
Controlled Trial of Captopril in Chronic Heart Failure: A Rest and Exercise Hemodynamic Study

BARRY L. KRAMER, M.D., BARRY M. MASSIE, M.D., AND NINA TOPIC, R.N.

SUMMARY Although many studies have shown acute hemodynamic improvement in patients with congestive heart failure treated with vasodilating drugs, long-term controlled studies with both hemodynamic and exercise capacity measurements are not available. We studied the converting-enzyme inhibitor captopril in 16 ambulatory patients in New York Heart Association functional class II–IV heart failure who were clinically stable on digoxin and diuretics. The acute response to open-label captopril was quantified by blood pool scintigraphy, right-heart catheterization at rest and during exercise, and measurements of exercise capacity. The patients were then randomized to maintenance therapy with captopril or matching placebo and were restudied after 3 months. The two groups were similar in their clinical characteristics and pretreatment rest and exercise hemodynamic measurements. Both displayed similar acute beneficial responses to captopril at rest, with a mean reduction in left ventricular filling pressure from 24 ± 9 to 14 ± 6 mm Hg (p < 0.001) and increases in cardiac index, from 2.1 ± 0.5 to 2.5 ± 0.61/min/m² (p < 0.01), and stroke index, from 25 ± 8 to 34 ± 8 ml/m² (p < 0.001). Directionally similar hemodynamic improvement was noted during exercise.

After 3 months, these beneficial hemodynamic changes were sustained only in the patients randomized to captopril. Concomitantly, the captopril patients increased their exercise capacity as measured by the duration of bicycle exercise (9.0 ± 2.2 vs 11.7 ± 1.4 min, p < 0.01), maximal work load (360 ± 80 vs 460 ± 50 kpm/min, p < 0.005) and oxygen consumption (12.9 ± 2.3 vs 15 ± 1.8 ml/kg/min). The placebo group showed either no change or a worsening over the 3 months compared to their pretreatment measurements. These findings demonstrate that captopril is an effective adjunctive agent for the treatment of chronic heart failure and that it produces long-term hemodynamic improvement together with an increase in exercise capacity.

VASODILATORS are commonly used to treat patients with severe congestive heart failure. The premise for this therapy has been the assumption that the acute hemodynamic improvement demonstrated with a variety of vasoactive drugs would be sustained with long-term treatment and accompanied by clinical improvement.1,2 Only a few uncontrolled studies have reported sustained hemodynamic benefit during chronic vasodilator therapy,3–9 although there is more evidence for functional improvement.10 Unfortunately, few adequately controlled trials have been performed, and these have not included both initial and follow-up invasive hemodynamic measurements.

The present study was designed to evaluate comprehensively the long-term therapeutic response to captopril, an angiotensin converting-enzyme inhibitor, in patients with chronic heart failure. Acute hemodynamic improvement after captopril administration has been well demonstrated,9,11–15 but the degree of long-term benefit is less clear. Our study was designed as a prospective, controlled, 3-month trial to answer the questions: Are the acute beneficial effects of captopril on cardiac function sustained? Do patients improve, as judged by objective measurements of exercise capacity, if their cardiac performance improves?
Methods

Patients

Sixteen male patients who were in New York Heart Association functional class II, III or IV chronic congestive heart failure were studied after giving informed consent to a protocol approved by the Committee on Human Research of the University of California, San Francisco. Their mean age was 60 years (range 48–72 years), and they had been in heart failure for a mean of 3.6 years (range 3 months to 10 years). All remained symptomatic despite therapy with digoxin, diuretics and, in three patients, other vasodilators. The etiology of heart failure was ischemic heart disease in 10 patients, coronary disease with a history of hypertension in two, rheumatic heart disease after mitral valve replacement in one and idiopathic cardiomyopathy in three. One patient had minimal aortic regurgitation and nine had auscultatory evidence of secondary mitral regurgitation.

All subjects were ambulatory outpatients who were clinically stable and on constant medical regimens for at least 2 weeks before entering the study. Vasodilators had been withdrawn at least 4 weeks earlier. To qualify for inclusion, patients had to be able to exercise on an upright bicycle for at least 3 minutes at a work load of 200 kpm/min and have an exercise end point consistent with heart failure (dyspnea or fatigue). Patients with exercise-limiting angina, claudication or pulmonary disease (as judged by FEV₁ < 70% or FEV₁/FVC < 70% of predicted) were excluded. Most of the subjects participating in this study were enrolled in an ongoing multicenter trial of captopril in congestive heart failure, and the results reported here represent the findings of ancillary studies performed at our center.

