Acute and Long-term Effects of Vasodilator Therapy on Resting and Exercise Hemodynamics and Exercise Tolerance

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SUMMARY The acute hemodynamic response to vasodilators in patients with chronic heart failure has been well characterized, but less is known about the long-term hemodynamic effects of vasodilator therapy. We measured hemodynamic variables at rest and during upright exercise in 11 patients during the initiation of therapy with oral hydralazine and sublingual isosorbide dinitrate and, in eight of these, after 3 months of continuous treatment. Marked initial increases in resting cardiac output and stroke volume and reductions in wedge pressure were sustained during chronic therapy. Similarly, the early improvement in exercise hemodynamic measurements persisted in most subjects.

Exercise tolerance, quantified as the maximum duration of treadmill exercise, increased modestly (7.7 ± 2.6 to 8.9 ± 3.3 minutes, 0.05 < p < 0.10) after several days on vasodilators and further (10.2 ± 3.7 minutes, p < 0.01) during long-term treatment. The acute hemodynamic effects of vasodilator therapy at rest or during exercise did not correlate well with the changes in exercise tolerance.

Our findings suggest that the combination of hydralazine and isosorbide dinitrate improves cardiac performance at rest and during exercise in patients with chronic heart failure and that this improvement persists during chronic therapy. In most patients, this hemodynamic improvement is accompanied by greater exercise tolerance.

THE USE of vasodilating drugs as therapy for chronic heart failure is an accepted adjunct to conventional therapy with digitalis and diuretics. However, little information is available about the long-term hemodynamic and exercise response to vasodilators and the clinical outcome of this therapy. The lack of a close correlation between acute changes in resting hemodynamic measurements and subsequent clinical response in some studies is particularly troublesome.

The present study was undertaken to examine prospectively the relationship between the acute and long-term hemodynamic effects of combined vasodilator therapy with hydralazine and isosorbide dinitrate and changes in exercise capacity. Several questions are addressed: Is acute improvement in resting cardiac performance sustained? What are the acute and chronic effects of this combination of vasodilators on exercise hemodynamic measurements? What are the effects of acute and chronic therapy with these agents on exercise capacity, and are they related to the hemodynamic findings? Some of this information is available. However, to our knowledge, this is the first study in which both resting and exercise hemodynamic effects of the hydralazine-nitrate combination are examined acutely and during long-term therapy. It also provides the first opportunity to relate these findings to changes in exercise tolerance.

Methods

Patient Population

Twelve patients in stable New York Heart Association functional class III or IV chronic congestive heart failure were studied prospectively. One patient could not tolerate either hydralazine or isosorbide dinitrate, and was dropped from the study. Patients with complicating noncardiac medical problems were excluded. In addition, patients with myocardial infarction within 6 months, those whose activity was limited by angina pectoris rather than dyspnea, and those with recent progression of heart failure symptoms were not included. Heart failure resulted from idiopathic cardiomyopathy in three and ischemic heart disease in eight. One patient had minimal aortic regurgitation by angiography and four patients had detectable mitral regurgitation, which was not thought to be significant, by clinical examination.

The mean age of the patients was 58 years (range 41-69 years), and the mean duration of heart failure was 3 years (minimum 8 months). All were referred because they remained symptomatic despite optimum therapy with digoxin (with plasma levels in the therapeutic range) and diuretics (furosemide, 80-640 mg/day).

