Prognostic Significance of Cardiopulmonary Exercise Testing for 10-Year Survival in Patients With Mild to Moderate Heart Failure

Akira Koike, MD; Yoshiharu Koyama, MD*; Haruki Itoh, MD; Hiromasa Adachi, MD**; Fumiaki Marumo, MD*; Michiaki Hiroe, MD*

Although a number of studies have investigated the prognostic significance of exercise variables, they have focused only on short-term prognosis in relatively severe heart failure. This study was carried out to determine whether the indices obtained during cardiopulmonary exercise testing have prognostic significance during a 10-year follow-up in mild to moderate heart failure. Three hundred and sixty-four consecutive patients with cardiac disease performed 4 min of 20-W warm-up, followed by a symptom-limited incremental exercise test on a cycle ergometer. In addition to the measurements of peak oxygen uptake (VO₂) and gas exchange (anaerobic threshold), the time constant of VO₂ kinetics during the onset of warm-up exercise was calculated using a single exponential equation. Data on mortality were available for follow-up in 260 patients. After 3,331±610 days of follow-up, 29 cardiovascular-related deaths occurred. The time constant of VO₂ in the nonsurvivors was 76.7±43.3 s and was significantly prolonged compared with that of survivors (55.3±30.6 s, p=0.001). Peak VO₂ and gas exchange threshold were both significantly lower in nonsurvivors than in survivors. Kaplan-Meier survival curves for 10 years of follow-up demonstrated a survival rate of 89.0% for patients with a normal VO₂ time constant (<80 s) and 71.7% for those with a longer time constant (>280 s), showing a significant difference in survival (p=0.0028).

Respiratory gas parameters obtained during exercise testing, particularly the time constant of VO₂ kinetics, were found to be useful for predicting long-term prognosis in patients with chronic heart failure. These results suggest that cardiopulmonary exercise testing could be more applicable in ambulatory patients with minimal symptoms or minimal functional impairment. (Jpn Circ J 2000; 64: 915–920)

Key Words: Cardiac patients; Oxygen uptake; Prognosis; Time constant

In spite of the rapid advances in intervention for coronary artery disease and medical therapy for heart failure, cardiovascular disease is still the leading diagnosis and cause of mortality. Until recently, risk stratification of heart failure was primarily based on the functional assessment and resting hemodynamic measurements. However, the former is subject to the physician’s bias, and the latter does not necessarily correlate with the clinical manifestations of heart failure. Hence, cardiopulmonary exercise testing is now becoming important for stratifying patients with heart failure and identifying those with poor prognosis. For these purposes, peak oxygen uptake (VO₂) measured at maximal exercise testing has been used as a gold standard.

Yet, measurement of peak VO₂ requires physical exhaustion, depends on subject motivation, and is easily influenced by the bias of the investigator. The main factor of decreased exercise capacity in heart failure is presumed to be an attenuated rise in cardiac output and the response (kinetics) of this increase has recently been found to be reflected in the kinetics of VO₂ during the onset of exercise.

A number of studies have examined the prognostic significance of exercise variables such as peak VO₂, heart rate and blood pressure at peak exercise, and the ratio of the increase in ventilation to the increase in carbon dioxide output (ΔVE/ΔVCO₂). However, these investigations have focused only on short-term prognosis in relatively severe heart failure. No former studies have evaluated whether analysis of the kinetics of VO₂ during the onset of exercise can be used to predict the prognosis of heart failure patients.

In the present study, we determined whether the standard exercise variables recognized to be useful for evaluating short-term prognosis in advanced heart failure have prognostic significance during a 10-year follow-up in mild to moderate heart failure. We also evaluated whether analysis of the VO₂ kinetics, a new marker of cardiopulmonary adaptation during exercise, could identify cardiac patients with lower prognosis during long-term follow-up.

