Detecting Abnormalities in Left Ventricular Function During Exercise by Respiratory Measurement

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The degree of exercise-induced cardiac dysfunction and its relation to the anaerobic threshold were evaluated in 23 patients with chronic heart disease. A symptom-limited exercise test was performed with a cycle ergometer with work rate increased by 1 W every 6 seconds. Left ventricular function, as reflected by ejection fraction, was continuously monitored with a computerized cadmium telluride detector after the intravenous injection of technetium-labeled red blood cells. The anaerobic threshold (mean, 727±166 ml/min) was determined by the noninvasive measurement of respiratory gas exchange. As work rate rose, the left ventricular ejection fraction increased but reached a peak value at the anaerobic threshold and then fell below resting levels. Ejection fraction at rest, anaerobic threshold, and peak exercise were 41.4±11.3%, 46.5±12.0%, and 37.2±11.0%, respectively. Stroke volume also increased from rest (54.6±17.0 ml/beat) to the point of the anaerobic threshold (65.0±21.2 ml/beat) and then decreased at peak exercise (52.4±18.7 ml/beat). The slope of the plot of cardiac output versus work rate decreased above the anaerobic threshold. The anaerobic threshold occurred at the work rate above which left ventricular function decreased during exercise. Accurate determination of the anaerobic threshold provides an objective, noninvasive measure of the oxygen uptake above which exercise-induced deterioration in left ventricular function occurs in patients with chronic heart disease. (Circulation 1989;80:1737-1746)

The heart’s pumping reserve, or maximum cardiac output, which reflects the severity of heart failure, does not necessarily correlate to ejection fraction or cardiac output measured at rest.1-3 Accordingly, exercise testing is important for evaluation of cardiac patients. Although determination of a patient’s aerobic capacity by the noninvasive measurement of peak oxygen uptake during exercise may provide this information,4 it may not be a reliable parameter to measure in cardiac patients because exercise duration and peak oxygen uptake are easily influenced by the subjects’ motivation and the philosophy of the physician who has the responsibility to terminate the exercise test.

Recently, it has been reported that the anaerobic threshold, which assesses the metabolic rate at which lactic acidosis occurs, can be used to identify the severity of chronic heart failure, noninvasively.2,5-8 The anaerobic threshold measurement has a great advantage over that of the maximal oxygen uptake because its determination does not require that the patients endure a maximal effort. While there are some reports9,10 that contradict the theory of the anaerobic threshold and it has been suggested that lactate increase during exercise is unrelated to some hemodynamic indexes of left ventricular function such as cardiac output or left ventricular filling pressure,11 other reports show hemodynamic correlation2,5,12 with the anaerobic threshold. Therefore, the exact relation between the anaerobic threshold and hemodynamic events during exercise in patients with chronic heart disease remains uncertain.

The development of exercise radionuclide angiography has expanded the diagnostic potential of exercise testing13-15 and made possible the simultaneous measurement of ejection fraction and gas exchange during exercise. In our study, we measured left ventricular ejection fraction beat-by-beat and compared the pattern of change in this cardiac function, as work rate was increased, to the anaerobic threshold.
TABLE 1. Physical Characteristics, Physiologic Data, and Cardiac Diagnosis of Patients

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<th>Age (yr)</th>
<th>Gender</th>
<th>Weight (kg)</th>
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<th>Rhythm</th>
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NYHA, New York Heart Association functional classification; AT, anaerobic threshold corresponding oxygen uptake; peak Vo2, oxygen uptake at peak exercise; max WR, maximum work rate; HHD, hypertensive heart disease; CAD, coronary artery disease; AR, aortic regurgitation; ASR, aortic stenoregurgitation; TR, tricuspid regurgitation; MSR, mitral stenoregurgitation; PR, pulmonary regurgitation; DCM, dilated cardiomyopathy; NSR, normal sinus rhythm; AF, atrial fibrillation.

Methods

Patient Population

Twenty-three patients with chronic heart disease (New York Heart Association functional classes I–III) were studied (Table 1). Seventeen patients were men and six patients were women (ages, 39–72 years; mean age, 60 years). The cardiac lesion of the subjects was ischemic heart disease with previous myocardial infarction in seven, ischemic heart disease without infarction in eight, valvular heart disease in five, hypertensive heart disease in two, and dilated cardiomyopathy in one. Seventeen patients had a sinus rhythm and six had atrial fibrillation. The etiology of valvular heart disease in five patients was rheumatic, and all these patients had multiple regurgitant valve lesions. Pure mitral stenosis or aortic stenosis was excluded. None of the patients had a myocardial infarction or unstable angina within 2 months preceding enrollment in the study.

