Acute Regional Circulatory and Renal Hemodynamic Effects of Converting-enzyme Inhibition in Patients with Congestive Heart Failure

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SUMMARY The acute effects of the angiotensin converting-enzyme inhibitor captopril on regional blood flow, renal hemodynamics and sodium excretion were studied in 12 patients with severe congestive heart failure. Converting-enzyme inhibition decreased systemic vascular resistance by 27% and increased cardiac index by 16%. Estimated hepatic blood flow decreased 17%, but renal blood flow increased 60%. The ratio of renal–systemic blood flow increased from 0.10 ± 0.01 to 0.14 ± 0.02 (p = 0.031). Although renal plasma flow increased from 202.8 ± 28.8 to 323.7 ± 42.7 ml/min (p = 0.008), the glomerular filtration rate did not change significantly from the mean pretreatment value of 82.1 ± 12.3 ml/min. The filtration fraction decreased from 41.3 ± 3.8% to 33.4 ± 4.5% (p = 0.050), while urinary sodium excretion doubled, from 34.5 ± 9.6 to 68.2 ± 19.6 μEq/min. The plasma renin activity increased from 12.6 ± 5.0 to 29.9 ± 8.4 ng/ml/hr (p = 0.030) as plasma aldosterone concentration decreased from 30.5 ± 6.5 to 11.3 ± 1.2 ng/dl (p = 0.010) and norepinephrine concentrations decreased from 774 ± 105 to 618 ± 85 pg/ml (p = 0.020). We conclude that converting-enzyme inhibition reverses renal vasoconstriction in congestive heart failure and redistributes regional blood flow. The natriuresis may be mediated by one or more of the following: improved renal plasma flow, reduction in filtration fraction, suppression of hyperaldosteronism, and lowering of circulatory catecholamine concentrations.

ANGIOTENSIN converting-enzyme inhibitors lower systemic vascular resistance and enhance myocardial function in patients with congestive heart failure,1-3 focusing attention upon the renin-angiotensin system as a cause of excessive vascular impedance. The peripheral vasoconstriction that develops in patients with this disorder occurs unequally in the various regional circulatory beds; renal vasoconstriction is particularly severe.4 The greater impairment of renal blood flow (RBF) than of glomerular filtration rate (GFR) may be a prime stimulus to the retention of sodium and water in heart failure.5,6 Because angiotensin II promotes renal vasoconstriction and sodium retention,7,8 we sought to determine whether converting-enzyme blockade in patients with advanced congestive heart failure might result in renal vasodilatation and natriuresis. Accordingly, we examined the renal plasma flow (RPF), creatinine clearance, urinary sodium excretion (U Na+,V) and plasma aldosterone concentrations of patients as they began therapy with the orally administered converting-enzyme inhibitor captopril. In addition, to extend earlier observations9,10 and establish whether redistribution of blood flow actually occurs after treatment, we measured the plasma clearance of indocyanine green (C10G) as an index of splanchnic perfusion.

The findings reported here suggest that the renin-angiotensin system impairs RBF and diminishes sodium excretion in patients with chronic heart failure, and indicate that therapy with converting-enzyme inhibitors causes redistribution of regional blood flow.

Methods

Twelve patients with symptoms and signs of severe congestive heart failure (New York Heart Association functional class III–IV) were studied. Clinical features of these patients are presented in table 1. All were normotensive. The duration of heart failure ranged from 6 months to 12 years (mean 3.9 years). Patients with recent myocardial infarction or predominant valvular pathology were excluded. The protocol of experiment had the approval of the Institutional Review Board for Human Research, and each patient gave informed consent.