Methods

Study Patients

Between July 1985 and February 1988, 364 consecutive patients with cardiac disease were evaluated using cardiopulmonary exercise testing at Tokyo Medical and Dental University and at Hokushin General Hospital. Patients with unstable angina, a myocardial infarction within the last month, documented lung disease, cerebrovascular disease, or orthopedic difficulty in pedalling a cycle ergometer were excluded from the study. All medications were withheld for 24 h before the exercise testing; there was no adverse effect.
attributable to this study design. The New York Heart Association (NYHA) functional classification of each patient was determined on the study day. The radiographic cardiothoracic ratio was determined within 1 month of the study day. The nature and purpose of the study and the risks involved were explained to the patients and informed consent was obtained from each prior to enrollment.

Exercise Protocol

A symptom-limited exercise test was performed using identical apparatus in both institutions without significant adverse outcomes. An upright, electromagnetically-braked cycle ergometer (Siemens-Elema AB, Solna, Sweden) was used for the exercise test. After a 4-min rest on the ergometer, exercise began with a 4-min warm-up at 20 W and 60 rpm, and the load was increased incrementally (by 1 W every 3, 4, or 6 s, depending on the patient’s age and daily activity). The heart rate and rhythm were monitored on a 12-lead electrocardiogram (System ML-8000, Fukuda Denshi Co, Ltd, Tokyo, Japan) throughout the test. Cuff blood pressures were measured every minute with an automatic manometer (STBP 680F, Collin Denshi, Aichi, Japan).

Expired Gas Analysis

$\dot{V}O_2$, carbon dioxide output ($\dot{V}CO_2$), and the 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 Sanei, Tokyo, Japan). This system consists of a mixing chamber (2.5 L), a polarograph analyzer and analyzer, and a hot wire spirometer. Gas exchange and flow measurements were corrected for ambient temperature, barometric pressure, and water vapor. From these measurements, $\dot{V}O_2$, $\dot{V}CO_2$ and minute ventilation (VE) were calculated every 10 s. The derived parameters such as ventilatory equivalent for oxygen ($VE/\dot{V}O_2$), ventilatory equivalent for carbon dioxide ($VE/\dot{V}CO_2$), and gas exchange ratio ($\dot{V}CO_2/\dot{V}O_2$) were computed simultaneously.

The gas exchange (anaerobic) threshold was visually determined mainly by the $V$-slope method, in addition to the following conventional criteria: (1) the $VE/\dot{V}O_2$ increases after remaining stable or decreasing, whereas the $VE/\dot{V}CO_2$ remains constant or decreases; and (2) the gas exchange ratio begins to increase more steeply after remaining stable or increasing mildly. The gas exchange threshold of all the subjects was determined by a single experienced physician within 1 week of the data collection.

$\dot{V}O_2$, $\dot{V}CO_2$, and VE at rest were determined as the average of 2 min with the subject sitting on the ergometer before starting exercise. Peak $\dot{V}O_2$, VE and $\dot{V}CO_2$ were defined as the average values obtained during the last 30 s of exercise. $\Delta VE/\Delta VCO_2$ was calculated as follows:

$$\Delta VE/\Delta VCO_2 = \frac{\text{Peak } VE - \text{VE at rest}}{\text{Peak } VCO_2 - \text{PCO}_2 \text{ at rest}}$$

Time Constant of $\dot{V}O_2$

The time constant of $\dot{V}O_2$: kinetics was determined by fitting a single exponential function to the response starting at the onset of exercise (Fig 1) with the resting $\dot{V}O_2$ defined as the baseline, using the following equation:

$$\dot{V}O_2(t) = \dot{V}O_2(b) + A(1-e^{-\frac{t}{\tau}}),$$

where $\dot{V}O_2(t)$ is $\dot{V}O_2$ at time $t$, $\dot{V}O_2(b)$ is the baseline $\dot{V}O_2$.

Fig 1. Changes in oxygen uptake ($\dot{V}O_2$) during 4 min of warm-up at 20 W followed by incremental exercise (1 W increase every 4 s) in a 45-year-old male patient with NYHA functional class I. The computer-derived line of the best fit to a single exponential model of the $\dot{V}O_2$: response during 20-W exercise is shown as a solid line. TC is the time constant of $\dot{V}O_2$.

at rest, $A$ is the amplitude of the $\dot{V}O_2$ response (increment above baseline), and $\tau$ is the time constant. The time constant ($\tau$) and amplitude ($A$) were derived by nonlinear regression analysis using least-squares and iterative techniques with a BMDP statistical software package.