The study design is summarized in table 1. It consisted of two phases. Initially, all 16 patients were treated with five doses of captopril while they underwent hemodynamic and radionuclide assessment of their acute response to drug. After a discharge dosage was determined, they were randomized to either an active drug or placebo group for a 3-month period, at the end of which they underwent repeat studies while receiving their blinded medication.

Acute Phase

Before hospitalization, patients performed a practice upright bicycle exercise test, pedaling to exhaustion on an electronically braked inertial ergometer beginning at a work load of 200 kpm/minute and increasing by 100 kpm/minute every 3 minutes until limiting dyspnea or fatigue. If a patient appeared ill at ease during exercise or stopped exercising at what was felt to be a submaximal level, a second test was performed. This preliminary assessment of maximal work load and exercise time was used to determine the timing of measurements during the subsequent hemodynamic studies. Measurements of oxygen consumption were not performed in conjunction with this test.

Patients were hospitalized 24 hours before the invasive studies to insure a stable medical regimen and diet. All medications were continued except for diuretics, which were withheld for at least 8 hours before each set of hemodynamic measurements. Right-heart catheterization was performed in the coronary care unit using a balloon-tipped thermodilution catheter, and a radial artery was cannulated. Patients were then allowed to rest for at least 1 hour before hemodynamics were measured. In both the supine and sitting positions, the transducers were set 5 cm below the angle of Louis. Baseline rest measurements of heart rate, mean and phasic arterial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure and cardiac output were obtained with the patient supine and then after sitting on the bicycle ergometer for 3–5 minutes. Exercise was then performed according to the protocol described above. During exercise, the ECG and arterial and pulmonary artery pressures were monitored continuously; pulmonary capillary wedge and right atrial pressures were recorded every minute. The pulmonary capillary wedge pressure at end expiration was used as a measure of left ventricular filling pressure, except in three patients in whom the pulmonary artery diastolic pressure was substituted for a technically unsatisfactory or unobtainable wedge pressure tracing. In these, concordance between the pulmonary artery diastolic and wedge pressures had previously been established. In the valve replacement patient, there had been no end-diastolic gradient across the mitral valve during a previous catheterization. Thermodilution cardiac output was measured in triplicate in the final 2 minutes of the highest completed exercise stage and, if the patient continued, again immediately before exercise was terminated. Arterial and pulmonary artery blood gas measurements were obtained at maximal exercise for calculation of the arteriovenous oxygen difference and oxygen consumption.

### Table 1. Study Protocol

<table>
<thead>
<tr>
<th>Acute phase</th>
<th>Long-term controlled phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehospitalization</td>
<td>Day 5</td>
</tr>
<tr>
<td>Medication stabilization</td>
<td>Discharged on randomized medication 50 mg tid</td>
</tr>
<tr>
<td>Day 1</td>
<td>Day 7</td>
</tr>
<tr>
<td>Preliminary exercise, determination of maximum work load</td>
<td>Dosage increased to 100 mg tid</td>
</tr>
<tr>
<td>Day 2</td>
<td>Days 7–82</td>
</tr>
<tr>
<td>Catheterization, pretreatment exercise hemodynamics</td>
<td>Regular follow-up</td>
</tr>
<tr>
<td>Day 3</td>
<td>Day 83</td>
</tr>
<tr>
<td>Captopril 25 mg q8h, rest hemodynamics, pre- and postcaptopril scintigraphy</td>
<td>Scintigraphy on randomized medication</td>
</tr>
<tr>
<td>Day 4</td>
<td>Day 84</td>
</tr>
<tr>
<td>Captopril 50 mg q8h, postcaptopril exercise hemodynamics</td>
<td>Recatheterization, rest and exercise hemodynamics on randomized medication</td>
</tr>
</tbody>
</table>
The patients rested overnight with the pulmonary artery catheter in place but without any changes in their medical regimens. The next morning, captopril, 25 mg orally every 8 hours, was begun. Resting hemodynamic measurements were monitored before and 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours after the initial dose. Blood pool scintigraphy was performed before and 90 minutes after the first dose of captopril by techniques described previously.\textsuperscript{17, 18} The scintigrams were analyzed for left ventricular ejection fraction by standard techniques and for end-diastolic and end-systolic volumes by a counts-based method similar to those described by Slutsy et al.\textsuperscript{19} and Dehmer et al.\textsuperscript{20} This volume technique has been validated in our laboratory and correlates closely with angiographic volumes (SEE = 18 ml\textsuperscript{19}).

