The Acute Effect of an Oral “Inotropic” Placebo on the Exercise Capacity of Patients with Chronic Cardiac Failure*

Srinivas Murali, M.D.; Barry F. Uretsky, M.D.; Judy A. Kolesar, R.N.; Anita M. Valdes, R.N.; and P. Sudhakar Reddy, M.D., F.C.C.P.

Uncontrolled studies have suggested that the newer oral phosphodiesterase inhibitors milrinone and enoximone acutely improve exercise performance in patients with severe chronic cardiac failure. To determine whether an oral placebo presented as an inotropic agent could acutely enhance exercise capacity, two separate groups of stable heart failure patients were studied by serial exercise testing and respiratory gas exchange analysis. Group 1 had nine patients studied four hours after a single oral dose of placebo, and group 2 had ten patients retested after one to two weeks of placebo therapy. No significant change was seen in the mean exercise time, mean peak oxygen consumption, and the mean oxygen consumption at anaerobic threshold after placebo administration in both group 1 and group 2 patients. Improvements in exercise time, peak oxygen consumption, and oxygen consumption at anaerobic threshold occurred in five patients in group 1 and seven patients in group 2. The improvements exceeded the baseline variability of 10 percent in three group 1 patients. Among group 2 patients, the increase in exercise time, peak oxygen consumption, and oxygen consumption at anaerobic threshold exceeded 10 percent in six, four, and four patients, respectively. Thus, stable chronic heart failure patients can achieve a true baseline exercise capacity. Small improvements in exercise performance seen acutely after oral inotropic drug therapy in individual heart failure patients must be interpreted with caution, as they may be due to a placebo effect.

Graded exercise testing with analysis of respiratory gas exchange has gained widespread use as an objective means of assessment of functional capacity in chronic cardiac failure patients. The determination of aerobic capacity or maximal oxygen consumption and anaerobic threshold is thought to be useful in assessing the severity and progression of heart failure and its response to therapeutic interventions. It has recently been reported that as a group, patients with chronic cardiac failure demonstrate an excellent reproducibility of their maximal exercise duration, peak oxygen consumption, peak heart rate, and peak systolic blood pressure during serial exercise testing. This implies that any improvement in exercise performance following drug therapy in cardiac failure can be attributed to the beneficial therapeutic effect of the drug.

Certain oral inotropic agents—in particular, the experimental phosphodiesterase inhibitors milrinone and enoximone—have been shown in uncontrolled studies to improve acutely the exercise capacity of chronic cardiac failure patients. It is not known whether such an acute improvement following drug intervention represents a true pharmacologic effect or a placebo effect. We describe the acute effect of an oral placebo presented as an inotropic agent on the exercise capacity of patients with severe cardiac failure.

*From the University of Pittsburgh School of Medicine, Pittsburgh. Manuscript received September 30; revision accepted February 1. Reprint requests: Dr Murali, 3494 Presbyterian University Hospital, Pittsburgh 15213.

Material and Methods

Patients

Two separate groups of patients were studied. Group 1 consisted of nine patients and group 2 of ten patients. All patients were participating in a phase 2 double-blind, placebo-controlled trial of the investigational phosphodiesterase inhibitor CI-914 hydrochloride. In accordance with the experimental drug protocol, each patient received placebo for one to two weeks before the double-blind randomization. The study patients had chronic, stable New York Heart Association functional class 3 to 4 cardiac failure. Each patient had had heart failure for at least six months and had persistent symptoms of dyspnea or fatigue despite treatment with digoxin, diuretics, and, in certain cases, angiotensin-converting enzyme inhibitors. The patient characteristics in each group are shown in Table 1.

