Long-term Vasodilator Therapy for Heart Failure: Clinical Response and its Relationship to Hemodynamic Measurements

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SUMMARY To assess the clinical efficacy of chronic vasodilator therapy for refractory congestive heart failure, the long-term follow-up (mean 13 months, range 3–30 months) was evaluated in 56 patients treated with hydralazine, usually in combination with nitrates. In the first 6 months, 73% improved subjectively and 59% improved by one or two New York Heart Association classifications; early improvement was usually sustained. Mortality was high, 22% at 6 months and 37% at 12 months, but was significantly lower in patients who had a clinical response to vasodilators (21% in responders vs 55% in nonresponders at 1 year). The only clinical indicator that differentiated responders from nonresponders was the presence or absence of symptomatic progression before initiation of vasodilator therapy. Pulmonary artery pressure, pulmonary capillary wedge (PCW) pressure and stroke work index (SWI) before and during vasodilator therapy correlated with clinical response and survival. Fifteen of 20 patients with PCW < 20 mm Hg and SWI ≥ 30 g-m/m² improved and survived, compared with two of 19 with PCW ≥ 20 mm Hg and SWI < 30 g-m/m². Patients who did not have acute hemodynamic improvement generally did not improve clinically, but neither the percentage change nor the absolute change in any hemodynamic variable predicted outcome in the remaining patients. The findings of this study indicate that vasodilators produce clinical improvement in many patients with refractory heart failure and that hemodynamic measurements are helpful in predicting the outcome of therapy.

THE USE of vasodilating drugs to treat patients with chronic congestive heart failure has become increasingly popular.1-3 Numerous studies have documented the acute hemodynamic efficacy of this approach,4-18 and several have shown that hemodynamic improvement persists for at least several months.17-18 However, only a few have reported even the short-term clinical response of these patients. More recently, improved exercise tolerance was shown in small groups of patients receiving vasodilators as part of blinded, placebo-controlled studies, but acute hemodynamic measurements were not reported.11, 20-22 Therapy with all of the commonly used vasodilating drugs has been associated with troublesome side effects in some patients,29 and each of these agents has the potential for producing hypotension, tachycardia and worsening of ischemia.24 Therefore, further information is needed concerning the clinical response and mortality of patients chronically receiving vasodilator therapy and on the relationship of outcome variables to the initial hemodynamic response to these medications.

In the present study, we evaluated long-term follow-up of 56 patients treated with oral hydralazine and nonparenteral nitrates for chronic, relatively stable congestive heart failure. We also analyzed the relationship of clinical response to the initial hemodynamic measurements and to the changes produced by vasodilator therapy.

Methods

Patients

We reviewed the charts of all patients who underwent right-heart catheterization and hemodynamic monitoring for the purpose of initiating vasodilator therapy during a 30-month period beginning January 1, 1976. Sixty-seven patients were identified who had had congestive heart failure secondary to left ventricular dysfunction for at least 6 months and who had not manifested any major change in clinical status before treatment. Patients with acute myocardial infarction or sudden worsening of failure in the 3 months before admission were excluded. Those with gradual progression of symptoms, such as increasing limitation of exercise tolerance or greater diuretic requirements, were included and classified as “worsening.” All patients were significantly symptomatic despite what was considered to be optimal therapy with digoxin and diuretics.

Fifty-nine of these were treated with oral hydralazine either alone (eight patients) or in combination with nitrates (51 patients). The remaining eight patients received a variety of vasodilating drugs and therefore, for the sake of uniformity, were not considered in this study. This report is based upon the 56 of these 59 patients in whom adequate follow-up data were available.

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Some of the pertinent clinical information concerning the patients is included in table 1. Thirty-seven males and 19 females were studied. The etiology of heart failure was ischemic heart disease in 34, primary myocardial disease in nine, hypertension in seven, rheumatic heart disease in four, and uncertain in two. The mean duration of heart failure was 3.5 years (range 6 months to 17 years). Before initiation of therapy, symptoms of heart failure were gradually worsening in 30 patients and stable in 26. When vasodilator therapy was instituted, 45 patients were in New York Heart Association (NYHA) class IV and 11 were in class III.\(^2\)

### Hemodynamic Measurements and Initiation of Vasodilator Therapy

Patients were admitted to the coronary care unit for hemodynamic monitoring and initiation of vasodilator therapy. All other medications were continued at their previous dosages.