Study Design

Patients were admitted to the hospital several days before the invasive studies and were maintained on a stable medical program and diet. They were continued on their regimen of digitalis and diuretics throughout the study, but all other vasoactive medications were discontinued. Exercise tolerance was evaluated by determining the time to limiting dyspnea or fatigue on a gradually progressive treadmill test (Naughton protocol) in which the work load was increased every 2 minutes. To avoid being misled by a conditioning effect of serial exercise tests, the baseline prevaso-
Long-term Follow-up

After discharge, all 11 patients who continued in the study were maintained on the same doses of vasodilators and other medications. They were examined monthly, and a treadmill exercise tolerance test was performed after 6 and 12 weeks of vasodilator therapy. After 3 months, the patients were readmitted while continuing their medication. After 24 hours in the hospital, right-heart catheterization and arterial cannulation were performed. Resting and exercise measurements were obtained on hydralazine and isosorbide dinitrate as described previously. Then, the vasodilators were discontinued and hydralazine and isosorbide dinitrate were increased by 100 kpm/min and by 100 kpm/min every 3 minutes until limiting dyspnea or fatigue. During each hemodynamic study, measurements were performed in the final 2 minutes at the highest work load completed during this preliminary test. Thus, on each regimen, hemodynamic measurements were compared at the same level of maximal or near-maximal exercise.

After these preliminary studies, patients were transferred to the coronary care unit, where a balloon-tipped thermodilution catheter was placed in the pulmonary artery and a radial artery was cannulated. After several hours, during which hemodynamic stability was established, supine and upright resting and upright exercise measurements of heart rate (HR), phasic and mean (M) arterial (AP), pulmonary artery (PA), right atrial (RA), and pulmonary capillary wedge (PCW) pressures, and cardiac output (CO) were performed. In both positions, the transducers were placed at a level 5 cm (vertical distance) below the sternal angle. The ECG and pressures were recorded continuously during exercise. CO was determined in triplicate during the predetermined 2-minute measurement period and again at maximal exercise (if the patient could continue). In nine patients, arterial and pulmonary artery blood gases were also drawn at maximal exercise to calculate oxygen consumption.

After the baseline exercise study, vasodilator therapy was instituted with a combination of oral hydralazine and sublingual isosorbide dinitrate, with nitroglycerin ointment applied at nighttime. The dosages of these medications were progressively increased during continuous hemodynamic monitoring until the resting cardiac index was more than 2.5 l/min/m² or had risen by 30% (whichever was greater) and wedge pressure was below 16 mm Hg, or until maximum doses of hydralazine, 100 mg every 6 hours, and isosorbide, 15 mg every 2 hours, were given. The final doses of these medications ranged from 50–100 mg of hydralazine every 6 hours and 5–15 mg of isosorbide dinitrate every 2 hours.

Resting and upright exercise measurements were then repeated, as described above, after 48–72 hours of vasodilator therapy, 2–3 hours after the preceding dose of hydralazine and 20–40 minutes after isosorbide dinitrate. Measurements were performed at approximately the same time of day and in the same relationship to meals and diuretic administration (always at least 6 hours earlier) as the baseline study. Body weight was monitored daily in the coronary care unit and did not fluctuate more than 1 kg.

The catheters were then removed, the medications continued, and the patients were permitted to ambulate. Twenty-four to 72 hours later, a repeat treadmill exercise test was performed to measure acute changes in exercise tolerance. To reduce physician bias, patients were asked to discontinue exercise when they experienced the same degree of dyspnea or fatigue that limited the earlier tests.

Calculations and Statistical Analysis

The following measurements were derived from hemodynamic variables:

Cardiac index (CI) = \( \frac{CO}{\text{body surface area}} \)

Stroke volume index (SVI) = \( \frac{CI}{HR} \)

Systemic vascular resistance (SVR) = \( \frac{\text{MAP} - \text{RAP}}{\text{CO}} \times 80 \)

\( \frac{O_2 \text{ content (ml/dl)} = O_2 \text{ saturation} \times \text{hemoglobin concentration} \times 1.34} \)

\( O_2 \text{ consumption (ml/min) = (arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content}) \times CO \)

The arterial and mixed venous (pulmonary artery) oxygen saturations were derived from the \( P_{O_2} \) measurements using a standard nomogram.8

The significance of the acute vasodilator effect on hemodynamic measurements at rest and on maximal oxygen consumption was assessed by paired \( t \) test. The relationship of acute and chronic effects of vasodilators on these measurements and on exercise tolerance was analyzed using two-way analysis of variance with a mixed-effects model and Neumann-Keuls multiple-range tests.