Table 1—Clinical Characteristics of the Study Patients*

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Acute Study)</td>
<td>(1-2 wk study)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>61 ± 8</td>
<td>59 ± 6</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>6/3</td>
<td>6/4</td>
</tr>
<tr>
<td>Etiology of CHF, ICM/DCM</td>
<td>8/1</td>
<td>7/3</td>
</tr>
<tr>
<td>NYHA class, 3/4</td>
<td>8/1</td>
<td>9/1</td>
</tr>
<tr>
<td>Mean EF, %</td>
<td>20 ± 5</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>CFH Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dig/Diuretics</td>
<td>9/9</td>
<td>10/10</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>

*ACE = angiotensin-converting enzyme; CHF = congestive heart failure; Dig = digoxin; DCM = dilated cardiomyopathy; EF = ejection fraction; ICM = ischemic cardiomyopathy; Rx = treatment.
Exercise Testing

Exercise testing in all of the patients was performed as part of the investigational drug protocol that was approved by the Biomedical Review Board of the University of Pittsburgh. After obtaining informed consent, each patient underwent maximal (symptom-limited) exercise treadmill testing with on-line measurement of oxygen consumption, carbon dioxide production, and minute ventilation. The exercise tests were conducted in an air-conditioned laboratory at least two hours after a light meal, using a programmable motorized treadmill (Quinton Instruments). The treadmill program employed the Naughton protocol consisting of incremental two-minute stages of graded exercise. Before the baseline exercise tests reported below, each patient underwent at least one test to become familiar with the laboratory personnel and the equipment. The ECG and heart rate were monitored continuously before and during the exercise test and during the recovery period. Blood pressure was measured at 90 seconds of each stage and at the end of exercise. All patients exercised to the point of exhaustion as determined by severe fatigue or dyspnea or both.

Gas Exchange Analysis

Oxygen consumption, carbon dioxide production, and minute ventilation during each exercise test were directly measured using a metabolic cart (MMC Horizon System, Sensormedics, Inc) while the patient breathed through a sealed mask and a nonbreathing, low-resistance two-way valve. The gas exchange analysis employed the mixing chamber technique with readouts at 15-second intervals. During each exercise test, the exercise time, peak oxygen consumption, and oxygen consumption at anaerobic threshold were measured. Peak oxygen consumption was defined as the oxygen consumption at the point when the patient stopped exercising because of symptoms. Oxygen consumption at anaerobic threshold was determined using the following previously described criteria: disproportion rate in carbon dioxide production, minute ventilation, and respiratory exchange ratio (relative to oxygen consumption), and disproportion increase in the ventilatory equivalent for oxygen (Fig 1). At least two of these criteria were satisfied in each patient in every exercise test.

Study Protocol

When results of two consecutive baseline exercise tests (one week apart) were within 10 percent of each other, each patient was presented with an oral placebo characterized as an inotropic agent for a third exercise test. Although the investigator knew that the drug administered was a placebo, the patient was told that this drug would "strengthen the heart muscle." This form of "deception" was approved by the University of Pittsburgh Biomedical Review Board. The mean of the two consecutive baseline exercise tests represented the baseline exercise test used for statistical purposes. Group 1 patients had a repeated exercise test four hours after the first dose of placebo ("acute study"). Group 2 patients had a repeated study one to two weeks after institution of placebo therapy ("one to two weeks' study"). The acute study was not part of the experimental drug protocol. All group 2 patients received one tablet of placebo twice a day.

Statistics

The combined results for all patients are expressed as mean ± SD. Comparison of baseline and postplacebo exercise tests used the Student's t test for paired data.

RESULTS

Short-term Study

There were no significant changes in the mean exercise time, mean peak oxygen consumption, and the mean oxygen consumption at anaerobic threshold in group 1 patients after administration of the first dose of placebo (Fig 2). Improvements in exercise duration, peak oxygen consumption, and the oxygen consumption at anaerobic threshold occurred in five patients. The degree of improvement exceeded the baseline variability of 10 percent in three patients. No patient improved more than 25 percent from baseline.

One to Two Weeks' Study

No significant changes were observed in the mean exercise time, mean peak oxygen consumption, and the mean oxygen consumption at anaerobic threshold after one to two weeks of placebo therapy, in group 2 patients, although there was a tendency for the patients to exercise longer after placebo administration (Fig 3). The exercise duration improved in seven patients, and in all but one, this improvement exceeded 10 percent. In three patients, the exercise time increased more than 25 percent from baseline. Improvements in the peak oxygen consumption and the oxygen consumption at anaerobic threshold occurred in seven patients.
and the improvements exceeded 10 percent in four patients. Improvements in the peak oxygen consumption and the oxygen consumption at anaerobic threshold did not exceed 25 percent in any patient.