In the 13 patients whose systolic arterial blood pressures remained above 85 mm Hg during the initial three doses, 50 mg of captopril was administered for the fourth dose the next morning. Three patients remained on 25 mg. The postcaptopril resting and exercise hemodynamic measurements were performed 90 minutes after the fourth dose using the same protocol. This procedure was followed so that these assessments were not made after the initial doses, which often have a more profound effect on blood pressure, and also so that they were obtained at the dosage of captopril on which the patients would be discharged. Cardiac output and arterial blood gases were measured at the same work load as during the baseline study and again at peak exercise in patients who exercised further. Captopril was administered in the same dosage 8 hours later. Patients were then randomized to captopril or matching placebo and discharged on the same dosage, given three times daily.

**Long-term Controlled Phase**

Patients were seen every 3–4 days for the initial 2 weeks. The medication dosage was increased under observation, so subjects were taking the target dosage of 100 mg three times daily or as close to it as the blood pressure permitted. Since the early blood pressure measurements may have permitted identification of patients taking active medication, the physician who monitored the titration phase did not participate in subsequent evaluations. The physician who followed the patients beyond week 2 and who performed the exercise tests did not see the patients or their blood pressure readings during the blinded titration phase. During the follow-up phase, an effort was made to maintain all medications at constant dosages. Diuretic dosages were adjusted upward if the patient had clinically evident fluid retention, or downward if prerenal azotemia was noted concomitant with a decrease in weight. The patients were then seen at 2–4-week intervals for a total of 12 weeks. At the end of this period, they underwent repeat radionuclide angiography 1½–3 hours after a medication dose. They were then admitted to the hospital for elective recatheterization. On the morning of admission, the treatment medication and diuretics were withheld. Right-heart and radial artery catheterization were performed. After at least a 1-hour stabilization period, hemodynamic measurements were recorded. Patients were then given their usual treatment medication (either captopril or placebo), and after 90 minutes, resting and exercise hemodynamic measurements were performed as described previously. Cardiac output and blood gas measurements were made at the same stage as before and, in subjects who exercised further, again at peak exercise. All patients were then given the option of receiving long-term captopril therapy.

**Calculations and Statistical Analysis**

The following measurements were derived from hemodynamic data:

\[
\text{Cardiac index (l/min/m}^2\text{)} = \frac{\text{cardiac output}}{\text{body surface area}}
\]

\[
\text{Stroke index (ml/m}^2\text{)} = \frac{\text{cardiac index}}{\text{heart rate}}
\]

\[
\text{Systemic vascular resistance (dyn-sec-cm}^{-5}\text{)} = \frac{\text{mean arterial pressure} - \text{right atrial pressure \times 80}}{\text{cardiac output}}
\]

\[
\text{Oxygen content (ml/dl)} = \text{oxygen saturation \times hemoglobin concentration} \times 1.34
\]

\[
\text{Oxygen consumption (ml/min)} = (\text{Arterial oxygen content} - \text{venous oxygen content}) \times \text{cardiac output}
\]

The arterial and pulmonary artery (mixed venous) oxygen saturations were derived from the Po2 measurements using a standard nomogram.

The significance of acute captopril effect on the various scintigraphic and hemodynamic measurements was determined by t test for paired samples. The effect of chronic treatment with captopril and placebo and its relationship to the acute response to open-label captopril was assessed using a two-way analyses of variance with a mixed-effects model and Newman-Keuls multiple range tests. All data are presented as the mean ± sd.

**Results**

**Acute Response to Captopril at Rest**

The acute effect of open-label captopril on the resting hemodynamic and radionuclide measurements is summarized in table 2. Hemodynamic data obtained 90 minutes after captopril administration and at the time of peak effect for each subject as judged by the greatest reduction in systemic vascular resistance and blood pressure, are shown. Peak effect was noted at 30 minutes in two subjects, at 1 hour in eight, at 90 minutes in three, and after 3–6 hours in three. In general, the changes at 90 minutes were comparable to those at
TABLE 2. Acute Response to Captopril at Rest: Hemodynamic and Radionuclide Measurements

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 16)</th>
<th>Group 1 (n = 8)</th>
<th>Group 2 (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre 90 min Peak</td>
<td>Pre 90 min Peak</td>
<td>Pre 90 min Peak</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(beats/min)</td>
<td>80 ± 11</td>
<td>78 ± 11</td>
<td>78 ± 8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>86 ± 9</td>
<td>72 ± 13†</td>
<td>64 ± 8‡</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>34 ± 11</td>
<td>27 ± 10‡</td>
<td>26 ± 8‡</td>
</tr>
<tr>
<td>LVFP (mm Hg)</td>
<td>24 ± 9</td>
<td>17 ± 9†</td>
<td>14 ± 6‡</td>
</tr>
<tr>
<td>MRAP (mm Hg)</td>
<td>10 ± 5</td>
<td>7 ± 4*</td>
<td>6 ± 4†</td>
</tr>
<tr>
<td>CI (l/m²)</td>
<td>2.1 ± 0.5</td>
<td>2.2 ± 0.4</td>
<td>2.5 ± 0.6‡</td>
</tr>
<tr>
<td>SVR (dyn-sec-cm⁻⁵)</td>
<td>1720 ± 510</td>
<td>1330 ± 480*</td>
<td>1050 ± 320†</td>
</tr>
<tr>
<td>EF (%)</td>
<td>19 ± 5</td>
<td>23 ± 5†</td>
<td>20 ± 6</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>383 ± 77</td>
<td>353 ± 75*</td>
<td>414 ± 66</td>
</tr>
</tbody>
</table>