Right-heart catheterization was performed with a balloon-tipped, triple-lumen catheter. Baseline measurements of right atrial (RA), pulmonary artery (PA) and pulmonary capillary wedge (PCW) pressures were obtained. Arterial pressure (AP) was monitored by sphygmomanometry in 26 patients and by an indwelling radial artery cannula in 30 patients. Mean arterial pressure (MAP) was determined electronically or estimated from the formula $MAP = D + (S - D)/3$, where $S$ is the systolic and $D$ the diastolic pressure. Mean systolic artery pressure (SAP) was estimated as $SAP = S - (S - D)/3$. Cardiac output (CO) was measured in triplicate using the thermodilution technique. From these measurements were calculated: cardiac index (CI, l/min/m\(^2\) = CO/body surface area (BSA); stroke volume index (SVI, ml/m\(^2\)) = CI/HR; stroke work index (SWI, g-m/m\(^2\)) = SVI × (SAP–PCW) × 0.0136; systemic vascular resistance (SVR, dyn-sec-cm\(^5\)) = 80 × (MAP–RA)/CO.

Vasodilator therapy with hydralazine and nitrates was initiated according to the protocol we have described previously.\(^1\) Maintenance doses were 200–400 mg of hydralazine daily and 5–20 mg of sublingual isosorbide dinitrate every 2–3 hours or 40–80 mg of oral isosorbide dinitrate every 4–6 hours. Hemodynamic monitoring was continued throughout the 36–72-hour period of medication adjustment. The measurements chosen to indicate the acute effect of vasodilators were those taken on the subsequent discharge regimen and were selected by an observer unaware of the patients’ clinical responses. Medication dosing was planned so that measurements could be obtained at the expected time of peak vasodilator effect. Care was taken to use measurements that were representative and removed in time from the administration of other potentially vasoactive medications (including diuretics) or from meals.

### Clinical Follow-up

Thirty-six patients were followed by the authors themselves or under their supervision. The referring physicians of the remaining patients were contacted to determine medication dosing, compliance and clinical status. In most cases, the patients were also interviewed to assess their subjective response and compliance. When the cause or nature of death was not known by the primary physician, relatives were contacted to obtain this information.

Patients were evaluated at two points in their clinical course after the institution of vasodilator therapy — early (1–6 months, mean 3 months) and at their latest physician visit (7–30 months, mean 13 months). The patients’ subjective responses to therapy were graded on a five-point scale (worsening, no change, and slight, moderate or marked improvement); NYHA clinical classifications were also assessed. Patients who had a symptomatic response were classified as improved even if they later died. The

### Table 1. Clinical Characteristics and their Relationship to Outcome

<table>
<thead>
<tr>
<th></th>
<th>Entire group</th>
<th>Improved‡</th>
<th>Unimproved</th>
<th>Survivors</th>
<th>Cardiac death</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>56</td>
<td>32</td>
<td>24</td>
<td>27</td>
<td>27</td>
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<tr>
<td>Age (years)</td>
<td>62</td>
<td>60</td>
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<td>64</td>
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<tr>
<td>Males</td>
<td>37</td>
<td>22</td>
<td>15</td>
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<td>Females</td>
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<tr>
<td>Coronary disease</td>
<td>33</td>
<td>19</td>
<td>14</td>
<td>16</td>
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<tr>
<td>Hypertension</td>
<td>21</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Duration of CHF (years)</td>
<td>3.5</td>
<td>3.4</td>
<td>3.6</td>
<td>3.3</td>
<td>3.7</td>
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<tr>
<td>NYHA class III</td>
<td>11</td>
<td>5</td>
<td>6</td>
<td>9*</td>
<td>*2</td>
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<td>NYHA class IV</td>
<td>45</td>
<td>27</td>
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<tr>
<td>Progressive CHF</td>
<td>30</td>
<td>8</td>
<td>22</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Stable CHF</td>
<td>26</td>
<td>24</td>
<td>2</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

*\(p < 0.05\).
†\(p < 0.001\).
‡Improved by one or more New York Heart Association classes.

