Severity and Pathophysiology of Heart Failure on The Basis of Anaerobic Threshold (AT) and Related Parameters

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Cardio-pulmonary exercise testing was performed in 99 normal subjects and 382 patients with cardiac disease in order to evaluate anaerobic threshold (AT) and related parameters as indices for assessing the severity of heart failure. AT could be determined easily during ergometer exercise testing with ramp protocol by monitoring minute ventilation (VE), oxygen uptake (VO₂) and carbon dioxide output (VCO₂). Peak VO₂ and the ratio of VO₂ rising to work rate increment (ΔVO₂/ΔWR) were also determined. There was good correlation between the AT determined by respiratory measurement and that determined by arterial lactic acid concentration (r = 0.93, n = 15). The reproducibility of AT was excellent between 2 testings with a 3-hour interval. AT (ml/min/kg) and peak VO₂ (ml/min/kg) declined with age, and males showed higher values than females in both indices. %AT, determined by the predicted AT values of each age and sex, decreased as NYHA class progressed as follows: 90.2 ± 15.4% in class I, 76.9 ± 13.8% in class II, and 59.7 ± 11.9% in class III. Although ΔVO₂/ΔWR was not influenced by age or sex, it also decreased as the severity of heart disease progressed. These results suggest that indices from cardiopulmonary exercise testing, especially AT, are closely related to the pathophysiology of heart failure, so that they are objective and reliable parameters for evaluation of the severity of heart failure and are sensitive enough to detect the efficacy of therapeutic intervention for heart failure.

Congestive heart failure is a clinical syndrome consisting of signs and symptoms that arise from congested organs and hypoperfused tissues. In the early stages of heart failure, hypoperfusion to the working muscles during exercise causes easy fatigue or malaise, i.e. exercise intolerance, a characteristic symptom of heart failure patients. Therefore, in evaluating the pathophysiologic state and severity of heart failure, it is important to consider oxygen kinetics and metabolic abnormality during exercise testing.

Muscular work elicits a complex interplay of diverse physiologic mechanisms designed to ensure that oxygen delivery is commensurate with oxygen demand. In patients with heart failure, the oxygen delivery system is compromised and aerobic capacity reduced because cardiac output cannot increase appropriately during exercise. Recently, anaerobic threshold (AT) was introduced as an index to evaluate exercise tolerance in patients with heart disease! AT is defined as the level of exercise oxygen consumption above which aerobic energy production is supplemented by anaerobic mechanisms leading to increased lactate production relative to the rate of glycolysis? Since a rapidly responding gas analysis device has been developed,

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  Peak VO₂
  ΔVO₂/ΔWR
  Heart failure
  Severity classification

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it has become possible to determine AT noninvasively by ventilatory measurement. We conducted this study for 3 purposes: to evaluate the accuracy and reproducibility of AT determined by ventilatory measurement during cycle ergometer exercise using ramp protocol; to establish the normal values of AT and its related parameters; and to evaluate the usefulness of AT as an index for the assessment of exercise tolerance and severity of heart failure patients.

MATERIALS AND METHODS

Normal subjects
Seventy-two men and 27 women with normal medical history and physical examination and on no medication volunteered to serve as control subjects. Prior to exercise testing, each subject underwent a medical examination including 12-lead ECG, spirometry and general medical check-up. All had a normal electrocardiographic response on a screening maximal cycle ergometer exercise test. The mean age of the normal subjects was 36.4 ± 15.6 years (mean ± SD, range 16 to 70). These normal subjects did not routinely engage in regular exercise.

Patient population
Two hundred forty-two men and one hundred forty women with heart disease participated in the study. The etiology of cardiac disease was valvular heart disease in 75, hypertensive heart disease in 64, ischemic heart disease in 138, cardiomyopathy in 26, congenital heart disease in 9, and others in 70. The mean age of the patients was 56.0 ± 13.0, ranging from 12 to 87 years old. Prior to exercise testing, all subjects underwent a physical examination, including 12-lead ECG, spirometry, and chest X-ray examination.

