Acute and Long-term Response to an Oral Converting-enzyme Inhibitor, Captopril, in Congestive Heart Failure

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SUMMARY Captopril (SQ 14,225), an oral angiotensin converting-enzyme inhibitor, was administered to 11 patients with severe congestive heart failure (CHF). Peak effect was observed at 1.5 hours after administration. At peak effect right atrial pressure fell from 3.4 to 0.0 mm Hg, pulmonary capillary wedge pressure (PCW) fell from 22.7 to 12.3 mm Hg, mean arterial pressure (MAP) fell from 79.5 to 62.1 mm Hg, systemic vascular resistance (SVR) fell from 1989 to 1370 dyn·sec·cm⁻⁵, pulmonary vascular resistance fell from 843 to 523 dyn·sec·cm⁻⁵, and cardiac index (CI) rose from 1.96 to 2.43 l/min/m². These were all statistically significant. Control plasma renin activity (PRA) was elevated (25.9 ng/ml/hr) and correlated with resting PCW (r = 0.65). The acute hemodynamic response was related to PRA: a fall in MAP (r = 0.74), a fall in PCW (r = 0.80), a fall in SVR (r = 0.45) and a rise in CI (r = 0.45). Eight patients were placed on chronic captopril therapy. After 2 or more months, their exercise time was significantly increased, from 6.8 to 11.7 minutes. Their cardiothoracic ratios showed a significant decrease, from 0.55 to 0.52, and most patients reported symptomatic improvement. Chronic response was not predicted by acute hemodynamic response. Captopril is therefore a vasodilator with both arterial and venous effects that are at least partially caused by inhibition of the renin-angiotensin system. It may be useful for the treatment of CHF.

SEVERE congestive heart failure (CHF) activates neural and humoral mechanisms. These increase systemic vascular resistance (SVR) to maintain arterial pressure in the face of a low cardiac output (CO). Increased activity of the renin-angiotensin system has been suspected because of the demonstration of increased plasma renin activity (PRA) in some instances of experimental and clinical heart failure. Consequent formation of angiotensin II could contribute to vasoconstriction and to stimulation of aldosterone secretion.

Because vasoconstriction may further depress left ventricular performance in CHF, vasodilator therapy has been used acutely to interrupt this cycle and chronically in an effort to improve outpatient management of CHF. The encouraging preliminary results with the use of nonspecific vasodilators such as nitrates, hydralazine and prazosin has led to interest in using agents that inhibit the conversion of angiotensin I to II (converting-enzyme inhibitors [CEI]). Not only could the drugs be effective therapeutically as vasodilators, but they also might provide insight into the role of the renin-angiotensin system in CHF.

In previous studies teprotide (SQ 20,881), an intravenously effective CEI, was demonstrated to produce acute vasodilatation and an increase in CO in patients with CHF. The acute hemodynamic response correlated with the PRA. The availability of an orally effective CEI has made it possible to assess the response to chronic inhibition of the renin-angiotensin system in CHF. The present report describes our preliminary experience with SQ 14,225 (captopril), administered to 11 patients with moderate-to-severe CHF.

Methods

Eleven patients with chronic congestive heart failure were studied (table 1). Ischemic heart disease was the cause of CHF in nine. Two patients had congestive cardiomyopathy of unknown cause. Coronary bypass surgery had been performed in patients 1, 3, 5 and 10. Patient 3 had undergone mitral valve replacement and patient 2 had undergone aortic valve replacement. At the time of study angina was not a major complaint of any patient and the prosthetic valves were functioning normally. All patients had had symptomatic CHF for at least 6 months. Five patients were in functional class IV (New York Heart Association [NYHA]) and six in class III. All were being treated with digitalis and diuretics. The study protocol was approved by the Committee on the Use of Human Subjects in Research. Informed consent was obtained from the patient before the study.

All patients were hospitalized for 3–5 days in a metabolic unit and placed on an 86-mEq sodium-restricted diet. Digitalis and diuretics were continued. Previous vasodilator therapy was stopped at least 3 days before study. Daily weights and morning blood samples for PRA were drawn on the 2 days before hemodynamic study.

Patients were studied in a fasting state. Digitalis and diuretics were withheld for at least 18 hours before study. A #7 thermodilution Swan-Ganz flow-directed, balloon-tipped catheter (Edwards Laboratory) was percutaneously inserted into an antecubital vein and passed to the pulmonary artery position. The brachial artery was cannulated using an
Amplatz 0.038 arterial catheter (B–D). Pressures were monitored on Bell and Howell 4-3271 transducers positioned at the level of the left atrium. ECG monitoring was continuous throughout the study. Pressure and ECG recordings were made on a Hewlett-Packard multichannel direct-writing recorder. 

