Normal Exercise Capacity in Patients with Severe Left Ventricular Dysfunction: Compensatory Mechanisms

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SUMMARY About one-third of patients who have severe left ventricular dysfunction can achieve normal levels of exercise. To elucidate the mechanisms that permit this to occur, we studied six patients with severe left ventricular dysfunction (average left ventricular ejection fraction 17 ± 2.5% [mean ± SEM]) who achieved nearly normal levels of exercise tolerance (greater than 11 minutes of treadmill exercise, Sheffield protocol). All patients had normal pulmonary function at rest and during exercise. Hemodynamics were measured at rest and during supine and upright exercise. The major mechanisms of the preserved exercise capacity in these patients were chronotropic competence, ability to tolerate elevated wedge pressures (33 ± 3 mm Hg) without dyspnea, ventricular dilation, and increased levels of plasma norepinephrine at rest and during exercise. Also, whereas peripheral vascular resistance was unchanged during supine exercise, it decreased by 50% during similar levels of upright exercise. As a consequence, increases in cardiac output from rest to exercise were greater during upright than supine exercise (100% vs 50%, respectively) (p < 0.05), and pulmonary wedge pressures were lower during upright than supine exercise (21 ± 5 mm Hg vs 33 ± 3 mm Hg). Thus, multiple mechanisms permit some patients with severe left ventricular dysfunction to achieve normal levels of exercise. These studies emphasize that left ventricular function must be assessed by direct measures rather than inferring function of the left ventricle from the results of an exercise tolerance test.

A PREVIOUS STUDY from our laboratory showed that exercise capacity in patients with severe left ventricular dysfunction varies widely. There are two major weaknesses in previous studies of exercise hemodynamics in patients with heart disease. First, the patient populations have usually not been homogeneous with regard to the severity of their cardiac dysfunction. Second, in most studies, only a few aspects of cardiac function have been examined and the hemodynamic measurements were obtained with patients either in the supine or upright position.

We studied patients with severe left ventricular dysfunction and normal exercise tolerance to determine the compensatory mechanisms that allowed them to achieve normal exercise levels. The patients were studied in both the supine and upright positions.

Materials and Methods

Patients

We studied six males (mean age 60 years, range 53–69 years) who had left ventricular ejection fractions less than 30% by gated isotope ventriculograms (range 7–25%) and nearly normal exercise tolerance by graded treadmill exercise test. Four patients had coronary artery disease and two had congestive cardiomyopathy. All of the coronary patients had evidence of previous infarction, but none had angina. All patients were being treated for congestive heart failure at the time of our study; all six patients were taking digitalis preparations and four were taking diuretics. All patients were on a salt-restricted diet. Patients with valvular heart disease, arrhythmias, or noncardiac disabilities that limit exercise were excluded. Approval of the protocol was obtained from the Human Use Committee of the University of Iowa, and each patient gave informed consent.

Graded Treadmill Exercise Test

All patients underwent physician-monitored graded treadmill exercise tests using the Sheffield modification of the Bruce protocol. A multilead ECG (12 standard leads and Frank X, Y, and Z leads) and cuff blood pressure were measured every 3 minutes during exercise. The exercise test was terminated if the patient complained of marked dyspnea or fatigue or achieved 85% of the maximal predicted heart rate.

Pulmonary Function Tests

Pulmonary function testing was performed and respiratory volumes were measured. In addition, two types of exercise pulmonary functions were determined in each patient. The first was a progressive upright bicycle test with an initial power output of 100 kpm/min. Each minute, the work load was increased by 100 kpm/min while a physician monitored the ECG, cuff blood pressure and ventilation. Oxygen consumption and carbon dioxide production were measured with oxygen and carbon dioxide analyzers after each minute of exercise. Exercise was terminated if the patient complained of significant dyspnea or fatigue. A second pulmonary exercise test was performed on a different day. Measurements were obtained at one-third and two-thirds maximal exercise (based on external load) in the upright posture. Each
level of exercise was continued for more than 3 minutes. Oxygen and carbon dioxide consumption, heart rate, brachial artery pressure, pulmonary artery pressure and mean pulmonary arterial wedge pressure were obtained at each level of exercise.

