Immediate and Sustained Hemodynamic and Clinical Improvement in Chronic Heart Failure by an Oral Angiotensin-converting Enzyme Inhibitor

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SUMMARY The hemodynamic effects of an oral angiotensin-converting enzyme inhibitor, captopril, were evaluated in 10 symptomatic patients with chronic congestive heart failure. In all patients there was a significant increase in cardiac output (average 28%), stroke volume (49%), and stroke work index (26%), along with a decrease in pulmonary capillary wedge pressure (48%), indicating improved left ventricular function. Modest decreases in heart rate and arterial pressure were also observed. In seven patients maintained on captopril therapy, repeated hemodynamic studies at 2 months revealed sustained effects. These beneficial hemodynamic effects were accompanied by clinical improvement and improved exercise tolerance during maintenance therapy. These findings suggest that captopril may be a useful therapeutic adjunct for the long-term management of patients with chronic congestive heart failure.

SYSTEMIC VASCULAR RESISTANCE, an integral part of left ventricular outflow resistance, is frequently elevated in patients with heart failure and low cardiac output. That pharmacologic manipulation of left ventricular outflow resistance can profoundly influence cardiac performance has been amply demonstrated.1-3 A reduction of systemic vascular resistance with vasodilator agents causes an improvement in cardiac function in patients with both acute and chronic heart failure.4-12 What causes an elevated systemic vascular resistance in a patient is difficult to determine; several neural, humoral or neurohumoral factors might be involved.13 In the presence of heart failure associated with low cardiac output, the renin-angiotensin system may be stimulated and increased levels of angiotensin might contribute to an increased systemic vascular resistance.14-17

In such circumstances, attenuation or inhibition of the effects of angiotensin would be expected to reduce systemic vascular resistance, thus improving cardiac performance. Indeed, with the use of saralasin, a specific competitive angiotensin antagonist, and of teprotide, an angiotensin-converting enzyme inhibitor, improvement in left ventricular function has been demonstrated in patients with chronic congestive heart failure. However, both saralasin and teprotide must be administered intravenously and therefore are not suitable for the long-term treatment of such patients. Captopril, which also inhibits the conversion of angiotensin I to angiotensin II, can be administered orally and therefore is more suitable for the long-term management of patients with chronic congestive heart failure. Preliminary studies suggest that this oral angiotensin-converting enzyme inhibitor produces beneficial hemodynamic responses in these patients.21-23 In this study we evaluated the immediate hemodynamic response to captopril and assessed whether the hemodynamic and clinical responses are sustained during maintenance therapy.

Materials and Methods

Patient Population

Ten patients with chronic congestive heart failure, nine males and one female, were studied. Their mean age was 54 years (range 36–73 years). All patients had been symptomatic for at least 1 year; seven patients were in class III and three in class IV (New York Heart Association [NYHA]) at the time of study. Seven patients had the diagnosis of ischemic heart disease based on either a history of documented myocardial infarction or the presence of severe three-vessel coronary artery disease determined by coronary arteriography. In two patients, the etiology of heart failure was unknown. In the remaining patient, who was the only patient who was hypertensive at the time of the study, hypertensive heart disease was the probable case of heart failure.

Study Protocol

In all patients, maintenance doses of digitalis and diuretics were continued during the study. However, on each of the 2 days of hemodynamic evaluation, diuretics were administered only in the evening, after completion of the daily protocol. Several patients had been treated with nonparenteral vasodilator drugs. All vasodilators, including nitrates, were discontinued for at least 5 days before the initiation of the study. While hospitalized, each patient was maintained on a 2-g sodium diet. Informed consent was obtained for each patient.

Before admission to the cardiac care unit, the
patients underwent upright treadmill exercise (seven patients) or supine bicycle exercise (three patients). After admission to the cardiac care unit, blood specimens were obtained after one-half hour of rest in the supine position for the measurement of control plasma renin activity by the method of Sealy et al.24

Right-heart catheterization was performed using a #7 thermodilution Swan-Ganz flow-directed balloon-tipped catheter inserted either percutaneously or by cut-down via an antecubital vein. With the use of this catheter, right atrial (RAP), pulmonary arterial (PAP), and pulmonary capillary wedge (PCW) pressures were recorded. Cardiac output (CO) was determined in triplicate by the thermodilution technique with the use of the same catheter.25 The variation in CO determination was less than 10%. Arterial pressure was recorded directly by cannulation of the radial artery. The following hemodynamic parameters were calculated:

\[
SV = \frac{CO}{HR}
\]

where \(SV\) = stroke volume and HR = heart rate.