Results

Acute Resting and Exercise Hemodynamic Findings

The acute effects of combined hydralazine and isosorbide dinitrate on resting and exercise hemodynamic measurements in the 11 patients completing the initial phase of the protocol are illustrated in figures 1 and 2.

With the patients resting in the supine position, there was no appreciable change in HR and a small but significant fall in MAP, from 82 ± 10 to 74 ± 9 mm Hg. CI and SVI increased by approximately 50%, from 2.3 ± 0.6 to 3.6 ± 0.9 l/min² and 27 ± 7 to 39 ± 7 ml/m², respectively, while the PCWP fell from 29 ± 5 to 19 ± 5 mm Hg.
Patients had shown notable clinical and exercise tolerance improvement.

The acute and long-term hemodynamic effects of the combination of hydralazine and isosorbide dinitrate at rest are shown in tables 1 and 2. Supine and upright resting measurements showed similar trends; therefore, only the supine measurements will be discussed. HR and MAP initially and at 3 months were similar, both on and off vasodilators. CI and SVI remained higher after 3 months of vasodilator therapy and fell rapidly to pretreatment levels when the drugs were discontinued. Similar trends were apparent with the vasodilator-induced decreases in SVR. In contrast, the PCWP and RAP after 3 months of therapy were significantly higher than after the initiation of treatment. However, the PCWP was still significantly lower than pretreatment levels.

The hemodynamic effects of vasodilators during exercise, again at the work load which represented maximal exercise before vasodilators, were also sustained (table 3, figure 3). HR during exercise was unchanged throughout. Exercise MAP fell acutely with vasodilators and remained slightly lower at 3 months, even after 48 hours off medication. CI and SVI remained increased to similar levels after 3 months and fell toward pretreatment values after vasodilators were withheld. SVR also remained lower and rose toward baseline off medication, but continued to be somewhat reduced even after 48 hours. At 3 months, only PCWP during exercise was significantly different from that during the initiation of vasodilators, although it was still lower than pretreatment or posttreatment levels.

Acute and Long-term Effects of Vasodilators on Exercise Tolerance

The effect of vasodilators on treadmill exercise tolerance is shown in figure 4. Exercise duration was similar at the 6-week and 3-month tests in the eight
patients studied at both times, so the 3-month measurements were used to illustrate chronic vasodilator effect, except in three subjects who underwent repeat testing only at 6 weeks. The individual responses were variable. Four patients did not improve (defined by an increase of at least 1 minute) either acutely or subsequently. Five patients showed an acute increase of at least a minute, and all had further improvement during long-term therapy. Two others showed no early change, but substantial late improvement. For the group, there was an increase from 7.7 ± 2.6 to 9.1 ± 3.3 minutes acutely (NS). During chronic therapy, exercise duration increased further, to 10.2 ± 3.7 minutes (p < 0.01).

Figure 5 illustrates the acute and long-term effects of vasodilators on maximal oxygen consumption. Two