**Discussion**

**Baseline Exercise Capacity**

Healthy subjects and patients with coronary artery disease are known to have a reproducible exercise capacity. This study clearly demonstrates that as a group, patients with severe chronic cardiac failure can also achieve a truly stable baseline exercise capacity. The exercise duration, peak oxygen consumption, and oxygen consumption at anaerobic threshold are reproducible (within a range of ±10 percent) in stable cardiac failure patients. The establishment of such a stable baseline is important for the purpose of assessing the efficacy of therapeutic interventions.

Administration of an oral placebo presented as an inotropic agent did not significantly change the peak oxygen consumption or the oxygen consumption at anaerobic threshold acutely, but there was a tendency for the patients to exercise somewhat longer after one to two weeks of placebo therapy. The maximal oxygen consumption (\(\dot{V}O_2\)max) is thought to be a more precise reflection of the aerobic exercise capacity than exercise time. In this study, the peak oxygen consumption was measured instead of the maximal oxygen consumption, since severe cardiac failure patients are often unable to attain a true maximal oxygen consumption during exercise testing. The lack of an acute change in the peak oxygen consumption and the oxygen consumption at anaerobic threshold following placebo therapy further confirm that stable cardiac failure patients have a reproducible exercise tolerance.

**“Inotropic” Placebo Effect**

In individual patients with chronic cardiac failure, the use of an oral “inotropic” placebo nevertheless does appear to improve acutely the exercise performance. The degree of improvement is usually less than 25 percent over baseline. This means that small improvements in exercise capacity seen acutely following oral inotropic drug administration in individual patients with cardiac failure must be interpreted with caution, since they may be due to a placebo effect rather than to the inotropic drug itself. The acute effect of oral placebo on the exercise capacity of cardiac failure patients has not been previously reported to our knowledge. A number of long-term placebo controlled studies have shown that cardiac failure patients can improve their exercise duration and maximal

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**Figure 2.** The acute response to the first dose of placebo. AT \(\dot{V}O_2\) = oxygen consumption at anaerobic threshold; \(B_1\) = baseline 1; \(B_2\) = baseline 2; \(B\) = mean of \(B_1\) and \(B_2\); \(P\) = 4 hours after a single dose of placebo; peak \(\dot{V}O_2\) = peak oxygen consumption.
oxygen consumption following long-term placebo administration. In the multicenter oral amrinone study, placebo-treated patients improved their exercise duration by 37 ± 10 percent from baseline. The placebo-controlled multicenter captopril trial demonstrated a 17 percent improvement in exercise time in the placebo-treated patients after four weeks of therapy. However, this improvement was no longer present at the end of 12 weeks. Likoff et al reported a 16 ± 27 percent increment in exercise time and a 6 ± 15 percent improvement in the maximal oxygen consumption after long-term placebo therapy.

One can only speculate as to why some patients improved their exercise performance following placebo therapy. Before placebo administration, all patients were adequately familiarized with both the equipment and the personnel in the exercise laboratory. It is likely that the patients were motivated to perform better following placebo administration. This may explain the greater degree of improvement in exercise duration compared with the peak oxygen consumption and the oxygen consumption at anaerobic threshold following placebo therapy. Another likely explanation is the training effect of serial exercise testing. It has been previously shown that a carefully supervised exercise program can improve exercise capacity even in patients with severely depressed left ventricular function.

Finally, errors in the measurement of the metabolic parameters could have been partially responsible. The measurement of peak oxygen consumption in severe chronic cardiac failure patients has a much wider range of uncertainty than what is observed in normal subjects. Similarly, there are pitfalls in the method used to measure the oxygen consumption at anaerobic threshold. The currently used criteria have an unacceptably wide range of reviewer variability. Also, all of the criteria were not satisfied in every exercise test in this study.

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