Post measurements were made during open-label captopril treatment. Group 1 was subsequently randomized to long-term captopril and group 2 to placebo. There were no significant differences in pre- or postcaptopril measurements between group 1 and group 2.

* p < 0.05 vs pre-captopril measurements.
† p < 0.01 vs pre-captopril measurements.

Abbreviations: MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; LVFP = left ventricular filling pressure; MRAP = mean right atrial pressure; CI = cardiac index; SI = stroke index; SVR = systemic vascular resistance; EF = radionuclide ejection fraction; LVEDV = left ventricular end-diastolic volume.

peak effect, except those in arterial pressure, systemic vascular resistance and cardiac and stroke indexes, which were, by definition, greater in magnitude at peak effect. Captopril caused a marked fall in mean arterial pressure, from 86 ± 9 to 64 ± 8 mm Hg (p < 0.001), with systolic pressures falling below 70 mm Hg in two subjects, although none experienced symptoms. Systemic vascular resistance exhibited a corresponding dramatic reduction, from 1720 ± 510 to 1050 ± 320 dyn-sec-cm⁻⁵ (p < 0.001). Left ventricular filling pressure decreased by a mean of 42%, from 24 ± 9 to 14 ± 6 mm Hg (p < 0.001). The increase in cardiac index was not significant at 90 minutes, but was at peak effect. Stroke index rose from 25 ± 8 to 29 ± 8 ml/m² (p < 0.05) at 90 minutes and by a maximum of 30%, to 34 ± 8 ml/m² (p < 0.001).

A comparison of the radionuclide measurements before and 90 minutes after the first dose of captopril (table 2) demonstrated a modest increase in ejection fraction, from 19 ± 5% to 23 ± 5% (p < 0.05) and a concomitant decrease in end-diastolic volume, from 383 ± 77 to 353 ± 75 ml (p < 0.05).

Acute Response to Captopril During Exercise

The effect of open-label captopril on the exercise hemodynamic measurements is summarized in table 3. No significant postural symptoms or hemodynamic changes were noted during the change from the supine to the upright position. During upright exercise, captopril improved cardiac performance at the same maximum work load achieved before treatment. Left ventricular filling pressure was significantly lower (31 ± 11 vs 36 ± 11 mm Hg, p < 0.005). Although exercise cardiac index did not significantly change acutely (3.9 ± 0.9 vs 3.7 ± 0.7 l/min/m²), it was achieved at a lower maximal heart rate (118 ± 16 vs 126 ± 13 beats/min, p < 0.005) and with a higher stroke index (34 ± 9 vs 30 ± 5 ml/m², p < 0.02). Of note is that systemic vascular resistance, even during exercise-induced vasodilation, was lower during captopril therapy (820 ± 220 vs 990 ± 190 dyn-sec-cm⁻⁵, p < 0.01) and mean arterial pressure was correspondingly lower as well (88 ± 14 vs 97 ± 20 mm Hg, p < 0.02).

Despite this acute hemodynamic improvement, exercise capacity did not change during the acute study. Exercise duration, maximal work load and maximal oxygen consumption were all similar before and after captopril.

Controlled Trial: Patient Groups and Clinical Response

The eight patients randomized to captopril and the eight maintained on placebo were comparable in terms of their ages (64 ± 4 vs 58 ± 7 years), etiology of heart failure, duration of heart failure (4.2 ± 2.8 vs 3.6 ± 3.0 years) and functional class (mean 2.8 vs 2.9). Five patients in each group were receiving antiarrhythmic therapy for ventricular ectopy, and no difference in the grade of ectopy was present between the two groups. No patient had a history of syncope or symptomatic arrhythmia during the year before the study. The pre- and postcaptopril measurements for the two groups are shown separately in tables 2 and 3. There were no significant differences between groups in the pre-captopril values of any of these indexes. At rest, captopril produced similar significant changes in each hemodynamic and radionuclide measurement except for heart rate, which did not change significantly in either group. During exercise, although the control measurements and directional changes were similar,
group 2 manifested a slightly greater hemodynamic response to open-label captopril. Thus, the decreases in exercise heart rate, arterial pressure, pulmonary artery pressure, left ventricular filling pressure and systemic vascular resistance produced by captopril all achieved statistical significance in group 2 but not in group 1. The baseline measurements of exercise capacity were slightly, but not significantly, lower in group 2 patients.