Abbreviations: NYHA = New York Heart Association; CHF = congestive heart failure.
cause of death was determined in nonsurvivors. Subjective response, change in NYHA class and survival were chosen as the primary outcome variables and were used to assess the efficacy of vasodilator therapy and to determine the relationship of initial clinical status and hemodynamic findings to outcome. Side effects and drug toxicity were also noted.

Vasodilator dosages were kept constant after discharge, except in nonresponders, in whom they were increased if tolerated. Medications were discontinued because of lack of efficacy in five patients and because of side effects in eight patients.

Data Analysis

Clinical and hemodynamic data were analyzed according to appropriate programs from the Biomedical Computer Programs (BMDP-77) statistical package. Contingency tables relating clinical characteristics to outcome variables were analyzed for significance by the chi-square statistic. The significance of changes in hemodynamic measurements before and after treatment was assessed using the paired t test. Analysis of the relationship of clinical and outcome variables to hemodynamic data was accomplished using analysis of variance. Survival curves were constructed and analyzed using the life-table method. All data are expressed as mean ± SD.

Results

Clinical Follow-up

Figure 1 is a summary of the findings at early follow-up (mean 3 months). Nine patients were considered improved by two NYHA classes and 23 by one NYHA class; 21 patients were considered unchanged or had only mild improvement and three were classified as having worsened. Because there were no clinical or hemodynamic differences between patients with various degrees of improvement, the five categories of subjective responses were combined into two: those who improved and those who did not. Forty-one patients (73%) thought they had improved in the initial months of treatment. Ten patients died of cardiac causes in the initial 6 months of therapy.

Figure 2 shows the initial and long-term follow-up in terms of improvement or lack of change in NYHA classification; eight of 10 early cardiac deaths occurred in patients who did not improve.

Thirty-six patients were followed for longer than 6 months (13 ± 5 months). Eleven patients died (one of noncardiac causes) in the first 6 months and follow-up was shorter than 6 months in nine others. Subjectively, 30 of these 36 patients felt that they were improved in the first 6 months of follow-up, and 28 of these felt that they continued to be better. The six that had not felt better initially continued to consider themselves unimproved. Overall, 78% of the 36 patients followed more than 6 months reported improvement at their last physician visit. The findings by NYHA classification were directionally similar (fig. 2). Of the 26 patients who were initially improved by at least one NYHA class, 23 (including all nine who improved by
two classes) continued to exhibit improvement. On the other hand, the 10 who did not respond early showed no late improvement. An additional 17 patients died of heart disease after the first 6 months of follow-up, giving a total cardiac mortality of 50% (27 of 54). As in the first 6 months of follow-up, most deaths came in patients who were not clinically improved.

Overall survival is plotted by the life-table method in figure 3. Two patients who died of noncardiac causes are excluded. Survival rates at 6, 12 and 18 months were 78%, 65% and 37%, respectively. Death was sudden in 10 and due to progressive heart failure in eight, myocardial infarction in five, nonspecified cardiac death in four, and carcinoma in two. Patients who were stable before vasodilator therapy had a significantly better survival than those who were worsening (fig. 4B). Patients who manifested clinical improvement during vasodilator therapy also fared better (fig. 4D), with a 79% 1-year survival, compared with a 55% 1-year survival in the nonresponders.

Because all but one of the patients were receiving diuretic therapy with furosemide, their diuretic requirements were examined to see if a change occurred. The mean diuretic dose had increased at early follow-up from 131 ± 137 mg to 154 ± 163 mg, an insignificant change overall. This increase primarily reflected a rise in dosage from 179 ± 181 mg to 222 ± 191 mg (p < 0.05) in nonresponders, as responders had no significant change in their diuretic dose. Similarly, in the patients followed longer than 6 months, the small and insignificant increase in furosemide dose from 126 ± 113 mg before vasodilator treatment to 149 ± 144 mg was accounted for by a significant increase in dosage, from 124 ± 192 to 272 ± 35 (p < 0.01) among unimproved patients. Again, patients showing an improvement in NYHA class had unchanged diuretic doses. Therefore, the clinical improvement in patients taking vasodilators was not a result of increased diuretic therapy. Digoxin doses were unchanged in both responders and nonresponders. The mean dose of vasodilating drugs was not significantly different in responders and nonresponders.