New York Heart Association functional classifications were as follows: 159 patients in class I, 182 in class II, and 41 in class III. The study excluded patients with angina pectoris who stopped during exercise testing due to chest pain. Also excluded were patients with respiratory dysfunction, abnormal thyroid function, obesity (30% more than ideal weight) or emaciation (20% less than ideal weight). These with pacemakers, and with orthopedic difficulty in pedaling a cycle ergometer were also excluded.

Exercise protocol
This study employed a symptom-limited ramp exercise test using an electromagnetically controlled cycle ergometer (Siemens-Elema 930B with ramp slope controller). After a 4-min rest on the ergometer, exercise began with a 4-min warm-up at 20 watts, 60 rpm, followed by 1 watt incremental loading every 6 seconds (Fig. 1). The ECG and heart rate (HR) were monitored throughout the testing by Stress Test System (ML-8000, Fukuda Densi, Tokyo). Cuff blood pressure was also measured every minute with an automatic indirect manometer (Stress Test Blood Pressure Monitor STBP-680F, Collin Denshi,
Fig. 2. The correlation between peak VO$_2$ corrected by body weight and age in healthy subjects (n = 99). Males showed higher peak VO$_2$ than females. Peak VO$_2$ decreased linearly with age in both sexes between 12 and 68 years.

Fig. 3. AT expressed as VO$_2$/body weight to age in 95 normal subjects. AT declined with age like peak VO$_2$, and males again showed higher AT than females.

Aichi).

**Expired gas analysis**

Expired O$_2$ and CO$_2$ and the rate of air flow were measured at rest (sitting on the ergometer) and throughout the exercise period using an Aerobic Processor 391 (Nihon Denki San-ei, Tokyo), consisting of a polarograph oxygen analyzer, infra-red carbon dioxide analyzer, and hot wire spirometer. Basic gas and flow measurements were corrected for ambient temperature, barometric pressure and water vapor. Each system was carefully calibrated before each study. Oxygen uptake (VO$_2$), CO$_2$ production (VCO$_2$) and minute ventilation (VE) were measured every 10 seconds. The derived parameters such as VE/VCO$_2$, VE/VO$_2$ and respiratory exchange ratio (R; VCO$_2$/VO$_2$) were computed simultaneously and displayed with VO$_2$ on a monitor during measurement using an NEC personal computer PC-9801 with software developed in our laboratory. This system enabled us to perform exercise testing easily and safely.

**Determination of AT and other parameters**

Gas exchange data were analyzed using an

NEC personal computer PC-9801 with our software. The AT point was determined visually by 2 experienced reviewers using the following criteria: 1) The VE/VO₂ curve, which was flat or decreasing, begins to rise as the VE/VCO₂ curve remains constant or decreases. 2) The R-work rate curve, which was flat or gently rising, changes to a steeper slope.

The ratio of increase in VO₂ to increase in work rate (ΔVO₂/ΔWR) was also determined by the computer using our software from increasing rate of VO₂ during ramp exercise. The peak VO₂ was defined as the average VO₂ at the last 30 seconds before the endpoint.

**Relationship between the AT determined by respiratory measurement and that determined by lactic acid**

To compare the AT determined by respiratory measurements and that determined by arterial lactic acid (ATLA), 15 patients were cannulated to brachial artery and underwent exercise testings. The arterial blood sample was obtained before and every 30 seconds throughout the testing. The ATLA was determined at the point where the lactic acid concentration-work rate curve began to rise.

**Reproducibility studies**

To confirm the reproducibility of ventilatory measurements and AT, 17 patients underwent 2 exercise testings with a 3-hour interval.

**Evaluation of the efficacy of drug treatment on heart failure patients**

The efficacy of a new inotropic agent, OPC-8212, was evaluated in 6 chronic heart failure patients using AT, peak VO₂ and ΔVO₂/ΔWR. After a 4-week control period, OPC-8212 was administered in a dose of 60 mg once a day and increased every 2 weeks up to 120 mg to get clinical improvement (dose titling period). This was followed by a long-term treatment period (average 4 months). A 4-week placebo period was added after the long-term treatment. Exercise testing was performed at the end of each period, and compared with NYHA functional class evaluation.

