Lack of relationship between the short-term hemodynamic effects of captopril and subsequent clinical responses

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ABSTRACT The role of hemodynamic monitoring during the initiation of vasodilator therapy for heart failure remains to be defined, despite the tremendous potential socioeconomic and clinical ramifications. We therefore performed resting and exercise hemodynamic studies before and during the initial 48 hr of captopril therapy in 14 stable patients with New York Heart Association Class II or III chronic congestive heart failure. Their clinical response to therapy was determined by evaluating changes in clinical status and the measured changes in exercise tolerance, heart size, and ejection fraction after 3 months. Significant improvement in each of these indexes was found for the group as a whole, but the baseline hemodynamics and the hemodynamic responses to captopril differed little between the patients showing marked improvement and those exhibiting little or no change. Correlations between the hemodynamic measurements and the changes in clinical class, exercise tolerance, heart size, and ejection fraction were generally poor. Even when they achieved significance, these correlations were too loose to allow prediction of the clinical efficacy of captopril in individual subjects. These findings indicate that the routine use of invasive hemodynamic monitoring during the initiation of captopril is unnecessary and potentially misleading, although such measurements remain valuable for diagnosis, the management of patients with complex conditions, and for investigation. The response to captopril may be best evaluated by serial measurements of exercise tolerance and heart size in addition to clinical assessment.


THE USE OF vasodilators as adjunctive agents in the management of patients with chronic heart failure has been widely accepted, based primarily on the short-term hemodynamic benefits and the resulting expectation that these would be associated with clinical improvement. While a growing body of data supports the clinical value of vasodilator therapy, the role of hemodynamic monitoring during its initiation remains unsettled. One reason for this is the scarcity of studies that include both hemodynamic measurements and objective assessments of clinical response. However, the potential ramifications of this question are enormous, both in terms of the spectrum and numbers of patients who might be treated with these drugs and in terms of length of hospitalization and the cost of intensive care unit monitoring.

In our study, the value of hemodynamic measurements in predicting the outcome of captopril therapy was prospectively assessed in a group of stable patients with moderately severe heart failure. To accomplish this, patients underwent hemodynamic studies while at rest and during exercise before and during the first 48 hr after the initiation of captopril therapy and these measurements were correlated with the subsequent changes in exercise tolerance, ejection fraction, and heart size over the next 3 months.

Methods

The study population consisted of 14 consecutive patients who presented with chronic stable congestive heart failure and underwent both resting and exercise hemodynamic measurements during the initiation of captopril therapy. Heart failure had been present for at least 3 months in all patients, and no patient had required hospitalization or adjustment in medication in the 30 days preceding the study. All subjects were men, with a mean age of 59 years (range 48 to 72). The causes of heart failure were coronary disease in nine patients, coronary and hypertensive disease in one, idiopathic cardiomyopathy in three, and rheumatic heart disease after mitral valve replace-
none were hypertensive at the time of study. Their mean pretreatment symptomatic classification, based on the subjective scale shown in table 1, was 3.1 ± 0.50 (range 2.0 to 4.0). All were on digoxin and furosemide (mean dosage 115 mg/day, range 40 to 400), and six were receiving adjunctive diuretic therapy with metolazone (n = 5) or spironolactone (n = 1). None had received vasodilators for the preceding 30 days.

To qualify for inclusion, patients were required to be capable of performing treadmill exercise. Patients in whom the exercise end point was not attributable to heart failure, including those with angina, claudication, or pulmonary disease (as indicated by a forced expiratory volume in 1 sec or a forced expiratory volume in 1 sec/forced vital capacity ratio below 70% of predicted) were excluded.

**Study protocol.** All patients were followed in a research clinic for 2 to 8 weeks before the initiation of captopril therapy to ensure clinical stability and consistency of their medical regimen. During the final 2 weeks of this period they underwent treadmill testing to determine their pretreatment exercise tolerance and a practice session on the upright bicycle ergometer. Patients were then hospitalized and baseline chest x-rays and radionuclide angiograms were obtained. On the second hospital day all underwent right heart catheterization and radial arterial cannulation. After hemodynamic stabilization, pretreatment resting and exercise hemodynamic measurements were recorded.

