Use of the Converting Enzyme Inhibitor Enalapril in Renovascular Hypertension
Effect on Blood Pressure, Renal Function, and the Renin-Angiotensin-Aldosterone System

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SUMMARY Thirteen patients were entered into a protocol to assess the safety and efficacy of enalapril (MK 421), 5 to 20 mg b.i.d., and hydrochlorothiazide, 50 to 100 mg daily, for the treatment of renovascular hypertension. Specifically monitored were the effects of therapy on blood pressure and pulse, renal function, and the renin-angiotensin-aldosterone axis. Enalapril and hydrochlorothiazide therapy produced excellent control of blood pressure with no adverse side effects. After approximately 8 weeks of therapy, renal vascular resistance was decreased and no adverse effects on glomerular filtration rate or renal blood flow were noted, except in one patient with a functional unilateral stenotic kidney. Patients receiving enalapril and hydrochlorothiazide showed stimulation of plasma renin activity and suppression of plasma angiotensin II, although the initial degree of suppression was not sustained in all patients during prolonged therapy. Although plasma aldosterone concentration was initially suppressed, the degree of suppression was not sustained. Nine patients have been followed for an additional 6 months; none have experienced further progression of renal disease, as assessed by repeated measurements of glomerular filtration and effective renal plasma flow. These results suggest that combined enalapril and hydrochlorothiazide therapy is safe and effective in the medical management of renovascular hypertension and that blood pressure control may be achieved in the absence of sustained interruption of the renin-angiotensin-aldosterone system. (Hypertension 8: 290-297, 1986)

KEY WORDS • glomerular filtration • renal plasma blood flow • renin-angiotensin-aldosterone system

That the converting enzyme inhibitors captopril and enalapril (MK 421) effectively lower blood pressure in patients with renovascular hypertension has been demonstrated repeatedly. The initial fall in arterial pressure appears to be proportional to the concurrent fall in plasma angiotensin II concentration for both drugs. Since the renin-angiotensin system plays a crucial part in the regulation of glomerular filtration rate when renal perfusion pressure is low, and short-term administration of a converting enzyme inhibitor destroys the integrity of this system, administration of a converting enzyme inhibitor to a patient with renovascular hypertension carries the risk of precipitating serious renal dysfunction. Indeed, both captopril and enalapril have been reported to precipitate serious deterioration in glomerular filtration rate, renal plasma flow, and renal blood flow in patients with critical bilateral renal artery stenosis, renal artery stenosis in the solitary kidney, and renal artery stenosis in the transplanted kidney. Furthermore, it has been suggested that converting enzyme inhibitors invariably worsen the already impaired function of the affected kidney, which raises questions concerning the potential safety of these two drugs in patients with renovascular hypertension.

It is equally clear, however, that the availability of converting enzyme inhibitors has improved markedly the medical management of renovascular hypertension. Usually, the blood pressure response to either captopril or enalapril is excellent, secondary aldosteronism is diminished, and compliance is improved due to the simplified and generally well-tolerated drug regimen. Side effects reported with use of captopril and other drugs containing mercapto groups (e.g., rashes, fever, taste disturbances, leukopenia,
and proteinuria) have not been reported with use of enalapril.23 Impressively, a compassionate use protocol that permitted substitution of enalapril for captopril in 66 renovascular hypertensive patients whose hypertension was uncontrolled or who suffered from adverse side effects of captopril has been reported without recurrence of side effects.25 Because enalapril has greater potency, longer duration of action, and a more favorable side effect profile than captopril, it could become the drug of choice for the medical management of renovascular hypertension.

To determine the relative safety of enalapril in the treatment of renovascular hypertension, a prospective study was initiated to characterize sequentially enalapril-mediated effects on the renin-angiotensin-aldosterone system and on renal function. Specifically monitored were the glomerular filtration rate and effective renal plasma flow using inulin and p-aminohippurate (PAH) clearance techniques. Of the 13 patients entered into the trial, all underwent at least two evaluations during 2 months of therapy and nine have undergone evaluations following 6 months of therapy.