### TABLE 1. Acute and Long-term Hemodynamic Effects of Hydralazine and Isosorbide Dinitrate at Rest (Supine)

<table>
<thead>
<tr>
<th></th>
<th>Pre-VD</th>
<th>Acute VD</th>
<th>Chronic VD</th>
<th>Off VD</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>76±13</td>
<td>78±11</td>
<td>77±9</td>
<td>76±6</td>
<td></td>
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<tr>
<td>AP (mm Hg)</td>
<td>83±11</td>
<td>72±9</td>
<td>77±11</td>
<td>82±14</td>
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<tr>
<td>CI (l/m²)</td>
<td>2.1±0.4</td>
<td>3.1±0.4</td>
<td>2.9±0.3</td>
<td>2.2±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>28±5</td>
<td>40±5</td>
<td>39±5</td>
<td>28±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>11±3</td>
<td>4±2</td>
<td>8±2</td>
<td>9±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVR ( dyn-sec-cm⁻²)</td>
<td>1480±390</td>
<td>920±130</td>
<td>1010±110</td>
<td>1460±250</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD; significance levels determined by two-way analysis of variance. Abbreviations: HR = heart rate; AP = mean arterial pressure; CI = cardiac index; SVI = stroke volume index; PCW = pulmonary capillary wedge pressure; RA = right atrial pressure; SVR = systemic vascular resistance; VD = vasodilators.

### TABLE 2. Acute and Long-term Hemodynamic Effects of Hydralazine and Isosorbide Dinitrate at Rest (Upright)

<table>
<thead>
<tr>
<th></th>
<th>Pre-VD</th>
<th>Acute VD</th>
<th>Chronic VD</th>
<th>Off VD</th>
<th>Significance (p)</th>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>75±12</td>
<td>84±14</td>
<td>82±12</td>
<td>80±12</td>
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<tr>
<td>AP (mm Hg)</td>
<td>79±11</td>
<td>69±13</td>
<td>76±10</td>
<td>80±12</td>
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<tr>
<td>CI (l/m²)</td>
<td>1.9±0.5</td>
<td>2.7±0.5</td>
<td>2.6±0.4</td>
<td>2.1±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVI (ml/m²)</td>
<td>24±6</td>
<td>32±6</td>
<td>32±5</td>
<td>26±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>26±5</td>
<td>15±4</td>
<td>21±4</td>
<td>27±4</td>
<td>&lt;0.001</td>
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<tr>
<td>RA (mm Hg)</td>
<td>9±3</td>
<td>3±3</td>
<td>6±3</td>
<td>8±4</td>
<td>&lt;0.001</td>
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<tr>
<td>SVR (dyn-sec-cm⁻²)</td>
<td>1880±370</td>
<td>1250±220</td>
<td>1370±230</td>
<td>1750±290</td>
<td>&lt;0.001</td>
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</table>

Values are mean ± SD; significance levels determined by two-way analysis of variance. Abbreviations: HR = heart rate; AP = mean arterial pressure; CI = cardiac index; SVI = stroke volume index; PCW = pulmonary capillary wedge pressure; RA = right atrial pressure; SVR = systemic vascular resistance; VD = vasodilators.

### TABLE 3. Acute and Long-term Hemodynamic Effects of Hydralazine and Isosorbide Dinitrate During Exercise

<table>
<thead>
<tr>
<th></th>
<th>Pre-VD</th>
<th>Acute VD</th>
<th>Chronic VD</th>
<th>Off VD</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>118±10</td>
<td>120±7</td>
<td>114±10</td>
<td>121±13</td>
<td></td>
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<tr>
<td>AP (mm Hg)</td>
<td>97±21</td>
<td>87±17</td>
<td>90±13</td>
<td>91±17</td>
<td>&lt;0.01</td>
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<tr>
<td>CI (l/m²)</td>
<td>2.7±0.8</td>
<td>4.4±0.9</td>
<td>4.4±0.9</td>
<td>3.1±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVI (ml/m²)</td>
<td>23±7</td>
<td>37±6</td>
<td>39±7</td>
<td>26±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>40±8</td>
<td>26±11</td>
<td>32±10</td>
<td>40±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>13±6</td>
<td>8±6</td>
<td>10±6</td>
<td>15±5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SVR (dyn-sec-cm⁻²)</td>
<td>1410±640</td>
<td>780±220</td>
<td>780±80</td>
<td>1040±330</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A-V O₂ diff (ml/dl)*</td>
<td>14.8±2.2</td>
<td>11.2±2.4</td>
<td>12.3±3.0</td>
<td>14.7±2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>O₂ consumption (ml/min)*</td>
<td>835±2.2</td>
<td>991±268</td>
<td>1100±415</td>
<td>932±305</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Exercise duration (min)†</td>
<td>6.7±1.9</td>
<td>7.7±2.0</td>
<td>8.8±2.5</td>
<td>8.3±2.5</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values indicated are mean ± SD; significance levels determined by two-way analysis of variance.

