Results of Long-term Vasodilator Therapy in Patients with Refractory Congestive Heart Failure

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SUMMARY The long-term effects of vasodilator therapy with oral hydralazine and long-acting nitrates were studied in 34 patients with refractory heart failure. Seven patients who had marginal hemodynamic improvement despite optimal hydralazine therapy were not maintained on vasodilators, and eight who had a favorable hemodynamic response subsequently discontinued hydralazine therapy because of side effects. Of these 15 patients, four (27%) died and 11 remained in New York Heart Association functional class III or IV at a mean follow-up of 10 ± 2 months (SEM). The 19 patients who received chronic therapy for 8 ± 2 months were divided into nine late responders (47%), who improved to functional class I or II, and 10 late nonresponders (53%), who remained in functional class III or IV. Only one of the nine late responders (11%) died, compared with seven of the 10 late nonresponders (70%) (p < 0.01). The actuarially determined survival at 1 year was 100% for late responders and 13 ± 12% for late nonresponders (p < 0.001).

No clinical variable could distinguish late responders from late nonresponders. Hemodynamic variables measured before vasodilator therapy showed that late responders had lower mean right atrial pressure (8 ± 1 vs 17 ± 3 mm Hg, p < 0.01) and lower mean pulmonary artery wedge pressure (20 ± 2 vs 30 ± 2 mm Hg, p < 0.005), higher stroke volume index (27 ± 2 vs 20 ± 1 ml/m², p < 0.005) and higher stroke work index (32 ± 4 vs 19 ± 2 g-m/m², p < 0.01) than late nonresponders. There were no significant differences in the acute response to vasodilators between the two groups.

We conclude that (1) a substantial portion of patients with refractory congestive heart failure either do not have a beneficial response to vasodilator therapy or discontinue it because of side effects; (2) about half of the patients who are maintained on chronic vasodilator therapy (or about one-fourth of the patients in whom therapy is initiated) had sustained clinical benefit; and (3) the initial hemodynamics, but not the clinical variables, are predictive of late mortality and late clinical response. Patients with evidence of more severe left ventricular dysfunction have an unfavorable course.

VASODILATOR drugs improve cardiac performance in patients with chronic congestive heart failure.1-11 Hydralazine, whose predominant effect is arteriolar vasodilation, has been shown to increase cardiac output in these patients.2,3,8-11 When hydralazine is combined with long-acting nitrates, left ventricular filling pressure is also reduced.8-10 Although combined vasodilator therapy acutely improves hemodynamics, the long-term results of such therapy are uncertain in patients with chronic heart failure, who have a poor prognosis.12-14 We undertook this study to examine the long-term clinical effects of vasodilator therapy with hydralazine and nitrates in patients with chronic refractory congestive heart failure and to determine whether the initial clinical or hemodynamic variables are predictive of the late response.

Methods

Patient Population

The study population consisted of 34 consecutive patients admitted to our institution for management of congestive heart failure who met the following criteria: (1) congestive heart failure refractory to conventional medical therapy with digitalis and diuretics; (2) New York Heart Association (NYHA) functional class III or IV; (3) absence of primary valvular heart disease, prosthetic valve malfunction or any other surgically correctable lesion; and (4) no change in clinical course during the preceding 3 months. All patients had multiple previous hospital admissions for treatment of
heart failure. Sixty-two percent of the patients were referred to our institution and 38% were admitted from the emergency room or cardiology clinic for further management of congestive heart failure. All patients were clinically stable at the time of initial study. There were 21 males and 13 females, mean age 52 ± 11 years (+ SEM). Twenty-one patients were in NYHA functional class IV and 13 patients were in class III. Congestive heart failure was caused by old myocardial infarction in 17 patients (50%), cardiomyopathy in nine patients (26%) and late heart failure after valve replacement in eight patients (24%). Previous myocardial infarction was defined by clinical, enzymatic and electrocardiographic criteria for transmural infarction. Prosthetic valve malfunction and primary valvular disease were excluded by cardiac catheterization and angiography in 12 patients.

Hemodynamic Measurements

Right atrial, pulmonary artery and pulmonary artery wedge pressures were measured in all patients by right-heart catheterization using a triple-lumen, balloon-tipped thermodilution catheter (Swan-Ganz Catheter, Edwards Laboratories). Systemic arterial pressure was measured directly using a small polyethylene catheter introduced into the brachial artery. Mean pressures were determined electronically. Cardiac output was measured in triplicate by the thermodilution technique using an analog computer (9520 Thermodilution Computer, Edwards Laboratories) and the mean value was used.