Exercise Protocol

A symptom-limited exercise test was performed with an electromagnetically braked cycle ergometer (Siemens-Elema 930B with ramp slope controller). After a 4-minute rest on the ergometer, exercise began with a 4-minute warmup at 20 W and 60 rpm, followed by 1-W incremental loading every 6 seconds (Figure 1). The electrocardiogram and heart rate were monitored throughout the test by 12-lead electrocardiogram (Stress System ML-8000, Fukuda Denshi, Tokyo). Cuff blood pressure was also measured every minute with an automatic indirect manometer (Stress Test Blood Pressure Monitor STBP-680F, Collin Denshi, Aichi, Japan). The brachial artery was cannulated in 15 of the patients to measure arterial lactate concentration at each minute during exercise (enzymatic method). Plasma norepinephrine and epinephrine concentrations were also determined every 2 minutes during exercise by high-performance liquid chromatography method in the patients with arterial cannulation. Cardiac output during a 4-minute rest period preceding exercise was measured by dye dilution method with indocyanine green16 using an ear photoelectric transducer, the output of which was analyzed by a special purpose computer (Cardiac Output Computer MLC-4200, Nihon-Koden, Tokyo). All medications were
withheld for 18 hours before the study. The end point of exercise for all the patients was leg fatigue or dyspnea. No patient experienced chest pain during exercise testing.

Expired Gas Analysis

Oxygen uptake (\(VO_2\)), carbon dioxide output (\(VCO_2\)), and rate of respiratory air flow were measured at rest (sitting on the ergometer) and throughout the exercise period using an Aerobic Processor 391 (Nihon Denki Sanrei, Tokyo), consisting of a mixing chamber (2.5 l), a polarograph oxygen analyzer, infrared carbon dioxide analyzer, and hot wire spirometer. The system was carefully calibrated before each study. Gas exchange and flow measurements were corrected for ambient temperature, barometric pressure, and water vapor. From these measurements, \(VO_2\), \(VCO_2\), and minute ventilation were calculated every 10 seconds. The derived parameters such as ventilatory equivalent for \(O_2\) (\(VE/VO_2\)), ventilatory equivalent for \(CO_2\) (\(VE/VCO_2\)), and gas exchange ratio (\(VCO_2/VO_2\)) were computed simultaneously and displayed with the change of \(VO_2\) on a monitor during measurement using a personal computer (NEC PC-9801) with software developed in our laboratory.

The anaerobic threshold was mainly determined by V-slope method\(^17\) in addition to the following conventional criteria\(^18,19\): 1) \(VE/VO_2\) increases after being flat or decreasing, whereas \(VE/VCO_2\) remains constant or is decreasing, and 2) the \(R\)(gas exchange

| Table 2. Anaerobic Threshold, \(O_2\) Uptake, and Hemodynamic Data at Rest and During Exercise |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | Rest            | 20 W pedaling   | AT              | Midpoint        |                  |
|                                |                 |                 |                 | between AT and   |                  |
| \(VO_2\) (ml/min)              | 228±49          | 486±69          | 607±106         | 727±166         | 924±201         |
| % Peak \(VO_2\) (%)             | 21.0±5.7        | 45.2±10.7       | 55.3±8.7        | 65.4±9.1        | 82.7±4.5        |
| Heart rate (beats/min)         | 78.1±12.3       | 87.1±13.3       | 93.7±13.4       | 97.7±12.8       | 116.3±13.0      |
| Sytolic blood pressure (mm Hg) | 136.9±19.2      | 158.9±28.3      | 167.1±30.3      | 169.1±27.8      | 178.7±30.6      |
| Diastolic blood pressure (mm Hg)| 79.1±10.9       | 84.0±15.3       | 83.8±10.9       | 84.7±14.7       | 87.1±17.6       |
| Ejection fraction (%)           | 41.4±11.3       | 44.2±12.1       | 45.6±12.1       | 46.5±12.0       | 41.9±11.8       |
| Stroke volume (ml/beat)        | 54.6±17.0       | 61.8±20.1       | 64.0±21.4       | 65.0±21.2       | 59.2±21.7       |
| Cardiac output (/min)           | 4.2±1.3         | 5.3±1.6         | 5.9±1.8         | 6.3±2.0         | 6.8±2.5         |
| End-diastolic volume (ml)      | 141.5±63.5      | 148.9±65.6      | 148.9±65.6      | 149.2±65.1      | 148.8±65.6      |
| End-systolic volume (ml)       | 86.9±52.6       | 87.1±53.9       | 84.9±52.2       | 83.3±49.8       | 89.5±52.7       |
| Epinephrine (pg/ml)            | 76.3±38.5       | 81.9±41.9       | 100.0±69.6      | 104.4±69.3      | 133.8±75.8      |
| Norepinephrine (pg/ml)         | 371.3±144.6     | 438.8±172.5     | 498.8±198.0     | 538.8±212.4     | 776.9±255.5     |
| Arterial lactate (mg/dl)       | 6.5±2.1         | 10.7±2.8        | 13.1±3.7        | 15.0±4.0        | 22.1±5.1        |

Values are given as mean±SD.

