Preservation of glomerular filtration rate in human heart failure by activation of the renin-angiotensin system

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ABSTRACT When renal perfusion pressure is reduced in experimentally induced low-output states, glomerular filtration rate is preserved by angiotensin II–mediated efferent arteriolar vasoconstriction, but available evidence in man suggests that angiotensin II supports renal function only to the extent that it preserves systemic blood pressure. We performed simultaneous assessments of cardiac and renal function in 56 patients with severe chronic heart failure before and after 1 to 3 months of converting-enzyme inhibition. Among the 29 patients with a pretreatment renal perfusion pressure under 70 mm Hg, patients with preserved renal function (creatinine clearance > 50 ml/min/1.73 m²) had markedly elevated values for plasma renin activity (11.8 ± 3.8 ng/ml/hr) and showed a significant decline in creatinine clearance after converting-enzyme inhibition (61.1 ± 3.0 to 45.9 ± 5.3 ml/min/1.73 m²; p < .05). In contrast, although similar with respect to all pretreatment demographic, hemodynamic, and clinical variables, patients with a creatinine clearance under 50 ml/min/1.73 m² had low values for plasma renin activity (3.4 ± 0.8 ng/ml/hr) and, despite similar drug-induced decreases in systemic blood pressure, showed no change in creatinine clearance after therapy with captopril or enalapril (32.6 ± 2.5 to 41.4 ± 3.8 ml/min/1.73 m²). Changes in creatinine clearance varied linearly and inversely with pretreatment values for plasma renin activity (r = −.64, p < .001); converting-enzyme inhibition effectively abolished the pretreatment difference in renal function seen in the high- and low-renin subgroups. In the 27 patients with a renal perfusion pressure of 70 mm Hg or greater, creatinine clearance did not vary significantly with plasma renin activity and was not altered by therapy. These data indicate that the renin-angiotensin system plays an important role in preserving glomerular filtration rate in patients with congestive heart failure in whom renal perfusion pressure is severely compromised and that this effect is achieved independently of the ability of this hormonal system to support systemic blood pressure.

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As cardiac output falls in patients with congestive heart failure, renal blood flow progressively decreases, but glomerular filtration rate is usually preserved until the terminal stages of the disease. Consequently, most patients with congestive heart failure have normal values for blood urea nitrogen and serum creatinine concentration, despite severe impairment of left ventricular function and substantial declines in renal perfusion pressure. The mechanism by which glomerular function is maintained in these patients, however, remains undefined. When renal perfusion pressure is reduced in experimental low-output states, glomerular filtration rate is preserved by selective efferent arteriolar vasoconstriction, which acts to increase glomerular capillary hydraulic pressure and filtration fraction. This intrarenal microcirculatory response is dependent on the presence of angiotensin II and does not occur when the actions of the hormone are pharmacologically blocked. Accordingly, when renal perfusion pressure is lowered in salt-depleted rats treated with converting-enzyme inhibitors, glomerular filtration can no longer be supported and declines in parallel with the fall in systemic blood pressure. It is not clear, however, whether the intrarenal activation of the renin-angiotensin system is similarly important in preserving glomerular filtration rate in patients with congestive heart failure.

The limited evidence that is available from the clini-
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A clinical laboratory has not been able to support a specific microcirculatory role for angiotensin II in man. When captopril and enalapril are administered to patients with congestive heart failure, creatinine clearance does not decline and may increase significantly, if treatment is accompanied by notable increases in renal blood flow.\textsuperscript{13-16} Compared with other vasodilators, such improved renal perfusion is particularly likely to occur after treatment with the converting-enzyme inhibitors, which cause drug-related increases in cardiac output to be selectively distributed to the kidneys.\textsuperscript{13} Glomerular filtration rate has been reported to deteriorate after treatment with captopril and enalapril only when therapy is accompanied by marked decreases in systemic blood pressure,\textsuperscript{17-19} but converting-enzyme inhibitors may not differ significantly in this regard from other vasodilator drugs that exert notable hypotensive effects in patients with congestive heart failure.\textsuperscript{20, 21}

These clinical observations suggest that angiotensin II preserves renal function only to the extent that the hormone maintains systemic blood pressure, and hence these findings do not support an intrarenal homeostatic role for the renin-angiotensin system in human heart failure.

