Effect of Isosorbide Dinitrate on Submaximal Exercise Capacity of Patients with Chronic Left Ventricular Failure

John R. Wilson, M.D., and Nancy Ferraro, R.N.

The effect of chewable isosorbide dinitrate on submaximal bicycle exercise capacity was evaluated in a double-blind randomized study involving 13 patients with chronic heart failure. All patients had impaired maximal exercise capacity ($V_o_2_{max} = 12.0 \pm 2.6$ ml/kg/min) due to fatigue and dyspnea but not angina. The administration of isosorbide dinitrate lowered the resting mean blood pressure ($82 \pm 9$ mm Hg to $78 \pm 10$ mm Hg, ($p < 0.03$)) and the resulting pulmonary wedge pressure ($26 \pm 5$ mm Hg to $12 \pm 6$ mm Hg, ($p < 0.01$)). Isosorbide dinitrate acutely improved exercise duration during upright bicycle exercise at a workload fixed at 50 percent of the maximal workload (placebo: $21.8 \pm 14.1$ min vs isosorbide dinitrate: $31.4 \pm 13.6$ min, ($p < 0.003$)) due to reduced exertional dyspnea. Administration of chewable isosorbide dinitrate acutely improved submaximal exercise tolerance in patients with chronic heart failure.

Patients with chronic heart failure are frequently limited during exercise even when they are asymptomatic at rest. Therefore, one of the key therapeutic objectives of vasodilator therapy in such patients has been to improve their exercise capacity. Heretofore, the effect of vasodilators on exercise capacity has been investigated primarily using maximal exercise testing. In contrast, relatively little is known about the effect of such agents on exercise performance at submaximal workloads. The only information available is based on changes in New York Heart Association functional classification. This method of assessing exercise performance relies heavily on subjective information and therefore is frequently unreliable and not reproducible. Since patients with heart failure are limited during daily activity at submaximal rather than maximal workloads, it is important to determine the effect of vasodilators on submaximal exercise capacity. Accordingly, the present study was undertaken to determine the acute effects of isosorbide dinitrate on submaximal exercise capacity in patients with chronic heart failure.

METHODS

Patients

Thirteen patients with chronic left ventricular failure were studied (Table 1). Nine patients had an ischemic cardiomyopathy and four patients an idiopathic cardiomyopathy. All patients were limited during exertion by fatigue and/or breathlessness, were receiving digoxin and furosemide, and had left ventricular ejection fractions <35 percent. Stable doses of digoxin and furosemide were continued unchanged throughout the study. However, these medications were administered each day after all exercise tests were completed. Written informed consent was obtained.

Protocol

Prior to any measurements, each patient underwent at least one trial maximal bicycle exercise test and two trials submaximal bicycle exercise tests to acquaint him with the equipment and with the exercise protocols. In addition, the blood pressure response to 5 mg chewable isosorbide dinitrate was evaluated 20 minutes following drug administration. Five patients had a 10 mm Hg or greater decrease in upright systolic blood pressure and were subsequently studied using 5 mg isosorbide dosages. The other eight patients were all studied using 10 mg dosages.

On the day prior to submaximal exercise testing, a Swan-Ganz catheter was inserted percutaneously via an antecubital vein and advanced to the pulmonary artery. Pulmonary wedge pressure and thermodilution cardiac outputs were measured. Blood samples for arterial and pulmonary venous

<table>
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<tr>
<th>Table 1—Patient Population</th>
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<tr>
<td>Mean</td>
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<tr>
<td>Age</td>
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<tr>
<td>Ejection fraction</td>
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<tr>
<td>Cardiac index</td>
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<tr>
<td>Pulmonary wedge pressure</td>
</tr>
<tr>
<td>Maximal exercise</td>
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<tr>
<td>Maximal $V_o_2$</td>
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<td>Duration</td>
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Oxygen saturation were obtained. Twenty minutes following instrumentation, maximal exercise testing was performed. Exercise was begun at a workload of 20 W and increased every 3 minutes by 20 W to symptomatic maximum. Samples for oxygen saturation were obtained at maximal exercise. Oxygen consumption was measured continuously for 5 minutes at rest and throughout exercise using a metabolic cart (Beckman). Oxygen extraction was calculated as (arterial saturation–mixed venous saturation)/arterial saturation.