Hemodynamic Monitoring

Pulmonary wedge pressures and pulmonary artery pressures were obtained using a #7F Swan-Ganz thermodilution catheter. Arterial pressure was monitored by inserting a straight, 20-cm #5F catheter into the brachial artery. Heart rate and rhythm were recorded by a standard 12-lead ECG and cardiac output was determined by the thermodilution and Fick methods.

Norepinephrine Levels

Arterial blood samples were drawn and packed in dry ice for later determinations of norepinephrine levels using a modification of a method described by de Champlain et al. One sample was obtained at rest and another at two-thirds maximal supine exercise.

Cardiac Imaging

Gated isotope ventriculograms were taken at rest and two-thirds maximal supine exercise in all patients. Red cells labeled in vivo with technetium-99m were used as the imaging agent. A small-field-of-view portable gamma camera with an all-purpose collimator (energy window 140 KeV and width ± 20%) was used to obtain the images, which were recorded on a computer. A time-activity curve composed of 16 frames (200,000 counts/frame) was obtained both at rest and during exercise in the 45° left anterior oblique projection. Rest and exercise left ventricular ejection fractions were calculated from the left anterior oblique projection using a method described by Burow et al. No significant ectopy was noted during acquisition.

Echocardiograms

Echocardiograms were performed at supine rest using an M-mode ultrasonoscope and a 2.25-MHz transducer focused at 7.5 cm. Recordings were made on a strip-chart recorder. Left ventricular end-diastolic dimensions were measured at a level immediately below the mitral valve. End-systolic dimensions and ejection fraction measurements were not made from the echocardiograms, as they may be unreliable in patients with ischemic heart disease.

Protocol

Upon admission, each patient related a complete medical history. Treadmill exercise tolerance tests done at least 1 week before the study suggested that the patients’ exercise tolerance was better than expected. A physical examination, chest x-ray and echocardiogram were performed, and a complete blood count, blood urea nitrogen, serum creatinine, sodium, potassium, chloride and bicarbonate were obtained. A practice session was held for each type of exercise (supine and upright) to familiarize the patients with the exercise procedure and the apparatus used to collect expired pulmonary gases. During this practice session, we determined the maximal level of exercise that each patient could achieve in the supine and upright postures. Submaximal levels of exercise (one-third and two-thirds maximal) were used to ensure steady-state conditions (more than 3 minutes of continuous exercise at one work load) during hemodynamic measurements. Isotope ventriculograms were also taken on day 1 at rest and at two-thirds maximal exercise.

On day 2, the patients were taken to the catheterization laboratory where Swan-Ganz and arterial catheters were placed through a right antecubital cutdown. A plethysmograph was placed on the left arm to measure forearm blood flow. All measurements were obtained at supine rest and, after the third minute, at one-third and two-thirds maximal steady-state exercise. The patient was allowed to recover for 15–45 minutes before the upright exercise tests. Samples were again obtained at upright rest and at one-third and two-thirds maximal steady-state exercise. After the upright exercise studies, the catheters were removed and the skin was sutured. On day 3, a graded treadmill exercise test was performed.

Calculations and Statistical Analysis

Peripheral vascular resistance was calculated as 80 • MAP/CO, where MAP = mean arterial pressure and CO = cardiac output. Forearm vascular resistance was calculated as MAP/FFBF, where FBF = forearm blood flow.

Differences between various treatments were determined by paired t test or analysis of variance. The significance of subgroup differences were assessed with Duncan’s test. Results are presented as mean ± SEM.

Results

Clinical Examination

All patients had a history of congestive heart failure. At the time of our study, none of the patients had physical findings (peripheral edema, increased systemic venous pressure, tachycardia or a third heart sound) or symptoms (dyspnea at rest or upon exertion) of advanced heart failure. Two patients had a 2/6 murmur of mitral regurgitation. The cardiothoracic ratio by chest x-ray averaged 0.54 ± 0.02, and there was no evidence of marked congestion or pleural effusion. The hemoglobin concentration (15.1 ± 0.2 g/dl), blood urea nitrogen (18.6 ± 2.7 mg/dl), and other blood chemistries were normal. Thus, the patients in this study had clinically compensated cardiac failure.

Graded Exercise Tolerance Test

All patients exercised for at least 12 minutes on the treadmill (Sheffield protocol). The average duration of treadmill exercise was 13.3 ± 0.7 minutes, and the maximal heart rate averaged 146 ± 11 beats/min.