In this study we provide evidence that the renin-angiotensin system plays an important role in preserving glomerular filtration rate in human heart failure and that this effect is achieved independently of the ability of this hormonal system to support systemic and renal perfusion pressure.

\section*{Methods}

\textbf{Patients.} Fifty-six patients (45 men and 11 women) with severe but clinically stable heart failure of at least 6 months' duration were hospitalized to permit invasural instrumentation and simultaneous measurements of hemodynamic, renal, and hormonal variables. All patients were referred for evaluation because of disabling dyspnea and fatigue despite therapy with digoxin and diuretics. The cause of heart failure was ischemic heart disease in 36 patients and primary dilated cardiomyopathy in 20 patients. All patients had a left ventricular ejection fraction less than 30% by radionuclide ventriculography. Seventeen patients had diabetes mellitus and 16 patients had a past history of systemic hypertension, but none had known intrinsic renal disease or a serum creatinine concentration greater than 2 mg/dl.

\textbf{Determination of cardiac function and glomerular filtration rate.} During the entire period of hospitalized observation, patients were fed a salt-restricted diet and were treated with constant doses of digoxin and diuretics; no other cardiac or vasoactive medications were given. After body weight and renal function were stable for 3 days, right heart catheterization and arterial cannulation were performed for measurement of intracardiac and systemic pressures, respectively, using procedures described in detail previously.\textsuperscript{22} For the next 24 hr, patients maintained bed rest without any change in therapy to permit hemodynamic stabilization, during which time urine was collected for determination of endogenous creatinine clearance, which was used as an index of glomerular filtration rate.\textsuperscript{5, 13} Immediately before completion of the 24 hr urine collection, blood samples were obtained for measurement of plasma renin activity (by radioimmunoassay), and the following hemodynamic variables were determined in triplicate (with a variation <10%): mean arterial pressure, heart rate, left ventricular filling pressure, mean right atrial pressure, and cardiac output. Left ventricular filling pressure was estimated by the mean pulmonary capillary wedge pressure or as the pulmonary arterial diastolic pressure after its identity with wedge pressure was established. Cardiac output was determined by the thermodilution method with iced injectate.

\textbf{Treatment with converting-enzyme inhibitors.} After completion of these hemodynamic, renal and hormonal measurements, all patients received long-term treatment with one of two converting-enzyme inhibitors, captopril (150 to 300 mg orally daily in 38 patients) or enalapril (20 to 40 mg orally daily in 18 patients). Therapy was continued for the next 1 to 3 months, during which time doses of digoxin, diuretics and the converting-enzyme inhibitors remained unaltered, and the salt-restricted diet was maintained. At the end of the treatment period, patients were rehospitalized and, after a 3 day period of observation during which medications remained constant, underwent repeat right heart catheterization and arterial cannulation, followed by a repeat determination of 24 hr endogenous creatinine clearance. On the next day, after completion of the 24 hr urine collection, hemodynamic variables were measured before and every 30 min for 4 to 6 hr after the regularly scheduled dose of captopril or enalapril. All of the procedures for the second evaluation were performed during uninterrupted converting-enzyme inhibition and were identical in all respects to that followed for the first study.

\textbf{Data analysis.} Mean systemic and pulmonary artery pressures were determined by electronic filtration. Creatinine clearance was corrected for body surface area and expressed as ml/min/1.73 m\textsuperscript{2}. Derived hemodynamic variables were calculated as follows: cardiac index = cardiac output/body surface area (liters/min/m\textsuperscript{2}); renal perfusion pressure = mean arterial pressure - mean right atrial pressure; systemic vascular resistance = 80 x (MAP - MRA P)/cardiac output (dyne-sec/cm\textsuperscript{5}), where MAP = mean arterial pressure and MRA P = mean right atrial pressure (both in mm Hg). The hemodynamic responses to long-term converting-enzyme inhibition were assessed at peak drug effect on left ventricular filling pressure and systemic vascular resistance (1.0 ± 0.5 hr after captopril and 3.0 ± 1.0 hr after enalapril).