Follow-up

During the follow-up period, most patients were prescribed the standard therapy of the 1980s for heart failure including digitalis, diuretics, and vasodilators. They did not participate in any special exercise training programs before the exercise testing or during the follow-up period. The patients were usually followed up every month at the outpatient clinic of the institution where the cardiopulmonary exercise testing was carried out.

The data on mortality were examined between September 1996 and January 1997 by looking through medical records from the outpatient clinic and/or conducting telephone interviews with the patients or their families. Data on 104 patients were not available for follow-up because of changes in their place of residence. Eleven patients had died of noncardiovascular-related diseases during follow-up: cancer in 5, chronic renal failure in 1, fulminant hepatitis in 1, drowning in 1, and other diseases in 3. After excluding these 115 patients, the data on the remaining 294 patients were used for analysis.

Cardiac deaths occurring within 24 h without antecedent symptomatic progression of heart failure were considered sudden. Deaths from progressive symptoms or hemodynamic deterioration were classified as progressive heart failure.

Statistics

Data are presented as the mean ± SD. Differences for clinical, hemodynamic and exercise variables between survivors and nonsurvivors were compared using the
Table 1  Clinical Characteristics of Patients With Cardiovascular Disease

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Survivors (n=220)</th>
<th>Nonsurvivors (n=29)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.8±13.3</td>
<td>54.8±13.5</td>
<td>63.2±9.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Male/female</td>
<td>151/98</td>
<td>134/86</td>
<td>17/12</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1.60±0.7</td>
<td>1.60±0.7</td>
<td>2.0±0.7</td>
<td>0.002</td>
</tr>
<tr>
<td>I</td>
<td>117</td>
<td>111 (50)</td>
<td>6 (21)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>106</td>
<td>89 (40)</td>
<td>17 (59)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>26</td>
<td>20 (9)</td>
<td>6 (21)</td>
<td></td>
</tr>
<tr>
<td>Radiographic CTR (%)</td>
<td>53.1±6.9</td>
<td>52.4±6.9</td>
<td>58.4±4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>84</td>
<td>71 (33)</td>
<td>13 (45)</td>
<td>NS</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>59</td>
<td>52 (24)</td>
<td>7 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>57</td>
<td>52 (24)</td>
<td>5 (17)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>49</td>
<td>45 (20)</td>
<td>4 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Hemodynamic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR at rest (beats/min)</td>
<td>73.8±14.7</td>
<td>74.1±14.9</td>
<td>72.0±13.1</td>
<td>NS</td>
</tr>
<tr>
<td>SBP at rest (mmHg)</td>
<td>139.9±22.3</td>
<td>139.4±23.6</td>
<td>143.7±24.5</td>
<td>NS</td>
</tr>
<tr>
<td>HR at peak exercise (beats/min)</td>
<td>136.9±29.5</td>
<td>138.6±29.4</td>
<td>124.3±27.8</td>
<td>0.016</td>
</tr>
<tr>
<td>SBP at peak exercise (mmHg)</td>
<td>193.8±33.4</td>
<td>194.4±33.9</td>
<td>188.7±29.2</td>
<td>NS</td>
</tr>
<tr>
<td>Time constant of V̇O₂(s)</td>
<td>58.0±33.1</td>
<td>55.3±30.6</td>
<td>76.7±43.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Gas exchange threshold (ml·min⁻¹·kg⁻¹)</td>
<td>16.0±3.7</td>
<td>16.2±3.7</td>
<td>14.1±2.7</td>
<td>0.010</td>
</tr>
<tr>
<td>Peak V̇O₂ (ml·min⁻¹·kg⁻¹)</td>
<td>23.2±6.9</td>
<td>23.8±6.9</td>
<td>18.7±4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∆VE/∆V̇CO₂</td>
<td>31.9±5.8</td>
<td>31.7±5.7</td>
<td>33.4±6.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD or number (%) of patients. CTR, cardiothoracic ratio; HR, heart rate; SBP, systolic blood pressure; V̇O₂, oxygen uptake; VE, ventilation; V̇CO₂, carbon dioxide output.