Relation of Baseline Clinical Status to Outcome

Among the 56 patients followed in this study, there was no apparent relationship between sex, age, etiology of heart failure, clinical evidence of accompanying mitral regurgitation or duration of heart failure and outcome (table 1). However, the number of patients with heart failure of some etiologies was small.

Patients initially in NYHA class IV had a significantly poorer survival rate, with nine of 10 early deaths and a higher proportion of overall deaths (table 1). The overall survival curves were not significantly different between these groups (fig. 4A). On the other hand, patients in NYHA class IV had a clinical
response similar to that of patients in class III, as assessed by both patient and physician. Thus, similar proportions of patients (five of 11 in class III, 27 of 45 in class IV) in both groups were improved by one NYHA class at early follow-up, and the proportions of patients considering themselves improved were also comparable.

Patients whose symptoms progressed fared much worse than those with stable heart failure (table 1); 24 of 26 patients with stable symptoms improved by at least one NYHA class, compared with only eight of 30 who were worsening (p < 0.001). A higher proportion of stable patients (14 of 24 vs 13 of 30) survived, but this difference was not statistically significant.

**Relationship of Pretreatment Hemodynamic Measurements to Clinical Status and Response to Treatment**

Patients in class III had lower PA pressures (33 ± 10 vs 41 ± 10 mm Hg, p < 0.025), lower PCW pressures (23 ± 7 vs 28 ± 7 mm Hg, p < 0.05), and higher CI (2.3 ± 0.4 vs 1.9 ± 0.4 l/min/m², p < 0.05) than patients in class IV. Patients who were stable before the study had lower PCW pressures than those with progressive heart failure (24 ± 5 vs 30 ± 8 mm Hg, p < 0.005), but otherwise were hemodynamically similar. There was no significant correlation between the pretreatment hemodynamic measurements and the other clinical characteristics listed in table 1.

Some of the initial hemodynamic variables were significantly related to the subsequent response to therapy. Patients who initially improved by at least one NYHA class had lower pretreatment PA pressures (37 ± 11 vs 43 ± 8 mm Hg, p < 0.05) and lower PCW pressures (24 ± 6 vs 32 ± 6 mm Hg, p < 0.001). Pretreatment CI and SWI and other hemodynamic measurements did not correlate with symptomatic response. Symptomatic status at late follow-up was correlated only with the PCW pressure.

Patients who died either during early follow-up or later tended to have both higher initial heart rates and lower mean arterial pressures, but these differences were significant only for blood pressure in patients who died during the initial 6 months (94 ± 19 mm Hg for survivors vs 81 ± 11 mm Hg for nonsurvivors, p < 0.05). The differences in PCW pressure and SWI between survivors and nonsurvivors were much more striking, both during early follow-up and overall (table 2).

Figure 5A illustrates the ability of the pretreatment PCW pressure and SWI to indicate the prognosis of these patients with vasodilator therapy. Patients are categorized by whether they improved by at least one