Materials and Methods

Thirteen hypertensive patients (3 women, 10 men; mean age, 52 years) were selected for this study. Each patient was diagnosed to have renovascular hypertension on the basis of an abnormal renal arteriogram plus either lateralized (ratio ≥ 1.5) or bilaterally elevated split renal vein renin determinations. All patients had to meet these criteria within 1 year of entrance into the protocol. To be included, each patient had to maintain a mean 5-minute recumbent diastolic (fifth phase) blood pressure greater than 95 mm Hg while receiving hydrochlorothiazide (HCTZ; 50 mg) therapy. Patient adherence to therapy was monitored by count of returned tablets. Excluded from study were patients with history, physical, or laboratory findings of moderate to severe cardiomyopathy, congestive heart failure, recent myocardial infarction, second or third degree heart block, overt diabetes mellitus, severe renal insufficiency (creatinine clearance < 25 ml/min/1.73 m²) or patients who were nonadherent to drug therapy. Informed consent was obtained according to the principles of the Declaration of Helsinki. All studies were approved by the Harry S Truman Memorial Veterans Hospital and the University of Missouri Health Sciences Center Joint Institutional Review Board (committee for research involving human subjects).

Patient Protocol

Due to the severity of hypertension often associated with a renovascular etiology, a placebo run-in period was not employed. All hypertensive patients were withdrawn from prior medication and placed on a regimen of 50-mg HCTZ monotherapy for 1 to 7 days. All patients were advised to follow a no-added-salt diet. An optional increase of HCTZ to 100 mg was allowed in patients with a creatinine clearance below 60 ml/min/1.73 m². All patients subsequently received enalapril therapy. Titration of enalapril progressed from 5 to 10 to 20 mg b.i.d. Each titration period ranged from 2 to 5 days, depending on the severity of the hypertension. Criteria for titrating drugs to the next dosage was a supine diastolic blood pressure greater than 90 mm Hg. Following the titration period (baseline) and a 2-week maintenance period (Maintenance 1), patients received combined enalapril and HCTZ therapy for an additional 4 weeks (Maintenance 2). Nine patients received therapy for an additional 6 months (Maintenance 3). Drug dosages for enalapril and HCTZ are shown in Table 1.

Forearm blood pressure was monitored using a standard mercury sphygmomanometer. Three pressures were recorded after the patient had been supine for 5 minutes and upright for 2 minutes. The three pressures were averaged to give a mean representation of the patient’s blood pressure. Mean arterial pressure was calculated as the diastolic pressure plus one third the pulse pressure. The mean heart rate was recorded from the average of three supine and upright determinations obtained before each blood pressure measurement. Two-hour recumbent humoral determinations were made between 0800 and 1200. Subsequently, renal clearances were performed. All studies were initiated during the HCTZ monotherapy period and repeated following the completion of each maintenance period.

Humoral Determinations

Supine plasma renin activity and plasma aldosterone level were determined by radioimmunoassay as previously described.25 Supine plasma angiotensin II level was determined by using a modification of the radioimmunoassay described by Koivunen et al.27 Specifically, blood samples were collected in chilled tubes containing ethylenediaminetetraacetic acid plus captopril (20 μg/ml blood), placed in ice, and then spun in a refrigerated centrifuge, and the plasma samples were stored frozen at −20°C. Before assay, the samples were thawed in an ice bath and 0.75 ml of each plasma sample was placed in a 12 × 75 polystyrene tube. To precipitate the proteins, 1.50 ml of cold absolute ethanol was added to each tube. The tubes were spun, and 400-μl aliquots of the supernatant were pipetted into a series of 12 × 75 polystyrene tubes for assay of angiotensin II. The tubes were evaporated to dryness with filtered air and stored at −20°C until assayed.

At the time of assay, 125I-angiotensin II (New En-
gland Nuclear, Boston, MA, USA) was diluted in a 0.1 M tris (hydroxymethyl)aminomethane (Tris) buffer (plus bovine serum albumin, 2.5 mg/ml; pH adjusted to 7.4). Synthetic [Asp\(^1\), Ile\(^3\)]angiotensin II (Vega Biotechnologies, Tucson, AZ, USA) was diluted in a standard tube. Each tube also received 0.5 ml of angiotensin II antiserum, diluted 1:160,000 in Tris buffer. The angiotensin II antiserum was produced by periodic injection of rabbits with angiotensin II conjugated to serum albumin, together with Freund's adjuvant. The tubes for the assay of angiotensin II also received \(^{125}\)I-angiotensin I and angiotensin II antiserum, as in our assay for plasma renin activity.\(^{26}\) Each tube was incubated in an ice bath for 18 hours, and then 1 ml of a solution of dextran-coated charcoal in barbital buffer (pH 7.4) was added to separate the free from the antibody-bound angiotensin. The samples were centrifuged, the supernatant was aspirated, and the charcoal pellets (free angiotensin) were counted in a well-type automated gamma counter.