Patients were divided into four groups on the basis of values for renal perfusion pressure (PP\textsubscript{ren}) and creatinine clearance (C\textsubscript{Cr}) at the start of the study:

- Group NP/NC = PP\textsubscript{ren} ≥ 70 mm Hg and C\textsubscript{Cr} ≥ 50 ml/min/1.73 m\textsuperscript{2}
- Group NP/LC = PP\textsubscript{ren} ≥ 70 mm Hg and C\textsubscript{Cr} < 50 ml/min/1.73 m\textsuperscript{2}
- Group LP/NC = PP\textsubscript{ren} < 70 mm Hg and C\textsubscript{Cr} ≥ 50 ml/min/1.73 m\textsuperscript{2}
- Group LP/LC = PP\textsubscript{ren} < 70 mm Hg and C\textsubscript{Cr} < 50 ml/min/1.73 m\textsuperscript{2}

Qualitative and quantitative differences among the groups were analyzed by the chi-square statistic and by a one-way analysis of variance, respectively; if the overall F test for the latter was significant, group means were differentiated by t test for independent variables. Changes in hemodynamic and renal functional variables during long-term treatment were compared with pretreatment values by the t test for paired data. Group data are expressed as mean ± SEM.
Results

Before treatment with a converting-enzyme inhibitor, we observed no significant relationship between glomerular filtration and any hemodynamic variable. Creatinine clearance varied independently of cardiac index, mean arterial pressure, renal perfusion pressure or systemic vascular resistance.

Patients with renal perfusion pressures of 70 mm Hg or greater. Among the 27 patients with a renal perfusion pressure of 70 mm Hg or greater, patients with higher values for creatinine clearance (≥50 ml/min/1.73 m²) were similar to those with lower values with respect to age, sex, cause of heart failure, dose of furosemide, and all hemodynamic variables (table 1). Both groups had low values for plasma renin activity (3.2 ± 1.0 ng/ml/hr in group NP/NC and 3.8 ± 0.8 ng/ml/hr in group NP/LC). Patients with a creatinine clearance under 50 ml/min/1.73 m², however, had a higher prevalence of diabetes mellitus than did patients with better renal function (64% vs 15%; p < .05).

After 1 to 3 months of converting-enzyme inhibition, groups NP/NC and NP/LC showed similar increases in cardiac index and decreases in mean arterial pressure, left ventricular filling pressure, mean right atrial pressure, heart rate, and systemic vascular resistance (all p < .05 to .001; table 2). Weight decreased and urinary sodium excretion increased significantly and similarly in both groups (both p < .05). Despite the marked and similar decreases in renal perfusion pressure, neither group showed significant changes in creatinine clearance (64.6 ± 3.7 to 63.1 ± 4.7 ml/min/1.73 m² in group NP/NC and 35.7 ± 1.4 to 34.7 ± 4.6 ml/min/1.73 m² in group NP/LC).

Patients with renal perfusion pressures less than 70 mm Hg. Among the 29 patients with a renal perfusion pressure under 70 mm Hg, patients with a creatinine clearance of 50 ml/min/1.73 m² or greater were similar to those with lower values with respect to age, sex, cause of heart failure, prevalence of diabetes mellitus, dose of furosemide, and all hemodynamic variables (table 3). Patients in whom creatinine clearance was relatively preserved (≥50 ml/min/1.73 m²), however, had higher values for plasma renin activity than did patients with worse renal function (11.8 ± 3.8 vs 3.4 ± 0.8 ng/ml/hr, respectively; p < .05). Values for creatinine clearance in these patients (groups LP/NC and LP/LC) varied linearly and directly with values for plasma renin activity (r = .49, p < .01; figure 1). Such a relationship was not observed in patients with a renal perfusion pressure of 70 mm Hg or higher (groups NP/NC and NP/LC; r = −.31, p > .10).