\(VO_2\), oxygen uptake; % peak \(VO_2\), the ratio of oxygen uptake to peak oxygen uptake.

Figure 1. Stylized representation of the exercise protocol. After a 4-minute rest on the ergometer, exercise began with a 4-minute warmup at 20 W and 60 rpm, followed by 1-W incremental loading every 6 seconds. Oxygen uptake (\(\dot{V}O_2\)), carbon dioxide output (\(\dot{V}CO_2\)), and minute ventilation (\(V_E\)) were measured every 10 seconds. Dye dilution cardiac output using indocyanine green was measured during a 4-minute rest period preceding exercise. Beat-to-beat left ventricular volume curve was obtained throughout the exercise. Arterial lactate concentration was measured at each minute, and plasma norepinephrine and epinephrine concentrations were determined every 2 minutes during exercise.
Monitoring of Left Ventricular Function

A computerized cardiac monitoring system (RRG-607, Aloka Co Ltd, Tokyo) was used for continuous monitoring of the left ventricular function. This system is composed of the cadmium telluride (CdTe) detector (A-116, Radiation Monitoring Devices, Boston), a preamplifier unit, a portable data acquisition unit, and central processing unit (NEC personal computer PC-9801). After the patient’s red blood cells were labeled with 30 mCi technetium-99m by semi-in-vivo method, the CdTe detector was positioned over the left ventricular region with a vest that was specially designed to hold the CdTe detector in place. The left ventricular region of interest was chosen as the position with the maximal ratio of stroke counts (end-diastolic counts minus end-systolic counts) to average counts (end-diastolic counts plus end-systolic counts divided by 2). Care was taken to avoid the right ventricle, left atrium, and pulmonary vasculature. A reference detector was placed over the right anterior chest for measure of change in background counts.

Data Analysis

The microcomputer calculated and displayed the count over the region of interest during the cardiac cycle at 50-msec intervals throughout the exercise test. To determine the appropriate factor to correct for background activity, a series of calibration studies were performed in which ejection fraction was obtained both by CdTe detector and by the gamma camera in a group of resting patients with mild-to-moderate left ventricular dysfunction. Using a fixed percentage of counts in the calculations, the best correlation with the gamma camera determinations was obtained when background activity was assumed to be 70% of end-diastolic counts. Left ventricular ejection fraction was therefore calculated as follows:

\[ EF = SC / (0.3 \times EDC) \]

where EF is ejection fraction, SC is stroke counts (end-diastolic counts minus end-systolic counts), and EDC is end-diastolic counts.

Stroke volume at rest was calculated from the cardiac output measured by dye dilution method; this was used to give absolute values to the radioactive counting technique for measurement of stroke volume. End-diastolic volume and end-systolic volume were calculated as follows:

\[ EDV = SV / EF \]
\[ ESV = EDV - SV \]

where EDV is end-diastolic volume, ESV is end-systolic volume, and SV is stroke volume.

Stroke volume, end-diastolic volume, and end-systolic volume during exercise were calculated from stroke counts, end-diastolic counts, and end-systolic counts by measuring the change of these parameters from rest. After the test, ejection fraction, stroke volume, end-diastolic volume, end-systolic volume, and cardiac output throughout the test were determined using 10 seconds averaging.

Statistical Methods

All data are given as mean±SD. Comparisons of left ventricular function obtained at rest and during exercise were made by analysis of variance for repeated measures. When the F test was significant, individual comparisons of resting values and those of each work level were made by Duncan’s multiple-range test. The comparison of the anaerobic threshold and \( V_o_2 \) at peak ejection fraction was made by paired t test. The significance level was set at \( p \) less than 0.05.

Results

Figures 2 and 3 show the respiratory gas exchange and left ventricular function in one patient during a progressive incremental exercise test to illustrate the typical results obtained. The anaerobic threshold was easily determined in all the subjects by respiratory gas measurements. The mean value for the anaerobic threshold was at an \( V_o_2 \) of 727±166 ml/min (Table 1). After \( V_o_2 \) was determined at 20 W pedaling and peak exercise, \( V_o_2 \) at the midpoint between 20 W pedaling and the anaerobic threshold and between the anaerobic threshold and the peak exercise were also determined. Parameters of left ventricular function corresponding to each time of those points were determined (Table 2).