The results were calculated from a log-logit transformation of the angiotensin standards versus the ratio of the bound counts of angiotensin for each standard to the bound counts of angiotensin for the zero angiotensin standard. Angiotensin I has 0.1 to 0.3% cross-reactivity with our angiotensin II antiserum, contributing between 0.7 and 2.1 pg/ml to the total immunoreactive angiotensin II concentration. Angiotensin II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe), the heptapeptide (Val-Tyr-Ile-His-Pro-Phe), and the pentapeptide (Tyr-Ile-His-Pro-Phe) cross-react 100% (mole-mole) with our angiotensin II antiserum. The heptapeptide, angiotensin III (Arg-Val-Tyr-Ile-His-Pro-Phe), cross-reacts 70% with our angiotensin II antiserum. However, 78 to 85% of the measured immunoreactive angiotensin II is probably the octapeptide, angiotensin II\(^{28,29}\). With this method, the recovery of angiotensin II added to human plasma samples averages 101% within an overall range from 75 to 600 pg/ml. Intra assay variation averaged 2.4% (\(n = 25\)) based on a mean (± SD) immunoreactive angiotensin II concentration of 79 ± 5.6 pg/ml; inter assay variation averaged 10.7% (\(n = 25\)).

Laboratory and Timed Clearance Studies

Serum and urine electrolytes and urinary protein were determined by autoanalyzer methods. The 24-hour urinary protein excretion was expressed as grams of protein per gram of creatinine to normalize for accuracy of collection. White blood cell count was determined by Coulter counter.

Timed renal clearance studies were performed as previously described by Bauer et al.\(^{30,31}\) Subjects were hydrated orally with tap water (20 ml/kg body weight; urine specific gravity < 1.010). Priming doses of mexitin (10% solution) and PAH (20% solution) were administered to obtain plasma concentrations of approximately 20 and 2 mg/dl, respectively. Inulin and PAH were infused to maintain initial plasma concentrations. After a 60-minute equilibration period, three timed urine collections (spontaneous voidings) were made at approximately 30- to 40-minute intervals. Plasma was obtained between each urine collection.

Calculations and Statistics

Clearances of creatinine, inulin, and PAH were calculated as (urine concentration/plasma concentration) \(\times\) urine flow rate (ml/min) and corrected for body surface area (1.73 m\(^2\)). Since there were no significant differences in urine flow rate or clearances from one collection period to another, all results were expressed as single mean values of triplicate determinations for each patient. Renal blood flow (ml/mm/1.73 m\(^2\)) was calculated from PAH clearance by using the peripheral venous hematocrit and assuming 74% renal extraction of PAH.\(^{32}\) To our knowledge, the effect of enalapril on the renal extraction of PAH is unknown; to the extent that enalapril may decrease PAH extraction, our calculated values for renal blood flow may have underestimated actual renal blood flow. Renal vascular resistance (dyn sec cm\(^{-1}\)/1.73 m\(^2\)) was calculated as equal to (mean arterial pressure/renal blood flow) \(\times\) 80,000.

A multiple comparison analysis was employed to compare Weeks 2 and 6 with baseline data. Wilcoxon's signed rank test was used with an \(a\) level of 0.05 for each comparison; an overall \(a\) level for the multiple comparison was selected at 0.025. Values are given as means ± SEM.

Results

Patient characteristics are presented in Table 2. Patients receiving enalapril excreted 114 ± 19 mEq of sodium per day during HCTZ monotherapy, as assessed by 24-hour urine collection. Mean urinary sodium excretion increased to 169 ± 15 mEq/day following 2 weeks of therapy (Maintenance 1) and was essentially unchanged (171 ± 16 mEq/day) following 6 weeks of therapy (Maintenance 2). These data suggest that the patients receiving combined enalapril and HCTZ therapy were consuming 4 to 5 g of dietary sodium per 24 hours during these two phases of the protocol.