After 1 to 3 months of converting-enzyme inhibition, groups LP/NC and LP/LC showed similar increases in cardiac index and decreases in mean arterial pressure, left ventricular filling pressure, mean right atrial pressure, heart rate, and systemic vascular resistance (all p < .05 to .001; table 4). Renal perfusion pressure declined to similarly low values in both groups (52.8 ± 2.1 mm Hg in group LP/NC and 50.2 ± 2.7 mm Hg in group LP/LC). In contrast to groups NP/NC and NP/LC, there were no notable changes in body weight or in urinary sodium excretion. In patients who had elevated pretreatment values for plasma renin activity (group LP/NC), creatinine clearance decreased significantly during long-term treatment with captopril and enalapril (61.1 ± 3.0 to 45.9 ± 5.3 ml/min/1.73 m²; p < .05), whereas in the patients with low pretreatment values for plasma renin activity (group LP/LC), creatinine clearance did not change significantly (32.6 ± 2.5 to 41.4 ± 3.8 ml/min/1.73 m²) during the 1 to 3 month treatment period. In contrast to the marked difference in renal function between the two groups at the start of the study, values for creatinine clearance after converting-enzyme inhibition in groups LP/NC and LP/LC did not differ significantly from each other. Changes in creatinine clearance during the course of therapy with captopril and enalapril in patients with a renal perfusion pressure less than 70 mm Hg varied linearly and inversely with pretreatment values for plasma renin activity (r = .64,
TABLE 2
Hemodynamic and biochemical responses to long-term converting-enzyme inhibition in patients with a renal perfusion pressure ≥70 mm Hg (groups NP/NC and NP/LC)

<table>
<thead>
<tr>
<th></th>
<th>CCr≥50 ml/min/1.73 m² (group NP/NC, n = 13)</th>
<th>CCr&lt;50 ml/min/1.73 m² (group NP/LC, n = 14)</th>
<th>p-ΔCEI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-CEI</td>
<td>LT-CEI</td>
<td>Pre-CEI</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>1.67±0.14</td>
<td>1.93±0.12</td>
<td>1.72±0.13</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>94.6±3.9</td>
<td>74.4±3.7</td>
<td>91.4±3.8</td>
</tr>
<tr>
<td>Left ventricular filling pressure (mm Hg)</td>
<td>27.7±1.6</td>
<td>13.3±2.2</td>
<td>27.1±1.2</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>9.9±0.8</td>
<td>4.5±1.2</td>
<td>9.9±1.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82.1±4.5</td>
<td>73.0±3.9</td>
<td>85.3±4.1</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne-sec-cm⁻²)</td>
<td>2519±199</td>
<td>1747±154</td>
<td>2349±194</td>
</tr>
<tr>
<td>Renal perfusion pressure (mm Hg)</td>
<td>84.7±3.8</td>
<td>69.9±3.7</td>
<td>81.5±3.7</td>
</tr>
<tr>
<td>CCr (ml/min/1.73 m²)</td>
<td>64.6±3.7</td>
<td>63.1±4.7</td>
<td>35.7±1.4</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>65.0±2.7</td>
<td>62.8±2.5</td>
<td>64.6±4.4</td>
</tr>
<tr>
<td>Urinary sodium excretion (meq/24 hr)</td>
<td>48.2±10.9</td>
<td>99.3±13.3</td>
<td>52.1±11.7</td>
</tr>
</tbody>
</table>

Pretreatment values for all hemodynamic variables in the two groups were not significantly different.

Urine was not collected for determination of creatinine clearance (CCr) and 24 hr urinary sodium excretion during LT-CEI in one patient in group NP/NC and in two patients in group NP/LC; the data shown for these two variables include only those patients with pretreatment and posttreatment data.

Significance of difference within each group comparing long-term response to converting-enzyme inhibition (LT-CEI) with pretreatment values (Pre-CEI): *p < .001; †p < .01; ‡p < .05. The last column designates significance of difference between the two groups in the magnitude of drug-induced changes (ΔCEI) during the study.