Control hemodynamic measurements were performed after a 1-hour rest period with catheters in place. Two sets of measurements were performed 15 minutes apart and varied no more than 10% from each other. Heart rate (HR) and right atrial (RAP), pulmonary arterial (PAP), occluded pulmonary wedge (PCW), and arterial (AP) pressures were recorded. COs by thermodilution were performed in triplicate using an Edwards 9150 thermodilution computer. PRA was measured by radioimmunoassay using RENAK kits (Roche Laboratories). After control values and blood samples had been obtained, captopril, 25 mg, was given orally. Intravascular pressures and CO were monitored every half hour for the first 2 hours and hourly thereafter for 6 hours more or until control values (± 10%) were reached. A second dose of captopril, 100 mg, was given and the same monitoring schedule was observed. Patients whose hemodynamic response to the 100-mg dose returned to control within 8 hours received a third dose of 150 mg orally. A third dose of 50 mg was given to patients who, at the end of the 8-hour observation after the 100 mg dose, still showed an alteration in hemodynamics from baseline.

Mean intravascular pressures were obtained by electronic integration and the following resistances (dyn-sec-cm⁻⁵) were calculated:

\[
\text{Systemic vascular resistance (SVR)} = \frac{\text{MAP} - \text{RAP}}{\text{CO}} \times 80
\]

\[
\text{Pulmonary vascular resistance (PVR)} = \frac{\text{PAP}}{\text{CO}} \times 80
\]

\[
\text{Pulmonary arteriolar resistance (PAR)} = \frac{\text{PAP} - \text{PCW}}{\text{CO}} \times 80
\]

Eight of the 11 patients studied acutely were then given a trial of chronic captopril therapy for 2 months or longer. Before and periodically during the trial period the patients underwent a complete history and physical examination, a radionuclear blood pool scan to measure left ventricular ejection fraction,¹⁸ a standard 6-foot posteroanterior (PA) chest x-ray to measure cardiothoracic (CT) ratio, and a treadmill exercise capacity test.¹⁹ The exercise protocol involved 2-minute periods of continuous exercise at progressively increasing treadmill speed and slope beginning at 1 mph and no slope.

All data were analyzed statistically by two-variable linear regression and paired t analysis.

Results

Resting Hemodynamics

All patients were normotensive, with mean arterial pressure averaging 79.5 mm Hg. PCW was elevated in all patients (mean 22.7 mm Hg) and cardiac index (CI) was reduced for the group, averaging 1.96 l/min/m² (table 2). RAP varied from –3 to 12 mm Hg (mean 3.4 mm Hg). This is lower than anticipated, given the severity of CHF, and probably occurred because the patients were hospitalized on salt restric-
tion and on diuretics. SVR averaged 1989 dyn-sec-cm\(^{-5}\) and PVR averaged 843 dyn-sec-cm\(^{-5}\).

**Acute Response to Captopril**

Peak response to oral captopril was observed at about 1.5 hours after administration. Figure 1 shows the change in SVR with time after administration of captopril. The combined curve represents 27 doses of the drug in 11 patients. Eleven patients received the 25-mg dose, nine the 100-mg dose, six the 150-mg dose and 1 the 50-mg dose (not represented graphically). Although there seems to be a more marked effect with the smallest dose, this is due to the individual patient response, which varied widely (table 2). Patients 2 and 3 had such a marked response to the 25-mg dose that no further doses were given. Patients with lesser responses were given the entire dose range, giving the illusion of decreased efficacy with the higher dose. For each patient the peak effect for the 25-mg dose was not significantly different from the peak effect with 100-mg or 150-mg dose. For the combined experience a significant drop in SVR appeared at 0.5 hours and remained significantly lower than control through hour 6 of observation. Figure 2 shows the change in PCW over time after giving captopril. PCW was significantly lower at 0.5 hours and remained so for as long as 7 hours after captopril.

At peak effect, RAP, PCW, MAP, SVR and PVR were all significantly reduced from control (table 2). CI was significantly increased and HR was slightly reduced, but not significantly so (fig. 3). PAR at peak

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**Table 2. Hemodynamic Effects of Captopril in 11 Patients with Congestive Heart Failure**

<table>
<thead>
<tr>
<th>Pt</th>
<th>State</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>CI (l/min/m(^2))</th>
<th>PWP (mm Hg)</th>
<th>RAP (mm Hg)</th>
<th>SVR (dyn-sec-cm(^{-5}))</th>
<th>PVR (dyn-sec-cm(^{-5}))</th>
<th>PAR (dyn-sec-cm(^{-5}))</th>
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<td>D* (100 mg)</td>
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<td>80</td>
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<td>3</td>
<td>1640</td>
<td>622</td>
<td>367</td>
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<td>83</td>
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<td>1455</td>
<td>747</td>
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<td>72</td>
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<td>334</td>
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<td>75</td>
<td>3.47</td>
<td>8</td>
<td>5</td>
<td>473</td>
<td>277</td>
<td>185</td>
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</table>