**Statistical approach**

Liner regression analysis was performed to determine the relationship of AT, peak VO₂ and ΔVO₂/ΔWR to age in normal subjects. To define abnormal exercise responses in each group of patients, group comparisons were made by use of analysis of variance. Chi-square test was applied to determine the statistical significance of the frequency of clinical signs in each group. All data are reported as the mean ± SD, and a value of p < 0.05 was considered indicative of a significant difference.
RESULTS

AT, Peak VO$_2$ and ΔVO$_2$/ΔWR in normal subjects

Figure 2 shows the relationship between peak VO$_2$ and age in normal subjects. Peak VO$_2$ declines with age and females showed lower peak VO$_2$ than males. The regression lines are expressed as follows: Peak VO$_2$ (ml/min/kg) = $-0.38 \times$ Age (year) + 52.1, $r = -0.69$, for males. Peak VO$_2$ (ml/min/kg) = $-0.23 \times$ Age (year) + 48.4, $r = -0.57$, for females. (Peak VO$_2$ (ml/min) = $-0.6 \times$ Age + 3116, $r = 0.60$, for males. Peak VO$_2$ (ml/min) = $-11.5 \times$ Age + 2021, $r = -0.57$, for females).

AT was detected satisfactorily in 95 out of 99 normal subjects. AT showed the same relationship to age, as did peak VO$_2$, as shown in Fig. 3. AT declines with age in subjects whose ages range from 12 to 68 years old. Females showed lower AT than males. The regression lines are expressed as follows: AT (ml/min/kg) = $-0.22 \times$ Age + 32.3, $r = -0.60$, for male. AT (ml/min/kg) = $-0.16 \times$ Age + 27.8, $r = -0.53$, for female. On the other hand, there was no relationship between age and ΔVO$_2$/ΔWR. ΔVO$_2$/ΔWR was 12.3 ± 1.6, and there was no apparent difference between male and female.

Relationship between the AT determined by respiratory measurement and that determined by lactic acid

Figure 4 demonstrates the comparability of AT estimated from gas exchange parameters and increases in arterial blood lactate levels (AT$_{L_{\text{LA}}}$). The means ± SD for all 15 subjects were 13.4 ± 2.7 ml/min/kg for AT by ventilatory measurements and 13.3 ± 2.7 ml/min/kg for AT$_{L_{\text{LA}}}$. Paired t-test analysis demonstrates that there is no statistical difference between the two methods for determining AT.

Reproducibility studies

Seventeen patients underwent two exercise testings with a 3-hour interval. Fig. 5 shows the relationship between the AT of the first and second trial. There was no significant difference between the 2 values.

AT, peak VO$_2$ and ΔVO$_2$/ΔWR in cardiac patients

Table I shows the values of AT, peak VO$_2$ and ΔVO$_2$/ΔWR in cardiac patients. Since AT and peak VO$_2$ decreased with age, these 2 values

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were expressed as %AT and %peak VO₂, namely percentages of predicted values at each age given by means of regression lines against age (Fig. 2 and Fig. 3). Fig. 6 illustrates the relationship of AT and peak VO₂ to NYHA functional classification. In normal subjects, %AT and %peak VO₂ were 100.2 ± 17.5% and 100.2 ± 15.9%, respectively. The %AT of NYHA class I, II, and III patients were 90.2 ± 15.4%, 76.9 ± 13.8%, and 5.97 ± 11.9%, and the peak VO₂ of NYHA class I, II, and III were 87.9 ± 15.8%, 73.4 ± 4.9% and 55.9 ± 12.3%, respectively. A significant decrease in %AT and %peak VO₂ was observed in accordance with the severity of the grade of disease (p < 0.001). Also ΔVO₂/ΔWR was lower in patients with a more severe functional class (p < 0.001). These results demonstrate that the amount of O₂ transported to the working muscle is restricted in patients with cardiac disease and that the degree of the restriction during exercise is closely related to functional class.

**AT and clinical observations at rest**

The incidences of third sound, hepatomegaly (palpable liver ≥ 1FB), and edema were compared in three groups divided by means of %AT (Group I: %AT ≥ 90, Group II: 90 > %AT ≥ 60, Group III; %AT < 60). Accordingly, the incidence of these clinical signs which are closely related to heart failure were significantly higher in group III as shown in Fig. 7 (p < 0.01). On the other hand, parameters like left ventricular diastolic dimension (LVDD) and fractional shortening (FS) from echocardiogram, CTR, and ejection fraction (EF) determined by cineangiogram showed poor relationship to exercise capacity (Table II).