TABLE 3
Pretreatment clinical and biochemical variables in patients with a renal perfusion pressure <70 mm Hg grouped according to pretreatment creatinine clearance

<table>
<thead>
<tr>
<th></th>
<th>CCr≥50 ml/min/1.73 m² (group LP/NC, n = 13)</th>
<th>CCr&lt;50 ml/min/1.73 m² (group LP/LC, n = 16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61.2±3.4</td>
<td>64.4±3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/2</td>
<td>12/4</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology of CHF</td>
<td>ICM 9, IDC 4</td>
<td>ICM 8, IDC 8</td>
<td>NS</td>
</tr>
<tr>
<td>History of systemic hypertension</td>
<td>2/13 (15%)</td>
<td>1/16 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2/13 (15%)</td>
<td>4/16 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>Furosemide dose (mg/day)</td>
<td>95±17</td>
<td>97±12</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>70.7±5.0</td>
<td>63.2±4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>11.8±3.8</td>
<td>3.4±0.8</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>CCr (ml/min/1.73 m²)</td>
<td>61.1±3.0</td>
<td>32.3±2.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Urinary sodium excretion (meq/24 hr)</td>
<td>40.1±10.4</td>
<td>41.1±10.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

p < .001; figure 2). Such a relationship was not observed in patients with a renal perfusion pressure of 70 mm Hg or higher (groups NP/NC and NP/LC; r = .04).

Discussion

In experimentally induced low-output states, renal hypoperfusion leads to the release of renin by the kidney,23, 24 which (by stimulating the synthesis of angiotensin II) serves to preserve renal function by supporting systemic blood pressure.5, 25, 26 Should this neurohormonal response fail to restore renal blood flow and perfusion pressure, however, the activation of the renin-angiotensin system will nevertheless attempt to support glomerular filtration by causing efferent arteriolar vasoconstriction, an intrarenal microcirculatory response that serves to increase glomerular capillary hydraulic pressure and filtration fraction.5, 6 When the effects of angiotensin II are pharmacologically blocked under these experimental conditions,
glomerular filtration rate falls markedly, not only because systemic blood pressure and renal perfusion pressure decline but because efferent arteriolar vasoconstriction cannot occur. These systemic and microcirculatory factors play important interdependent roles in the maintenance of renal function in the dog and the rat. Should renal perfusion pressure be maintained, the fall in filtration fraction after converting-enzyme inhibition will be of little consequence; similarly, marked drug-induced hypotension will result in little renal impairment if the renin-angiotensin system is left intact. Glomerular filtration rate declines in the experimental laboratory only when both renal perfusion pressure is reduced and the intrarenal actions of angiotensin II are abolished.

It is not clear, however, that the physiologic events that occur in experimental low-output states are important in the clinical setting, since little is known about the control of glomerular filtration rate in human heart failure. As cardiac output declines in patients with cardiac failure, the kidney elaborates renin. Such activation of the renin-angiotensin system may be a transient phenomenon during periods of clinical decompensation, but as left ventricular performance deteriorates and the normal homeostatic mechanisms

**TABLE 4**

<table>
<thead>
<tr>
<th>Hemodynamic and biochemical responses to long-term converting-enzyme inhibition in patients with a renal perfusion pressure &lt;70 mm Hg (groups LP/NC and LP/LC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCr&lt;50 ml/min/1.73 m² (group LP/NC, n = 13)</td>
</tr>
<tr>
<td>Pre-CEI</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
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</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne-sec-cm&lt;sup&gt;-5&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Renal perfusion pressure (mm Hg)</td>
</tr>
<tr>
<td>CCr (ml/min/1.73 m²)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
</tr>
<tr>
<td>Urinary sodium excretion (meq/24 hr)</td>
</tr>
</tbody>
</table>

Pretreatment values for all hemodynamic variables in the two groups were not significantly different. Urine was not collected for determination of creatinine clearance (CCr) and 24 hr urinary sodium excretion during LT-CEI in two patients in group LP/LC; the data shown for these two variables include only those patients with pretreatment and posttreatment data sets. Other notes and abbreviations as in table 2.