\[
SWI = SVI \times (MSP - PCW) \times 0.036
\]

where \(SWI\) = stroke work index, \(SVI\) = stroke volume index and \(MSP\) = mean systolic pressure.

\[
SVR = \frac{MAP - PCW/CO \times 80}{SWI}
\]

where \(SVR\) = systemic vascular resistance and \(MAP\) = mean arterial pressure.

\[
PVR = \frac{PAP - PCW/CO \times 80}{SVR}
\]

where \(PVR\) = pulmonary vascular resistance.

After control hemodynamic measurements on day 1, the patients received 25 mg of oral captopril (SQ 14–225, the Squibb Institute, Princeton, New Jersey). Hemodynamic measurements were then repeated every half hour through 2 hours and then every hour for 6 hours. Control measurements were again obtained and 50 mg of oral captopril was administered. Changes in hemodynamics were again monitored for 8 hours. On day 2, after control hemodynamic measurements, 100 mg of oral captopril was given and hemodynamic measurements were repeated for 8 hours. The patients were then discharged on the dose of captopril that produced the best hemodynamic response. Seven of the 10 patients received maintenance therapy of captopril for 8 weeks, after which they were readmitted to the hospital. One patient was not put on maintenance therapy because of the difficulties in weekly follow-up that were needed according to the protocol, and one patient discontinued captopril by himself. One other patient with severe congestive heart failure (NYHA class IV) due to multiple previous myocardial infarctions had a good hemodynamic response to captopril while in the hospital, but died suddenly within 24 hours of discharge. Patients continued their maintenance doses of digitals and diuretics during this period. Before hemodynamic changes on maintenance therapy of captopril were evaluated, treadmill or supine bicycle exercise was repeated. Blood specimens were also drawn for determination of plasma renin activity during maintenance therapy. Hemodynamic studies were performed in the same way as during the initial study. Hemodynamics were monitored for 8 hours after each of at least two maintenance doses of captopril.

Statistical analysis was performed using two-way analysis of variance with multiple-range test and mixed-effects model.

Results

Initial Hemodynamic Studies (table 1)

The control CO, HR, intravascular and intracardiac pressures, SVR, PVR, SV and SWI were similar before each dose of captopril (25, 50 and 100 mg). The hemodynamic changes after oral captopril were characterized by a significant reduction in HR, RAP, PAP, PCW, and SVR and an increase in CO, SV and SWI. The maximum changes in these hemodynamic variables after 25, 50 or 100 mg of oral captopril were quantitatively similar (fig. 1). The maximum increases in CO, SVI and SWI after 25 mg of captopril were 28%, 49% and 26%, respectively, and similar increases in CO, SV and SWI appeared after the 50- and 100-mg doses. PCW decreased by an average of 46% after the 25-mg dose; it decreased to a similar extent after the 50- or 100-mg dose. The magnitude of decrease in SVR (−41%), MAP (−23%), HR (−14%), and RAP (−27%) after the 25-mg dose was almost identical to that after the 50-mg or 100-mg doses.

Figure 2 shows changes in hemodynamics for each patient after 25 mg of oral captopril. HR and MAP decreased in all patients (fig. 2A). Most patients had only a modest decrease in arterial pressure; in two patients, however, it fell markedly. PCW decreased markedly in all patients and CO increased significantly in all but one patient (fig. 2B). SVR decrease in all patients. Despite a fall in arterial pressure, SWI increased (fig. 2C). A significant correlation was found between the initial level of SVR and the magnitude of increase in CO (\(r = 0.81, p < 0.0005\)) (fig. 3). A correlation was also found between the relative changes in SVR and CO (\(r = 0.72, p < 0.0005\)).

The time course and duration of action were similar for all three doses of captopril. A substantial increase in CO and a fall in PCW occurred at one-half hour and the peak effects were usually observed at 1.5 hours. The hemodynamic effects lasted for at least 6 hours in all patients. The maximum decrease in MAP and SVR also tended to occur usually at 1.5 hours; however, some degree of hypotension was observed as long as 6 hours after a single oral dose.

Initial plasma renin activity (PRA) varied considerably and ranged from 0.5–35.3 ng/ml. There was no correlation between initial PRA and control SVR.

