Oxygen Deficit During Exercise Testing in Heart Failure*
Relation to Submaximal Exercise Tolerance

Andrew M. Cross, Jr, MD; and Michael B. Higginbotham, MD

Measurements of oxygen deficit during submaximal exercise were correlated with the anaerobic threshold (as measured by gas exchange analysis), peak work rate on a ramp protocol, and the ability to perform constant work rate exercise in 10 male patients with New York Heart Association class 2 congestive heart failure and 12 age- and gender-matched normal controls. All subjects performed a maximal ramp exercise test for measurement of the anaerobic threshold. In addition, several 15-min constant work rate exercise sessions were conducted to evaluate oxygen deficit, measured as the area between the “ideal” square curve of oxygen consumption at the onset of constant work rate exercise and the actual exponentially shaped curve. Since the oxygen deficit significantly correlated with the plateau oxygen consumption during the 25-W constant work rate exercise ($r=0.61$, $p=0.002$), the oxygen deficit was normalized by the rectangular area of 15-min oxygen consumption above baseline. This normalized value significantly correlated with the inverse of the anaerobic threshold ($r=0.51$, $p<0.0001$). The logarithm of the normalized oxygen deficit significantly correlated with the maximum ramp work rate ($r=-0.86$, $p<0.0001$) and the highest constant work rate sustained for 15 min ($r=-0.82$, $p<0.0001$). In addition, the time to reach plateau oxygen consumption for the 25-W exercise significantly correlated with the inverse of the anaerobic threshold ($r=-0.78$, $p<0.0001$), the maximum ramp work rate ($r=-0.76$, $p<0.0001$), and the highest constant work rate sustained for 15 min ($r=-0.74$, $p<0.0001$). Thus, the oxygen deficit seen in patients with heart failure during constant work rate exercise results from abnormally slow oxygen uptake kinetics and correlates with exercise capacity as measured by anaerobic threshold (via gas exchange analysis) and maximal and submaximal exercise tolerance. Oxygen deficit warrants further evaluation as a submaximal index of functional capacity in patients with heart failure. (Chest 1995; 107:904-08)

NYHA=New York Heart Association

Key words: anaerobic threshold; congestive heart failure; constant work-load exercise testing; oxygen deficit

Graded maximal exercise testing and gas exchange analysis are increasingly used in patients with heart failure for evaluation of functional capacity, response to therapy, and prognosis.1-4 While graded testing has the advantage of being practical to administer and provides a good index of maximal oxygen uptake, the significance of data generated during submaximal work rates remains somewhat obscure. Using graded maximal exercise testing, patients with heart failure have been observed to have lower anaerobic thresholds and lower oxygen consumption/work rate relationships compared with normal individuals.5-7 It has been suggested that these differences in exercise response are related to an increased contribution by anaerobic metabolism at lower work rates in patients with heart failure.5 It has also been suggested that these phenomena may have a functional relevance to submaximal exercise tolerance.8,9 At the onset of constant work rate exercise, there is a delay in the rise of oxygen consumption to a higher steady state, resulting in an incurred oxygen deficit.10-15 This oxygen deficit appears to be related to anaerobic metabolism, exercise intensity, and exercise endurance in both athletes and untrained normal individuals.16-18

Recent data suggest that compared with normal individuals, patients with heart failure have slower oxygen uptake kinetics and a greater oxygen deficit during the onset of work at a given load that are correlated with markers of increased anaerobic metabolism.19 However, oxygen deficit in patients with heart failure has not been studied sufficiently to determine its relationship to sustainable levels of submaximal work. Significant correlations among delayed oxygen uptake kinetics, anaerobic threshold, and sustainable levels of submaximal work would suggest a potential role for low-level submaximal exercise testing in the determination of functional...
capacity in patients with heart failure.

The purpose of this study was to examine oxygen deficit at the onset of exercise in a mixed population of patients with heart failure and normal subjects, and to correlate the oxygen deficit with the anaerobic threshold (as measured by gas exchange analysis) and the amount of work that can be performed for sustained periods of time.