One hour following maximal exercise testing, repeat baseline hemodynamic measurements were made. The preselected dose of chewable isosorbide dinitrate was administered. Hemodynamic measurements were repeated 20 minutes later.

The following day, a submaximal bicycle exercise test was performed at 8 A.M. Patients exercised at 50 percent of their maximal workload until exhaustion. Twenty minutes prior to exercise, either the predetermined dose of isosorbide dinitrate or a placebo was administered in random fashion. Four hours later, the alternate agent was administered. Twenty minutes later, submaximal exercise was repeated. The first agent was isosorbide in six patients and placebo in seven patients. The supervising physician and nurse were not informed of the agent administered. Heart rate and cuff blood pressure were measured every three minutes and recorded by the nurse, but not reported to the physician. Mean blood pressure was calculated as diastolic blood pressure + 1/3 of the pulse pressure.

Statistical Analysis

All data are expressed as mean ± standard deviations. Differences were assessed using Student's t-test for paired data. The relationship between variables was assessed by linear regression analysis.

RESULTS

Results are summarized in Tables 1 and 2, and Figure 1.

Maximal Exercise

The maximal exercise VO2 was 12.0 ± 2.6 ml/kg/min, maximal workload 46 ± 13 W and maximal exercise duration 6.0 ± 1.8 min. All patients exhibited >70 percent peripheral oxygen extraction during maximal exercise.

Hemodynamic Effects of Isosorbide

Isosorbide dinitrate dose was 5 mg in five patients and 10 mg in eight patients. Twenty minutes following administration, the pulmonary wedge pressure decreased from 26 ± 5 mm Hg to 12 ± 6 mm Hg (p < .01) and cardiac output increased from 3.2 ± .6 L/min to 3.6 ± .6 L/min (p < .05). The pulmonary wedge pressure decreased ≥ 5 mm Hg in all patients.

Effects on Submaximal Exercise

Following placebo administration, patients exercised for 21.8 ± 14.1 min (4.0-47.25 min) to a peak heart rate of 123 ± 16 beats/min and peak mean blood pressure of 94 ± 14 mm Hg. Exercise produced marked fatigue in all patients, moderate dyspnea in 11 patients and minimal dyspnea in two patients.

Isosorbide administration decreased the resting upright mean blood pressure from 82 ± 9 mm Hg to 78 ± 10 mm Hg (p < .03). Submaximal exercise duration increased to 31.4 ± 13.6 minutes (10.0 to 55.5 min) (p < .003 compared with control) (Fig 1) due to reduced exertional dyspnea. Exercise capacity improved in ten of 13 patients. In the ten patients who showed improvement, five received isosorbide dinitrate as the first medication whereas five received a placebo first. No change in peak exercise heart rate (124 ± 17 beats/min) or peak mean blood pressure (94 ± 15 mm Hg) was noted (Table 2).

Table 2—Effect of Isosorbide Dinitrate on Submaximal Exercise Capacity

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate (beats/min)</th>
<th>Mean BP (mm Hg)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>91 ± 10</td>
<td>82 ± 9</td>
<td></td>
</tr>
<tr>
<td>Peak exercise</td>
<td>123 ± 18</td>
<td>94 ± 14</td>
<td>21.8 ± 14.1</td>
</tr>
<tr>
<td>Isosorbide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>91 ± 14</td>
<td>78 ± 10*</td>
<td>31.4 ± 13.6†</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>124 ± 17</td>
<td>94 ± 15</td>
<td></td>
</tr>
</tbody>
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*p < 0.03 compared with placebo.

\( p < 0.003 \) compared with placebo.
Determinants of Exercise Response

There was no relationship between the change in submaximal exercise duration produced by isosorbide dinitrate and the maximal \( \dot{V}O_2 \) \( (r = -0.20, p = \text{NS}) \), the resting pulmonary wedge pressure \( (r = 0.05, p = \text{NS}) \), or the submaximal exercise duration following placebo administration \( (r = -0.41, p = \text{NS}) \).

Discussion

Previous investigators have examined the effects of nitrates on exercise capacity in patients with chronic heart failure utilizing maximal exercise testing.\(^6,7\) During normal daily activities, however, patients are limited almost exclusively at submaximal rather than maximal levels of exertion.\(^8\) Consequently, one of the key objectives of vasodilator therapy should be to improve submaximal exercise capacity. Whether such improvement occurs has heretofore not been determined.