*Data available for only seven patients.

†Duration of exercise on upright bicycle during catheterization.

Abbreviations: A-V O₂ diff = arteriovenous oxygen difference; others as in table 1.
patients did not have baseline measurements and two others did not have repeat catheterizations. Oxygen consumption at maximal exercise increased with acute vasodilator therapy in the nine patients, from $820 \pm 199$ to $992 \pm 284$ ml/min ($p < 0.05$). In the seven patients with both acute and chronic measurements, maximal oxygen consumption increased slightly, from $835 \pm 212$ to $991 \pm 268$ ml/min ($p < 0.05$) with acute therapy, and increased further, to $1100 \pm 415$ ml/min ($p < 0.01$ from pretreatment) with chronic therapy, before falling to $932 \pm 305$ ml/min after vasodilators were discontinued for 48 hours ($p < 0.05$ from chronic therapy values; not significantly different from pretreatment) (table 2). The increase in oxygen consumption at maximal exercise reflected an increase in CO; the arteriovenous oxygen difference actually fell from $14.8 \pm 3.0$ to $11.2 \pm 2.4$ ml/dl acutely. During chronic vasodilator therapy, the arteriovenous oxygen difference increased to $12.3 \pm 3.0$ ml/dl, especially in the improving patients, but remained lower than the pretreatment measurements. After drug withdrawal, the arteriovenous oxygen difference again increased, to $14.7 \pm 2.9$ ml/dl. Patients who sustained no change in their exercise tolerance also had little change in maximal oxygen consumption. Resting oxygen consumption did not change significantly either acutely or at recatheterization. Arterial saturation remained above 94% at rest and during exercise, indicating that changes in arteriovenous oxygen difference reflected changes in mixed venous oxygen content. No effect of vasodilators on arterial oxygen saturation was noted.

Relationship of Hemodynamic Measurements to Changes in Exercise Tolerance

As noted above, seven patients had an improved exercise tolerance and four did not (figs. 2 and 3). Acutely, these nonresponding patients sustained increases in both resting and exercise SVIs comparable to the improved patients. Resting PCWP fell similarly, with one exception. The highest exercise PCWPs during therapy were in three patients who did not improve. The fourth nonresponder did have a marked fall in exercise PCWP acutely. This man also

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**Figure 3.** The exercise hemodynamic findings in the eight recatheterized patients. A marked increase in stroke volume index (SVI) was seen acutely with vasodilators (Acute VD) and was sustained during long-term therapy (Chronic VD). Pulmonary capillary wedge (PCW) pressure during exercise was also reduced acutely by vasodilators and remained below control levels after 3 months. However, exercise PCW pressure appeared to be somewhat higher during chronic therapy, compared with the early measurements, particularly in the nonresponders (dashed lines).

**Figure 4.** The early and long-term effect of vasodilators (VD) on exercise tolerance, quantitated by the duration of treadmill exercise with the Naughton protocol. The mean duration of exercise increased from 7.7 ± 3.6 minutes to 8.9 ± 3.3 minutes after several days on vasodilators, and further, to 10.2 ± 3.7 minutes, during chronic therapy. The four patients who did not display an improvement of 1 minute are shown by the dashed lines. The crosses indicate the three patients who were not recatheterized.