METHODS

Subjects

Ten adult (age ≥18 years) male patients with dilated cardiomyopathy, left ventricular ejection fraction <40% (as measured by radionuclide ventriculography), and New York Heart Association (NYHA) class 2 congestive heart failure were recruited from a population followed up by the Duke University Medical Center Heart Failure Service, Durham, NC. Twelve normal men were recruited from employees of Duke University and from a population of volunteers enrolled in the Duke Geriatrics Databank. Patients and volunteers were excluded if valvular heart disease, significant obstructive or restrictive lung disease, or exercise-induced ischemia was present. The protocol was approved by the Duke University Medical Center institutional review board, and informed consent was obtained from all participants.

Exercise Testing

After familiarization with the exercise equipment, subjects first performed maximal cycle exercise for determination of their anaerobic thresholds and maximal work rates. This was done using a ramp protocol in which the work rate was progressively increased at a rate of 7.5 to 15 W/min, adjusted so that exhaustion occurred within approximately 10 min. On separate days, subjects performed constant work rate exercises for the evaluation of oxygen deficit and the highest constant work rate sustainable for 15 min. The initial constant work rate was 25 W. The work rate of each successive exercise was increased by 25 W until a full 15-min exercise could not be completed. The time between successive exercises was no fewer than 3 days to avoid a training effect. Subjects performed one to eight constant work rate exercise depending on their ability to sustain exercise for 15 min at higher work rates. Each constant work rate exercise was initiated by a 1-min ramp from no pedaling to the preset work rate. Measurements obtained during the study included blood pressure, heart rate, continuous electrocardiographic monitoring, oxygen consumption, carbon dioxide production, and minute ventilation. Exercise was performed on an electronically braked stationary ergometer. Gas exchange analysis was completed using a metabolic cart (Medical Graphics CPX, Medical Graphics, St. Paul, Minn).

Gas Exchange Analysis

Anaerobic threshold was determined from gas exchange analysis during ramp exercise. Three criteria were used to visually detect the anaerobic threshold:20 (1) the point of a progressive increase in the ratio of minute ventilation to oxygen consumption, without an increase in the ratio of minute ventilation to carbon dioxide production; (2) the point of a progressive increase in end-tidal partial pressure of oxygen without a decrease in end-tidal partial pressure of carbon dioxide; and (3) the point of an abrupt increase in the respiratory exchange ratio (carbon dioxide production/oxygen consumption). The time at which the anaerobic threshold occurred was determined to be the point of agreement between at least two of the three criteria.

The oxygen consumption curve during constant work rate exercise was plotted vs time. The oxygen deficit was determined by measuring the area between the ideal square curve of oxygen consumption at the onset of the constant work rate exercise and the actual exponentially shaped curve (Fig 1). The ideal curve represents the theoretical instantaneous response of oxygen consumption at the onset of constant work rate exercise in a perfect system. The 15-min exercise oxygen consumption was measured as the area under the oxygen consumption curve during 15 min of constant work rate exercise, over and above the baseline oxygen consumption (Fig 1). The area was calculated using an integration algorithm written in C language on a computer (Digital Equipment Corporation AXF 3000). All determinations of anaerobic threshold and oxygen deficit were done independently by a single investigator.

Statistical Analysis

Independent nonpaired, two-tailed t tests were performed to compare measurements obtained in patients with heart failure with those obtained from normal subjects. Correlation analysis was used to determine the relationship between measurements obtained during maximal exercise and those obtained from constant work rate exercise. A p value less than 0.05 was considered significant.

RESULTS

The clinical characteristics of the study population...
Table 1—Clinical Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD) age, yr</td>
<td>51.1±11.7</td>
</tr>
<tr>
<td>Mean (± SD) resting ejection fraction</td>
<td>0.22±0.09</td>
</tr>
<tr>
<td>Etiology of heart failure, No. of patients</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>4</td>
</tr>
<tr>
<td>Hypertensive cardiovascular disease</td>
<td>1</td>
</tr>
</tbody>
</table>

are summarized in Table 1. The mean (± SD) ages of the patients and the normal subjects were 51.1 ± 11.7 years and 47.2 ± 9.5 years, respectively. The patients with heart failure had a mean (± SD) ejection fraction of 0.22 ± 0.09. The etiology of heart failure was judged to be coronary artery disease in five patients, idiopathic in four patients, and hypertensive cardiovascular disease in one patient.