Patients' 5-minute recumbent and 2-minute upright systolic blood pressure, diastolic blood pressure, and heart rate responses to enalapril and HCTZ therapy are given in Table 3. Both systolic and diastolic blood pressures were well controlled. Although there was a significant difference between recumbent and upright systolic pressure measurements at baseline and following the first maintenance period (\(p < 0.025\)), no such difference existed following the second maintenance period. Upright heart rate was significantly higher than recumbent heart rate throughout all phases of the protocol (\(p < 0.005\)).

In nine patients with renovascular hypertension who have completed an additional 6 months of enalapril and HCTZ therapy (Maintenance 3), both recumbent and
Table 2: Characteristics of 13 Patients Receiving Combined Enalapril and Hydrochlorothiazide Therapy

<table>
<thead>
<tr>
<th>Patient no, sex, age (yr)</th>
<th>Renal vein renin (ng ANG I/ml/hr)</th>
<th>Split renal vein renin ratio</th>
<th>Angiographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td></td>
</tr>
<tr>
<td>1, M, 59</td>
<td>39</td>
<td>59</td>
<td>1.5</td>
</tr>
<tr>
<td>2, M, 63</td>
<td>8</td>
<td>13</td>
<td>1.6</td>
</tr>
<tr>
<td>3, M, 61</td>
<td>42</td>
<td>2.6</td>
<td>1.6</td>
</tr>
<tr>
<td>4, M, 66</td>
<td>7</td>
<td>14</td>
<td>2.0</td>
</tr>
<tr>
<td>5, M, 49</td>
<td>35</td>
<td>66</td>
<td>1.9</td>
</tr>
<tr>
<td>6, M, 63</td>
<td>59</td>
<td>24</td>
<td>2.5</td>
</tr>
<tr>
<td>7, F, 28</td>
<td>32</td>
<td>19</td>
<td>1.7</td>
</tr>
<tr>
<td>8, M, 49</td>
<td>15</td>
<td>29</td>
<td>1.9</td>
</tr>
<tr>
<td>9, M, 56</td>
<td>20</td>
<td>12</td>
<td>1.7</td>
</tr>
<tr>
<td>10, M, 60</td>
<td>17</td>
<td>10</td>
<td>1.7</td>
</tr>
<tr>
<td>11, F, 21</td>
<td>28</td>
<td>74</td>
<td>2.6</td>
</tr>
<tr>
<td>12, M, 63</td>
<td>4</td>
<td>11</td>
<td>2.8</td>
</tr>
<tr>
<td>13, F, 39</td>
<td>25</td>
<td>35</td>
<td>1.4</td>
</tr>
</tbody>
</table>

ANG I = angiotensin I, RRA = right renal artery, AS = atherosclerotic disease, LRA = left renal artery, FM = fibromuscular disease.

Upright systolic and diastolic blood pressures have remained well controlled. Furthermore, there has been no orthostatic change in blood pressure.

Enalapril and HCTZ therapy was associated with a significant increase in plasma renin activity at Week 2 of maintenance therapy (Table 4). Although the mean increase in plasma renin activity was sustained at Week 6, the increase was not significant at the p < 0.025 level. Plasma angiotensin II concentration was decreased significantly at Week 2 of maintenance therapy. Although there was a mean decrease in plasma angiotensin II concentration at Week 6 of maintenance therapy, this decrease was not significant (p = 0.17). Five of the 13 patients demonstrated a 42 pg/ml mean increase in the immunoreactive angiotensin II concentration from Week 2 to Week 6 of maintenance therapy. Plasma aldosterone level was significantly decreased at Week 2 of maintenance therapy. Although the mean decrease in plasma aldosterone was sustained at Week 6 of maintenance therapy, the decrease was not significant. Nine patients demonstrated a 4.2 ng/dl mean increase in plasma aldosterone concentration from Week 2 to Week 6 of maintenance therapy.

Enalapril and HCTZ therapy was not associated with clinically significant changes in serum sodium level: baseline, 136 ± 1 mEq/L; Maintenance 1, 138 ± 1 mEq/L; Maintenance 2, 138 ± 1 mEq/L.