Table 2  Univariate Cox Proportional Hazards Survival Analysis of Association Between Cardiopulmonary Indices and Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>χ²</th>
<th>p value</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak V̇O₂</td>
<td>15.29</td>
<td>&lt;0.001</td>
<td>0.880 (0.825-0.938)</td>
</tr>
<tr>
<td>Radiographic CTR</td>
<td>13.00</td>
<td>&lt;0.001</td>
<td>1.101 (1.045-1.161)</td>
</tr>
<tr>
<td>Time constant of V̇O₂</td>
<td>10.57</td>
<td>0.001</td>
<td>1.015 (1.006-1.024)</td>
</tr>
<tr>
<td>Gas exchange threshold</td>
<td>6.72</td>
<td>0.010</td>
<td>0.849 (0.750-0.961)</td>
</tr>
<tr>
<td>HR at peak exercise</td>
<td>6.23</td>
<td>0.013</td>
<td>0.986 (0.975-0.997)</td>
</tr>
<tr>
<td>∆VE/∆V̇CO₂</td>
<td>2.12</td>
<td>0.145</td>
<td>1.044 (0.985-1.106)</td>
</tr>
<tr>
<td>SBP at rest</td>
<td>0.82</td>
<td>0.364</td>
<td>1.007 (0.992-1.023)</td>
</tr>
<tr>
<td>SBP at peak exercise</td>
<td>0.68</td>
<td>0.410</td>
<td>0.993 (0.984-1.006)</td>
</tr>
<tr>
<td>HR at rest</td>
<td>0.58</td>
<td>0.446</td>
<td>0.990 (0.986-1.016)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CTR, cardiothoracic ratio; HR, heart rate; SBP, systolic blood pressure; V̇O₂, oxygen uptake; VE, ventilation; V̇CO₂, carbon dioxide output.

Unpaired t-test or chi-square analysis, where appropriate. Comparisons of parameters among 4 groups of different cardiac etiologies were performed using analysis of variance (ANOVA), which was followed by a post-hoc test (Fisher's PLSD). A Cox proportional hazards model was used to measure the impact of exercise test results on survival time. We divided subjects into 2 groups according to the time constant of V̇O₂: patients with a time constant ≥80s (n=42) and patients with a time constant less than 80s (n=189). Eighty seconds was selected as the cut-off point because in our previous report the upper limit (mean+2SD) of the V̇O₂ time constant during mild-intensity exercise in middle-aged (60 years) normal subjects was found to be 78±32. Similarly, the subjects were divided into 2 groups according to the percentage of peak V̇O₂ (% peak V̇O₂ ≥80, n=102; % peak V̇O₂ <80, n=149) or the percentage of gas exchange threshold (% gas exchange threshold ≥80, n=104; % gas exchange threshold <80, n=112). The % peak V̇O₂ was calculated by dividing peak V̇O₂ by predicted peak V̇O₂, which was calculated based on a normal Japanese population. The % gas exchange threshold was determined by the same method: Differences in survival between the 2 groups were detected by the Kaplan–Meier method and compared using the logrank test. For all comparisons, p<0.05 was considered statistically significant.

Results

The clinical characteristics and exercise data of the study patients are presented in Table 1. In the comparisons of parameters among the 4 groups of different etiologies, patients with valvular disease had a significantly higher cardiothoracic ratio as compared with those with the other diseases (p<0.0001 by ANOVA, p<0.001 by Fisher’s PLSD). There was also a significant difference in peak V̇O₂ among the 4 groups (p=0.001). However, there was no difference in the time constant of V̇O₂ (p=0.21).

After 3,331±610 days of follow-up, 29 cardiovascular related deaths occurred: 8 patients had a sudden cardiac death, 7 died of acute myocardial infarction, 7 died of progressive heart failure, and 7 died of cerebrovascular diseases. There was no significant difference in the etiology of heart disease between survivors and nonsurvivors. On the day of the exercise testing, the mean age of the nonsurvivors was 63.3±9.6 years, which was significantly higher than that of the survivors (54.8±13.5 years). NYHA functional class and
cardiothoracic ratio were also higher in nonsurvivors than in survivors (2.0±0.7 vs 1.6±0.7, p=0.002; 58.4±4.8 vs 52.4±6.9, p<0.001, respectively).