The anaerobic threshold was detectable in all subjects. Anaerobic threshold normalized by body mass (milliliter per kilogram per minute) less favorably correlated with the maximal ramp and the highest sustained constant work rates (r=0.78, r=0.77) compared with measurements evaluated without normalization (r=0.84, r=0.82). Therefore further analysis was performed without adjustment for body mass. There was no significant difference in body mass between the patients with heart failure and normal subjects (83.1 ± 20.5 kg vs 77.7 ± 9.5 kg, p=0.42). Normal subjects attained significantly higher work rates (191 ± 44 W vs 87 ± 24 W, p <0.0001) and anaerobic thresholds (1,480 ± 500 mL/min vs 870 ± 290 mL/min, p=0.002) with ramp exercise compared with patients with heart failure. With constant work rate exercise, normal subjects completed 15-min sessions at significantly higher work rates compared with patients with heart failure, with a range of 75 to 200 W (mean, 137 W) vs 25 to 75 W (mean, 50 W) (p<0.0001). Since the 25-W, 15-min constant work rate exercise was the only test that all subjects completed, subsequent comparisons were made only at this level.

The oxygen deficit during the 25-W exercise significantly correlated with the steady-state oxygen consumption (r=0.61, p=0.002). To account for the effect of higher steady-state oxygen consumptions causing higher measurements of oxygen deficit, the oxygen deficit was normalized by the rectangular area bordered by the baseline oxygen consumption and the steady-state oxygen consumption during the period of 15-min constant work rate exercise. This allowed for assessment of oxygen deficit as related to the delay in reaching the plateau oxygen consumption, independent of the magnitude of the plateau oxygen consumption.

For the entire study population, the normalized oxygen deficit significantly correlated with the inverse of the anaerobic threshold (r=0.81, p<0.0001) (Fig 2). Graphically, there appeared to be an exponential relationship between the normalized oxygen deficit and work rate, and logarithmic analysis provided the most significant correlations. The logarithm of the normalized oxygen deficit significantly correlated with the maximum ramp work rate (r=−0.86, p<0.0001) and the highest constant work rate sustained for 15 min (r=−0.82, p<0.0001), as illustrated in Figure 3. In addition, the time to reach plateau oxygen consumption for the 25-W exercise significantly correlated with the inverse of the anaerobic threshold (r=−0.78, p<0.0001), the maximum ramp work rate (r=−0.76, p<0.0001), and the highest constant work rate sustained for 15 min (r=−0.74, p<0.0001). The normalized oxygen deficit for the 25-W exercise was higher in the patients with heart failure compared with the normal subjects (0.13 ± 0.07 vs 0.03 ± 0.03, p=0.0003). Similarly, the time to reach plateau oxygen consumption was longer in the patients with heart failure (8.6 ± 3.3 min vs 2.7 ± 2.5 min, p=0.0001).
DISCUSSION

In this study, we investigated the relationship between gas exchange variables measured during maximal exercise and those measured during constant work rate submaximal exercise in normal subjects and patients with heart failure. The major finding of our study was that during a very low level (25 W) submaximal exercise test, differences in oxygen uptake kinetics were evoked that significantly correlated with indices of submaximal and maximal exercise tolerance. This finding not only confirms the relationship of oxygen uptake kinetics to the level of impairment, but raises the possibility that low-level exercise testing may be developed as a safe and easily performed substitute for maximal testing in evaluating functional capacity in patients with heart failure.

The degree of anaerobic metabolism present at the beginning of exercise has been central to many of the mechanisms proposed to explain delayed oxygen consumption responses. A delay exists in the ability of aerobic metabolism to supply the sudden increase in energy requirements of the working muscles at the beginning of exercise, causing an increase in anaerobic metabolism and higher lactate levels at the onset of exercise. Exercise training has the effect of decreasing the delay in oxygen consumption and lowering the lactate response at the onset of exercise. Factors that may contribute to an improved response of oxygen consumption include improved capacity for mitochondrial respiration, greater availability of oxygen stores, and a higher proportion of slow-twitch muscle fibers. Since congestive heart failure causes skeletal muscle changes similar to deconditioning, with atrophy and a higher proportion of fast-twitch fibers, it likely has an effect on the early stages of exercise opposite that of exercise training.