Table 3: Systemic Hemodynamic Response to Combined Enalapril and Hydrochlorothiazide Therapy

<table>
<thead>
<tr>
<th>Patient position</th>
<th>Baseline (n = 13)</th>
<th>1 (n = 13)</th>
<th>2 (n = 13)</th>
<th>3 (n = 9)</th>
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</thead>
<tbody>
<tr>
<td>Recumbent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>164 ± 8</td>
<td>133 ± 5*</td>
<td>128 ± 5*</td>
<td>134 ± 7†</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>101 ± 2</td>
<td>81 ± 2*</td>
<td>80 ± 3*</td>
<td>80 ± 3*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>87 ± 4</td>
<td>83 ± 4</td>
<td>82 ± 3</td>
<td>78 ± 5</td>
</tr>
<tr>
<td>Upright</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>152 ± 7</td>
<td>124 ± 5*</td>
<td>125 ± 6†</td>
<td>133 ± 7†</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>102 ± 3</td>
<td>81 ± 2*</td>
<td>78 ± 3*</td>
<td>85 ± 2*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>99 ± 4</td>
<td>96 ± 4</td>
<td>95 ± 4</td>
<td>88 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± SEM. BP = blood pressure. See Table 1 for key to other terms. *p < 0.005, †p < 0.01, ‡p < 0.5, compared with baseline values.

Table 4: Humoral Response to Combined Enalapril and Hydrochlorothiazide Therapy in 13 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n = 13)</th>
<th>1 (n = 13)</th>
<th>2 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (ng ANG I/ml/hr)</td>
<td>11.0 ± 2.9</td>
<td>21.2 ± 5.0*</td>
<td>28.7 ± 7.0†</td>
</tr>
<tr>
<td>ANG II (pg/ml)</td>
<td>78 ± 14</td>
<td>32.6 ± 6†</td>
<td>47 ± 12</td>
</tr>
<tr>
<td>ALDO (ng/dl)</td>
<td>13.7 ± 2.3</td>
<td>8.0 ± 1.2†</td>
<td>9.9 ± 1.0†</td>
</tr>
</tbody>
</table>

Values are means ± SEM. PRA = plasma renin activity, ANG I = angiotensin I, ANG II = plasma angiotensin II concentration, ALDO = plasma aldosterone concentration. See Table 1 for key to other terms. *p < 0.025, †p < 0.05, ‡p < 0.01, compared with baseline values.
The addition of enalapril to HCTZ therapy was associated with significant increases in serum potassium level: baseline, 3.5 ± 0.1 mEq/L; Maintenance 1, 3.9 ± 0.1 mEq/L; Maintenance 2, 4.1 ± 0.1 mEq/L (p < 0.01). Enalapril and HCTZ therapy was not associated with clinically significant changes in white blood cell count (baseline, 7900 ± 400/ml; Maintenance 1, 7200 ± 500/ml; Maintenance 2, 7400 ± 400/ml) or urinary protein excretion (baseline, 0.18 ± 0.06 g/g creatinine; Maintenance 1, 0.17 ± 0.06 g/g creatinine; Maintenance 2, 0.13 ± 0.04 g/g creatinine).

Although mean arterial pressure decreased markedly, there were no significant changes in mean inulin or PAH clearances or renal blood flow following Week 2 or 6 of maintenance therapy (Table 5). Renal vascular resistance, however, was reduced significantly by Week 6 of maintenance therapy. Serum creatinine level was increased and creatinine clearance was decreased at Week 2 of maintenance therapy, compared with baseline values; however, these changes were not sustained at Week 6.

In nine patients with renovascular hypertension who have completed 6 months of enalapril and HCTZ therapy, inulin and PAH clearances have remained stable: inulin clearance, 62 ± 6 ml/min/1.73 m² (a 5 ml/min/1.73 m² mean decrease compared with baseline); PAH clearance, 270 ± 29 ml/min/1.73 m² (a 32 ml/min/1.73 m² mean decrease compared with baseline).