Six of eight group 1 patients were maintained on 100 mg three times daily. One patient was initially maintained on 50 mg three times daily but had his dosage further decreased to 12.5 mg because of persistent symptomatic hypotension. Another group 1 patient exhibited early hypotension and was inadvertently maintained on 12.5 mg three times daily for the entire 12-week period despite becoming mildly hypertensive after week 4. Seven of eight group 2 patients were maintained on the 100-mg dose of placebo; one was treated with 50 mg three times daily because of low blood pressure.

All eight group 1 patients completed the study. Although six of the seven who underwent recatheterization demonstrated hemodynamic improvement and increased exercise capacity, only four reported marked or moderate subjective improvement and the others considered themselves unchanged. Diuretic dosages were unchanged in seven patients and reduced in one patient. Other than the hypotension in two patients, which resolved at lower captopril dosages, the only adverse reactions were a mild taste alteration in one subject and a drop in platelet count to 40,000–60,000 in another, which may have been related to alcohol abuse or other medications. No captopril patient experienced syncope or symptomatic arrhythmias. Only four patients in group 2 completed the follow-up period. One experienced syncope in week 3 after complaining of orthostatic dizziness, and was dropped from the study. He remained stable during follow-up but refused subsequent tests. Three died during the study period. One of these had experienced gradually progressive heart failure despite increased diuretics and a therapeutic digoxin level. He had been maintained on procainamide because of ventricular ectopy, but was hospitalized elsewhere during week 6 for a syncopal episode and died suddenly 2 days after discharge. The second patient died suddenly during week 4, at a time when he felt considerably improved. He also had been taking antiarrhythmic agents for ventricular ectopy. The third patient had exhibited progressive deterioration despite increased diuretics and was withdrawn from the study during week 5, but died suddenly several days later after having been started on hydralazine and nitrates. Postmortem examinations were performed on two patients. Both had severe coronary artery disease and extensive left ventricular fibrosis from healed myocardial infarctions. No acute cause of death was apparent. The third patient who died was thought to have a primary cardiomyopathy on clinical grounds. Another group 2 patient exhibited progressive biventricular failure but stabilized when his daily furosemide dosage was increased from 80 to 480 mg. The other three placebo patients reported no change in symptoms.

**Controlled Trial: Long-term Hemodynamic and Radionuclide Measurements**

Seven of eight group 1 patients and the four continuing group 2 patients agreed to elective recatheterization. The salient findings are shown in table 4 and

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**Table 3. Acute Response to Captopril During Exercise: Hemodynamic and Exercise Capacity Measurements**

<table>
<thead>
<tr>
<th>Metric</th>
<th>All patients (n = 16)</th>
<th>Group 1 (n = 8)</th>
<th>Group 2 (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>p</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>126 ± 18</td>
<td>118 ± 16</td>
<td>0.005</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>97 ± 20</td>
<td>88 ± 14</td>
<td>0.02</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>50 ± 12</td>
<td>46 ± 16</td>
<td>0.05</td>
</tr>
<tr>
<td>LVFP (mm Hg)</td>
<td>36 ± 11</td>
<td>31 ± 11</td>
<td>0.005</td>
</tr>
<tr>
<td>MRAP (mm Hg)</td>
<td>14 ± 5</td>
<td>13 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>CI (l/m²)</td>
<td>3.7 ± 0.7</td>
<td>3.9 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>SI (ml/kg)</td>
<td>30 ± 5</td>
<td>34 ± 9</td>
<td>0.02</td>
</tr>
<tr>
<td>SVR (dyn·sec·cm⁻¹)</td>
<td>990 ± 190</td>
<td>820 ± 220</td>
<td>0.01</td>
</tr>
<tr>
<td>Exercise time (min)</td>
<td>8.8 ± 2.2</td>
<td>8.5 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum load (kpm/min)</td>
<td>350 ± 85</td>
<td>356 ± 90</td>
<td>NS</td>
</tr>
<tr>
<td>VO₂ (ml/kg)</td>
<td>12.4 ± 3.0</td>
<td>12.7 ± 2.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Post measurements were made on open-label captopril. Group 1 was subsequently randomized to long-term captopril and group 2 to placebo.

There were no significant differences in pre- or postcaptopril measurements between group 1 and group 2.