Subjects were hospitalized and maintained on an 86 mEq/day sodium diet for at least 3 days before study. During this period and before diuretic drugs were stopped, urine was collected over 24 hours for determination of daily sodium excretion. Digitalis, diuretics and all medications other than clinically necessary antiarrhythmic agents were withheld for at least 1 day before the hemodynamic studies. Within 1 week of admission, patients underwent right-heart catheterization with Swan-Ganz catheters (Instrumentation Laboratories). A radial arterial cannula and urinary bladder catheter were placed in each patient. Pressures were measured using Bentley model 508 strain-gauge transducers and recorded on a direct-writing Hewlett-Packard multigraph. Mean pressures
were obtained by electronic integration with zero reference at the level of the midaxillary line; heart rate was determined from the simultaneous ECG signal. Cardiac output was quantified by thermodilution, using a cardiac-output computer (Instrumentation Laboratories, model 601) and averaging at least three replicate determinations that varied less than 10%.

Effective RPF was determined in nine patients by the clearance of p-aminohippurate (CPAH). A priming injection of 0.04 mg/kg was followed by a constant infusion of 2 mg/min through a forearm venous cannula. Forty-five minutes of equilibration were allowed before clearance measurements were started. The clearance of endogenous creatinine (Ccr) was used as an index of GFR. Hepatomesenteric blood flow was estimated in 11 patients by measuring CSG according to methods described by Wiegand et al. After a single bolus injection of indocyanine green, 0.5 mg/kg, via the pulmonary arterial catheter, blood was sampled from the right atrial port at 5-minute intervals for 25 minutes.

Patients were studied in the recumbent, postabsorptive state without premedication. Systemic hemodynamic data were collected until three successive determinations 15 minutes apart demonstrated homeostasis. Three consecutive 20-minute collections of urine and four plasma samples were used to determine CPAH, Ccr and UNaV. Captopril (SQ14225, Squibb Institute of Medical Research), 100 mg, was then given as a single oral dose and hemodynamic data were recorded 60, 90 and 120 minutes thereafter. Renal dynamics and CICG were measured 1–2 hours after captopril. Peripheral venous blood was sampled before and 2 hours after drug administration to determine plasma renin activity and plasma concentrations of norepinephrine and aldosterone.

Hemodynamic indexes were derived from pressure and output values according to standard formulas. Systemic hemodynamic measurements obtained during the control period and 1–2 hours after captopril administration were averaged to provide comparisons with the renal dynamics and CICG results. RBF was derived as RPF/(1 – hematocrit). Renal vascular resistance was calculated as ((AP – RA) × 80)/RBF, where AP = mean arterial pressure and RA = mean right atrial pressure. The filtration fraction (FF) was calculated as the ratio (GFR/RPF) × 100.

ICG and PAH concentrations were measured by spectrophotometric methods, creatinine concentration by an autoanalyzer method, and sodium by flame photometry. Plasma renin activity was assayed in peripheral venous blood by radioimmunoassay of angiotensin I generation. Plasma aldosterone concentration was quantified by direct radioimmunoassay, and norepinephrine concentration by a modified radioenzymatic assay.

Data before and after captopril were compared and evaluated by the paired t test and the Wilcoxon-Mann-Whitney rank-sum statistic for gaussian and non-gaussian distributions, respectively, and expressed as the mean ± SEM. The Pearson product-moment correlation coefficient was computed for effects on selected variables. Statistical significance was accepted at the 95% confidence level (p < 0.05).

Results

Central Hemodynamic Measurements

Acute hemodynamic benefit was evident in these patients (table 2). Mean blood pressure decreased with treatment from 80.5 ± 3.3 to 69.7 ± 3.6 mm Hg (p = 0.003), and the heart rate slowed from 81 ± 3 to 76 ± 3 beats/min (p = 0.030). The systemic vascular resistance decreased from 1701 ± 136 to 1240 ± 81 dyn-sec-cm⁻⁴ (p = 0.004). The cardiac index improved from 1.9 ± 0.1 to 2.2 ± 0.1 L/min/m² (p = 0.011). Both left- and right-heart filling pressures were reduced after captopril; the mean pulmonary capillary wedge pressure decreased from 27.0 ± 2.4 to 18.7 ± 2.2 mm Hg (p = 0.001) and the mean right
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**Mean ± SEM**