Exercise initiation requires rapid acceleration of circulatory oxygen transport that may acutely depend on an increase in stroke volume. The circulatory response in patients with heart failure is depressed due to reduced cardiac reserve and in turn reduced capacity to increase stroke volume. Decreased cardiac reserve may also play a role in the alteration of oxygen uptake kinetics observed in the patients with heart failure.

The relationship we demonstrated between oxygen deficit and anaerobic threshold is consistent with past observations. Subjects with higher exercise tolerances on graded maximal exercise testing have lower oxygen deficit at the onset of constant work rate exercise. Oxygen deficit also has been related to the increase in lactate level during constant work rate exercise. While anaerobic threshold and maximal work rate performed on graded exercise testing correlate with the ability to sustain endurance exercise, for example, marathon running, these indices have not been correlated previously with sustained work in patients with heart failure. Such a relationship is supported in our study by the logarithmic correlation between oxygen deficit at low-level constant work and the ability to sustain higher levels of constant work for a prescribed period of time. Although the choice of 15 min of constant work rate exercise was arbitrary, we believed it to be a logical empiric exercise interval, and one that reflected functional capacity commonly obtained historically from patients with congestive heart failure. Many patients in this study were not able to complete 15 min of exercise at more than 50 W intensity, which is a relatively low work rate for a normal individual.

Limitations

In our study, all of the patients with heart failure had NYHA class 2 symptoms and were able to exercise to some extent. This allowed for all anaerobic thresholds to be easily identified by gas exchange analysis. Detection of anaerobic threshold may be more difficult in patients with severe symptoms, who demonstrate anaerobic metabolism in very early stages of exercise or at rest, and do not have the abrupt alteration in respiratory gas exchange variables that determine the anaerobic threshold. We also found a steep logarithmic rise in the oxygen deficit within the group of patients with heart failure, which was associated with impaired exercise capacity. The work rate was likely too high to demonstrate more gradual changes in oxygen deficit. Although 25 W is a relatively low work rate, it requires a level of oxygen consumption that is above the anaerobic threshold in many patients with heart failure. The sharp rise in anaerobic metabolism associated with exercise above the anaerobic threshold is probably reflected by a sharp rise in the oxygen deficit. Exercise at lower work rates may provide oxygen deficit data that are more evenly distributed. Such low-intensity exercise testing may also be more applicable to patients with more severe symptoms, ie, NYHA class 3. Conversely, exercise testing in patients with minimal symptoms using lower work rates may not be useful, since the distribution of their responses would be closer to those of the normal individuals. This study included only men and therefore the results may not be totally applicable to a female population of patients with heart failure. It is likely that the absolute magnitude of the exercise responses in women would be different but with similar correlational relationships. This hypothesis obviously requires further investigation.

Although this study revealed significant relationships between oxygen deficit and submaximal exer-
Exercise tolerance, there was not any insight into the mechanisms of delayed oxygen kinetics at the onset of exercise. Such an evaluation requires more sophisticated techniques compared with those used in this study, and it was not included as part of the main focus of this study.

Other significant limitations include the small sample size and the lack of reproducibility studies. These issues along with the need for a more homogeneous patient population should be addressed in future studies.

**Conclusions**

Abnormal oxygen uptake kinetics appear to account for the abnormal oxygen consumption/work rate relationship during exercise in patients with heart failure, are related to anaerobic threshold, and correlate with submaximal levels of sustainable exercise. These observations provide a strong theoretic basis for the measurement of gas exchange variables during low submaximal exercise protocols in the evaluation of functional capacity in patients with heart failure. Future studies should evaluate the reproducibility of measurements obtained during submaximal constant work rate exercise and also monitor changes in these measurements as they are repeated over time.

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**References**

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