Follow-up Results

Clinical Evaluation

Seven of the 10 patients remained on maintenance captopril therapy for 8 weeks before reevaluation of hemodynamic performance. Three patients were taking 25 mg of captopril twice daily, two patients were
TABLE 1. Initial Hemodynamic Effects of Oral Captopril in 10 Patients with Chronic Heart Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control1</th>
<th>25 mg</th>
<th>Control2</th>
<th>50 mg</th>
<th>Control3</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>78 ± 15</td>
<td>67 ± 15</td>
<td>77 ± 9</td>
<td>67 ± 13</td>
<td>77 ± 13</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>92 ± 19</td>
<td>71 ± 20</td>
<td>88 ± 16</td>
<td>72 ± 20</td>
<td>90 ± 21</td>
<td>70 ± 20</td>
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<tr>
<td>PCW (mm Hg)</td>
<td>29 ± 8</td>
<td>15 ± 6</td>
<td>27 ± 6</td>
<td>15 ± 5</td>
<td>28 ± 5</td>
<td>15 ± 5</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>41 ± 9</td>
<td>28 ± 6</td>
<td>40 ± 10</td>
<td>28 ± 5</td>
<td>38 ± 7</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>11 ± 4</td>
<td>8 ± 4</td>
<td>12 ± 6</td>
<td>6 ± 4</td>
<td>11 ± 7</td>
<td>6 ± 5</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>3.96 ± 1.68</td>
<td>5.05 ± 1.78</td>
<td>4.57 ± 1.89</td>
<td>5.34 ± 1.95</td>
<td>4.03 ± 2.02</td>
<td>5.53 ± 1.95</td>
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<tr>
<td>SVR (dyn-sec-cm⁻²)</td>
<td>1798 ± 653</td>
<td>1066 ± 362</td>
<td>1554 ± 633</td>
<td>1089 ± 309</td>
<td>1812 ± 728</td>
<td>1066 ± 366</td>
</tr>
<tr>
<td>SWI (g-m/m²)</td>
<td>31 ± 11</td>
<td>39 ± 8</td>
<td>33 ± 12</td>
<td>41 ± 11</td>
<td>32 ± 10</td>
<td>38 ± 10</td>
</tr>
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</table>

Statistical analysis

<table>
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<tr>
<th>Variable</th>
<th>CO</th>
<th>PCW</th>
<th>HR</th>
<th>MAP</th>
<th>SVR</th>
<th>SWI</th>
<th>PAP</th>
<th>RAP</th>
</tr>
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<tbody>
<tr>
<td>Controls 1 vs 2 vs 3</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>Control1 vs 25 mg</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
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<tr>
<td>Control1 vs 50 mg</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
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<tr>
<td>Control1 vs 100 mg</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
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</tr>
<tr>
<td>25 mg vs 50 mg vs 100 mg</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</table>

Statistical analysis was performed using two-way analysis of variance with a multiple range test and mixed effects model. A Student-Newman-Keuls multiple comparison test to compare the three drug-dose responses and the three controls was used when the analysis of variance was significant (p < 0.05).

Abbreviations: CO = cardiac output; PCW = pulmonary capillary wedge pressure; HR = heart rate; MAP = mean arterial pressure; SVR = systemic vascular resistance; SWI = stroke work index; MPAP = mean pulmonary artery pressure; RAP = right atrial pressure.

One patient could do neither because of severe peripheral neuropathy, and the other because of the worsening of a previously present hemiparesis. Exercise duration on the treadmill while on maintenance captopril therapy increased in each patient by an average of 48% (before therapy 3.3 minutes, after therapy 4.9 minutes). In the one patient who performed supine bicycle exercise, exercise duration increased by 3.3 minutes.

Hemodynamic Evaluation

The hemodynamic measurements after initiation of captopril and at 8 weeks of maintenance therapy in

![Figure 1. Percent changes from control in cardiac output (CO), pulmonary capillary wedge pressure (PCW), stroke work index (SWI), systemic vascular resistance (SVR), mean arterial pressure (MAP), right atrial pressure (RAP) and heart rate (HR) after 25, 50 and 100 mg of oral captopril. Magnitude of changes in hemodynamics after each dose level was similar.](http://circ.ahajournals.org/Downloadedfrom)
seven patients are summarized in table 2. The beneficial hemodynamic response during the initial evaluation was sustained at 8 weeks. Thus, CO, SV and SWI remained elevated and PCW, RAP, MAP, PAP and SVR remained decreased. HR tended to decrease after captopril during both the initial and follow-up studies. SV increased initially in all seven patients and this increase was maintained at 8 weeks. Similarly, PCW decreased in all patients initially and remained low at the time of restudy (fig 4).