Captopril therapy was begun at a dosage of 25 mg orally tid, with resting measurements being recorded at 30, 60, 90, 120, 180, 240, 360, and 480 min after dosing. The fourth dose was increased to 50 mg orally tid in patients whose blood pressures allowed such an increase. Exercise hemodynamic measurements were recorded again 90 min after the fourth dose.

Patients were discharged on captopril 50 mg tid and had their dosage increased to 100 mg tid after 1 to 2 weeks. The patients were seen at monthly intervals, and at the end of 3 months of continuous captopril therapy, they underwent repeat treadmill testing, chest x-ray, and radionuclide angiography.

**Methods of evaluation.** Clinical classification was rated by the criteria shown in table 1, which were developed to permit recognition of more subtle changes than the New York Heart Association classification, although they remain subjective. A reduction in classification of 1.0 or greater was considered a positive response.

Exercise tolerance was measured by a modified Naughton protocol in which the workload was progressively increased in 2 min stages. The baseline duration was determined by averaging two consecutive pretreatment test results that differed by less than 2 min and was required to be between 6 and 16 min. A positive response was defined as an increase of 2 min or more, since this represented the upper limit of variability in the base-line studies and was greater than that seen in any patient treated with placebo in a previously published controlled study. The radionuclide angiograms were obtained with the equilibrium blood pool technique with the use of red blood cells labeled in vivo. The method used in our laboratory has been described in detail previously.

Measurements of mean right atrial, phasic and mean pulmonary arterial, and mean pulmonary capillary wedge pressures were made with a flow-directed thermomulation catheter. Blood pressure was measured through the radial arterial line. Cardiac output was determined at least in triplicate by thermodilution. Exercise hemodynamic measurements were made during upright bicycle exercise, beginning at a workload of 200 kilopond-meters/min and increasing by 100 kilopond-meters/min every 3 min. The same protocol was used after captopril. In the three subjects who completed an additional stage, the ventricular filling pressures and pulmonary arterial pressures from the same stage as during the pretreatment maximum were compared, but the heart rate, arterial pressure, and cardiac output from the highest completed stage were used. Cardiac output and stroke volume were indexed for body surface area. Systemic vascular resistance (SVR) was calculated as follows:

\[ \text{SVR (dynes-sec-cm}^{-5}) = \frac{\text{AP} - \text{RA}}{\text{CO}} \times 80 \]

**Determination of the relationship between initial measurements and subsequent response.** To determine the value of hemodynamic measurements in predicting the results of the therapy, the correlations between the hemodynamic measurements and the change in clinical class, exercise tolerance, ejection fraction, and cardiothoracic ratio at 3 months were examined. In addition, as a second way of assessing the value of the hemodynamic findings, the mean values of the patients who showed clinical improvement and increases in exercise tolerance were compared with values in those who did not with unpaired t tests. Seven patients underwent recatheterization after 3 months of treatment, and the hemodynamic measurements made after a dose of captopril at this time were also examined in relation to the clinical response.

All measurements are expressed as mean ± SD. Changes were considered statistically significant if the null hypothesis was rejected with a probability of .05 or below. However, since multiple correlations between the same variables were examined, the Bonferroni correction was used. Thus, since changes in 12 hemodynamic measurements were correlated with changes in four outcome variables, a significance level of .001 (.05/48) was required for the correlations.