Abbreviations: VO₂ = derived oxygen consumption at maximal work load; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; LVFP = left ventricular filling pressure; MRAP = mean right atrial pressure; CI = cardiac index; SI = stroke index; SVR = systemic vascular resistance.
Table 4. Acute and Long-term Resting Hemodynamic Response to Captopril and Placebo

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>3 Months</th>
<th>Probability matrix*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>I Pre 1½ hrs</td>
<td>II Pre 1½ hrs</td>
<td>I vs II</td>
</tr>
<tr>
<td>Group 1 (Captopril)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77 ± 8</td>
<td>73 ± 5</td>
<td>74 ± 6</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>87 ± 9</td>
<td>70 ± 8</td>
<td>87 ± 14</td>
</tr>
<tr>
<td>LVFP (mm Hg)</td>
<td>25 ± 10</td>
<td>16 ± 8</td>
<td>23 ± 9</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.1 ± 0.5</td>
<td>2.3 ± 0.4</td>
<td>2.2 ± 0.5‡</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>28 ± 7</td>
<td>32 ± 8</td>
<td>30 ± 7‡</td>
</tr>
<tr>
<td>Group 2 (Placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>89 ± 13</td>
<td>85 ± 6</td>
<td>76 ± 8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>82 ± 7</td>
<td>69 ± 12</td>
<td>77 ± 9</td>
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<tr>
<td>LVFP (mm Hg)</td>
<td>30 ± 4</td>
<td>20 ± 6</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>1.9 ± 0.5</td>
<td>2.1 ± 0.9</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>22 ± 8</td>
<td>25 ± 7</td>
<td>19 ± 7</td>
</tr>
</tbody>
</table>

*The significance of within-group differences over time, as assessed by analysis of variance, are shown.
†Indicates significant difference between group 1 and group 2.

Abbreviations: See table 2.

Figures 1–3. Since the captopril dosage was increased during chronic therapy and patients were hospitalized at the time of the first study but not the second, the acute and 3-month measurements are not strictly comparable. Furthermore, captopril pharmacokinetics and pharmacodynamics may well change over time. Table 4 shows measurements obtained at the same time (90 minutes) after captopril. However, in order to evaluate the question of hemodynamic tolerance over time, the peak acute effects are compared with the long-term 90-minute measurements in figures 1–3.

The acute responses in the recatheterized patients are very similar to those in the complete patient groups. At rest, the long-term responses to captopril were very similar to the acute responses (table 4, column II vs column IV for group 1). Thus, heart rate did not change significantly at either point, although it tended to decrease on drug. Left ventricular filling pressure, cardiac index and stroke index continued to improve from baseline (table 4, column I for group 1) at 3 months and were not different from the acute captopril values (table 4, column II for group 1). However, mean arterial pressure tended to rise over time, and the 3-month mean value was significantly higher than the acute value (79 ± 12 vs 70 ± 8; table 4, columns I vs II for group 1).

Figure 1. Pretreatment, acute captopril and 3-month follow-up measurements of mean arterial pressure (MAP) and systemic vascular resistance (SVR) at rest. The captopril group is shown by solid circles and the placebo group by open circles. Changes with captopril are shown by solid lines and those with placebo by dashed lines. Both groups exhibited dramatic falls in MAP with acute open-label captopril, but returned to near-baseline levels after 3 months of randomized therapy. SVR remained lower than baseline after 3 months in the captopril group, and at that time it was also significantly lower than that of the placebo group. *p < 0.05; ***p < 0.001, pre- vs postcaptopril values.

Figure 2. Pretreatment, acute captopril and 3-month follow-up measurements of left ventricular filling pressure (LVFP) and stroke index (SI) at rest. Symbols are as in figure 1. In the captopril-treated group, resting LVFP fell acutely from 25 ± 9 to 12 ± 5 mm Hg, and remained lower (17 ± 7 mm Hg) after 3 months, whereas in the placebo group, the initial decrease after open-label captopril from 27 ± 7 to 17 ± 6 mm Hg was not sustained at 3 months (28 ± 4 mm Hg) on placebo. Similarly, resting SI rose acutely in both groups but remained higher only during captopril treatment. Although both groups initially had similar measurements, the differences between the groups are significant at 3 months. *p < 0.05; **p < 0.001, pre- vs postcaptopril values.
column II vs IV for group 1), although it represented an 8-mm Hg fall from pretreatment levels. Even when the long-term measurements were compared with peak acute responses (figs. 1–3), there was no evidence of loss of beneficial effect.

After 3 months, the premedication measurements obtained approximately 12 hours after the last dose of captopril were not significantly different from baseline (table 4, columns I vs III for group 1). In contrast, the placebo group showed no response to medication at 3 months, with the post captopril measurements similar to the pretreatment baseline values and the predose measurements (table 4, column IV vs columns I and III for group 2). In general, hemodynamics tended to deteriorate over time in group 2, although the change did not achieve significance in the small number of recatheterized subjects. As a result, left ventricular filling pressure, cardiac index and stroke index were significantly better in group 1 than in group 2 after 3 months, whereas there had been no significant difference initially.