Pulmonary Function Test

No patient had evidence of limiting pulmonary disease at rest or during exercise testing (table 1). During supine or upright exercise, oxygen consumptions and
TABLE 1. Results of Pulmonary Function Test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (l)</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>(97 ± 6%)*</td>
</tr>
<tr>
<td>FEV1</td>
<td>(77 ± 5.1%)*</td>
</tr>
<tr>
<td>Maximal exercise</td>
<td></td>
</tr>
<tr>
<td>Work load (kpm/min)</td>
<td>650 ± 56</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>148 ± 11</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>(87 ± 6%)*</td>
</tr>
<tr>
<td>Oxygen consumption (ml/kg/min)</td>
<td>112 ± 6</td>
</tr>
<tr>
<td></td>
<td>(71 ± 3%)*</td>
</tr>
<tr>
<td>Two-thirds maximal exercise</td>
<td></td>
</tr>
<tr>
<td>Arterial Po2 (mm Hg)</td>
<td>87 ± 5</td>
</tr>
<tr>
<td></td>
<td>(94 ± 6)†</td>
</tr>
<tr>
<td>Arterial PcO2 (mm Hg)</td>
<td>34.5 ± 2</td>
</tr>
<tr>
<td></td>
<td>(30.3 ± 2)†</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.42 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>(7.49 ± 0.02)‡</td>
</tr>
<tr>
<td>VO2/pulse</td>
<td>10 ± 1</td>
</tr>
<tr>
<td></td>
<td>(11 ± 1)‡</td>
</tr>
<tr>
<td>VE/VO2</td>
<td>33 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>(27 ± 3)‡</td>
</tr>
</tbody>
</table>

*Percent predicted.
†Value at rest.
‡Normal value from Sheffield.11

Abbreviations: FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; kpm = kilopond meters; VO2 = oxygen uptake; VE = ventilatory equivalent; Po2 = oxygen tension; PcO2 = carbon dioxide tension.

Discussion

We previously reported a poor correlation between left ventricular function assessed by left ventricular ejection fraction and exercise tolerance determined by a graded exercise test. The present study indicates that the primary mechanisms that influence exercise capacity are (1) the ability to tolerate very elevated pulmonary artery wedge pressures without symptoms, (2) preserved chronotropic response to exercise, (3) ventricular dilation, (4) augmented stroke volume and decreased peripheral vascular resistance with upright exercise, (5) increased cardiac output particularly with upright exercise, and (6) increased levels of circulating catecholamines at rest and during exercise.

Compensatory Mechanisms

Tolerance of High Pulmonary Wedge Pressures

During supine exercise, wedge pressures increased to levels that frequently produced pulmonary edema. However, even with pulmonary wedge pressures that averaged 33 mm Hg, no patient had clinical signs of pulmonary edema and none was limited by dyspnea during exercise. Only fatigue prevented additional exercise. Two mechanisms could have permitted our patients to tolerate the abnormally high pulmonary venous pressures: increased pulmonary lymphatic flow, which allows accelerated fluid removal,22 and chronic changes in capillary walls, which inhibit transudation of fluid into the interstitial space. Studies in animals suggest that increased pulmonary lymphatic flow is probably the major factor.

Chronotropic Competence

Impaired chronotropic response to exercise has been implicated as contributing to the inability of patients with cardiac failure to perform normal levels of exercise.23 Compared with age-matched controls, our patients showed normal heart rate response at two-thirds maximal exercise (fig. 1, table 1). Thus, a normal chronotropic response to exercise contributed to our patients’ exercise tolerance.

Ventricular Enlargement

All but one patient had an abnormally large left ventricular diameter by echocardiography. Three of the six patients had a cardiothoracic ratio greater than 0.5 by chest x-ray. Because stroke volume increases as the ventricle dilates, even if fractional shortening remains constant, ventricular dilation was an important compensatory mechanism in our patients.

Stroke Volume

In normal subjects, the contribution of changes in stroke volume to changes in cardiac output during exercise has been carefully examined. Thadani and Parker21 showed in normal males (mean age 46 years) that stroke volume changed little during supine submaximal exercise, but increased by 67% during upright exercise. The results in our patients with severe left ventricular dysfunction are similar to those reported by Thadani and Parker in normal subjects. Stroke volume...
changed little during supine exercise, but increased by 62% during upright exercise. Thus, an increase in stroke volume during upright exercise contributed to the increase in cardiac output achieved by our patients. Studies in patients with heart failure usually have not included measurements of stroke volume during both supine and upright exercise.