**Results**

**Hemodynamic response to captopril therapy.** The pretreatment and postcaptopril hemodynamic measurements and the captopril-induced changes are listed in table 2. The postcaptopril resting measurements used were those obtained at the time of the peak decrease in mean arterial pressure after the initial 25 mg dose and were always recorded between 30 and 90 min after dosing. In patients at rest the mean left ventricular filling pressure fell markedly (27 ± 3 to 18 ± 5 mm Hg; p < .001), while cardiac and stroke indexes rose (2.0 ± 0.5 to 2.5 ± 0.5 ml/m²; p < .001 and 25 ± 7 to 32 ± 8 ml/m²; p < .001). Both arterial pressure and systemic vascular resistance fell significantly and heart

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**TABLE 1**

<table>
<thead>
<tr>
<th>Symptomatic classification</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>Always symptomatic at rest, not ambulatory</td>
<td></td>
</tr>
<tr>
<td>4.5</td>
<td>Usually symptomatic at rest</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>Frequently symptomatic at rest</td>
<td></td>
</tr>
<tr>
<td>3.5</td>
<td>Occasionally symptomatic at rest</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>Frequently symptomatic with limited activity</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>Symptomatic with mild-to-moderate activity</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Symptomatic only with moderate activity</td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>Symptomatic only with strenuous activity</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>Asymptomatic from congestive heart failure</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2
Hemodynamic effects of captopril

<table>
<thead>
<tr>
<th></th>
<th>Rest Before captopril</th>
<th>After captopril</th>
<th>Change (%)</th>
<th>Exercise Before captopril</th>
<th>After captopril</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>84 ± 8</td>
<td>80 ± 7</td>
<td>-5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>128 ± 18</td>
<td>118 ± 14</td>
<td>-8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>87 ± 11</td>
<td>68 ± 6</td>
<td>-22&lt;sup&gt;a&lt;/sup&gt;</td>
<td>96 ± 18</td>
<td>87 ± 18</td>
<td>-7</td>
</tr>
<tr>
<td>CI (l/min/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>2.0 ± 0.5</td>
<td>2.5 ± 0.5</td>
<td>+23&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.8 ± 0.9</td>
<td>3.8 ± 0.7</td>
<td>0</td>
</tr>
<tr>
<td>SI (ml/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>25 ± 7</td>
<td>32 ± 8</td>
<td>+28&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30 ± 7</td>
<td>32 ± 7</td>
<td>+7</td>
</tr>
<tr>
<td>LVFP (mm Hg)</td>
<td>27 ± 8</td>
<td>18 ± 5</td>
<td>-33&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37 ± 9</td>
<td>34 ± 10</td>
<td>-8</td>
</tr>
<tr>
<td>SVR (dyne-sec-cm&lt;sup&gt;-2&lt;/sup&gt;)</td>
<td>1700 ± 500</td>
<td>1070 ± 230</td>
<td>-37&lt;sup&gt;b&lt;/sup&gt;</td>
<td>960 ± 280</td>
<td>870 ± 210</td>
<td>-10</td>
</tr>
</tbody>
</table>

HR = heart rate; AP = mean arterial pressure; CI = cardiac index; SI = stroke index; LVFP = left ventricular filling pressure; SVR = systemic vascular resistance.

<sup>a</sup>p < .05; <sup>b</sup>p < .001 for before vs after captopril.

rate declined slightly. The changes in exercise hemodynamics after captopril were less marked, with only the change in heart rate achieving significance.

Clinical response to captopril. All 14 patients were maintained on captopril. Ten received a total of 300 mg daily, while four were maintained on 150 or 75 mg doses because of persistent hypotension. Diuretic dosage was decreased in six patients, but no other adjustments in medication were made.

The outcome of therapy at 3 months in the individual patients is shown in table 3. At 3 months clinical class had improved from 3.1 ± 0.6 to 2.3 ± 0.5 (p < .001). Individual responses were variable, with eight subjects improving by 1.0 or more class (clinical responders) and six by 0.5 or not at all (clinical nonresponders). After 3 months on captopril, exercise tolerance rose from 10.2 ± 2.6 to 12.7 ± 2.4 min (p < .001). It increased in 12 of 14 patients, by more than 2 min in nine (the exercise responder group) and by less than 2 min in five (the exercise nonresponders). Ejection fraction rose from 0.19 ± 0.05 to 0.24 ± 0.06 (p < .01), with 11 of 14 patients exhibiting increases. Cardiothoracic ratio fell from 0.60 ± 0.04 to 0.57 ± 0.05 (p < .05), with nine of 14 patients exhibiting a decrease.