<sup>1</sup>p < .001; <sup>2</sup>p < .01; <sup>3</sup>p < .05.
FIGURE 2. Relationship between pretreatment plasma renin activity and the change in creatinine clearance during long-term converting-enzyme inhibition in patients with severe chronic heart failure with a renal perfusion pressure less than 70 mm Hg.

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That maintain peripheral perfusion are exhausted, plasma renin activity becomes persistently elevated in proportion to the decline in systemic blood pressure and in parallel to the fall in renal perfusion.30 Despite the decrease in renal blood flow, however, glomerular filtration is relatively preserved in patients with congestive heart failure (because of a marked increase in filtration fraction), but the mechanisms responsible for this compensatory response are unknown. We might expect (by analogy to experimentally induced low-output states) that angiotensin II–efferent arteriolar vasoconstriction plays an important role in this phenomenon, and indeed, filtration fraction declines significantly when patients with heart failure are treated with converting-enzyme inhibitors.13–17 Yet, glomerular filtration rate does not fall and may even increase after therapy with captopril or enalapril, as renal blood flow rises markedly concomitant with a pronounced decrease in renal vascular resistance.13–16 These observations suggest that in patients with congestive heart failure, the renin-angiotensin system (activated in response to renal hypoperfusion) contributes to a further decline in renal blood flow and thereby exerts detrimental effects on renal function in these patients.15, 30 These findings do not indicate that the ability of angiotensin II to preserve glomerular filtration rate by an intrarenal mechanism (established in the experimental laboratory) is clinically important.

Our findings are the first to provide evidence that activation of the renin-angiotensin system acts specifically to support glomerular filtration rate in patients with congestive heart failure. In our study, patients with a normal renal perfusion pressure (≥70 mm Hg) showed low levels of plasma renin activity, despite marked decreases in cardiac output, vigorous diuretic therapy, and restriction of dietary salt; this observation supports the primacy of systemic blood pressure in the stimulation of renin release in heart failure and is consistent with the findings of other investigators.38, 29 When treated with converting-enzyme inhibitors, these patients (groups NP/NC and NP/LC) showed no change in creatinine clearance, regardless of the pretreatment level of renal function and despite further decreases in renal perfusion pressure. In contrast, our patients with low renal perfusion pressures (<70 mm Hg) frequently had markedly elevated levels of plasma renin activity, and these levels were directly and linearly correlated with values for creatinine clearance before the trial as well as the changes in creatinine clearance during the trial. Hypoperfused patients with a high plasma renin activity had a relatively preserved glomerular filtration rate before treatment (group LP/NC) and showed marked deterioration in renal function after converting-enzyme inhibition, whereas patients with a low plasma renin activity had a markedly depressed glomerular filtration rate before treatment (group LP/LC), which did not decline after therapy with captopril or enalapril, despite decreases in renal perfusion pressure similar to those we observed in group LP/NC. By suppressing the synthesis of angiotensin II, converting-enzyme inhibition effectively abolished the pretreatment difference between groups LP/NC and LP/LC with respect to creatinine clearance. These observations strongly support an important role for the renin-angiotensin system in the maintenance of glomerular filtration rate in some patients with severe heart failure in whom renal perfusion is compromised and suggest that this homeostatic function is achieved independently of its systemic vasoconstrictor effects.

Our findings differ from those of previous investigators, who were unable to discern an independent role of angiotensin II in the support of glomerular filtration rate in patients with congestive heart failure. In their short-term trials with captopril, Pierpont, Powers, Mujias, and their co-workers17–19 observed notable declines in glomerular filtration rate and noted (as we did) the most marked deterioration in renal function after converting-enzyme inhibition in patients with the most elevated levels of plasma renin activity before treatment. These high-renin patients, however, were also the most likely to experience severe hypotension.
during the initiation of therapy, and consequently these investigators concluded that the observed decline in renal function was related to the fall in renal perfusion pressure secondary to the loss of angiotensin’s systemic vasoconstrictor effects. This hypothesis was further supported by the work of Dzau, Creager, and their colleagues. When these investigators minimized the hypotensive effects of captopril by the withdrawal of diuretic therapy, they observed no change or even increases in glomerular filtration rate. Unfortunately, interventions that replete total body sodium not only reduce the hypotensive effects of converting-enzyme inhibition but also diminish the dependence of the renal microvasculature (particularly the efferent arterioles) on angiotensin II; converting-enzyme inhibition produces little change in filtration fraction in salt-replete states, even if renal perfusion pressure falls. Because changes in sodium balance would be expected to influence systemic and intrarenal vascular sensitivity to angiotensin II in a similar fashion, previous investigators could not distinguish a role for the hormone independent of its systemic pressor actions.