Derived hemodynamic variables were calculated as follows: cardiac index (1/min/m²) = cardiac output/body surface area; stroke volume index (SVI) (ml/m²) = cardiac index/heart rate; stroke work index (g-m/m²) = (mean systolic pressure [MSP] — mean pulmonary artery wedge pressure) × SVI × 0.0136, where MSP was estimated from the formula D + 2(S − D)/3; systemic vascular resistance (dyn-sec-cm⁻⁴) = 80(mean arterial pressure — mean right atrial pressure)/cardiac output.

Vasodilator Protocol

Digitalis and diuretic preparations were continued without change during the acute drug trial. Control measurements of pressures and cardiac output were performed at 30-minute intervals until a stable baseline was reached. Hydralazine was then administered orally at an initial dose of 50–75 mg. The dosage was increased every 3–4 hours in 25-mg increments, provided that heart rate did not increase by ≥ 15 beats/min, mean arterial pressure did not decrease by ≥ 15 mm Hg, diastolic blood pressure was not reduced below 55 mm Hg in patients with coronary artery disease, and patients did not develop limiting side effects such as angina, postural hypotension, headache or gastrointestinal disturbance. The optimal dose of hydralazine was that which resulted in the greatest increase in stroke volume without provoking unwanted side effects or symptoms. When necessary, the dosage of hydralazine was adjusted within the range that produced a favorable hemodynamic response (as discussed below) to help control side effects. If the mean pulmonary arterial wedge pressure exceeded 20 mm Hg after optimal therapy with hydralazine, long-acting nitrates in the form of sublingual isosorbid dinitrate, starting at a dose of 5 mg and increasing in 5-mg increments every 2 hours, or nitroglycerin ointment, starting at a dose of 1–2 inches and increasing in increments of 1 inch every hour, were added until mean pulmonary arterial wedge pressure was decreased to 15 mm Hg or side effects occurred. Hemodynamic monitoring was continued for 24 hours while patients were maintained on optimal vasodilator therapy to allow stabilization and to determine the interval with which drugs had to be administered. Final measurements of pressures and cardiac output were then obtained. Patients in whom stroke volume index increased by 20% or more during optimal hydralazine therapy were considered to have had a beneficial response and were maintained on the drug. If stroke volume increased by less than 20%, patients were not considered to have had a beneficial response to hydralazine and were not maintained on long-term therapy. Before discharge from the hospital, patients were observed for an additional 24–48 hours while receiving vasodilator therapy.

Follow-up

The latest clinical follow-up of living patients was at least 6 months after the initial drug trial. Complete follow-up was obtained in 32 patients by regular clinic visits and examination by one of the authors or in two cases by telephone contact with both the patient and his primary physician. Patients who died within 6 months while receiving vasodilator therapy were included in the analysis; follow-up time was considered to be the interval between the initiation of therapy and the terminal event. The response to therapy in such patients was determined by functional class at the time of the last clinic follow-up visit.

Late clinical response was assessed according to NYHA functional classification. A patient was considered to be a late responder if he was in functional class I or II and a late nonresponder if he was functional class III or IV.

Statistical analysis of the results was performed using the two-tailed t tests for paired and unpaired values and chi-square analysis. Actuarially determined survival was evaluated using methods previously described.

Results

Acute Hemodynamic Response

Optimal therapy with hydralazine failed to increase stroke volume index by 20% in seven of the 34 patients (21%) (fig. 1). Therapy was limited by an increase in heart rate in five patients, by a reduction in arterial pressure from 120/64 to 86/44 mm Hg in one patient with coronary artery disease, and by the onset of
nausea and vomiting in one patient whose stroke volume was unchanged by the administration of 225 mg of hydralazine. Overall, there was no significant change in mean pulmonary artery wedge pressure, stroke volume index, stroke work index, or systemic vascular resistance in these seven patients. Cardiac index increased from 2.7 ± 0.2 to 3.2 ± 0.3 l/min/m² (mean ± SEM) (p < 0.05) due to an increase in heart rate from 88 ± 2 to 104 ± 3 beats/min (p < 0.001).

Hydralazine increased stroke volume index by more than 20% in 27 patients (79%). Twelve (44%) of these patients required additional long-acting nitrates to decrease mean pulmonary artery wedge pressure. In this group vasodilator therapy reduced mean arterial pressure from 89 ± 3 to 85 ± 3 mm Hg (NS) and increased heart rate from 86 ± 2 to 93 ± 3 beats/min (p < 0.005). Mean pulmonary artery wedge pressure was reduced from 27 ± 2 to 20 ± 2 mm Hg (p < 0.001). Cardiac index increased from 2.0 ± 0.1 to 3.3 ± 0.2 l/min/m² (p < 0.001), and stroke work index increased from 25 ± 2 to 40 ± 3 g-m/m² (p < 0.001). Systemic vascular resistance decreased from 1836 ± 80 to 1130 ± 57 dyn-sec-cm⁻² (p < 0.001).