Relationship of pretreatment measurements to 3 month responses. The correlations between the pretreatment hemodynamic measurements and the subsequent changes in clinical class, exercise tolerance, ejection fraction, or cardiothoracic ratio were all nonsignificant. Table 4 lists the various measurements made before instituting captopril therapy in the groups of patients classified as responders and nonresponders by clinical criteria and exercise tolerance. There were no significant differences, except for a slightly lower initial mean arterial pressure in the group in which exercise tolerance increased.

Relationship of the short-term hemodynamic effects of captopril to the 3 month responses. Table 5 lists the correlation coefficients between the short-term changes in the various hemodynamic measurements in patients on captopril and the subsequent changes in exercise tolerance, clinical class, cardiothoracic ratio, and ejection fraction. Very few of these correlations were significant, even before the Bonferroni correction was applied, and none of the relationships were close enough to allow prediction of responses in individual patients. Only the correlation between the initial change in arterial pressure and the subsequent change in clinical class (r = - .86) achieved significance at the .001 level required by the Bonferroni correction. Clinical class improved more in the patients in whom blood pressure fell the least initially. The only appreciable relationship between any exercise hemodynamic mea-
massie et al.

TABLE 4
Relationship of pretreatment measurements to 3 month response

<table>
<thead>
<tr>
<th></th>
<th>Exercise tolerance</th>
<th>Clinical class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resp</td>
<td>Nonresp</td>
</tr>
<tr>
<td></td>
<td>HR (bpm)</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>85 ± 14</td>
<td>89 ± 9</td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>85 ± 11</td>
<td>96 ± 12</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>1.9 ± 0.3</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>24 ± 5</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>LVFP (mm Hg)</td>
<td>27 ± 10</td>
<td>23 ± 9</td>
</tr>
<tr>
<td>SVR (dynes-sec-cm⁻²)</td>
<td>1700 ± 200</td>
<td>1890 ± 4010</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.20 ± 0.06</td>
<td>0.19 ± 0.5</td>
</tr>
<tr>
<td>CT ratio</td>
<td>0.60 ± 0.08</td>
<td>0.59 ± 0.02</td>
</tr>
<tr>
<td>Clinical class</td>
<td>3.2 ± 0.7</td>
<td>2.9 ± 0.4</td>
</tr>
</tbody>
</table>

Exercise

|                         |                |
| Cl (l/min/m²)           | 3.5 ± 1.0      | 4.2 ± 0.6      | 3.8 ± 0.8      | 3.8 ± 1.1       |
| SI (ml/m²)              | 30 ± 2         | 31 ± 4         | 30 ± 5         | 31 ± 10         |
| LVFP (mm Hg)            | 39 ± 10        | 34 ± 5         | 39 ± 10        | 34 ± 5          |
| Exercise tolerance (min)| 9.9 ± 3.1      | 10.8 ± 0.7     | 10.0 ± 3.0     | 10.7 ± 12       |

Resp = responders; Nonresp = nonresponders; others as in table 2.

*Significant difference between responders and nonresponders (p < .05).

Measurement and the subsequent response was that between the captopril-induced decline in left ventricular filling pressure and the improvement in clinical class (r = .63).

Table 6 and figure 1 present the changes in the various hemodynamic indexes for the responders and nonresponders. There were several statistically significant differences between the responders and nonresponders, but these were usually small and overlap existed between the groups. The greatest difference was in the short-term change in blood pressure. Mean arterial pressure fell by 10 mm Hg in the patients who improved by at least 1.0 clinical class, but dropped much further (28 mm Hg; p < .001) in those who did not. In fact, the arterial pressure decreased less in the responders, as defined by each of the outcome categories, although the other differences were not significant.