The mean ejection fraction at rest was 41.4±11.3%. As work rate increased, the ejection fraction in most of the subjects increased to its highest value at the point of the anaerobic threshold, averaging 46.5±12.0%. Above the anaerobic threshold, ejection fraction decreased, reaching 37.2±11.0% at peak exercise (Figures 4 and 6). Ejection fraction at the anaerobic threshold was significantly higher than those at rest and the other levels of work except for the midpoint between 20 W pedaling and the anaerobic threshold. Figure 5 shows the relation between \( V_o_2 \) at the peak ejection fraction (or if there is not a peak, at the last point at which ejection fraction remained constant) and \( V_o_2 \) at the anaerobic threshold. \( V_o_2 \) at the peak ejection fraction averaged 715±196 ml/min, showing no difference from the anaerobic threshold by paired t test.

The response pattern of stroke volume during exercise was similar to ejection fraction (Figure 6). Stroke volume increased from a mean value of 54.6±17.0 at rest to 65.0±21.2 ml/beat at the anaerobic threshold and decreased to 52.4±18.7 ml/beat at peak exercise. While cardiac output increased linearly from 4.2±1.3 l/min at rest to 6.3±2.0 l/min at the anaerobic threshold, the slope of cardiac output as a function of work rate decreased above
above the anaerobic threshold. End-systolic volume at the anaerobic threshold was significantly lower than those at rest and the other levels of work except for the midpoint between 20 W pedaling and the anaerobic threshold.

Arterial lactate concentration was measured every minute in 15 patients (Figure 8). On average, lactate gradually increased with increasing work rate and rapidly increased above the anaerobic threshold. Epinephrine and norepinephrine were also measured every 2 minutes (Figure 9). The pattern of these responses were similar to that of lactate.

In 22 patients, cardiac output was also measured by dye dilution method during 20 W pedaling, and this was compared with that calculated by the CdTe detector calibrated with the dye dilution method cardiac output measured at rest. Cardiac output at 20 W pedaling measured by dye dilution method and by the CdTe detector were 5.2±1.7 and 5.3±1.6 l/min, respectively, and were well correlated (r=0.86).

**Discussion**

It has been suggested that anaerobic metabolism occurs during exercise when oxygen supply to the working muscles cannot be increased sufficiently to maintain aerobic metabolism. Wasserman and McIlroy\(^3\) termed the threshold of rapid arterial blood lactate increase with increasing work rate, the anaerobic threshold, and postulated that it could be detected by analysis of gas exchange. The anaerobic threshold, therefore, is considered to be the parameter that represents the highest level of VO\(_2\) that a subject could perform without developing a sustained lactic acidosis. Many investigators have recently used the anaerobic threshold measurement to estimate the degree of cardiovascular impairment\(^5,7,8\) and effectiveness of therapy.\(^2,22,23\) In general, the magnitude of the anaerobic threshold reduction has correlated well with the degree of hemodynamic abnormality.\(^5,7,8\)

Recent studies\(^13-15\) have suggested that the ejection fraction during exercise increases compared with rest in normal persons but does not change or decreases in patients with heart disease (particularly coronary artery disease). However, only a few investigators evaluated the change of the ejection fraction below and above the anaerobic threshold. In 1985, Boucher et al.\(^24\) measured the ejection fraction during exercise in normal subjects by radionuclide angiography and concluded that above the anaerobic threshold, the left ventricular ejection fraction response may be highly variable, and a uniform increase is not necessarily expected. There are many factors that may influence the anaerobic threshold such as arterial oxygen content, oxygen delivery to the working muscle, or muscle metabolism. Therefore, in normal persons, the main factor that determines the anaerobic threshold may not necessarily be the limitation in cardiac function.

Wasserman and Whipp\(^18\) reported that with work step increments of more than 1 minute duration, the
anaerobic threshold is less clearly identifiable than during an incremental exercise test in which work rate is increased more rapidly. However, with use of the conventional multigated equilibrium radionuclide angiography, left ventricular ejection fraction must be calculated from the summation of several hundred individual cardiac cycles, making determinations over brief time intervals difficult. A more reliable system that enables us to measure the left ventricular function during a rapid incremental exercise test, such as when work rate is increased in ramp pattern, is needed to evaluate the exact relation between the anaerobic threshold and exercise hemodynamic pattern. Recent studies have reported the usefulness of the nuclear detector, a portable nonimaging device for measuring left ventricular function both at rest and during exercise. Excellent correlation between the left ventricular ejection fraction measured with a CdTe detector and that recorded with the gamma camera or contrast ventriculography has been shown by several studies. This device has also been shown to accurately evaluate left ventricular function in patients with atrial fibrillation.