| Table 2. Relationship of Pretreatment Hemodynamic Measurements to Subsequent Response |
|--------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | HR (beats/min) | AP (mm Hg) | PA (mm Hg) | PCW (mm Hg) | CI (l/min/m²) | SWI (g-m/m²) |
| Early change in NYHA class     |                |            |            |              |                |                |
| Improved                       | 82 ± 14        | 91 ± 16    | 37 ± 11    | 24 ± 6       | 2.0 ± 0.4      | 30 ± 14        |
| Unimproved                     | 89 ± 15        | 93 ± 20    | 43 ± 8     | 32 ± 6       | 2.0 ± 0.5      | 26 ± 13        |
| Early subjective response      |                |            |            |              |                |                |
| Improved                       | 85 ± 15        | 92 ± 17    | 38 ± 10    | 25 ± 7       | 2.0 ± 0.4      | 30 ± 13        |
| Unimproved                     | 88 ± 14        | 90 ± 20    | 44 ± 8     | 32 ± 5       | 2.0 ± 0.6      | 24 ± 13        |
| Late change in NYHA class      |                |            |            |              |                |                |
| Improved                       | 84 ± 14        | 91 ± 18    | 36 ± 12    | 23 ± 6       | 2.0 ± 0.4      | 30 ± 12        |
| Unimproved                     | 87 ± 13        | 100 ± 22   | 41 ± 10    | 30 ± 7†      | 2.2 ± 0.7      | 35 ± 18        |
| Late subjective response       |                |            |            |              |                |                |
| Improved                       | 84 ± 3         | 95 ± 21    | 37 ± 12    | 24 ± 6       | 2.1 ± 0.4      | 32 ± 14        |
| Unimproved                     | 88 ± 15        | 87 ± 10    | 43 ± 10    | 31 ± 8       | 2.2 ± 0.8      | 26 ± 12        |
| Early survival                 |                |            |            |              |                |                |
| Alive                          | 85 ± 14        | 94 ± 19    | 39 ± 11    | 26 ± 6       | 2.0 ± 0.5      | 30 ± 14        |
| Cardiac death                  | 90 ± 19        | 81 ± 11    | 43 ± 8     | 35 ± 6†      | 1.9 ± 0.3      | 18 ± 6†        |
| Overall survival               |                |            |            |              |                |                |
| Alive                          | 82 ± 12        | 96 ± 18    | 37 ± 10    | 24 ± 5       | 2.2 ± 0.4      | 34 ± 14        |
| Cardiac death                  | 89 ± 17        | 88 ± 17    | 43 ± 9     | 31 ± 7†      | 1.9 ± 0.4      | 23 ± 11†       |

* p < 0.05.
† p < 0.001.
‡ p < 0.001.

Abbreviations: HR = heart rate; AP = mean arterial pressure; PA = mean pulmonary artery pressure; PCW = pulmonary capillary wedge pressure; CI = cardiac index; SWI = stroke work index.
NYHA class and whether they survived. Most patients with both SWI \( \geq 30 \text{ g-m/m}^2 \) and PCW below 30 mm (nine of 13) improved and survived, whereas 11 of 16 with both SWI < 30 g-m/m² and PCW \( \geq 30 \text{ mm} \) never improved and subsequently died. The outcome of patients with SWI \( \geq 30 \text{ g-m/m}^2 \) and PCW < 30 mm and those with PCW \( \geq 30 \text{ mm} \) but SWI < 30 g-m/m² were more variable, but generally an initial PCW \( \geq 30 \text{ mm} \) correlated with a failure to improve (28 of 32 with PCW < 30 mm Hg improved vs five of 22 with PCW \( \geq 30 \text{ mm} \), \( p < 0.001 \)) and a SWI < 30 g-m/m² correlated with cardiac death (21 of 35 with low SWI died vs six of 19 with SWI \( \geq 30 \text{ g-m/m}^2 \), \( p < 0.05 \)).

Relationship of Hemodynamic Changes During Initiation of Vasodilator Therapy to Subsequent Clinical Response

Table 3 lists the hemodynamic measurements during the initiation of vasodilator therapy. The typical hemodynamic response to hydralazine and nitrates was noted. Heart rate was essentially unchanged and blood pressure decreased modestly. PA and PCW pressure both decreased significantly, while CI, SWI and PCW all increased markedly due to a decrease in systemic resistance.