The long-term exercise hemodynamic data showed similar trends, although the findings did not always achieve statistical significance (fig. 3). Left ventricular filling pressure measured at the pretreatment maximal work load fell initially and remained lower during captopril treatment than during placebo. Maximum cardiac index did not change acutely but was significantly higher after 3 months in group 1, as was stroke index.

The scintigraphic findings also showed significant differences between groups 1 and 2 (fig. 4). Ejection fraction rose modestly in both groups after the initial captopril dose, but this improvement persisted only on active medication. Similarly, left ventricular end-diastolic volume remained smaller only in patients given captopril.

**Controlled Trial: Effect on Exercise Capacity**

Although open-label captopril did not affect any of the indexes of exercise capacity acutely, significant increases were noted after long-term captopril therapy (fig. 5). Exercise time lengthened from 9 ± 2.2 to 11.7 ± 1.4 minutes (p < 0.01), maximal work load increased from 360 ± 80 to 460 ± 50 kpm/min (p < 0.005) and maximal oxygen consumption increased from 12.9 ± 2.3 to 15 ± 1.8 ml/min/kg (p < 0.001) in group 1. Group 2 showed no change or a slight worsening in each of the measurements. Six of the seven restudied group 1 patients showed improvement in these indexes, the only exception being the one who eventually became hypertensive but whose dosage, 12.5 mg three times daily, was inadvertently not increased appropriately.

**Discussion**

The long-term use of vasodilating drugs to treat patients with chronic congestive heart failure has gained popularity, primarily as a result of the theoretical appeal of this approach and the numerous studies demonstrating acute hemodynamic improvement with these agents.1 2 The underlying assumption has been that the acute hemodynamic benefit would be sustained during chronic therapy and translated into a reduction in exer-

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**Figure 3.** Hemodynamic measurements during exercise. Symbols are as in figure 1. (left) Left ventricular filling pressure (LVFP) at the pretreatment maximal work load. There was a trend toward lower LVFP at the same level of exercise in the captopril group, but it did not achieve statistical significance. The cardiac index (CI) and stroke index (SI) values are those obtained at maximal exercise. CI did not change acutely with captopril in either group, but rose during long-term captopril therapy. SI increased acutely in both groups, although the change was not significant (p < 0.05), and increased further after 3 months on captopril. *p < 0.05, pre- vs postcaptopril values.

**Figure 4.** Left ventricular ejection fraction (EF) rose modestly, but significantly, with open-label captopril, from 20 ± 6% to 23 ± 6% in group 1, 19 ± 4% to 23 ± 5% in group 2, and remained higher (24 ± 8%) only during chronic active therapy. End-diastolic volume (EDV) also fell in both groups and remained lower on captopril. *p < 0.005; **p < 0.01, pre- vs postcaptopril values. Measurements are at rest.
Drugs, including nitrate preparations, hydralazine, prazosin, trimazosin, minoxidil, and captopril. The initial improvement in cardiac performance, however, has generally not been accompanied by an immediate increase in exercise capacity. During maintenance therapy with isosorbide dinitrate, prazosin, trimazosin, and the combination of hydralazine and nitrates, exercise tolerance has improved in heart failure patients. However, none of the controlled studies have examined the long-term effect of a vasodilator on both invasive measurements of cardiac function and on exercise capacity. Additionally, the long-term effectiveness of several of these drugs remains controversial, perhaps because patients develop a tolerance to them. Long-term follow-up studies have presented a less optimistic picture than the initial reports.

Captopril is the first oral converting-enzyme inhibitor to be studied in heart failure. The initial reports documenting its acute effectiveness gained considerable attention and provided some evidence of sustained hemodynamic and clinical improvement with maintenance captopril therapy. Ader et al. documented persistent hemodynamic benefit at rest in seven patients restudied after 2 months of therapy, five of whom had an accompanying increase in treadmill exercise tolerance. Other groups have reported small numbers of patients with chronic heart failure who increased their exercise tolerance after 1-20 weeks of therapy. Dzau et al. showed improved hepatic and renal function and an increase in left ventricular ejection fraction in seven patients treated for a mean of 6 months, and Faxon et al. noted sustained improvement in functional class after a mean of 1 year.

Our protocol was designed as a controlled study to examine the hemodynamic effects of chronic captopril administration at rest and during exercise to relate these hemodynamic findings to measurements of exercise capacity. We also measured left ventricular function and size by scintigraphy.