Mean ± SEM

- Control: 79.5 ± 3.06, 77.36 ± 3.53, 1.96 ± 0.14, 22.73 ± 1.94, 3.36 ± 1.42, 1989 ± 271, 843 ± 97, 322 ± 36
- D*: 62.09 ± 3.92, 72.82 ± 4.01, 2.34 ± 0.20, 12.27 ± 1.21, 0.00 ± 1.05, 1372 ± 198, 523 ± 74, 276 ± 38

*p* values:

- NS: 0.01
- 0.01
- 0.01
- 0.02
- 0.02
- NS

*Abbreviations: MAP = mean arterial pressure; HR = heart rate; CI = cardiac index; PWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; PAR = pulmonary arteriolar resistance.*
FIGURE 1. Change in systematic vascular resistance (ΔSVR) with time after various doses of captopril in 11 patients with con
gestive failure. Standard error of the mean is shown for combined data. SVR is significantly reduced for 6 hours after ad-
ministration of drug.

FIGURE 2. Change in pulmonary capillary wedge pressure (ΔPCW) after captopril in 11 patients with con-
gestive heart failure. PCW is reduced for 7 hours after administration of drug.

effect tended to fall, but values after captopril were not
significantly different from control.

All the patients tolerated the acute testing without
ill effects. They remained asymptomatic even when a
marked fall in blood pressure occurred (table 2).

Plasma Renin Activity

PRA varied from 0.6–89.7 ng/ml/hr, averaging
25.9 ng/ml/hr (fig. 4). Control PCW correlated with
PRA (r = 0.65, p < 0.05). There was a weak correla-
tion between PRA and control CI (r = 0.41, p >
0.10). No meaningful correlation existed between
PRA and control values for MAP, RAP, HR, SVR
and PVR. The acute hemodynamic response to cap-
topril was related to PRA: a fall in MAP (r = 0.74,
p < 0.01), a fall in PCW (r = 0.80, p < 0.01), a fall
in SVR (r = 0.45, p < 0.10), a fall in PVR (r = 0.50,
p > 0.10) and a rise in CI (r = 0.45, p > 0.10).

Chronic Response to Captopril

Eight patients were placed on chronic captopril
therapy (25, 50, 100 or 150 mg every 8 hours) for at
least 2 months while their previous digitalis and diuretic therapy was reinstituted. By NYHA classification, six of eight patients showed symptomatic improvement (Table 3). Exercise tolerance measured by treadmill exercise testing improved in six patients. Patients 6 and 7 were limited by noncardiac disabilities and patient 10, who did improve, stopped because of angina, which occurred only after his exercise tolerance improved with treatment of his failure. The improved exercise tolerance was statistically significant ($p < 0.02$) for those limited by cardiac symptoms.

CT ratios measured by independent observers on standard 6-foot PA chest x-rays were significantly reduced after 2 months of therapy. The mean control CT ratio was $0.55 \pm 0.02$, compared with a mean CT ratio of $0.52 \pm 0.02$ after 2 months of treatment ($p < 0.05$). However, ejection fraction (EF) as measured by gated blood pool scans did not change significantly after chronic captopril therapy.

Systolic and diastolic arterial pressures by cuff measurements during chronic therapy were slightly but insignificantly lower than pressures measured in the control period. Orthostatic hypotension was not observed. HR also was somewhat lower on treatment, but the difference was not statistically significant.

**Discussion**

Captopril acted hemodynamically as a vasodilator, with both arterial and venous affects. MAP, SVR, PCW and RAP fell and the Frank-Starling curve was shifted upward and to the left. Two recent reports showed a similar acute hemodynamic response to a single dose of captopril in patients with CHF. The hemodynamic response to captopril was similar to that previously reported from this laboratory with intravenous infusion of teprotide (SQ 20,881) and also similar to the response to intravenous infusion of nitroprusside and oral administration of the combination of hydralazine and isosorbide dinitrate. The venous effect of captopril and these other regimens becomes apparent when compared with the response to hydralazine and minoxidil, which also have a selective arterial vasodilator effect. These latter agents do not reduce RAP or produce as great a fall in PCW as was observed after captopril.

Captopril inhibits the conversion of inactive angiotensin I to active angiotensin II. The renin-angiotensin activity, as measured by PRA, varied widely in the group of patients studied. As might be expected, the acute hemodynamic response to captopril was directly and significantly related to the control PRA. This relationship is similar to that of teprotide. The absence of a correlation between control PRA and acute hemodynamic response to captopril noted in a previous report probably can be attributed to the fact that PRA ranged only up to 7.3 ng/ml/hr in that study. Our series included four

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**FIGURE 3.** Changes in pulmonary capillary wedge pressure (PCW) and cardiac index (CI) from control to peak effect (1.5 hours) after captopril in 11 patients with congestive heart failure.