The data were examined to determine whether the measurements during vasodilator therapy or the magnitude of change produced by vasodilators predicted the subsequent clinical response (table 4). Patients manifesting early improvement in NYHA class had significantly lower PA pressures (28 \( \pm 9 \) vs 37 \( \pm 8 \) mm Hg, \( p < 0.001 \)) while taking vasodilators. Similar differences in these measurements were present between patients who felt improved and those who did not (table 4). CIs during vasodilator therapy were similar in the improved and unimproved groups, but SWI was somewhat higher in improved patients. There were no significant relationships between the initial hemodynamic measurements on vasodilators and late symptomatic status. Significant relationships were present between PCW pressure and SWI and both early and overall mortality (table 4). A plot of SWI vs PCW on vasodilators (fig. 5B) indicates how these measurements predicted subsequent response and survival. Fifteen of 20 patients with SWI \( \geq 30 \text{ g-m/m}^2 \) and PCW < 20 mm Hg during vasodilator therapy improved and were long-term survivors, compared with five of 34 with either SWI < 30 g-m/m² or PCW > 20 mm Hg (\( p < 0.001 \)) and only two of 17 with both of these abnormalities.

Although both the pretreatment and initial vasodilator measurements were useful in predicting which patients would improve and survive, the actual magnitude of change in the hemodynamic measurements was helpful primarily in selecting a small group of clinical nonresponders. Patients who did not improve hemodynamically almost invariably experienced no symptomatic improvement. Nine of 11 subjects who manifested no change in PA or PCW pressures and all four who had less than 10% increase in cardiac output failed to improve. However, among patients who did experience a hemodynamic response to vasodilators, neither the absolute change nor the percentage change in any hemodynamic variable correlated well with subsequent clinical response. While improving patients and survivors had a greater reduction in PA and PCW pressures, these differences were not statistically significant (table 4).

Adverse Reactions to Vasodilator Therapy and Discontinuation of Therapy

Side effects and drug toxicity were not uncommon during vasodilator therapy with the combinations of
TABLE 4.  Relationship of Initial Hemodynamic Measurements on Vasodilators to Subsequent Response

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Vasodilators</th>
<th>Change</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>86 ± 15</td>
<td>88 ± 15</td>
<td>+4%</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>92 ± 18</td>
<td>81 ± 14</td>
<td>−10%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean PA pressure (mm Hg)</td>
<td>40 ± 10</td>
<td>32 ± 10</td>
<td>−19%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PCW pressure (mm Hg)</td>
<td>27 ± 7</td>
<td>19 ± 7</td>
<td>−29%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RA pressure (mm Hg)</td>
<td>12 ± 7</td>
<td>11 ± 7</td>
<td>−12%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.0 ± 0.5</td>
<td>2.8 ± 0.6</td>
<td>+46%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>24 ± 7</td>
<td>33 ± 8</td>
<td>+42%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroke work index (g-m/m²)</td>
<td>28 ± 13</td>
<td>36 ± 12</td>
<td>+41%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systemic resistance (dyn-sec/cm⁵)</td>
<td>1900 ± 500</td>
<td>1210 ± 400</td>
<td>−33%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: PA = pulmonary artery; PCW = pulmonary capillary wedge; RA = right atrial.

TABLE 3.  Hemodynamic Changes During Initiation of Vasodilator Therapy

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>Vasodilators</th>
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In the past several years, several vasodilating drugs have been shown to produce acute hemodynamic improvement in patients with chronic heart failure. However, this, in part, reflected the reluctance of physicians to discontinue therapy in patients with mild or even moderate side effects when they were apparently responding. Therapy was also discontinued in five other patients, all of whom were clinical nonresponders. As a result of this selection process, it is not surprising that mortality was significantly higher in the 15 patients who discontinued vasodilator therapy (fig. 4C).

**Discussion**

**Present Status of Vasodilator Therapy for Chronic Heart Failure**

In the past several years, several vasodilating drugs have been shown to produce acute hemodynamic improvement in patients with chronic heart failure. However, this, in part, reflected the reluctance of physicians to discontinue therapy in patients with mild or even moderate side effects when they were apparently responding. Therapy was also discontinued in five other patients, all of whom were clinical nonresponders. As a result of this selection process, it is not surprising that mortality was significantly higher in the 15 patients who discontinued vasodilator therapy (fig. 4C).
Few studies have evaluated the clinical efficacy of vasodilator therapy and none have examined its long-term results. Although the drugs used for vasodilator therapy have been chosen for their acute hemodynamic effect, little information is available concerning the relationship between the immediate hemodynamic changes and the results of chronic therapy. Recently, Fitchett and associates reported hemodynamic measurements and short-term (4 months) clinical follow-up in a small group of patients given hydralazine.\(^7\) Hemodynamic improvement occurred in almost all patients and was sustained in the seven who were restudied. In contrast, after several doses, prazosin appears to have a relatively weak hemodynamic effect at rest,\(^3\) but it has been shown to produce a sustained improvement in exercise capacity.\(^2\)

