduction of intrarenal angiotensin II following ACE inhibition has been proposed as a mechanism of acute renal insufficiency in these patients. In our patients, similar degrees of depression of plasma angiotensin II concentration occurred in patients in whom renal failure developed and in those with stable renal function. This observation does not exclude participation of angiotensin II in the pathogenesis of the renal failure, as circulating angiotensin II levels may not be an accurate reflection of the intrarenal level. Experiments by Anderson et al. support the role of angiotensin II in maintaining renal hemodynamics. In those experiments, ACE inhibition abolished the renal autoregulation that normally occurred after renal artery stenosis. This effect was largely corrected by an infusion of angiotensin II into the stenosed renal artery. Similar changes of renal function have been shown in the two-kidney, one clip Goldblatt model of hypertension in the rat. In this model, glomerular filtration was compromised in the stenosed kidney following ACE inhibition, whereas the contralateral normal kidney showed a marked increase in glomerular filtration rate.

The present prospective study using 99mTc-DTPA clearance as an index of glomerular filtration has confirmed that this situation also prevails in humans. In patients with unilateral renal artery disease, 99mTc-DTPA clearance was suppressed in the kidney with renal artery stenosis following ACE inhibitor therapy and increased in the normal kidney. The net effect in these patients was a preservation of total renal function; serum creatinine concentration remained unchanged despite marked reduction in function of the stenosed kidney. In contrast, patients with bilateral renal arterial disease showed a reduction in total renal function, reflected by a fall in 99mTc-DTPA clearance and a rise in serum creatinine concentration. Following the introduction of ACE inhibitor therapy in these patients, serum creatinine concentration rose to a higher level and subsequently remained stable. That all patients with bilateral renal artery stenosis did not experience ARF may have been due to the variable degree of stenosis of the renal vessel. In patients with more severe renal artery stenosis, angiotensin II--induced efferent arteriolar vasocostriction may be the only mechanism for maintaining glomerular filtration, whereas with lesser degrees of arterial stenosis, additional mechanisms may compensate for the reduced angiotensin II during ACE inhibition and result in preservation of filtration, albeit at a reduced level.

The ACE inhibition in the patients studied prospectively was induced with either captopril or enalapril. Although it is possible that these agents have differing renal toxicology, we attribute the effects on renal func-

### Table 3. Split Renal Function Before, During, and After Treatment with Enalapril or Captopril

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Arteriogram results</th>
<th>99mTc-DTPA clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Atheromatous bilateral RAS</td>
<td>Left 24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right 25</td>
</tr>
<tr>
<td>Captopril</td>
<td>Fibromuscular RAS</td>
<td>Left 66</td>
</tr>
</tbody>
</table>

The reduction in function observed during ACE inhibition recovered to pretreatment levels following ACE inhibitor withdrawal. See Table 2 for key to abbreviations.
tion to ACE inhibition per se and have thus combined data from patients receiving either agent.

Hricik et al. report one case of ARF in a patient with renal artery stenosis during treatment with captopril, in whom subsequent challenge with enalapril also led to ARF. Recently, Watson et al. suggested that diuretic therapy may contribute to renal failure during ACE inhibition, citing patients with renovascular hypertension in whom renal failure developed and in whom cessation of diuretic therapy improved renal function. All our patients studied retrospectively who experienced renal failure had received diuretic therapy. In the prospective study, however, five patients received monotherapy with ACE inhibitor. Diuretic therapy may increase the dependence of renal autoregulation on angiotensin II–mediated mechanisms, thus increasing the sensitivity of kidneys with low perfusion pressure to ACE inhibitors.

The long-term consequences of reduction in glomerular filtration in a stenosed kidney caused by ACE inhibitors are not known. In this series, all patients with ARF had a return of renal function to pretreatment levels when ACE inhibitors were withdrawn. Two patients studied prospectively also had return of renal function in the stenosed kidneys after 2 and 4 months of ACE inhibition. Similar observations were made by Wenting et al. in patients with unilateral renal artery stenosis studied by split renal function before, during, and after ACE inhibitor therapy. The loss of renal function does not appear to be irreversible, at least over a period of months. Longer term use of ACE inhibitors needs to be studied further before irreversible parenchymal damage or thrombosis of the stenosis can be excluded as potential complications in patients with renovascular hypertension.

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