**Figure 5.** Maximal oxygen consumption during exercise in seven recatheterized subjects. A small but statistically significant increase, from $820 \pm 199$ to $992 \pm 284$ ml/min, was present acutely (Acute VD). After 3 months (Chronic VD), a further rise to $1100 \pm 415$ ml/min was noted. Oxygen consumption fell quite rapidly toward control levels, to $932 \pm 305$ ml/min, shortly after vasodilators were stopped (Off VD). Most of these changes were due to increased maximal consumption in responding patients (solid lines).
had a 0.9-minute early increase in exercise tolerance and a 190-ml acute increase in maximal oxygen consumption. He had noticeable clinical improvement in the initial 3 weeks, and then, after a severe episode of chest pain, worsened, so that his exercise capacity was at the pretreatment level by 6 and 12 weeks. His clinical course may have reflected an unproved myocardial infarction.

At recatheterization (fig. 3), the nonresponders again differed from the patients who improved by having the highest exercise PCWP while on chronic vasodilator therapy. Their resting PCWP on vasodilators and exercise PCWP after medication was discontinued also tended to be higher. Resting and exercise SVI on treatment did not discriminate these subjects, but after vasodilators were stopped, the nonresponders did have the lowest exercise SVI.

Clinical Response to Chronic Vasodilator Therapy

The patient's symptomatic response paralleled the exercise response. All patients with increased exercise tolerance improved by one functional classification, and the others did not change or worsened.

All patients remained on hydralazine and isosorbide dinitrate, but the dosages of medication were increased from 400 to 600 mg daily in two nonresponders, without notable clinical effect. The dosage of hydralazine was reduced from 400 to 300 mg daily in two responders with gastrointestinal side effects. Five of 11 patients complained of headaches and nausea in early therapy, but these side effects lessened with chronic treatment and dose reduction.

Diuretic dosage was adjusted upward in two nonresponders, but was otherwise unchanged. No patient had more than a 3-pound weight fluctuation during chronic follow-up.

Discussion

Background

Vasodilator therapy has become popular for treating patients with severe congestive heart failure. A variety of both available and investigational drugs produce acute improvement in resting hemodynamic measurements in this setting.1, 2, 9-22 Most patients with chronic heart failure experience symptoms predominately with exertion, so it is noteworthy that several recent studies have demonstrated that cardiac performance during exercise is also improved acutely by vasodilators.23-29

Less information is available about the clinical response to chronic vasodilator therapy. Aronow and co-workers reported a modest improvement in exercise tolerance in controlled studies using both prazosin and trimazosin.30, 31 They did not measure hemodynamics in their patients. Other studies, though usually not controlled, revealed better exercise tolerance during vasodilator therapy, but these also did not include hemodynamic measurements, especially during exercise, either after several days of treatment or during chronic therapy. Therefore, the clinical response to vasodilators in relationship to the hemodynamic response in individual patients has not been examined. The well-documented tachyphylaxis with prazosin, which has been shown to be clinically effective in several studies, indicates the need for such data.32-34 We recently noted a variable long-term clinical response to hydralazine and nonparenteral nitrates, which in individual subjects could not be predicted from the acute resting hemodynamic effects of these drugs.3

The present study was designed to examine the acute and chronic hemodynamic effects of treatment with hydralazine and isosorbide dinitrate, both at rest and during exercise. Using these data, we have demonstrated the sustained efficacy of vasodilator therapy and gained some insight into the hemodynamic correlates of the variable individual clinical responses to therapy.

Acute Hemodynamic Measurements

Our acute resting hemodynamic findings in these patients are similar to those previously reported.18-19 The combination of hydralazine, a predominant arteriolar dilator, and isosorbide dinitrate, which primarily acts on the venous bed, markedly improves CO and ventricular filling pressures.

Although the acute exercise hemodynamic effects of hydralazine and nitrates given individually have been reported,29-37 with combined therapy, only noninvasive measurements of CO after a single dose of medication have been published.38 We found that combined therapy produced beneficial hemodynamic changes during upright exercise similar to those noted at rest. The increase in exercise SVI, from 26 ± 10 to 38 ± 10 ml/m², and the fall in exercise PCWP, from 40 ± 8 to 28 ± 9 mm Hg, were not only impressive for the group as a whole, but were noted individually.