The institution of vasodilator therapy frequently entails hospitalization and right-heart catheterization. Further, vasodilating drugs are associated with side effects and have the potential to produce serious adverse reactions.\(^2\) Therefore, further data documenting the clinical efficacy of vasodilator therapy and reliable criteria for choosing patients who are likely to benefit from it are needed.

**Findings**

In the present study, many patients with severe, relatively stable chronic heart failure improved during the first 6 months of vasodilator therapy, both subjectively (73%) and by their physician’s evaluation of their NYHA class (59%). This improvement persisted during more long-term follow-up in most surviving patients.

There was no control group of patients who did not receive vasodilators in this study and the evaluations of clinical response were subjective, so it is not possible to ascribe the improvement to vasodilator therapy with absolute certainty. However, several factors suggest that this was the case. The patients were either symptomatically stable or gradually worsening. Heart failure had been present for a mean of 3½ years, and in no case for less than 6 months. Such patients are not likely to manifest significant spontaneous improvement. Further, the improvement, when it occurred, tended to be sustained. The change in status also could not be explained by a change in medications other than vasodilators. In particular, diuretic dosage was not changed in the patients who experienced improvement, although it was increased in those who deteriorated. Vasodilators were discontinued in 15 patients because of adverse effects or at the wish of the referring physician; these patients fared significantly worse than those who remained on therapy. Only one was symptomatically improved after discontinuation of therapy, although five had shown improvement earlier.

Previous investigators have suggested a sustained beneficial response to vasodilators, including a sustained increase in exercise capacity with prazosin and trimazosin.\(^2,\)\(^3\) Other investigators have confirmed that the hemodynamic changes produced by hydralazine and nitrates are sustained.\(^1,\)\(^7\)\(^-\)\(^9\) While these findings are not necessarily equivalent to clinical improvement, they do suggest that vasodilators are chronically effective. Because hemodynamic measurements were not repeated, we cannot be certain that the initial drug effects were sustained.

The mortality rate of this group of patients was substantial (22% at 6 months and 35% at 12 months). Again, without a comparable control group it is difficult to speculate whether vasodilators resulted in a change in prognosis. The patients who discontinued vasodilator therapy had a significantly higher mortality than those who remained on therapy (fig. 4C). However, these patients do not constitute an adequate control group, as medications were often stopped at least in part due to a lack of response.

Although no comparable group of patients has been reported, the prognosis of patients with chronic heart failure has been examined. Mortality rates ranged from 39–80% in the initial 1–2 years of follow-up in comparably ill patients.\(^20\)\(^-\)\(^25\) In the Framingham study,\(^3\) the natural history of congestive heart failure was examined prospectively, and 20.5% and 14.0% 1-year rates and 61.5% and 43.3% 5-year mortality rates for men and women, respectively, after the first occurrence of heart failure were reported. While these latter mortality rates are substantially lower than ours, this is probably because our patients were already refractory to conventional therapy and had had heart failure for a mean of 3½ years. Of particular interest is the significantly better survival of patients who showed a clinical response to vasodilators, 79% of whom were alive after 1 year (fig. 4D). However, it is not clear whether these patients represent a subgroup whose prognosis was actually improved by vasodilators or whether their potential to manifest symptomatic improvement merely indicated better cardiac reserve and a better prognosis.
Predictors of Response to Vasodilator Therapy

Because the response to vasodilators was variable, we sought to determine whether any clinical or hemodynamic variables were predictive. Clinically, only the lack of progressive heart failure indicated a better response. In patients with gradually worsening heart failure, most of whom did not show clinical improvement, it seems likely that any initial hemodynamic improvement may have been obscured by further deterioration of cardiac function.