One method of distinguishing the systemic and intrarenal actions of angiotensin II would be to infuse an antagonist or inhibitor of the hormone directly into the renal artery in doses that do not exert systemic hemodynamic effects. Precisely such an approach has been utilized in the experimental laboratory, but it is difficult to employ for prolonged periods of time in severely ill patients. In the present study we developed a different approach to the problem by examining the hemodynamic and renal functional effects of interference with the renin-angiotensin system during long-term converting-enzyme inhibition. We have previously shown that the linear relationship between plasma renin activity and the drug-induced decline in mean arterial pressure seen after first doses of captopril and enalapril is abolished during long-term therapy with these drugs; that is, there is little relation between pretreatment plasma renin activity and the decline in systemic blood pressure after 1 to 3 months of treatment. This observation permits us to compare the effects of angiotensin suppression on renal function in high- and low-renin subgroups without the need to correct for significant differences in the magnitude of drug-induced hypotension and systemic vasodilation. This long-term approach also has the advantage of being more clinically relevant than short-term intervention studies.

Our findings support the concept that renal perfusion pressure is an important determinant of renal function in patients with congestive heart failure. In patients with a pretreatment renal perfusion pressure greater than 70 mm Hg, converting-enzyme inhibition resulted in an expected, marked natriuretic response, as reflected by an increase in urinary sodium excretion and a decrease in body weight. These responses were similar to those that are observed after experimental angiotensin II blockade and occurred despite marked decreases in systemic blood pressure that might have been expected to limit any natriuretic effect. No natriuresis or change in body weight occurred after converting-enzyme inhibition, however, in patients with a pretreatment renal perfusion pressure less than 70 mm Hg, despite decreases in systemic blood pressure that were quantitatively smaller than those seen in patients with higher renal perfusion pressures; such changes occurred independently of renal function or hormonal status. These observations suggest that absolute posttreatment levels of renal perfusion pressure are more important than changes in this variable in determining the natriuretic response to converting-enzyme inhibition. In contrast to its primacy in determining changes in urinary sodium excretion, however, renal perfusion pressure appeared to be of secondary importance in the determination of glomerular filtration rate. Our patients with low-renin heart failure in group LP/LC did not show notable declines in glomerular filtration rate, despite a fall in renal perfusion pressure to very low levels. This is consistent with experimental observations; in rats treated with an angiotensin II antagonist, marked decreases in renal perfusion pressure did not cause a deterioration in renal function if the synthesis of angiotensin II was suppressed but produced marked decreases in glomerular filtration rate when the renin-angiotensin system was activated by salt-depletion.

We attempted to exclude patients in this study who had intrinsic renal disease, but patients in group NP/LC had very low values for glomerular filtration rate despite high renal perfusion pressures. Although renal blood flow was undoubtedly reduced in these individuals, the degree of renal hypoperfusion was probably similar to that of patients in groups NP/NC and LP/NC (in whom glomerular filtration rate was preserved) because all three groups had similar pretreatment values for cardiac output; thus these individuals lacked an apparent circulatory cause for their depressed renal function. We suspect that these patients had intrinsic renal disease, a hypothesis supported by our finding that this cohort had a very high prevalence of diabetes mellitus and systemic hypertension and required somewhat larger doses of diuretics to maintain stable weights before entry into the study (table 1).
It is difficult to separate the contribution of cardiac and renal factors in the pathogenesis of the azotemia seen in many patients with severe heart failure, particularly since hypertension and diabetes frequently coexist with advanced left ventricular dysfunction. Our observations indicate that, contrary to previous speculation,13 such patients are not predisposed to further functional renal deterioration after converting-enzyme inhibition, as long as the renin-angiotensin system is not activated and renal perfusion pressure is not excessively compromised. These patients, however, should be distinguished from patients in group LP/LC, whose depressed glomerular filtration rate may be related to the marked decreases in renal perfusion pressure but who (inexplicably) do not show an elevation of plasma renin activity. Future studies are needed to measure filtration fraction in this cohort; if it is decreased, to determine why the renin-angiotensin system fails to be appropriately activated; and to evaluate whether interventions that enhance intrarenal angiotensin II biosynthesis may serve to ameliorate azotemia.