In the present study, left ventricular function was evaluated with the computerized CdTe detector, which allows beat-to-beat assessment of the radionuclide time-activity curve. It was shown that the anaerobic threshold strongly correlates with the \( V\text{O}_2 \) above which left ventricular function decreases during exercise in patients with chronic heart disease. These findings support previously observed relations between the anaerobic threshold and...
the severity of exercise impairment in cardiac patients.

However, several potential limitations should be considered in the evaluation of the data obtained by this technique. The CdTe detector that we used in this study has the advantage of being light in weight (250 g). The ejection fraction after 10 minutes recovery correlated well with that at rest, before exercise, suggesting that the detector did not dislocate during exercise. Although ejection fraction, stroke volume, and cardiac output throughout the test were calculated using 10 seconds averaging to evaluate the exact relation between the anaerobic threshold and left ventricular function during exercise, 20 seconds averaging might be better for patients with atrial fibrillation to reduce the effects of statistical noise caused by the variability of the cardiac cycle length.

Background counts during exercise were measured by a reference detector placed over the right anterior chest; however, the absolute value of background counts may be affected by changes in the position or the orientation of the detector. Therefore, we used a fixed percent (70%) of end-diastolic counts as background activity to calculate ejection fraction. Recently, this method has been used and reported by several investigators. From the reference detector, the mean increase in background counts at the anaerobic threshold and at peak exercise were 5.1±4.0% and 6.3±5.1%, respectively, from the resting value, which did not appear to differ for different cardiac lesions. This suggests that a fixed percent of end-diastolic counts might lead to underestimation of ejection fraction, stroke volume, and cardiac output during exercise. Another problem is a constant position of the detector over the chest that does not consider cardiac motion during exercise. However, we do not think these problems affect the observed relation between the anaerobic threshold and the point above which left ventricular function decreases during exercise. Because positional changes would be unlikely to result in a systematic error, a change in background activity would have a small effect on the absolute value and, therefore, on the pattern of change of indexes of left ventricular function during exercise.

It has been previously reported that ejection fraction decreases at peak exercise relative to rest in patients with coronary artery disease. Most of the patients with coronary artery disease in the present study had ST segment depression during exercise, particularly above the anaerobic threshold. The decreases in ejection fraction in these patients may be related to the occurrence of asymp-
tomatic ischemia, although electrocardiographic changes do not necessarily represent deterioration in global left ventricular function. Ischemia might also be responsible for the decrease in ejection fraction during exercise in the two patients with aortic valve disease.

Eight patients in the present study were without documented coronary artery disease (Table 1). All of these patients decreased ejection fraction at peak exercise compared with the resting value except for one patient with hypertensive heart disease, whose ejection fraction at rest was 39.8% and at peak exercise was 52.9%. For the remaining patients without documented coronary artery disease, the deterioration of left ventricular function during exercise may be due in part to increased preload and/or failure of systemic vasodilation to produce sufficient afterload reduction during exercise.

In some patients, the ejection fraction did not rise after the start of exercise. It may be that the ejection fraction of patients with severe congestive heart failure or severe coronary artery disease does not increase with exercise. Nevertheless, it decreased as peak VO_2 was approached.
We measured arterial lactate concentration in 15 patients every minute during exercise. It was not as easy to determine the anaerobic threshold point by lactate as by respiratory measurement. It has been reported that the lactate-to-pyruvate ratio should be used to determine the anaerobic threshold rather than lactate. Also, the initial increase in lactate may not cause an intracellular acidosis since the first lactate produced appears to be buffered by intracellular non-HCO₃⁻ buffers.

We used the V-slope method to determine the anaerobic threshold because it does not rely on the magnitude of the ventilatory adjustment for metabolic acidosis and, in contrast to other gas exchange methods previously described to measure the anaerobic threshold, is relatively insensitive to breathing irregularities. This is particularly important in study of patients with congestive heart failure because some show oscillatory changes in ventilation during exercise, making methods for measuring the anaerobic threshold, which are sensitive to breathing irregularities, relatively less reliable.

These studies demonstrate that accurate determination of the anaerobic threshold, measured noninvasively, provides a method that can be used to objectively detect the work rate above which the exercise-induced decrease in left ventricular function occurs in patients with chronic heart disease.

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