**FIGURE 4.** Relationship between control plasma renin activity (PRA) and mean arterial pressure (MAP) before and at peak effect (1.5 hours) after captopril in 11 patients with congestive heart failure. The greatest drop in MAP was seen in patients with the highest PRA ($r = 0.74$).
patients with PRA above 20 ng/ml/hr who responded most dramatically to the drug.

Despite the strong evidence for the role of renin in determining the response to CEI, other factors must be involved because even patients with low PRA had some acute response to the drug. Captopril has also been shown to be effective in treating low-renin hypertension. Converting enzyme is also active in the degradation of bradykinins, which are powerful vasodilator substances and could have contributed to the vasodilator effect of captopril.

Oral captopril produced a sustained hemodynamic effect consistent with the previously reported pharmacologic half-life of the drug. Indeed, as previously suggested, the duration of effect rather than the peak effect was increased when the dose was increased in any given patient. These results are consistent with the vasodilator effect being dependent on inhibition of angiotensin II formation, which is complete even at low doses of captopril, rather than on a direct action of the drug on vascular tone. Since all patients included in the study were on treatment with digitalis and diuretics the therapy may have played a role in stimulating the renin-angiotensin system and enhancing the response to captopril. The temporal hemodynamic response to captopril was somewhat unusual. An early peak effect, as reflected by a fall in MAP and SVR, appeared to moderate at 2 hours and then the effect again became accentuated (fig. 1). This change did not reach statistical significance, but nonetheless raises the possibility that two or more mechanisms with different time courses contribute to the vasodilator effect of the drug in these patients.

The response to chronic oral therapy with captopril has been gratifying in these preliminary studies. Side effects of the drug have not been observed and most patients have objective and subjective evidence of improvement. Chronic response to captopril was not necessarily dependent on a high PRA or a good acute response to the drug. Patient 3, who responded dramatically in the acute study, did not show a particularly good chronic response, whereas patients 4 and 9, who had low PRA and a small acute response, had an excellent chronic response. These data must be viewed with caution, however, because the chronic therapy was not placebo-controlled or blinded.

If captopril is a clinically effective vasodilator in patients with heart failure, it might have certain advantages over the less specific vasodilators currently used, hydralazine, isosorbide dinitrate and prazosin. By reducing angiotensin II, which is a factor in the heightened SVR, captopril may have a more favorable effect on blood flow distribution than a drug with less selective vascular effects. In addition, inhibition of

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**Table 3. Response to Chronic Captopril Therapy in Eight Patients with Congestive Heart Failure**

<table>
<thead>
<tr>
<th>Pt</th>
<th>State</th>
<th>HR (supine) (beats/min)</th>
<th>BP (supine) (mm Hg)</th>
<th>Exercise time (min)</th>
<th>EF by blood pool scan</th>
<th>CT ratio</th>
<th>NYHA class</th>
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<td>3</td>
<td>Control</td>
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<td>0.75</td>
<td>0.24</td>
<td>0.61</td>
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<td></td>
<td>Month 5</td>
<td>64</td>
<td>83/59</td>
<td>3.22</td>
<td>0.18</td>
<td>0.56*</td>
<td>IV</td>
</tr>
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<td>4</td>
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<td>102/80</td>
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<td>0.52</td>
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<td>0.47*</td>
<td>I</td>
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<td>12.25†</td>
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<td>88</td>
<td>94/66</td>
<td>11.47</td>
<td>0.11</td>
<td>0.56</td>
<td>II</td>
</tr>
<tr>
<td>Total</td>
<td>Control</td>
<td>80 ± 4</td>
<td>108 ± 2/68 ± 3</td>
<td>6.75 ± 1.82</td>
<td>0.24 ± 0.02</td>
<td>0.55 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>74 ± 4</td>
<td>103 ± 5/66 ± 2</td>
<td>11.70 ± 2.61</td>
<td>0.25 ± 0.03</td>
<td>0.52 ± 0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p* NS NS 0.02 NS 0.05

*Month 2.
†Exercise stopped for noncardiac symptoms; not included in analysis.
Abbreviations: HR = heart rate; BP = blood pressure; EF = ejection fraction; CT ratio = cardiothoracic ratio; NYHA = New York Heart Association.
aldosterone formation, and possible inhibition of antidiuretic hormone secretion could contribute to improved renal handling of salt and water. Furthermore, if vasodilator drugs such as hydralazine increase PRA in patients with heart failure, captopril might be useful as adjunctive therapy to counteract the vasoconstrictor effect of this homeostatic mechanism.

In summary, captopril is an effective oral angiotensin converting-enzyme inhibitor that may be therapeutically useful in the treatment of CHF. Further studies are needed to confirm its beneficial effects and to explore possible adverse effects.

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