Renovascular hypertension, a heterogeneous disease, can be subdivided into the following four categories based on angiographic and humoral determinations:

1. Unilateral renovascular hypertension angiographic evidence of unilateral involvement and unilateral renal vein renin lateralization with a ratio greater than 1.5.
2. Asymmetrical bilateral renovascular hypertension: angiographic evidence of bilateral involvement, in which one side is more severely involved, and lateralization ratio greater than 1.5 of split renal vein renin to the more involved side.
3. Unilateral renovascular disease plus contralateral renal parenchymal (small kidney) disease: angiographic involvement on only one side, with a small contralateral kidney secondary to renal parenchymal disease, and nonlateralizing, high split renal vein renin.
4. Symmetrical bilateral renovascular disease. Symmetrical angiographic involvement of both sides and nonlateralizing, high split renal vein renin.

Based on these definitions, eight patients had unilateral renovascular hypertension, four had asymmetrical bilateral renovascular hypertension, and one had unilateral renovascular disease plus contralateral renal parenchymal disease (a small, contracted kidney, thought to be secondary to chronic pyelonephritis). No patient had symmetrical bilateral renovascular disease. No significant changes in mean inulin or PAH clearances were noted with enalapril and HCTZ therapy in patients with either unilateral renovascular hypertension or asymmetrical bilateral renovascular hypertension (Table 6); however, the patient with unilateral renovascular disease plus contralateral renal parenchymal (small kidney) disease had a 50% reduction in inulin clearance and a 30% reduction in PAH clearance at the end of the maintenance period. This degree of deterioration in renal function has remained stable through 6 months of therapy (inulin clearance, 41 ml/min/1.73 m²; PAH clearance, 225 ml/min/1.73 m²).

### Table 5 Renal Function Response to Combined Enalapril and Hydrochlorothiazide Therapy in 13 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Maintenance 1</th>
<th>Maintenance 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>122 ± 4</td>
<td>98 ± 3*</td>
<td>96 ± 3*</td>
</tr>
<tr>
<td>Plasma creatinine (mg/dl)</td>
<td>1.3 ± 0.1</td>
<td>1.6 ± 0.1*</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Cₘ (ml/min/1.73 m²)</td>
<td>85 ± 8</td>
<td>65 ± 5*</td>
<td>85 ± 10</td>
</tr>
<tr>
<td>Cₑ (ml/min/1.73 m²)</td>
<td>79 ± 8</td>
<td>70 ± 10</td>
<td>74 ± 8</td>
</tr>
<tr>
<td>Cₚₐₜ (ml/min/1.73 m²)</td>
<td>292 ± 31</td>
<td>333 ± 48</td>
<td>298 ± 32</td>
</tr>
<tr>
<td>RBF (ml/min/1.73 m²)</td>
<td>713 ± 68</td>
<td>786 ± 109</td>
<td>699 ± 71</td>
</tr>
<tr>
<td>RVR (dyn sec cm⁻²)</td>
<td>15.2 ± 1.4</td>
<td>12.5 ± 1.7</td>
<td>12.6 ± 1.4‡</td>
</tr>
</tbody>
</table>

Values are means ± SEM MAP = mean arterial pressure, Cₘ = creatinine clearance, Cₑ = inulin clearance (glomerular filtration rate); Cₚₐₜ = p-aminohippurate clearance (effective renal plasma flow); RBF = renal blood flow, RVR = renal vascular resistance. See Table 1 for key to other terms.

### Table 6 Renal Function Response to Combined Enalapril and Hydrochlorothiazide Therapy According to Category of Renovascular Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Baseline</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral renovascular hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 8)</td>
<td>64 ± 5</td>
<td>58 ± 10</td>
</tr>
<tr>
<td>Cₘ</td>
<td>258 ± 32</td>
<td>314 ± 60</td>
</tr>
<tr>
<td>Asymmetrical bilateral renovascular hypertension (n = 4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cₘ</td>
<td>108 ± 18</td>
<td>101 ± 22</td>
</tr>
<tr>
<td>Cₚₐₜ</td>
<td>360 ± 77</td>
<td>402 ± 103</td>
</tr>
<tr>
<td>Unilateral renovascular hypertension + contralateral renal hypertension (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cₘ</td>
<td>82 ± 41</td>
<td></td>
</tr>
<tr>
<td>Cₚₐₜ</td>
<td>295 ± 206</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SEM Cₘ = inulin clearance (glomerular filtration rate); Cₚₐₜ = p-aminohippurate clearance (effective renal plasma flow). See Table 1 for key to other terms.
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treatment of renovascular hypertension. Indeed, all 13 patients receiving this therapy had good blood pressure control within 2 weeks of initiating therapy (supine diastolic blood pressure < 90 mm Hg). No side effects were reported; no patient exhibited leukopenia or a clinically important change in urinary protein excretion. Nine patients who have been followed on enalapril and HCTZ therapy for 6 months have maintained excellent blood pressure control without any side effects.