Peripheral Vascular Resistance

Vascular resistance in nonexercising skeletal muscle normally increases during exercise. This also occurred in our patients with heart failure. In patients with heart failure, vasodilation is limited during exercise. In our patients, total systemic vascular resistance did not change during supine exercise, but de-
increased significantly during upright exercise. With upright exercise, the magnitude of the decrease in total systemic vascular resistance was similar to that in normal subjects performing similar levels of exertion (table 2).

Why did total systemic vascular resistance decrease during upright exercise and not change during supine exercise? During exercise, the response of the total systemic vascular resistance represents a balance between metabolic vasodilation in exercising muscle and reflex vasoconstriction triggered by somatic afferents. Normally, inhibitory cardiac afferents modulate the reflex vasoconstriction triggered by muscular exercise and somatic pressor reflexes.24, 25 As a result, total systemic vascular resistance decreases during exercise because metabolic vasodilation in exercising muscles predominate. However, cardiac afferent input is impaired in patients with heart failure. This would be expected to augment the somatic pressor vasoconstrictor reflex and thereby limit decreases in total systemic vascular resistance during exercise. This could explain the failure of total systemic vascular resistance to decrease during supine exercise in patients with heart failure.

How could the cardiac afferents contribute to a significant decrease in total systemic vascular resistance during upright exercise? Normally, cardiac afferent input decreases during upright tilt because cardiac filling pressures and volume decrease.25 Consequently, with exercise, the percent change in cardiac dimensions is increased relative to that during supine exercise. This greater change in cardiac dimensions may help activate the cardiac afferent sensory endings, which discharge during systole with a frequency that depends largely on the mechanics of ventricular contraction. It is difficult to prove that this hypothesis explains the mechanism for the restoration of the vasodilator response to exercise in the upright position in patients with heart failure. The important point is that the normal decrease in vascular resistance during upright exercise in patients with heart failure may contribute to the increase in stroke volume and preservation of exercise capacity in these patients.

Cardiac Output

An inadequate cardiac output response to exercise is a common characteristic of patients in heart failure.4, 5, 7-9 Our patients, although unable to increase cardiac output to normal levels with exercise, doubled their cardiac output with upright exercise. Increases in cardiac output during supine exercise were more limited. These differences in exercise cardiac output during supine and upright exercise are probably modulated by significant differences in peripheral vascular resistance that occurred during these two states.

Plasma Norepinephrine

Plasma norepinephrine levels were above normal at rest and increased substantially during exercise. This increase in catecholamines has also been reported by Chidsey et al.,2 and is a significant compensatory mechanism in patients with left ventricular dysfunction.

Advantages and Problems of the Experimental Design

There are several advantages to our experimental design. The patients were similar with respect to the severity of left ventricular dysfunction and exercise tolerance. In addition, no patient was accepted into the study if exercise performance was limited by pulmonary disease or other noncardiac factors. Each patient was familiarized with the supine and upright exercise procedures. Maximal exercise was determined to calculate the two-thirds maximal exercise level. All measurements were obtained in the steady state so as to eliminate dynamic variations seen with progressive exercise. Invasive hemodynamic monitoring was performed in both the supine and upright postures. Measurements of oxygen consumption and pulmonary artery saturation indicate that during upright and supine exercise, comparable levels of cardiovascular stress were achieved. Thus, comparisons between upright and supine exercise hemodynamics are reasonable. Our measurements can also be compared with those in normal subjects.

One problem with our study is that we did not study normal controls. Our purpose was not to delineate normal from abnormal, but to evaluate compensatory mechanisms in patients with severe left ventricular dysfunction. Extensive values for normal subjects are available (table 2). A second problem is that the patients were taking various medications. Because our patients were in well-compensated congestive heart failure, it would have been unethical to discontinue their medications. Consequently our results pertain only to patients receiving adequate medical therapy. Although the study group was small, the responses of all of our patients were similar; thus, studies done in a larger group of patients would probably yield similar conclusions.

Acknowledgment

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References

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