Hydralazine was discontinued before hospital discharge because of side effects in three of these 27 patients (fig. 1). One patient developed a drug fever, one had intolerable anorexia and nausea, and one developed angina secondary to drug-induced tachycardia.

### Long-term Follow-up

Twenty-four patients were discharged from the hospital and continued to receive vasodilator therapy. These patients were followed for 10 ± 8 months (range 1–26 months) (fig. 1). The mean daily dose of hydralazine was 243 ± 43 mg (range 150–450 mg). Twelve patients (50%) required additional long-acting nitrates: nine received sublingual isosorbide dinitrate (mean 54 ± 6 mg/day) and three received nitroglycerin ointment (mean 4 inches every 6 hours). Hydralazine therapy was subsequently discontinued in five patients because of late side effects (fig. 1). A lupus syndrome developed after 4 months of therapy in one patient who was receiving 300 mg/day, drug fever after 1 month in another and intolerable anorexia and nausea within 2 weeks in three patients.

The 15 patients who were not maintained on long-term vasodilator therapy because of an equivocal acute hemodynamic response or side effects were followed for 10 ± 2 months. All patients remained markedly limited by symptoms and all were considered to be in NYHA class III or IV on follow-up. The actuarial curve (fig. 2) shows that 1-year survival was 69 ± 9% in this group.

Of the 19 patients who tolerated chronic vasodilator therapy, nine (47%) showed sustained improvement, to functional class I or II, after a follow-up of 12 ± 2 months (fig. 1). The doses of vasodilators and diuretics were unchanged in this group of patients during the follow-up period. Two of the late responders recently relapsed to functional class III after 9 and 11 months of therapy; one of these two patients subse-

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**Figure 1.** Flow diagram illustrating the clinical course of the 34 patients who underwent hemodynamic study to evaluate the long-term effects of vasodilator therapy. FC = New York Heart Association functional class.

**Figure 2.** Actuarial curves for survival in various subgroups. There is no significant difference in survival at 1 year between the 15 patients who did not receive long-term therapy and the 19 patients who received vasodilators. The nine late responders had a significantly lower mortality than the 10 late nonresponders.
quently died of end-stage heart failure while receiving vasodilator therapy. Ten patients (53%) remained in functional class III or IV at a mean follow-up of 5 ± 2 months on vasodilator therapy (fig. 2). None of these patients had substantial clinical improvement, even for short periods of time, after the initiation of therapy, and the dose of diuretics was subsequently increased in six patients. Eight of these late nonresponders required readmission to the hospital because of worsening heart failure, and seven of the 10 patients (70%) subsequently died while receiving vasodilator therapy, including five who died within 6 months of the initial hemodynamic study. Three of the seven patients died suddenly and four died of end-stage congestive heart failure. The late mortality was significantly higher (p < 0.01) in the late nonresponder than in the late responders (table 1). Follow-up was significantly longer for the late responders because of the early mortality in the late nonresponders. Actuarially determined survival at 12 months was 100% for the nine late responders and 13 ± 12% for the 10 late nonresponders (p < 0.001) (fig. 2). Survival for the group of 19 patients who received chronic therapy (56 ± 11%) (and for the subgroups of late responders and late nonresponders) was not significantly different from that of the 15 patients who did not receive long-term therapy (69 ± 9%).

Analysis of Late Responders and Nonresponders

Table 1 shows initial clinical characteristics of the nine late responders and 10 late nonresponders. There was no significant difference between the two groups with respect to age, sex, etiology of heart failure, initial functional class, clinical events leading to hospitalization or mean hydralazine dose. Seven of the late nonresponders required additional long-acting nitrates, compared with one of the late responders (p < 0.01). A comparison of initial hemodynamic measurements showed that late responders had significantly lower mean right atrial pressure (p < 0.01), lower mean pulmonary artery wedge pressure (p < 0.005), higher stroke volume index (p < 0.005) and higher stroke work index (p < 0.01) than the late nonresponders (table 2, fig. 3). There was no significant difference between late responders and late nonresponders with respect to initial heart rate, mean arterial pressure, cardiac index and systemic vascular resistance (table 2).