Adverse Effects

During the initial hemodynamic study, profound bradycardia and hypotension were observed after the first 25-mg dose in two patients. In the same two patients who received larger doses, the hypotension and bradycardia were much less severe. One other patient developed symptoms of postural hypotension at the end of the first week of maintenance therapy (50 mg three times daily) and was found to have orthostatic hypotension. The symptoms and hypotension resolved with a lowering of the drug dosage.

Discussion

The purpose of the present study was to evaluate the hemodynamic effects of captopril, an oral angiotensin converting enzyme inhibitor, in patients with chronic congestive heart failure. Results indicate that this drug may be beneficial for the treatment of chronic heart failure. Almost all patients in this study had a substantial decrease in pulmonary and systemic venous pressure, the major determinants of the signs and symptoms of pulmonary and systemic venous congestion. There was also a concomitant increase in CO, SV and SWI, suggesting improved cardiac performance (fig. 5). These beneficial hemodynamic effects lasted in most patients for at least 6 hours after a single oral dose. Therefore, the frequency of administration need not exceed three or four times daily; such a regimen is usually well tolerated by most patients.

This study also demonstrates that during maintenance therapy, the hemodynamic effects of captopril were sustained. All seven patients in whom hemodynamics were reevaluated at the end of 8 weeks of therapy still had an elevated CO and decreased PCW. Changes in SVR, HR and arterial pressure were also similar to those observed after initiation of therapy. These findings suggest that tachyphylaxis to captopril does not occur in patients with chronic heart failure.

Improved left ventricular function with captopril was associated with clinical improvement. Six of the seven patients on maintenance therapy experienced improvement in their effort tolerance. Exercise duration on the treadmill or bicycle also increased considerably. The duration of the maintenance therapy in this study, however, was relatively short and longer follow-up will be needed to evaluate the long-term effects of captopril therapy on exercise tolerance in patients with chronic heart failure. Furthermore, changes in exercise tolerance on maintenance therapy

**Figure 2.** Captopril (25 mg) induced changes in A) heart rate (HR) and mean arterial pressure (MAP); B) pulmonary capillary wedge pressure (PCW) and cardiac output (CO); and C) systemic vascular resistance (SVR) and stroke work index (SWI) in all 10 patients during initial hemodynamic evaluation.
were evaluated while the patients were ambulatory and the influence of conditioning cannot be entirely eliminated. Nevertheless, concomitant improvement in hemodynamics suggests that the increased exercise tolerance was related to the improved resting left ventricular performance.

Although captopril produces an immediate and sustained beneficial hemodynamic response in patients with chronic heart failure, the mechanism is not entirely clear. Its hemodynamic effects are very similar to those of teprotide.19, 20 Some investigators have postulated that in patients with chronic congestive heart failure the renin-angiotensin system is

| Table 2. Hemodynamic Measurements After Initiation of Captopril and at 8 Weeks of Maintenance Therapy in Eight Patients |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Control                          | Immediate response | Eight weeks   | Control vs immediate response | Control vs eight weeks |
| HR                              | 78 ± 16          | 67 ± 15        | 73 ± 17         | < 0.05          | < 0.05          |
| MAP                             | 89 ± 16          | 70 ± 15        | 68 ± 9          | < 0.05          | < 0.05          |
| PCW                             | 29 ± 9           | 16 ± 4         | 13 ± 7          | < 0.05          | < 0.05          |
| PAP                             | 40 ± 10          | 28 ± 7         | 27 ± 14         | < 0.05          | < 0.05          |
| RAP                             | 12 ± 3           | 9 ± 3          | 5 ± 2           | < 0.05          | < 0.05          |
| CO                              | 3.54 ± 1.66      | 4.38 ± 1.30    | 5.09 ± 1.54     | < 0.05          | < 0.05          |
| SV                              | 46 ± 20          | 68 ± 22        | 72 ± 26         | < 0.05          | < 0.05          |
| SWI                             | 28 ± 12          | 36 ± 8         | 35 ± 7          | NS              | NS              |
| SVR                             | 1933 ± 753       | 1175 ± 384     | 1084 ± 327      | < 0.05          | < 0.05          |

Abbreviations: SV = stroke volume; other abbreviations as in table 1.