- **Before**: 80.5 ± 3.3, 1.9 ± 0.1, 1701 ± 136, 344 ± 48, 20.2 ± 3.5, 82 ± 12, 41 ± 4, 34.5 ± 9.6, 1.8 ± 0.4, 14.5 ± 4.6, 30.5 ± 6.5, 774 ± 106
- **After**: 69.7 ± 3.6, 2.2 ± 0.1, 1240 ± 81, 553 ± 82, 14.4 ± 5.8, 97 ± 16, 33 ± 5, 68.2 ± 19.6, 1.5 ± 0.3, 31.0 ± 7.5, 11.3 ± 1.2, 618 ± 85

**p** = 0.003, 0.011, 0.004, 0.020, 0.010, 0.240, 0.050, 0.050, 0.051, 0.030, 0.010, 0.020

Abbreviations: BP = blood pressure; CI = cardiac index; SVR = systemic vascular resistance; RBF = renal blood flow; RVR = renal vascular resistance; GFR = glomerular filtration rate; FF = filtration fraction; UNaV = sodium excretion; CICG = indocyanine green clearance; PRA = plasma renin activity; Ald = plasma aldosterone concentration; Nor = plasma norepinephrine concentration.
atrial pressure decreased from 9.3 ± 1.6 to 7.1 ± 1.1 mm Hg (p = 0.050). Although the mean pulmonary arterial pressure was lowered from 38.5 ± 2.6 to 31.8 ± 2.9 mm Hg (p = 0.003) 1–2 hours after drug ingestion and the total pulmonary resistance decreased from 930 ± 101 to 625 ± 37 dyn-sec-cm⁻⁶ (p = 0.003), the pulmonary arteriolar resistance was unchanged from the initially elevated value of 265 ± 18 dyn-sec-cm⁻⁶.

Splanchnic Blood Flow

As arterial blood pressure declined, CICG was reduced slightly, from 1.8 ± 0.4 to 1.5 ± 0.3 ml/kg/min (p = 0.051), despite the improvement in cardiac output and the decrease in systemic vascular resistance (table 2). This estimate of hepatomesenteric blood flow suggests that no splanchnic vasodilatation developed.

Renal Hemodynamic Measurements

RBF averaged 344 ± 48 ml/min before treatment. During the 1–2 hours after captopril ingestion, RBF increased 60%, to 553 ± 82 ml/min (p = 0.020) (fig. 1). The increment in cardiac output (CO) during this period was 460 ml/min, 45% of which (208 ml/min) was evidently delivered to the kidneys. The ratio of renal-to-systemic blood flow (RBF/CO) increased from 0.10 ± 0.01 to 0.14 ± 0.02 (p = 0.031) after drug administration. The calculated renal vascular resistance was reduced 29% during therapy, from 20.2 ± 3.5 to 14.4 ± 5.8 × 10⁸ dyn-sec-cm⁻⁶ (p = 0.010). In patient 10, the only patient who had an initial plasma creatinine concentration greater than 1.5 mg/dl, RBF decreased after captopril. The acute effects of captopril therapy on renal hemodynamics and function are shown in figure 2. RPF increased from 202.8 ± 28.8 to 323.7 ± 42.7 ml/min (p = 0.008). GFR averaged 82.1 ± 12.3 ml/min before captopril and 97.2 ± 15.5 ml/min 1–2 hours after therapy (p = 0.244). The pretreatment GFR did not predict the response to converting-enzyme inhibition (r = 0.19, NS); indeed, among the three patients in whom GFR was reduced after therapy, one (no. 10) had the lowest initial creatinine clearance (34.5 ml/min) and another (no. 4) had the highest creatinine clearance (152.5 ml/min). Although no consistent change in GFR was discerned, a relationship was identified between the percentage increases in RBF and in GFR for the individual patients (r = 0.86, p = 0.003). The decrease in blood pressure did not correlate with variations in GFR. FF decreased from 41.3 ± 3.8% to 33.4 ± 4.5% (p = 0.050).