**The efficacy of the drug treatment**

Figure 8 shows the time course of functional class, AT, peak VO₂, and ΔVO₂/ΔWR showed almost the same changing pattern as that of functional class in each case.

**DISCUSSION**

**Methodological considerations**
TABLE II  THE RELATIONSHIP BETWEEN INDICES OBTAINED AT REST AND SEVERITY OF EXERCISE INTOLERANCE

<table>
<thead>
<tr>
<th></th>
<th>Echocardiogram</th>
<th>Chest X-P</th>
<th>Cineangiogram</th>
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<tr>
<td></td>
<td>LVDD (mm)</td>
<td>FS (%)</td>
<td>CTR (%)</td>
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<tr>
<td><strong>Group I</strong></td>
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<tr>
<td>%AT &gt; 90%</td>
<td>47.0 ± 7.2</td>
<td>35.7 ± 7.8</td>
<td>50.7 ± 6.2</td>
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<td>(n = 22)</td>
<td>(n = 22)</td>
<td>(n = 90)</td>
<td>(n = 7)</td>
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<td><strong>Group II</strong></td>
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<tr>
<td>60 &lt; %AT &lt; 90%</td>
<td>51.8 ± 10.5</td>
<td>33.0 ± 9.3</td>
<td>51.9 ± 7.2</td>
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<td>(n = 46)</td>
<td>(n = 46)</td>
<td>(n = 147)</td>
<td>(n = 21)</td>
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<tr>
<td><strong>Group III</strong></td>
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<tr>
<td>%AT &lt; 60%</td>
<td>51.1 ± 6.7</td>
<td>32.4 ± 10.4</td>
<td>54.1 ± 6.9</td>
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<td>(n = 20)</td>
<td>(n = 19)</td>
<td>(n = 36)</td>
<td>(n = 11)</td>
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Group I: %AT > 90, Group II: 90 > %AT > 60, Group III: %AT < 60. Mean NYHA Functional Classes of each group were 0.73 ± 0.71, 1.46 ± 0.75, 2.44 ± 0.55, respectively. Only CTR showed a significant statistical difference among the three groups (p < 0.05).

Fig. 8. Correlation between NYHA Functional Classification, AT, peak VO₂, and ΔVO₂/ΔWR as affected by drug therapy. Of the 3 latter parameters, AT seems to be the most sensitive to changes in the NYHA Functional Class. (C: Control period, DT: Dose titling period, LT: Long-term treatment period, P: Placebo period. In one case, AT was not clearly determined in the control and dose titling periods.)
Maximal oxygen uptake (\(\dot{V}O_2\text{max}\)) has been considered one of the most reliable indices of exercise tolerance.\(^5\) \(\dot{V}O_2\text{max}\) should be determined at the plateau value in \(\dot{V}O_2\), while the work rate continues to increase. In other words, direct measurement of \(\dot{V}O_2\text{max}\) requires the patient to exercise to physical exhaustion. This procedure is accompanied by risks, and it is actually very rare for \(\dot{V}O_2\) to level off during incremental exercise in patients with heart failure. We, therefore, employed not \(\dot{V}O_2\text{max}\) but peak \(\dot{V}O_2\) which represents the highest \(\dot{V}O_2\) value obtained in each testing.

Peak \(\dot{V}O_2\) is influenced not only by the subject's motivation but also the philosophy of the personnel supervising the test concerning when a test should be terminated. AT is one of the objective indices obtained from submaximal exercise testing and is not influenced by patient motivation. Since AT has a close relationship with endurance performance\(^6\) \(\dot{V}O_2\text{max}\)\(^7\) and oxidative capacity in skeletal muscle\(^8\) it has been used as a measure of endurance capacity.