Our findings need to be interpreted in the context of important methodologic assumptions. We assumed an identity between systemic blood pressure and renal artery pressure, a valid hypothesis only in the absence of renal artery stenosis, which was excluded clinically (but not angiographically) in our patients. We used creatinine clearance as an index of glomerular filtration rate, but because creatinine is secreted by the tubules, creatinine clearance may overestimate true glomerular filtration rate, especially in patients with poor renal function.49 Were this the case in the present study, however, we would have underestimated (rather than overestimated) the deterioration in renal function seen in our patients in group LP/NC. We did not measure renal blood flow and thus could not calculate glomerular plasma flow or filtration fraction. We recognize that glomerular plasma flow is an important determinant of glomerular filtration rate,41 but since cardiac output and systemic vascular resistance decreased similarly in our four subgroups, it appears likely that the four cohorts also experienced similar changes in renal plasma flow. Even if this was not the case, renal blood flow and renal function become dissociated by interventions that suppress angiotensin II biosynthesis40, 42 so that the renal distribution of cardiac output is no longer a determinant of changes in creatinine clearance during treatment with captopril or enalapril. Finally, we did not measure filtration fraction, and thus we cannot confirm that filtration fraction declined in our patients in group LP/NC; such data would help localize the role for angiotensin II that we defined in the present study to the level of the efferent arteriole. Such a site of action, however, appears to provide the only possible explanation for our findings. The only other major known renal microvascular site of action of angiotensin II is the glomerular mesangial cell,43 which mediates changes in the ultrafiltration coefficient,44, 45 an important determinant of glomerular function.41 Converting-enzyme inhibition, however, increases the ultrafiltration coefficient,6 which would serve to counterbalance (rather than explain) the deterioration in renal function that we observed in our patients in group LP/NC.

In conclusion, our findings suggest that the renin-angiotensin system plays an important role in the preservation of glomerular filtration in patients with congestive heart failure in whom renal perfusion pressure is severely compromised. The elaboration of renin by the kidney in these patients appears to be a beneficial compensatory mechanism that serves to preserve renal function by actions that are independent of the hormone’s ability to support systemic blood pressure. Our data cannot clearly define the precise site of this beneficial effect, but previous experimental work suggests that it is likely exerted at the level of the efferent arteriole, which constricts under the influence of angiotensin II and thereby serves to increase glomerular capillary hydraulic pressure. In such patients, converting-enzyme inhibition is accompanied by a marked deterioration in renal function. Such drug-induced azotemia, however, is generally well tolerated and does not constitute a reason to discontinue effective treatment in the patient with severe chronic heart failure who has improved symptomatically. Furthermore, the magnitude of azotemia can usually be ameliorated by reducing the dose of concomitantly administered diuretics. Such an intervention, by deactivating the renin-angiotensin system, greatly decreases the role of angiotensin II in the preservation of glomerular filtration rate and thereby reduces the degree to which renal function can be expected to decline after converting-enzyme inhibition. Finally, this compensatory intrarenal mechanism is likely to be clinically important only in patients with heart failure in whom renal perfusion pressure is very low and is further reduced by drug treatment. Should therapy be accompanied by minimal hypotensive effects, the significance of this efferent arteriolar mechanism probably diminishes dramatically. Under such circumstances, the ability of converting-enzyme inhibition to increase the ultrafiltration coefficient may lead to an improvement in glomerular filtration rate despite a marked fall in filtration fraction.5, 15-17
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