Table 1 shows a comparison of cardiopulmonary exercise variables between survivors and nonsurvivors. Peak VO2 was obtained in all 249 patients, but the gas exchange threshold could not be determined in 33 patients (25 survivors and 8 nonsurvivors). The time constant of VO2 could not be calculated in 18 survivors, mainly because of excessive noise and the relatively long, 10-s sampling interval of the device. Although resting heart rate and systolic blood pressure did not differ between these 2 groups, heart rate at peak exercise was lower in nonsurvivors. The time constant of VO2 obtained during 4 min of 20-W exercise was significantly longer in nonsurvivors (76.7±43.3 s) than in survivors (55.3±30.6 s), showing a delayed VO2 response at the onset of exercise in the former. Nonsurvivors achieved a significantly lower gas exchange threshold (14.1±2.7 vs 16.2±3.7 mL·min⁻¹·kg⁻¹) and lower peak VO2 (18.7±8.4 vs 23.8±6.9 mL·min⁻¹·kg⁻¹) than survivors. However, there was no significant difference in ΔVE/ΔVCO2.

Table 2 shows the univariate Cox proportional hazards analysis of association between cardiopulmonary indices and survival time. With this analysis, cardiothoracic ratio, peak exercise heart rate, VO2 time constant, gas exchange threshold, and peak VO2 were found to be significant prognostic indices of survival. When all these indices were entered into a multivariate analysis, no significant independent predictor was detected. However, with multivariate analysis, the prognostic power of the VO2 time constant was found to be independent of peak VO2.

Kaplan–Meier survival was assessed using ≥80 s and <80 s of VO2 time constant as a cut-off point (Fig 2). The survival curves for 10 years of follow-up (4,019 days) demonstrated a survival rate of 89.0% for patients with the shorter VO2 time constant (<80 s) and 71.7% for those with a longer time constant (≥80 s). The difference in survival between the 2 groups was statistically significant (p=0.0028).

Discussion

Main Findings

In the present study, the parameters obtained during cardiopulmonary exercise testing, especially the time constant of VO2 kinetics, were newly found to be powerful predictors for 10-year survival in heart failure patients. A number of investigators have attempted to test the prognostic significance of the parameters obtained during exercise testing, in addition to the significance of functional assessment and resting cardiac function.10–11 Mancini et al10 and Stelken et al11 have demonstrated that patients with higher peak VO2 have an excellent prognosis. However, the heart failure in their subjects was relatively severe, and their follow-up period was only 2 years at the longest. The present study is the first to investigate the significance of respiratory gas indices during exercise for predicting long-term prognosis in patients with less severe heart failure.

Prognostic Significance of Hemodynamic and Exercise Variables

The radiographic cardiothoracic ratio is a common parameter for screening patients with heart failure and we found it to be another potentially useful index for predicting long-term prognosis. Prognostic information in the ratio suggests the importance of enlargement of the left and/or right ventricle for long-term prognosis.

Several investigators have emphasized the prognostic significance of the hemodynamic variables at peak exercise11 but the present study failed to find any prognostic value in either peak exercise heart rate (when adjusted by age) or peak exercise systolic blood pressure. Chua et al recently examined the relation between the ventilatory response during symptom-limited treadmill exercise testing and mortality over a 2-year follow-up in heart failure patients. In their study, the ratio of ΔVE/ΔVCO2 became higher with the severity of heart failure and was found to be an independent prognostic marker. The low left ventricular ejection fraction of their subjects (mean ejection fraction was 28%) and the advanced heart failure in their study (mean NYHA functional class was 2.5) both contrast with the present findings. In our subjects with less severe heart failure, the prognostic power of ΔVE/ΔVCO2 was not significant. We used a mixing chamber rather than a breath-by-breath system for gas exchange analysis. The slope of ΔVE/ΔVCO2 was calculated simply by the values of 2 points (resting and peak exercise values), not by the least-squares linear regression. These methodologies might have blunted the sensitivity of ΔVE/ΔVCO2 as a prognostic index. Also, the prognostic power of indices obtained during cardiopulmonary exercise testing may depend on the severity of heart failure and etiology of heart disease of the recruited subjects.
Clinical Implications of the VO₂ Time Constant