Sodium Excretion (table 2, fig. 2)

All patients were initially in sodium-retentive states as judged by their lesser excretion of sodium (46.8 ± 11.8 mEq/day) than intake (86 mEq/day). The rate of urine flow did not change significantly, from the initial value (1.2 ± 0.2 to 1.4 ± 0.1 ml/min), but UNaV doubled, from a mean control figure of

![Figure 1](http://circ.ahajournals.org/)

**Figure 1. Renal blood flow in each subject before and after therapy with captopril (mean ± SEM).**

34.5 ± 9.6 to 68.2 ± 19.6 μEq/min 1–2 hours after therapy (p = 0.050). There was no significant correlation between this increase in UNaV and changes in RBF, GFR or FF.

**Plasma Renin Activity and Aldosterone and Norepinephrine Concentrations (table 2)**

The plasma renin activity of these patients before treatment ranged from 1.3–35.0 ng/ml/hour, and increased from a mean value of 14.5 ± 4.6 to 31.0 ± 7.5 ng/ml/hr (p = 0.030) after captopril. This response is compatible with the negative-feedback control of renal renin release and implies effective enzyme inhibition. The pretreatment venous plasma renin activity correlated with the improvement in systemic vascular resistance (r = −0.64, p = 0.033), cardiac index

![Figure 2](http://circ.ahajournals.org/)

**Figure 2. Renal hemodynamic response to captopril. The renal plasma flow (RPF), glomerular filtration rate (GFR), filtration fraction (FF) and urinary sodium excretion (UNaV) are given as the mean ± SEM.**
(r = 0.69, p = 0.019) and renal FF (r = -0.72, p = 0.044). The plasma aldosterone concentration was reduced from the elevated average initial value of 30.5 ± 6.5 to 11.3 ± 1.2 ng/dl after captopril (p = 0.010), indicating acute suppression of hyper-aldosteronism. The plasma norepinephrine concentration decreased from 774 ± 105 to 618 ± 85 pg/ml during this period (p = 0.020).

Discussion

The acute hemodynamic changes after angiotensin converting-enzyme inhibition in these patients with low-output congestive heart failure are consistent with the results of earlier studies.9,10 The lowering of a markedly elevated pulmonary capillary wedge pressure and elevation of depressed cardiac index are accompanied by reduction of systemic vascular resistance in a fashion very similar to the effects of other vasodilator drugs.15,18 We have shown that the magnitude of the acute hemodynamic actions is a function of the basal plasma renin activity.9,10 Such observations contribute to the bulk of evidence that the renin-angiotensin system plays an important role in maintaining the intense peripheral vasoconstriction often seen in patients with severe heart failure. While it is intriguing to speculate that interference with the generation of the naturally occurring vasoconstrictor substance angiotensin II might be responsible for the effects of converting-enzyme inhibitors, these agents also block degradation of the intrinsic vasodilator bradykinin.19-21 Because the activity of the kallikrein-kinin system was not measured, we cannot exclude accumulation of bradykinin as a cause of vasodilatation.

Previous investigations using both teprotide8 and captopril19 have identified modest limb venodilatation and essentially no arteriolar dilatation in either the limb or pulmonary circuits, despite a major reduction of total systemic vascular resistance. These findings indicate that selective vasodilatation must develop in other regional vascular beds. Other studies in normotensive, sodium-depleted dogs not in heart failure have shown that redistribution of regional blood flow develops after angiotensin inhibition; renal perfusion is enhanced at the expense of cutaneous, skeletal muscular and hepatomesenteric flow.22 To investigate further the regional vasodilatory actions of converting-enzyme inhibition in heart failure, we measured indexes of hepatomesenteric and renal perfusion. C\textsubscript{ICO} was lower in our patients than in normal subjects18 and failed to increase after converting-enzyme inhibition. We did not measure the hepatic extraction ratios of this indicator; therefore, its clearance is a limited measure of splanchnic perfusion. Wiegand et al.12 however, found C\textsubscript{ICO} to be a useful indirect method that, in this setting, should reliably estimate directional changes in hepatic blood flow. Hepatomesenteric vascular resistance cannot be calculated from C\textsubscript{ICO} without knowledge of the simultaneous hepatic venous capillary wedge pressure. It seems most unlikely, though, that splanchnic vasodilatation contributes to the decline in total systemic vascular resistance after captopril. Mechanisms other than overactivity of the renin-angiotensin system must limit hepatic perfusion in patients with congestive heart failure. The effect of chronic therapy with captopril on hepatic metabolic function could change requirements of other drugs.