To determine AT by ventilatory measurement, there are 2 major technical problems. First, there should be a continuous, rapid-response gas analyzer which gives data on a breath-by-breath basis or at least every 10 seconds. A 30-second delay would create unacceptable fluctuations in the \(\dot{V}O_2\) reading. For example, in 10-min exercise testing for subjects with 2000 ml/min peak \(\dot{V}O_2\), a 30-second delay would create roughly a 100 ml/min difference in \(\dot{V}O_2\). Second, one must employ the ramp protocol in which the work rate is increased continuously so that \(\dot{V}O_2\) kinetics are characterized by linear first-order dynamics. Otherwise it would be difficult to determine the AT point and read the values of parameters. If one had employed a 3-min incremental protocol like Bruce’s multi-step protocol, \(\dot{V}O_2\) would reach steady-state values with in 3 min during the early stage (below AT level) but not within 3 min in the late stages (above the AT level). Thus the pattern of \(\dot{V}O_2\) kinetics changes during testing, making it very difficult to analyze ventilatory gas dynamics. Wasserman and Whipp\(^2\) reported that with work increments greater than 1 min in duration, the ventilatory anaerobic threshold is less clearly defined than during a rapid incremental exercise test.

Many investigators have published papers on the relationship between AT as determined by ventilatory measurement and that by arterial lactic acid concentration\(^5,10,11\) Most of them found good correlation between the two. The reproducibility of AT was also established by a few investigators. In this paper, we confirmed the basic validity of AT.

Few reports have attempted to establish AT standards for ergonomics in Japan. It is well known that exercise tolerance decreases with age\(^12\) but there was no report on the exercise capacity of heart failure patients which took the predicted values for each subject into consideration. Although some papers have shown decreased AT in patients with heart disease\(^10,11\) this is the first to prove that not only absolute but relative values of AT in cardiac patients are closely related to the functional classification considering the sex and age of subjects.

\(\dot{V}O_2/\DeltaWR\) is an index related to oxygen delivery to the working muscle and is significantly low in patients with pulmonary or peripheral vascular disease\(^13\). Failure of the circulatory system to deliver adequate oxygen to the working muscles requires that energy be generated by anaerobic mechanisms. When oxygen delivery cannot meet the demand for increasing work rate, \(\dot{V}O_2/\DeltaWR\) becomes smaller. Although \(\dot{V}O_2/\DeltaWR\) had no relationship to age and sex, unlike AT and peak \(\dot{V}O_2\), it decreased as NYHA functional classification advanced.

\(AT\) as an objective index to evaluate severity of heart failure and efficacy of therapy

NYHA classification is not a golden standard to estimate the severity of heart failure because it is mainly based on the patient's subjective symptoms. Patients tend to compare themselves and their symptoms with healthy subjects of the same age. In specific cases, for example, the exercise tolerance of NYHA class II 20-year-old patients may exceed that of a healthy 75-year-old. Also, of course, the plots of AT, which restricted by cardiac function in NYHA class II patients, are scattered widely since the definition of class II includes many patients whose exercise tolerance range widely.

Recently, many novel cardioactive agents and vasodilators have been developed for treatment of cardiac failure. The final goal for treatment of cardiac failure is to extend life span and improve quality of life. Therefore, survival trials such as CONCENSUS trial study\(^14\) and the study to

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\(AT\) and related parameters in normality and heart disease

evaluate quality of life using exercise testing are essential in evaluating the efficacy of a drug. In evaluating the effect of OPC-8212 in heart failure patients, we found that AT and $\Delta VO_2/\Delta WR$ were objective and sensitive indices for estimating the patient's severity of heart failure.

In this report, we confirmed the findings of other reports$^{15}$ that indices of cardiac function at rest do not represent appropriately the severity of heart failure. For these reasons, performing cardio-pulmonary exercise testing to obtain objective indices such as AT is important in evaluating exercise tolerance and severity of heart failure.

Conclusion
Cardio-pulmonary exercise testing is one of the most important clinical examinations for evaluating the severity of heart failure, since exercise intolerance is an essential symptom closely related to its pathophysiology. Moreover, AT and related parameters such as $\Delta VO_2/\Delta WR$ are linked to the abnormal oxygen kinetics of heart failure, and these indices are sensitive and accurate enough to determine objectively the severity of heart failure. It is also necessary for accurate and safe testing to use a carefully calibrated rapid-response gas analyzer and real-time monitoring of ventilatory parameters employing ramp protocol. AT is a useful index for evaluation not only of severity of heart failure but of the efficacy of therapeutic intervention for heart failure.

REFERENCES
3. WASSERMAN K: The anaerobic threshold measurement to evaluate exercise performance. Am