Our findings are consistent with some reports evaluating the exercise hemodynamic effects of these drugs and differ from others. Rubin et al.40 noted a significant improvement in CO at maximum supine bicycle exercise, but no change in left ventricular filling pressure after 48 hours of treatment with hydralazine. In contrast, Franciosa and Cohn41 found no change in CO, but they administered only single doses of a combination of oral hydralazine and isosorbide dinitrate. Another group found both a rise in CO and a decrease in PCWP after 48 hours of hydralazine, but some of their patients had exercise-induced angina pectoris.27 With oral isosorbide dinitrate, Franciosa and Cohn46 did not find a significant change at maximum exercise, but they did observe a lower PCWP at a submaximal work load.48 Stephens et al.47 noted significant improvements in both CI and left ventricular filling pressure after sublingual isosorbide dinitrate, while Moscovitz et al.24 using nitroglycerin ointment, reported an increase in CI but no significant change in PCWP. The more impressive exercise hemodynamic findings in the present study may reflect the advantage of combined therapy and individual dose titration, the generally longer duration of treat-
Hemodynamic Findings During Chronic Therapy

Our results indicate that the hemodynamic effects of the hydralazine-isosorbide dinitrate combination are sustained during chronic therapy. Thus, the increases in CO and SVI and reductions in SVR at 3 months are almost identical to those observed initially, both at rest and during exercise. At rest and with exercise, PCWP was also lower than control at 3 months, but had risen somewhat from the acute levels. Each of the measurements returned toward the pretreatment levels when the medications were discontinued; only exercise SVR remained significantly different from control after 48 hours.

Although the few reports concerning the long-term hemodynamic response to hydralazine and nitrates were conducted with these drugs given individually and are limited to resting measurements, they also suggest that these medications remain effective during chronic therapy. This is in contrast to several reports that suggest that tachyphylaxis occurs rapidly with prazosin, another frequently used vasodilator.

Acute and Long-term Effects of Vasodilator Therapy on Exercise Capacity

Our findings suggest that combination therapy with hydralazine and isosorbide dinitrate results in improved exercise capacity. At 6 weeks and 3 months, the mean duration of treadmill exercise was significantly greater than pretreatment. Maximal oxygen consumption also increased after 3 months. Several studies have demonstrated comparable improvement in exercise performance during chronic vasodilator therapy.

We also noted a small, but statistically significant, acute increase in maximal oxygen consumption during upright bicycle exercise and a trend toward an increase in the duration of symptom-limited treadmill exercise after only several days of treatment. These findings differ from reports that have not shown an acute increase in exercise capacity with hydralazine or nitrates, alone or in combination.

Our results would be more definitive if a control group had been used or if an end point more independent of motivation, such as anaerobic threshold, had been used. One controlled study demonstrated a small improvement in exercise tolerance in the placebo-treated group. However, pretreatment measurements were always obtained after at least one practice exercise run. During later tests, the patients were asked to determine their own exercise end point, thereby lessening investigator bias. Further support for the validity of ascribing the changes in exercise capacity to vasodilator therapy is provided by the rapid fall in maximal oxygen consumption soon after the drugs were discontinued.

The discrepancy between our results and those of other studies could reflect differences in study protocol and patients. Both Franciosa and Cohn and Moskowitz et al. tested patients after only one dose of medication and used a single dosage that was not individualized according to the hemodynamic findings, as we did. Patients of Rubin et al. received treatment for up to 48 hours, but they administered only one drug and used supine bicycle exercise. The subjects apparently were also more incapacitated; they achieved far lower maximal work loads and oxygen consumption.