Symptom-limited maximal exercise tests have long been used for estimating the severity of the disease process, but the focus has concentrated on objective information obtained from submaximal rather than maximal exercise. The great advantage of the VO₂ kinetics is that it can be measured objectively, without maximal effort on the part of the patient. Factors determining the VO₂ kinetics during the onset of exercise are the increase in cardiac output, blood flow distribution to the exercising muscles (vasodilator capacity of the vascular smooth muscle), O₂ extraction in the muscles, and the pulmonary function. We recently noted that cardiac patients with lower left ventricular ejection fraction have slower kinetics of VO₂ response during the onset of exercise. Administration of coronary vasodilator has also been found to speed the VO₂ kinetics in patients with coronary artery disease.

As the present study did not include patients with lung disease, the longer VO₂ time constant in nonsurvivors strongly suggests an insufficient cardiac reserve and/or insufficient vasodilator capacity in the skeletal muscle. Impairment of the vasodilator capacity of the vascular smooth muscle in the extremities would imply atherosclerosis or endothelial dysfunction in the systemic vasculature, including coronary and cerebral arteries. Thus, measurement of the VO₂ time constant during the onset of exercise could help identify patients with lower survival resulting from myocardial infarction and cerebrovascular diseases along with progressive heart failure.

It was found that the etiology of heart disease significantly affects the cardiovascular ratio and peak VO₂. However, the time constant of VO₂ was not influenced by the etiology of the disease. These results indicate an advantage of the VO₂ time constant as a prognostic index and multivariate analysis showed that its prognostic power was also significant in patients of all ages. Evaluation of cardiac function, such as by echocardiography, left ventriculography, or ¹³¹I-metaiodobenzylguanidine (MIBG) scintigraphy can provide useful information in order to select cardiac patients with poor prognosis, but these techniques are invasive, expensive, or limited to the measurement of resting cardiac function. Exercise testing with gas exchange analysis noninvasively and cost-effectively provides useful information on cardiovascular function during exercise. In particular, analysis of VO₂ kinetics provides a new and useful parameter for the evaluation of circulatory adjustments at the onset of exercise.

Study Limitations

The medical history of each subject could not be fully obtained because of disposal of old clinical records. Beta-blockers and/or angiotensin-converting enzyme inhibitors might have been added during the 10 years in some subjects. As far as we could discover, 6 patients underwent coronary artery bypass graft surgery, and 17 patients underwent other cardiac surgery, including valve replacement, during the follow-up period. Although these events were not considered in the present study, the relatively low mortality could be partly attributed to the surgical therapy in addition to the newer medical therapy.

The VO₂ kinetics during the onset of exercise partly depend on the intensity of exercise. Although the kinetics are assumed to progressively decelerate and become more complicated as the work rate increases during heavy exercise (especially above the gas exchange threshold), the work rate used for determining the kinetics in the present study was only 20 W. However, exercise testing at a slightly higher work rate might have been more appropriate in order to accurately obtain the time constant of VO₂, as it would enhance the signal-to-noise ratio of the time course of VO₂.

The time constant of VO₂ could not be determined in 18 subjects because of an inability to fit data with a single exponential model. This might be the result of a noise caused by an irregular breathing pattern or it might also be attributed to the basic methodology used. The respiratory gas variables during exercise were measured using a simple system composed of a mixing chamber because of the unavailability of a gas analyzer capable of measuring variables on a breath-by-breath basis in Japan in the 1980s. The accuracy and time resolution of our device were sufficient to analyze the VO₂ kinetics in most of our patients. However, use of newer devices and higher exercise intensities may reduce the incidence of exercise data with time constants that cannot be calculated.

Conclusions

Respiratory gas indices obtained during exercise testing, particularly the time constant of VO₂, were found to be useful for predicting long-term prognosis. The time constant of VO₂ kinetics provides objective, noninvasive and inexpensive guidance for identifying patients with worse prognosis without requiring maximal effort by the patient. Our results suggest that cardiopulmonary exercise testing could be more applicable in ambulatory patients with minimal symptoms or minimal functional impairment.

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