Comparison of the magnitude of change in pressures and cardiac output in response to vasodilator therapy revealed no significant differences between the two groups for any variable. Measurements performed after the optimal dose of hydralazine and nitrates showed that late responders had significantly higher stroke volume index (p < 0.05) and lower right atrial pressure (p < 0.05) than did late nonresponders (table 2).

The initial hemodynamic variables for the nine late responders were compared with those of the seven patients who failed to show an adequate hemodynamic response to oral hydralazine. There was no significant difference between the groups for any of the variables measured.

Discussion

These data show that almost half the patients with refractory heart failure who respond acutely to vasodilators and are able to tolerate long-term therapy experience substantial clinical improvement. The likelihood of clinical improvement as well as subsequent mortality can be predicted by initial hemodynamic values. However, 44% of our patients either failed to respond to therapy acutely or were forced to discontinue vasodilators because of side effects. Mortality in these patients was considerable, whether long-term vasodilator therapy was undertaken or not.

Hemodynamic monitoring was necessary to determine the vasodilator regimen that resulted in optimal unloading conditions. The dose of hydralazine that produced the most beneficial hemodynamic response ranged from 150-450 mg. Such variability in dosage requirement was reported by Packer et al.18 In addition, only 12 of 24 (50%) of our patients required long-acting nitrates to reduce pulmonary artery wedge pressure below 20 mm Hg. The use of venodilators in patients whose left ventricular filling pressure is not elevated has been shown to reduce cardiac output by the Starling mechanism.19

The acute changes in cardiac performance in our patients after treatment with hydralazine and nitrates are similar to those previously reported.2 5 6 11 However, the 21% incidence of an equivocal hemodynamic response to hydralazine exceeds that noted in the past. Had we used changes in cardiac index rather than

### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Late responders (n = 9)</th>
<th>Late non-responders (n = 10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 3</td>
<td>55 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/5</td>
<td>5/5</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology of CHF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Initial NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referral</td>
<td>6</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>ER or clinic</td>
<td>3</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Hydralazine dose (mg/day)</td>
<td>213 ± 20</td>
<td>248 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1</td>
<td>7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>12 ± 2</td>
<td>5 ± 2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (11%)</td>
<td>7 (70%)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Abbreviations: ER = emergency room; NYHA = New York Heart Association.
stroke volume index to define a favorable response, three of the seven nonresponders would have had a favorable response to therapy. Because the increase in cardiac index in these patients was due to a substantial increase in heart rate rather than to an improvement in left ventricular performance, hydralazine was discontinued. Although little information is available about the long-term effects of changes in heart rate in patients with congestive heart failure, a chronic increase in heart rate could be deleterious, particularly to patients with underlying coronary artery disease.

Hydralazine was discontinued because of intolerable side effects in eight of our 34 patients (24%). The most common side effects were gastrointestinal; anorexia, nausea and vomiting were the major symptoms. The high incidence of side effects in this study is probably related to the relatively high dose of hydralazine (243 ± 43 mg/day) required in our patients and the fact that gastrointestinal symptoms are more likely to occur because of splanchnic congestion in patients with heart failure. Important additional side effects seen in this series were drug fever, the lupus syndrome and tachycardia-induced angina. No patient developed clinically significant orthostatic hypotension or a peripheral neuropathy. The relatively high incidence of side effects with hydralazine has been reported.20, 21

In our series, 47% of patients who increased stroke volume acutely and tolerated long-term vasodilator therapy (26% of the entire population) had sustained symptomatic relief. One of the nine late responders had no symptoms of heart failure 26 months after the initiation of therapy and is considered to be in NYHA functional class I. Although late responders have experienced relief of symptoms for up to 26 months, how long this improvement can be maintained is uncertain. The fact that two of the late responders who were in class II recently relapsed back into class III suggests a gradual attrition over time.

Although overall mortality for the 19 patients who received long-term therapy was poor (actuarial survival of 56% at 12 months), improvement in functional class was associated with relatively good survival; only one of the late responders had died during a follow-up

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**TABLE 2. Hemodynamics in Late Responders vs Late Nonresponders**