Our acute resting hemodynamic findings in the entire group of 16 patients are similar to those reported in previous studies. Left ventricular filling pressure decreased by 42%, while cardiac and stroke indexes increased 22% and 30%, respectively. The acute effects were most prominent in indexes of preload. Captopril also exerted a beneficial effect during upright exercise, attenuating the increase in left ventricular filling pressure, modestly increasing cardiac and stroke indexes and further augmenting the vasodilating stimulus of exercise. In general, the exercise hemodynamic changes were not as impressive as those seen at rest. In part, this difference probably resulted from the timing of the exercise measurements, which were all performed at 90 minutes after drug administration — not always the time of peak drug response. The acute hemodynamic improvement was associated with significant decreases in left ventricular end-diastolic and end-systolic volumes and a modest increase in ejection fraction. As with other vasodilators, there was no short-term change in exercise capacity despite the hemodynamic improvement.

The beneficial effects of captopril were sustained only in patients randomized to active drug treatment (group 1). Left ventricular filling pressure and end-diastolic volume were significantly lower and cardiac index, stroke index and ejection fraction were higher after 3 months than before captopril therapy and were generally similar to the acute captopril values. After 3 months, all of these measurements were similar to control values in the placebo group. Furthermore, although the two groups initially had similar measurements, after 3 months the captopril group had significantly lower heart rates and left ventricular filling pressures, as well as higher cardiac and stroke indexes. Likewise, only group 1 patients continued to have increased left ventricular ejection fractions and decreased ventricular volumes compared with those before captopril.

The findings were similar with the exercise hemodynamic measurements: Only group 1 showed sustained improvement. Most important, exercise capacity improved only in group 1 patients. The duration of upright bicycle exercise, the maximal work load, and maximal oxygen consumption all improved significantly after 3 months of captopril treatment, but not on placebo. The only patient receiving captopril who did not increase his exercise capacity was the man whose dosage was not increased from 12.5 mg three times daily despite the subsequent rise in his blood pressure.

![Figure 5](http://circ.ahajournals.org/)

**Figure 5. Changes in exercise capacity.** None of these variables were affected acutely, after four doses of captopril. After 3 months, however, exercise duration, work load, and oxygen consumption all rose in the captopril group and did not change or worsened in the placebo group.
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In contrast, no group 2 patient had an improved exercise capacity.

All eight group 1 patients completed the study and either improved symmetrically or remained clinically stable. In group 2, one patient was withdrawn after a syncopal episode in week 3 and only four others survived the randomized period. Only one of the group 2 patients felt symptomatically improved.

Other than the acute hypotension during the initiation of captopril, the drug was well tolerated. Arterial pressure gradually rose toward pretreatment values during chronic therapy, so six of the eight patients could be maintained on 100 mg three times daily after the first week. Two captopril patients as well as one placebo subject were maintained on reduced dosages. At recatheterization, arterial pressure in group 1 was not significantly lower than at baseline despite a persistently lower systemic resistance. The only other adverse reactions to captopril were a mild loss of taste in one patient and a reversible decrease in platelet count in another.

Implications

Several salient points can be derived from these results, and these in turn raise some unresolved questions. Clearly, captopril therapy is chronically effective, producing both continued hemodynamic benefit and improved exercise capacity. Although the number of patients is small and further studies are needed for confirmation, the short-term clinical course of some heart failure patients is apparently improved during captopril therapy. However, continued therapy is required to sustain the hemodynamic effects of the drug. Thus, 12 hours after the last dose, measurements return to the pretreatment levels, even though full responsiveness to the medication is retained. Thus, not surprisingly, there does not appear to be an improvement in underlying cardiac function during chronic therapy. Our findings differ from those reported in preliminary form by Nicholls et al., who found no deterioration when captopril was withdrawn for as long as 48 hours. This may in part be explained by differences in protocol, since our patients were outpatients at the time of recatheterization.

More perplexing is the seemingly greater effect of captopril on left ventricular preload than on cardiac output. This is consistent with our previous observations, but is somewhat surprising because captopril, as a competitive antagonist of angiotensin-converting enzyme, would be expected to have its major effect on the arteriolar resistance bed. Thus, despite the limited effect of angiotensin II on the veins, captopril functions as a venodilator. This probably results from indirect effects of captopril on other vasoactive substances, such as bradykinin, catecholamines and prostaglandins.

Finally, the time course of exercise improvement is of interest. Hemodynamic improvement at rest occurs immediately during captopril, but exercise capacity did not increase until the 3-month measurements. This dissociation between the hemodynamic and functional responses has been noted with other vasodilators. We and others have speculated elsewhere about the mechanism of this phenomenon. It most likely reflects either a delay in the improvement of oxygen delivery to the exercising muscle or a lag in the ability of the periphery to use its enhanced supply, but further studies in this area are needed.

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