Figure 3. Correlation between initial level of systemic vascular resistance (SVR) and percent change in cardiac output (%ΔCO) after captopril therapy.

Figure 4. Changes in stroke volume (SV) and pulmonary capillary wedge pressure (PCW) after initiation (I) and 8 weeks of treatment (L) compared with control (C) in all seven patients who were on maintenance captopril therapy. Increased SV and decreased PCW observed initially were sustained at 8 weeks.

Figure 5. Changes in stroke volume and left ventricular filling pressure (LVFP) during captopril therapy. After each dose level, stroke volume increased along with a decrease in LVFP, indicating improved left ventricular function.
stimulated and enhanced angiotensin activity may contribute to the elevated SVR frequently found in patients with low CO.15-17. 26 attenuation of the effects of angiotensin II, therefore, would be expected to cause a reduction in SVR and thereby improve left ventricular performance. A fall in SVR and an increase in CO were consistently observed after administration of captopril in this study. These findings suggest that captopril might have caused a reduction in circulating levels of angiotensin II in these patients. However, in the present study only a general correlation was found between the magnitude of fall in SVR and the initial level of PRA. Furthermore, no correlation was found between the initial level of SVR and the control PRA, a finding reported previously.19, 20 these observations suggest that the reduction of SVR by captopril may not be entirely caused by a decrease in the levels of circulating angiotensin II. For example, captopril has been shown to inhibit the degradation of bradykinin.27, 28 Therefore, kinin-induced vasodilation with reduced SVR is possible.

Diet, sodium output and the use of diuretics were not controlled in the present study, so the varying state of sodium balance may have contributed to these wide variations in PRA. Furthermore, the mechanism for an elevation of SVR in congestive heart failure may be multifactorial.13 Augmented sympathetic activity with consequent arteriolar constriction and increased stiffness of the vascular walls caused by sodium and water retention may also be important factors.29

A significant reduction in RAP and PCW was observed in both acute and chronic studies. The mechanism of this fall, however, is unclear. It is generally accepted that angiotensin causes constriction of resistance or precapillary vessels, while the veins or capacitance vessels are relatively insensitive to the direct constricting effect of angiotensin.30-33 During the systemic administration of angiotensin, however, peripheral venous tone and central venous pressure consistently increased.34-37 This vasoconstricting effect of angiotensin can be prevented by regional nerve block, suggesting that reflex neural mechanisms might be responsible.34 Captopril may cause vasoconstriction by inhibiting this indirect vasoconstricting effect of angiotensin. In patients with chronic heart failure, circulating norepinephrine levels fall after the administration of angiotensin-converting enzyme inhibitors.19, 23 the fall in systemic and pulmonary venous pressures with captopril may be partly due to the attenuation of norepinephrine-induced vasoconstriction.

A modest but significant decrease in HR was also observed after the administration of captopril in our patients. The explanation for this relative bradycardia is not clear. Cardio-acceleration after systemic administration of angiotensin has been reported previously.38 Irrespective of the underlying mechanisms for angiotensin-induced cardio-acceleration, its inhibition by captopril might explain the decrease in HR observed in the present study. A reduction in HR, with a concomitant decrease in arterial pressure and PCW, may be beneficial in terms of metabolic cost, particularly in patients with ischemic heart disease. Although changes in coronary hemodynamics or myocardial metabolism were not investigated in this study, myocardial consumption also probably decreased. Improved left ventricular performance with captopril in these patients, therefore, most likely occurred at a lower metabolic cost. Davis et al.21 recently reported their experience with captopril and observed a similar time course of action and decrease in the PCW. However, they did not observe a significant reduction in HR.21

The patients in this study tolerated captopril well. Two patients, however, developed marked bradycardia and hypotension at the initiation of therapy, although these effects were largely attenuated with continued therapy. One patient also developed postural hypotension during maintenance therapy and the dose of captopril was reduced. Nevertheless, hypotension remains a potential complication and caution must be exercised to avoid hypotension, particularly at the initiation of therapy.

In summary, captopril produces beneficial hemodynamic and clinical effects in normotensive chronic heart failure patients. Since the hemodynamic effects of captopril appear to persist during maintenance therapy, it may be a useful therapeutic adjunct for the long-term treatment of chronic heart failure.

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