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>After therapy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
<td>LNR</td>
</tr>
<tr>
<td>Heart rate</td>
<td>81 ± 3</td>
<td>90 ± 4</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>92 ± 6</td>
<td>87 ± 4</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>8 ± 1</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>Mean pulmonary pressure (mm Hg)</td>
<td>32 ± 4</td>
<td>43 ± 3</td>
</tr>
<tr>
<td>Mean pulmonary artery wedge pressure (mm Hg)</td>
<td>20 ± 2</td>
<td>30 ± 2</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.2 ± 0.2</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>27 ± 2</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>Stroke work index (g-m/m²)</td>
<td>32 ± 4</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn-sec-cm⁻⁵)</td>
<td>1977 ± 206 1766 ± 76</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Abbreviations: LR = late responders; LNR = late nonresponders.
of 12 ± 2 months. Survival was significantly better in the late responders than in the late nonresponders; seven of 10 late nonresponders died. The difference in survival between the late responders and late nonresponders was probably due at least in part to the severity of the underlying myocardial dysfunction. There was no significant difference in survival between the 19 patients who received vasodilators and the 15 patients who did not. Further comparison revealed that late responders had somewhat higher and late nonresponders lower survival at 1 year than did the untreated patients; however, neither difference was significant. Although the increased mortality in late nonresponders compared with untreated patients is of concern because it raises the possibility that vasodilators had an adverse effect on survival, a more likely explanation is that the patients not receiving long-term therapy had a lesser degree of myocardial dysfunction (as evidenced by less severe initial hemodynamic abnormalities). Whether long-term vasodilator therapy affects survival in patients with chronic, severe congestive heart failure remains uncertain.

Few reports of long-term therapy of congestive heart failure with hydralazine and nitrates have been available. Massie et al.8 followed eight patients who received chronic hydralazine and nitrate therapy for a mean of 6 months (range 3–10 months) and noted symptomatic improvement to NYHA functional class II in five of the eight patients (63%). Fitchett et al.8 noted early symptomatic improvement in eight of 13 patients treated with oral vasodilators. This improvement was confirmed by hemodynamic studies performed 6 weeks after initiation of therapy. Pierpont et al.10 reported follow-up data on nine patients with severe heart failure who had shown an initial hemodynamic response to combined vasodilator therapy with hydralazine and nitrates. At a mean of 6 months, five of the nine had improved symptomatically and four remained clinically unchanged; two of the nine patients died during the follow-up period. In these studies the total number of patients with refractory heart failure in whom vasodilator therapy had been attempted was not stated.

In our series, late responders could not be separated from late nonresponders on the basis of age, sex, functional class, etiology of heart failure or clinical events leading to hospitalization. Also, both groups had a similar acute response to therapy. The latter finding may be influenced by the fact that only patients who increased stroke volume by at least 20% were included in the analysis and there was little chance for hemodynamic differences between the groups to emerge. However, our data show that late nonresponders had higher initial right atrial and pulmonary artery wedge pressures and lower stroke work and stroke volume indexes than did the late responders. It is likely that the more severe hemodynamic abnormalities noted in the late nonresponders were the result of more severe underlying left ventricular dysfunction. Thus, it appears that even with improved loading conditions, patients with evidence of more severe underlying myocardial dysfunction cannot maintain cardiac performance at a level that results in sustained relief of symptoms of heart failure, and mortality is high in this group.

There were no differences in initial hemodynamics between the seven patients who had an equivocal hemodynamic response to hydralazine therapy and the nine late responders. However, the patients who were not maintained on vasodilators had an unfavorable clinical course and all remained in functional class III or IV at late follow-up. Thus, an adequate acute response to hydralazine, as well as less severe underlying myocardial dysfunction, appears to be essential for long-term symptomatic improvement.

Our study shows that only some patients with chronic refractory congestive heart failure experience sustained relief of symptoms and improvement in functional capacity with long-term vasodilator therapy. Hemodynamic monitoring is necessary to determine the drug requirements needed to produce optimal unloading conditions. Such monitoring identifies patients whose acute hemodynamic response to therapy is equivocal and helps determine whether arterial dilators or venodilators or both are required, as well as the ideal dose of the drugs. Moreover, initial hemodynamics provide a useful guide to the late clinical outcome such that patients with less severe hemodynamic abnormalities are more likely to benefit from long-term vasodilator therapy. The finding that about 25% of the patients who had a positive hemodynamic response to hydralazine had to discontinue therapy because of side effects indicates that vasodilator drugs that are better tolerated by patients with heart failure are needed.

Our study shows that patients with advanced congestive heart failure have a poor prognosis whether they are maintained on vasodilators or conventional therapy alone. About half of the patients who had a beneficial acute response to vasodilator drugs and who tolerated therapy experience significant symptomatic relief with long-term vasodilator therapy. Conversely, about half the patients who showed a beneficial hemodynamic response to hydralazine and who tolerated chronic therapy had no change in functional class, indicating that early hemodynamic response is not necessarily translated to long-term clinical improvement. The severity of underlying myocardial dysfunction appears to have strong influence on the clinical response to vasodilator drugs and is a potent predictor of mortality.

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