Enalapril and HCTZ therapy was associated with marked increases in plasma renin activity, a predictable marker of drug adherence to converting enzyme inhibitors. Plasma aldosterone concentration was suppressed. The addition of enalapril to baseline HCTZ therapy produced a clinically important increase in serum potassium level (from 3.5 to 4.1 mEq/L), which is in agreement with previous reports that angiotensin converting enzyme inhibitor therapy ameliorates hypokalemia associated with the secondary aldosteronism accompanying renovascular hypertension.1 5

The principal mechanism responsible for sustained blood pressure reduction with angiotensin converting enzyme inhibitors is thought to be related to sustained reduction in plasma angiotensin II concentration. Although a mean reduction in angiotensin II was observed, the levels were not completely suppressed (the minimal concentration of angiotensin II detectable in our laboratory is <20 pg/ml). This finding suggests a potential role for non-renin-mediated antihypertensive mechanisms, such as inhibition of bradykinin degradation or stimulation of vasodilator prostaglandin synthesis.39

Blaine et al.34 recently have reported that enalaprilat (the active diacid metabolite of enalapril), administered to sodium-deficient, conscious dogs, produced a prompt decrease in blood pressure associated with a marked increase in plasma renin activity and a decrease in plasma immunoreactive angiotensin II to 35% of control level. The subsequent infusion of a statine-containing renin inhibitor produced no further change in blood pressure, although plasma immunoreactive angiotensin II levels fell essentially to zero. When the order of drug administration was reversed, the infusion of the renin inhibitor produced a decrease in blood pressure that was associated with reduction of plasma renin activity and plasma immunoreactive angiotensin II to near zero levels. The subsequent infusion of enalaprilat produced an additional decrement in blood pressure without further decreasing plasma immunoreactive angiotensin II levels. These data, demonstrating dissociation between the effects of enalaprilat on blood pressure and the renin-angiotensin system, clearly suggest that enalaprilat lowers blood pressure by additional (nonrenin) mechanisms.

Converting enzyme inhibition with enalapril is reported to be associated with marked suppression of angiotensin converting enzyme activity, which recovers slowly over a 72-hour period.35-37 Although in the present study plasma angiotensin II concentration was initially suppressed, compared with baseline, the degree of suppression was not sustained in all patients after 6 weeks of therapy. There are several possible mechanisms by which converting enzyme inhibition may not be associated with continually suppressed levels of angiotensin II. First, despite low levels of angiotensin converting enzyme, the levels may be sufficiently high to catalyze the reaction of angiotensin I to angiotensin II, since high levels of substrate (angiotensin I) are available. Second, a non-converting enzyme system might convert high levels of circulating angiotensin I to angiotensin II. Tonin, a serine protease, is an enzyme that has been shown to convert angiotensin I into angiotensin II.38 Third, the observed increase in plasma angiotensin II concentration might reflect an increase in the immunoreactive angiotensin II peptide fragments (5 through 7) and not the octapeptide (angiotensin II). However, this latter hypothesis would require dissociation between the production of the octapeptide and the other immunoreactive peptide fragments. Such a physiological dissociation in the metabolism of these peptides would be difficult to explain.