Methods

In the present study, this question was examined in a double-blind randomized trial. Bicycle exercise at a fixed percentage of a patient's maximal workload was selected to assure that exercise was similarly strenuous in all patients. This laboratory has previously noted that exercise at 50 percent of maximal workload in patients with heart failure increases the \( \dot{V}O_2 \) to approximately 65 percent to 80 percent of maximal \( \dot{V}O_2 \).\(^9\) The absolute workload used in this study (10 to 30 W) is equivalent to walking at 2 mph or light housework.\(^9\) Maximal exercise capacity was determined using an incremental bicycle exercise protocol similar to that described by Franciosa et al.\(^1\) Oxygen extraction during exercise exceeded 70 percent in all patients consistent with patients performing at close to peak aerobic capacity.\(^11\) Maximal oxygen consumption was less than 16.0 ml/kg/min in all patients, indicating moderate to severe exercise impairment.\(^1\)

Effect on Submaximal Exercise Capacity

The results of the present study indicate that administration of isosorbide dinitrate acutely increases submaximal exercise capacity in patients with chronic heart failure. Following placebo administration, patients exercised for 4 to 47 minutes. Isosorbide administration increased exercise duration an average of ten minutes, improvements being observed in ten of the 13 patients.

This improvement was ascribed by most patients to a reduction in exertional dyspnea. Although fatigue primarily terminated exercise during all submaximal exercise tests, moderate dyspnea usually occurred during the placebo exercise test and contributed to the exercise limitation. Following isosorbide administration, dyspnea was reduced, and patients were usually able to tolerate fatigue longer.

Mechanism of Improved Exercise Capacity

These improvements in submaximal exercise capacity and exertional dyspnea are most likely due to decreased intrapulmonary pressure during exercise. Franciosa et al.\(^12,13\) have demonstrated that isosorbide decreases submaximal exercise pulmonary wedge pressure. This reduction in wedge pressure may alter lung mechanics during exercise, possibly by reducing interstitial edema. It is unlikely that nitrates improve skeletal muscle oxygen delivery during exercise since they do not alter systemic lactate levels during submaximal exercise\(^12\) or lactate levels and oxygen content in blood draining the exercising limb.\(^13\)

The ability of nitrates to acutely improve submaximal exercise capacity helps to explain the effects of nitrates on maximal exercise capacity. Acute administration of nitrates does not improve maximal upright exercise capacity.\(^5,7\) However, chronic administration improves maximal upright exercise capacity\(^5,6\) due to increased oxygen extraction at peak exercise rather than to reduced pulmonary wedge pressure or increased cardiac output.\(^5\) Since nitrates acutely improve submaximal exercise capacity, this should allow patients to become more active. It has been observed that chronic submaximal exercise training can significantly increase maximal exercise capacity by increasing peripheral oxygen extraction during exercise.\(^14,15\) Consequently, the increased activity levels produced by chronic isosorbide administration would be anticipated to indirectly increase maximal exercise capacity.

Limitations

It would have been of interest to measure hemodynamic responses to submaximal exercise to assure that chewable isosorbide dinitrate reduces pulmonary wedge pressures throughout exercise. This was not performed since previous studies indicate that isosorbide dinitrate reduces wedge pressures at submaximal workloads.\(^5,6\) However, hemodynamic measurements were made at rest to assure that the dose of isosorbide administered was hemodynamically effective. Hemodynamic effects persist for three hours following chewable isosorbide administration.\(^16\)
Clinical Implications

This study supports the use of nitrate therapy to improve the functional capacity of patients with chronic cardiac failure. In addition, the finding that the acute administration of nitrates improves submaximal exercise capacity where maximal exercise capacity reportedly is not changed24 raises major questions about current methods of assessing the efficacy of vasodilator therapy. At present, maximal exercise testing is the principle objective parameter used to assess the effect of a vasodilator on exercise tolerance.17 The data suggest that vasodilator therapy may improve submaximal exercise capacity considerably more than maximal exercise capacity. If this is the case, submaximal exercise testing should be used in combination with maximal exercise testing to assess the effects of a vasodilator on exercise tolerance. Further studies investigating this possibility are needed.

References

7 Massie BM, Kramer B, Haughom F. Acute and long-term effects of vasodilator therapy on resting and exercise hemodynamics and exercise tolerance. Circulation 1981; 64:1218-26