RBF was severely reduced in our patients and increased toward normal after therapy with captopril. Increments in RBF also occur in both sodium-depleted and low-cardiac-output dogs after intrarenal arterial infusion of a specific antagonist of angiotensin II, saralasin.23-25 Similar results have been reported in these animal models after converting-enzyme inhibition.26 Because angiotensin II is a potent renal vasoconstrictor, even in subpressor doses, we assume that the increase in RBF in our study resulted from angiotensin inhibition; however, a role for kinins cannot be excluded.18

Renal perfusion accounted for only 10% of the cardiac output in our patients, roughly half the normal proportion.8 After therapy with captopril, the fraction of the cardiac output measured as RBF increased significantly, to 14%. Because this implies that nearly half of the increment in output was distributed to the kidneys, preferential renal vasodilatation must have developed, which suggests not only that the renin-angiotensin system plays a dominant part in renal vasoconstriction in congestive heart failure, but also that redistribution of regional blood flow occurs after converting-enzyme inhibition. Dzau et al.27 recently reported that captopril increased RBF in azotemic patients with congestive heart failure after 1 week of therapy, but concurrent systemic hemodynamic measurements were not described. Previous studies with the inotropic agents isoproterenol,28 dopamine29 and amrinone30 in patients with heart failure have shown increases in RBF; in contrast to the findings with captopril, the ratio of RBF to cardiac output was not increased with these cardiotoxic drugs. Cogan et al.31 reported experience with the vasodilator drugs nitroprusside and hydralazine. With both drugs, hemodynamic improvement was accompanied by increased RBF, but there was no significant redistribution of blood flow to the renal vascular beds. This regional selectivity of the arteriolar vasodilatation after converting-enzyme inhibition distinguishes these agents from conventional vasodilator drugs.

The 60% increase in RBF was not accompanied by a significant rise in GFR, although there was a trend in this direction. Several factors in addition to RBF influence GFR, including the hydrostatic pressure gradient across the glomerular capillary membrane (\(\Delta P\)), the counteracting colloid oncotic pressure (\(\Delta \pi\)), and the glomerular capillary ultrafiltration coefficient (\(K_f\)).32 In our patients, \(\Delta P\) may have decreased either because of reduced systemic arterial pressure or as a result of disproportionate lowering of resistance in postglomerular efferent arterioles. Previous work suggests that angiotensin II constricts predominantly the efferent arterioles and that angiotensin inhibition in high-renin states increases RBF without ap-
precisely increasing GFR.\footnote{Because GFR did not decrease, any decline in $\Delta P$ was partially counterbalanced by changes favoring an increase in GFR. Angiotensin infusion reduces $K_7$ in rats;\footnote{Angiotsin infusion decreases $K_7$ in rats.} therefore, converting-enzyme inhibition might be expected to increase $K_7$. On the other hand, intrarenal bradykinin infusion decreases $K_7$. Thus, the overall effect of captopril on $K_7$ is difficult to predict. GFR is also dependent upon RPF, and proportional changes in GFR correlated with the percentage increase in RPF during captopril therapy. The lack of a significant increase in GFR suggests that potential positive influences of RPF and $K_7$ may have been offset by negative changes in $\Delta P$. Our findings differ from those of Dzau and colleagues,\footnote{Our findings differ from those of Dzau and colleagues.} who reported an increase in GFR. In their patients, the severely depressed GFR increased concomitantly with a substantial increment in RPF after captopril therapy. This difference in results may reflect the greater pretreatment impairment of renal function in azotemic subjects.}