Our results indicate that improvement in exercise performance follows a variable time course. Although the improvement in exercise hemodynamics with vasodilators is no greater with chronic therapy, exercise tolerance continues to improve in many patients. This may reflect an increasing ability to use the increased CO during the chronic stage of therapy compared with the acute stage. Although the further increase in maximal oxygen consumption at 3 months did not achieve statistical significance compared with acute measurements, maximal oxygen consumption was higher in each of the improving patients at 3 months than acutely due to a progressive increase in arteriovenous oxygen difference and no further increase in cardiac output. Two possible mechanisms have been suggested for the phenomenon. First, increased CO during the acute stage of therapy may not be distributed to exercising muscle, but instead may be shunted to nonexercising tissues. Direct measurements of regional blood flow would be required to demonstrate this. A second explanation is that there is increased oxygen delivered to the periphery, even acutely, but local conditions initially prevent its use.

In patients with chronic heart failure, Zelis et al. demonstrated peripheral circulatory abnormalities that could impair local oxygen delivery. Furthermore, the oxidative capacity of skeletal muscle increases with conditioning. Our patients may well have an impaired capacity to utilize oxygen, which limits exercise even if delivery is acutely increased, and this may improve with progressive activity during chronic therapy. Also of interest is the rapid fall in maximal oxygen consumption when vasodilators were discontinued, which paralleled the return of the hemodynamic measurements to pretreatment levels. This finding, together with the widening arteriovenous oxygen difference, suggests that cardiac output may again become the limiting factor to exercise capacity during chronic therapy.

Not all patients had an improvement in exercise tolerance. One patient who did not respond probably had a new clinical event. The three others who did not respond may have experienced further deterioration of cardiac function, but their hemodynamic measurements after vasodilators were similar to pretreatment levels. The group as a whole, and these three patients in particular, had somewhat higher left and right ventricular filling pressures at 3 months than they had initially. This may have reflected subclinical fluid retention. Increased activity of the renin-angiotensin system has been demonstrated in patients receiving vasodilators for heart failure and could produce this...
effect. It may also have resulted from some decrease in vascular responsiveness, most likely to the isosorbide dinitrate.

Almost all patients manifested beneficial acute hemodynamic responses to hydralazine-isosorbide dinitrate therapy. However, the acute hemodynamic effects of these drugs, either at rest or during exercise, did not predict the chronic changes in exercise tolerance. The only hemodynamic correlate of the subsequent failure to respond clinically was the exercise PCWP, which remained greater than 40 mm Hg in three of four nonresponders; the fourth was the man who probably suffered a subsequent myocardial infarction. At recatheterization, the three patients who failed to improve their exercise tolerance again had the highest exercise PCWPs. It is not possible to draw conclusions from this small number of patients, but these findings suggest that the presence of persistently high left ventricular filling pressures during exercise may be associated with a failure to improve exercise capacity. This may not be a direct cause-and-effect relationship, because some subjects with higher wedge pressures at 3 months did continue to improve their exercise tolerance. Perhaps the development of such extremely high pressures during exercise in the nonresponders precluded them from increasing their normal activities and, therefore, from undergoing a conditioning effect from their higher cardiac output.

Clinical Implications

Our findings support the long-term use of vasodilators in refractory heart failure. They indicate that the combination of hydralazine and isosorbide dinitrate produces improvement in exercise and resting cardiac performance and that these beneficial effects persist for at least 3 months during chronic therapy. The hemodynamic improvement correlates with clinical improvement and increased exercise tolerance in most patients. Patients who continue to have very high PCWPs during upright exercise appear less likely to respond; therefore, it might be worthwhile to evaluate other drugs.

Acknowledgment

The authors express their appreciation to Susan Musser for her secretarial work, to the nurses of the coronary care unit for their invaluable assistance in the care of the patients, and to Dr. J. David Bristow for his advice and encouragement.

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Circulation. 1981;64:1218-1226
doi: 10.1161/01.CIR.64.6.1218

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