Enalapril and HCTZ therapy was not associated with reductions in insulin clearance, a sensitive marker of glomerular filtration rate, or PAH clearance, a sensitive marker of effective renal plasma flow in renovascular hypertensive patients with unilateral or bilateral (but asymmetrical) disease. Changes in the plasma creatinine level and creatinine clearance were more variable but, in general, paralleled changes in insulin clearance. Although renal blood flow did not change, renal vascular resistance was reduced. These two anatomical variants of renovascular hypertension are probably the most common clinical forms of the disease. In such patients, overall renal function obviously was not dependent on the renal blood flow to the most severely involved kidney. Unexpectedly, the patients with unilateral renovascular hypertension had lower mean insulin and PAH clearances than did the patients with asymmetrical bilateral renovascular hypertension. These data suggest that the contralateral kidney in patients with unilateral renovascular hypertension had experienced marked nephrosclerosis, whereas the contralateral kidney in patients with asymmetrical bilateral renovascular hypertension was relatively protected from pressure-associated end-organ damage.

In contrast to the more common anatomical forms of renovascular hypertension, the patient treated with enalapril and HCTZ therapy who had unilateral renovascular disease and a small contracted contralateral kidney (hence, a functional unilateral stenotic kidney) showed a marked reduction in insulin and PAH clearance. In this patient, the deterioration in renal function may have been related to angiotensin II inhibition with loss of autoregulatory control of renal perfusion32; her circulating level of angiotensin II fell from 114 pg/ml to less than 20 pg/ml and remained at this level throughout the 6 weeks of maintenance therapy. Sequential follow-up studies over 6 months, however, have not demonstrated progressive deterioration of either glomerular filtration rate or effective renal plasma flow. Although we did not study any patient with criti-
cal bilateral renovascular hypertensive disease, a similar result could be anticipated. Our results, demonstrating the efficacy and safety of enalapril therapy in the majority of patients with renovascular hypertension, are consistent with prior reports.6,9 Total kidney function generally is well preserved.

Recently, Wenting et al.22 have reported marked reduction of glomerular filtration (as assessed by 99mTc-diethylenetriamine pentaacetic acid [DTPA] renal scan) in the affected kidney of seven of 14 patients with unilateral renovascular hypertension treated with captopril, 150 mg/day, for 3 to 5 weeks. Split renal function studies have also been reported in 10 patients with renovascular hypertension who received 10 to 40 mg of enalapril for 3 months.8 In the affected kidney, renal plasma flow (as assessed by 125I-iodipirurate sodium) fell 37%, from 162 to 102 ml/min, whereas renal plasma flow increased from 298 to 437 ml/min in the contralateral kidney. Overall effective renal plasma flow increased, but overall creatinine clearance decreased (from 105 to 88 ml/min).

Although we did not measure split renal function, we believe it is premature to conclude that the use of converting enzyme inhibitors invariably worsens affected kidney function in renovascular hypertensive patients. Inulin clearance is a sensitive marker of glomerular filtration rate; it is unlikely that an affected, stenotic kidney of relatively normal size and function would undergo major deterioration without manifesting an abrupt worsening of inulin clearance. Indeed, the split renal function studies performed by Wenting et al.22 found no deterioration in 99mTc-DTPA uptake in the affected kidney of the other seven patients studied with unilateral renovascular hypertension. Clearly, further prospective studies are required to define the subgroup of renovascular hypertensive patients at risk from converting enzyme inhibition therapy.

Renovascular hypertension is clearly an asymmetrical disease that has a heterogeneous effect on the extent of renovascular involvement (variation in extent of stenosis and number of renal arteries involved), as well as on the extent of renal ischemia ( unilateral versus bilateral elevation of renal vein renins). Only when there is a preexisting severe compromise in renal function, in which the primary functional dependence resides with the stenotic kidney, is the patient's overall renal function at risk from angiotensin II converting enzyme inhibition therapy.

Nine patients have now completed at least 6 months of combined enalapril and HCTZ therapy. All have demonstrated excellent blood pressure control and stable renal function. Since renovascular disease is a dynamic, probably progressive disease, these medically managed patients will require frequent follow-up to assess change in renal function. Since blood pressure control may decelerate the rate of atherogenic progression, surgical intervention may not be required for preservation of renal function.

We conclude that combined enalapril and HCTZ therapy is an effective antihypertensive regimen for most patients with renovascular hypertension and that prolonged blood pressure control is not dependent on sustained interruption of the renin–angiotensin–aldosterone system. Renal function deteriorated only in the patient with a functional unilateral stenotic kidney, a predictable complication of this class of antihypertensive agents. If the long-term safety of enalapril is confirmed, it will become an important mode of therapy for the treatment of renovascular hypertension.

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