The absolute sodium excretion doubled after therapy with captopril. The factors regulating renal sodium excretion are too complex to allow ready explanation of the mechanism of this natriuresis. Sodium reabsorption in the proximal tubule varies with the peritubular oncotic pressure.\footnote{Sodium reabsorption in the proximal tubule varies with the peritubular oncotic pressure.} In both experimental and human heart failure, renal sodium avidity is associated with a high FF and a presumed increase in peritubular oncotic pressure.\footnote{In both experimental and human heart failure, renal sodium avidity is associated with a high FF and a presumed increase in peritubular oncotic pressure.} Consequently, the decrease in FF observed here may have led to a decrease in this pressure, which would reduce proximal sodium reabsorption and favor natriuresis. Similar findings have been reported in a low-output animal model after converting-enzyme inhibition.\footnote{Similar findings have been reported in a low-output animal model after converting-enzyme inhibition.} Other studies of vasodilators in heart failure,\footnote{Other studies of vasodilators in heart failure.} however, have not shown increased sodium excretion despite a reduction in FF, which suggests that a decrease in arterial pressure adversely affected natriuresis. It is noteworthy, therefore, that sodium excretion doubled in patients given captopril, notwithstanding reduction in blood pressure below that reported by other investigators. Angiotensin has also been reported to cause sodium retention by directly influencing tubular sodium transport mechanisms.\footnote{Angiotensin has also been reported to cause sodium retention by directly influencing tubular sodium transport mechanisms.} Inhibition of these actions of angiotensin may contribute to sodium excretion. An increase in GFR and, hence, in filtered sodium, is a known cause of natriuresis. The three patients in whom GFR decreased, however, still had greater $U_{Na}V$; therefore, it seems unlikely that changes in GFR enhanced sodium excretion.

Alternatively, the decrease in aldosterone may contribute to the natriuresis. The attenuation of aldosterone excess in these patients is consistent with earlier findings\footnote{The attenuation of aldosterone excess is consistent with earlier findings.} and represents an expected consequence of removing the stimulus of circulating angiotensin II on adrenal mineralocorticoid release. Improvement in RBF may also have enhanced excretion of aldosterone. It seems unlikely that decreased aldosterone concentrations resulted from increased hepatic metabolism,\footnote{It seems unlikely that decreased aldosterone concentrations resulted from increased hepatic metabolism.} because the $C_{ICG}$ data suggest that hepatic function did not improve acutely. As aldosterone exerts its influence on distal renal tubular sodium retention over much longer periods than studied here,\footnote{As aldosterone exerts its influence on distal renal tubular sodium retention over much longer periods than studied here.} the suppression of hyperaldosteronism may play a more important role during sustained captopril therapy than in this short-term trial. The dosages of diuretics and potassium supplements could be reduced, as this has occurred in some of our patients on chronic therapy.\footnote{The dosages of diuretics and potassium supplements could be reduced, as this has occurred in some of our patients on chronic therapy.} The observed reduction of norepinephrine concentrations indicates direct inhibition of catecholamine generation or interruption of reflex arcs because of improved cardiac function. Decreased adrenergic activity might be germane to the release of renal vasoconstriction or to natriuresis. The relative importance of these mechanisms to natriuresis remains to be determined.

We acknowledge that a placebo-treated control group was not included in the experimental design. It is difficult for patients with severe heart failure to undergo these studies twice (i.e., once with placebo and once with drug). Because the study involved a short, well-defined time interval and we demanded a stable control period, we think that the responses were the result of acute drug intervention.

We feel that the foregoing data substantiate earlier assertions that myocardial performance may significantly improve in patients with chronic heart failure given the converting-enzyme inhibitor captopril. This salutary result appears to develop as a consequence of selective peripheral vasodilatation in which blood flow to the kidneys is increased preferentially over that to the splanchnic circulation and limbs. The greater improvement in RPF than in GFR is reflected in a lower renal FF and substantial natriuresis ensues. These acute systemic and renal hemodynamic effects represent partial corrections of the abnormalities occurring in congestive heart failure. Continuation of these responses during sustained oral therapy might be augmented by suppression of mineralocorticoid excess and might prove useful in the long-term management of patients with this illness.

References

Acute regional circulatory and renal hemodynamic effects of converting-enzyme inhibition in patients with congestive heart failure.


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