Of note is that the short-term changes in resting cardiac index were identical in those who appeared to improve the most and those who showed less change during continued therapy and that the filling pressure responses in the two groups differed very little. The maximum exercise cardiac index rose from 3.7 to 4.1 in the patients who subsequently increased their exercise tolerance by at least 2 min, while it fell in those who did not (p < .01). However, there were no significant differences in the exercise cardiac output response when the patients were stratified according to the other outcome criteria. Otherwise, analysis of exercise hemodynamics yielded few significant findings.

Relationship between hemodynamic measurements at 3 months and clinical responses. Only seven patients underwent recatheterization during maintenance therapy and they exhibited significant hemodynamic improvement. These findings have been published previously.

Five of these met the criteria for exercise tolerance and were considered clinical responders. They showed the greatest beneficial changes in both resting and exercise hemodynamics.

Discussion

Numerous previous studies have demonstrated that captopril is an effective drug in many patients with

TABLE 5
Correlations between hemodynamic changes induced by captopril and 3 month response

<table>
<thead>
<tr>
<th></th>
<th>Δ Exercise</th>
<th>Δ Clinical class</th>
<th>Δ CT ratio</th>
<th>Δ Ejection fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔHR (bpm)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.43</td>
<td>0.50</td>
<td>0.14</td>
<td>-0.45</td>
</tr>
<tr>
<td>ΔAP (mm Hg)</td>
<td>0.47</td>
<td>-0.86&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.24</td>
<td>0.62&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ΔCI (l/min/m²)</td>
<td>0.18</td>
<td>-0.01</td>
<td>-0.45</td>
<td>0.05</td>
</tr>
<tr>
<td>ΔSI (ml/m²)</td>
<td>0.43</td>
<td>-0.31</td>
<td>0.07</td>
<td>0.23</td>
</tr>
<tr>
<td>ΔLVFP (mm Hg)</td>
<td>-0.30</td>
<td>0.10</td>
<td>0.19</td>
<td>-0.35</td>
</tr>
<tr>
<td>ΔSVR (dynes-sec-cm⁻²)</td>
<td>0.58&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.56&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.49</td>
<td>0.40</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔCI (l/min/m²)</td>
<td>0.27</td>
<td>-0.29</td>
<td>-0.33</td>
<td>0.14</td>
</tr>
<tr>
<td>ΔSI (ml/m²)</td>
<td>0.23</td>
<td>-0.48</td>
<td>-0.27</td>
<td>0.47</td>
</tr>
<tr>
<td>ΔLVFP (mm Hg)</td>
<td>-0.31</td>
<td>0.63&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.10</td>
<td>-0.40</td>
</tr>
</tbody>
</table>

Abbreviations are as in tables 2 and 4.

*For these correlations absolute change in the hemodynamic variables and outcome measurements were used. Correlations between the percent changes were generally poorer.

<sup>a</sup>p < .05; <sup>b</sup>p < .01; <sup>c</sup>p < .001.
TABLE 6  Relationships of short-term hemodynamic effects of captopril to 3 month response

<table>
<thead>
<tr>
<th>Exercise tolerance</th>
<th>Clinical class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resp</td>
<td>Nonresp</td>
</tr>
<tr>
<td>Rest</td>
<td></td>
</tr>
<tr>
<td>ΔHR (bpm)</td>
<td></td>
</tr>
<tr>
<td>ΔAP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>ΔCI (l/min/m²)</td>
<td></td>
</tr>
<tr>
<td>ΔSI (ml/m²)</td>
<td></td>
</tr>
<tr>
<td>ΔLVFP (mm Hg)</td>
<td></td>
</tr>
</tbody>
</table>

Values given are the actual changes in each measurement. The per-
cent change can be calculated using the baseline measurements given in
table 4, examined by the same procedures. They did not provide better
separation between responders and nonresponders.

Abbreviations are as in tables 2 and 4.