Hemodynamic measurements were more helpful in discriminating responders from nonresponders. Patients with the worst cardiac function were least likely to respond. Subjects with high PA pressures and high PCW pressures (≥ 30 mm Hg) showed little improvement and had a high mortality. Patients with low SWI (< 30 g·m/m²) had a significantly worse mortality. The combination of these two measurements correlated highly with subsequent outcome.

Hemodynamic measurements after the initiation of vasodilator therapy were also useful in predicting response and survival. Patients whose PCW remained above 20 mm Hg had a significantly smaller chance of improving and a higher mortality. Patients whose SWI remained below 30 g·m/m² also had a significantly higher mortality. Conversely, 90% of patients in whom SWI was above 30 g·m/m² and PCW was below 20 mm Hg during vasodilator therapy, improved and 80% were long-term survivors. A similar relationship between survival and the severity of the hemodynamic derangement has been reported in patients with chronic heart failure.4, 38

Unfortunately, the indicators often used to evaluate the efficacy of vasodilator therapy, such as the absolute change or percentage change in one or more hemodynamic variables, did not predict response as well. This reflected the fact that nearly all patients manifested a substantial increase in CI and SWI and some decrease in PA and PCW pressures, whether or not they improved clinically or survived long-term. In some patients, these measurements remained abnormal despite substantial improvement. While in many subjects, this failure of the hemodynamic changes to predict outcome may have resulted from progressive deterioration, the hemodynamic changes also did not correlate well with clinical outcome in the subgroup with relatively stable symptoms. Fitchett et al.18 found hemodynamic improvement in most patients given hydralazine, but the clinical response varied considerably. Other reports also indicate that the correlation between the acute hemodynamic effects of vasodilators and subsequent response may not be close.17, 27, 38

The finding that the few patients who had no increase in CI and nine of 11 of these with no decrease in PA or PCW pressures during vasodilator therapy did not improve has important clinical implications. Such patients should probably be evaluated on a different therapeutic regimen before hemodynamic monitoring is discontinued.

One possibility that deserves further investigation is that some of the nonresponding patients would have improved on still higher doses of hydralazine. Packer et al.39 showed that individual doses of as much as 800 mg may be required to increase CO. We did not administer more than 400 mg/day initially and did not increase the dose beyond 600 mg/day in nonresponders.

Clinical Implications

Clearly, further long-term studies using objective as well as subjective methods of evaluation are necessary. Optimally, such studies should be controlled. Because other vasodilating medications act, at least in part, by mechanisms different from those of the drugs we studied, our results cannot be assumed to characterize the outcome of therapy with other vasodilators. Nonetheless, our findings indicate that vasodilator therapy with a combination of hydralazine and nonparenteral nitrates provides symptomatic relief in many patients with severe, chronic heart failure. This improvement was sustained in some for as long as 30 months. The more rapid the progression of symptoms and the more severe the initial hemodynamic derangement, however, the less favorable the response. Therefore, use of these drugs in patients with less advanced disease may produce more consistent improvement. It is also obvious that whether or not vasodilators affect long-term prognosis, treated patients with NYHA class IV or severe class III heart failure continue to have a high mortality rate.

Our data confirm the prognostic value of hemodynamic studies in patients with chronic heart failure. Measurements before and during vasodilator treatment provide helpful information concerning symptomatic response and survival. In addition, a lack of acute hemodynamic improvement with vasodilators made subsequent clinical improvement unlikely. However, the correlation between the magnitude of the acute hemodynamic changes produced by vasodilators and subsequent clinical response was less good. Perhaps the effect of vasodilators on other variables, such as left ventricular volume and ejection fraction or exercise hemodynamic measurements, will be more helpful in predicting efficacy.

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References

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37. Walsh W, Greenberg B: Late results of oral hydralazine in refractory heart failure. (abstr) Circulation 60 (suppl II): II-130, 1979
B Massie, T Ports, K Chatterjee, W Parmley, J Ostland, J O'Young and F Haughom

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