There was essentially no difference in the pretreatment
hemodynamic profile or in heart size, ejection frac-
tion, clinical class, or exercise tolerance between the
responders and nonresponders. More importantly, es-
sentially all of the correlations between the short-term
hemodynamic responses and the changes in outcome
measurements (shown in table 5) were insignificant or,
if significant, they were too loose to permit prediction
of response in individual subjects. The only possible
exception was the inverse relationship between the
magnitude of the initial blood pressure drop and the
subsequent improvement (reduction) in clinical class,
which was the least objective of the outcome mea-
sures. The inverse relationships between the initial
reduction in blood pressure and systemic resistance
and the various measurements of clinical response are
difficult to explain. They may indicate that compensat-
ed patients in whom the renin-angiotensin system is
less active ultimately improve more. Levine and Cohn12
have reported the opposite relationship be-
tween the short-term change in blood pressure and
chronic congestive heart failure. However, sever-
al practical issues arise with the use of captopril, just as
with other vasodilators. Foremost among these are the
role of hemodynamic measurements during the initi-
ation of therapy and the proper approach to the follow-
up and the objective assessment of response in these
patients.

Value of hemodynamic measurements. Hemodynamic
measurements have frequently been used to study the
short-term response to vasodilator drugs, both to con-
firm the rationale for their use and to provide data
about their differing mechanisms of action.17 This infor-
mation has been used, sometimes erroneously, to
justify long-term treatment with new drugs. Little in-
formation is available about the relationship between
the short-term hemodynamic effects of vasodilators
and the subsequent clinical response.18 The studies ex-
amining this relationship have not found the short-term
hemodynamic measurements to be predictive,12, 15, 19–20
but few of these studies were prospective or included
systematic, objective assessments of response in stable
patients whose subsequent course could be considered
to reflect drug effect rather than the natural history of
the underlying disease or associated interventions.
Despite this dearth of information, short-term hemody-
namic monitoring is frequently instituted to evaluate the
clinical efficacy of vasodilator therapy.

Our findings do not support the value of this ap-
proach for stable, ambulatory patients treated with the
angiotensin converting–enzyme inhibitor captopril.

FIGURE 1. The short-term resting hemodynamic effects of captopril in
the nine patients considered exercise responders because their exercise
tolerance subsequently improved by more than 2 min (stippled bars) are
compared with those in five in whom it improved less or not at all
(hatched bars). The data are percent change from the pretreatment
values. The only significant difference was the 6 beats/min decline in
heart rate in the responders, with no change in the nonresponders.
The lesser drops in arterial pressure and systemic vascular resistance in
the responders did not achieve significance. Of note was the lack of dif-
fences in the short-term responses of cardiac index and left ventricular
filling pressure between the groups. A similar lack of hemodynamic
differences was present when the responses were classified by the
change in clinical class, ejection fraction, or cardiothoracic ratio.

Vol. 69, No. 6, June 1984
subsequent changes in exercise tolerance \( (r = .67) \), but their correlation predominantly reflected changes in three patients with extremely poor baseline tolerance who were below the entry limits for our study. In addition to the lack of close correlations between the hemodynamic responses and outcome of therapy, there were few differences in the short-term hemodynamic effects of captopril at rest in the responders compared with the nonresponders, whether evaluated as absolute or percent changes.

In a previous study examining the relationship between the short-term hemodynamic effects of hydralazine and nitrates and the subsequent change in exercise tolerance, we noted that the magnitude of the reduction in left ventricular filling pressure during exercise might be the most helpful measurement in predicting the response to treatment.\(^{24}\) In the present study, left ventricular filling pressure also fell to a greater extent in the responders, and this difference was significant in the groups categorized by change in clinical class. The responders also differed significantly in their change in exercise cardiac index. However, the actual correlations between these short-term changes in exercise hemodynamics and subsequent responses to therapy were too loose to make the measurements predictive. The one positive finding was that the hemodynamic changes observed at the 3 month recatheterization did agree with the other assessments.

Several qualifications to these findings should be emphasized. The study population was narrowly defined to include only stable, normotensive patients who were capable of exercise and whose limiting symptoms were due to heart failure. This permitted us to assume that changes during follow-up were likely to reflect the effects of captopril. Such patients may not be representative of those described in most published studies of vasodilator drugs, and the short-term hemodynamic changes may be more predictive of clinical response in sicker subjects. A second qualification is that our results are valid only for captopril and should not be extrapolated to other drugs. Captopril is unique among the currently available vasodilators in that it has multiple hormonal as well as circulatory actions.\(^{28}\) Some of these, such as the inhibition of aldosterone production, may take time to become fully manifest; thus, they would not be expected to affect the short-term hemodynamic response as much as the clinical outcome. Others, such as the transient changes in plasma or tissue kinin and prostaglandin activity, may produce short-term hemodynamic effects but not be involved in the long-term clinical response.\(^{28-30}\) It should be noted, however, that although captopril is a unique drug, evidence for the predictive value of short-term hemodynamic measurements for other drugs is lacking.\(^{20-24, 26}\)

Several limitations of the present study should also be mentioned. The number of subjects is relatively small. Our inability to demonstrate a significant relationship between the short-term hemodynamic responses and the outcome of therapy may represent a type 2 statistical error. Important associations may have been missed. However, given the weak correlations that were found, it is very unlikely that the short-term measurements would turn out to be predictive of the clinical response in individual subjects. It should be noted that most patients were usually maintained on 50 or 100 mg tid dosages of captopril, while in the short-term hemodynamic evaluation patients on 25 mg doses at rest and 50 mg doses during exercise were followed. We cannot exclude the possibility that better correlations would have been found if we had used the higher dosages initially, but this is often not feasible because patients may develop acute hypotension. Furthermore, several studies have demonstrated a flat dose-response curve during the short-term hemodynamic evaluation of captopril.\(^{11, 12, 31}\) Ten of our patients were evaluated after both 25 mg and 50 mg doses, and there were no differences in their hemodynamic responses. Finally, this study was uncontrolled and the clinical evaluations and possibly even the exercise measurements are somewhat subjective. However, it should be noted that in our previous blinded, controlled evaluation of captopril no patient receiving placebo exhibited a 2 min improvement in exercise tolerance, so we feel this degree of response represents drug effect. Furthermore, the short-term hemodynamic measurements were not known to the physician administering the exercise tests or clinical evaluations.

Measurements of plasma renin activity were not made in these patients because they were not hospitalized for the period of dietary stabilization that is required to obtain meaningful values. Others have reported mixed results in correlating plasma renin with short-term hemodynamic responses,\(^{12, 25, 27, 32}\) but the relationship between plasma renin levels and long-term clinical response is poor.\(^{25, 27}\)

Implications. Our results suggest that routine hemodynamic measurements during the institution of captopril therapy are unnecessary, since they provide little predictive information about the subsequent response. In light of these findings, the value of routine hemodynamic monitoring with other drugs should be carefully assessed. The lack of a need to hospitalize and invasively monitor patients could result in a considerable
reduction in cost and inconvenience and may permit more widespread use of vasodilators in less symptomatic patients.

Undoubtedly, hemodynamic measurements retain an important role in the treatment of some heart failure patients. They should still be made when questions of which vasodilators can be administered. Hemodynamic efficacy.

Finally, hemodynamic measurements remain a valuable tool for evaluating reduction in cost and inconvenience and may permit other patients whose conditions are complex or rapidly deteriorating. They may help prevent undesirable hemodynamic responses and increase the safety with which vasodilators can be administered. Hemodynamic measurements performed after several months of continuous therapy have been shown to correlate with the degree of improvement. Finally, hemodynamic measurements remain a valuable tool for evaluating new drugs and investigating mechanisms of action, but they should not be used as the sole criteria for therapeutic efficacy.

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