Prognostic Impact of Ventilatory Efficiency in Heart Disease Patients With Preserved Exercise Tolerance

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Background The minute ventilation/carbon-dioxide output ($\dot{V}_E/\dot{V}_{CO_2}$) slope as a marker of cardiac events has been established in patients with severe heart failure, but it is not known whether it is useful for other heart diseases.

Methods and Results The present study investigated 215 patients with various heart diseases (age 59 ± 11 years; ischemic heart disease, $n=89$; dilated cardiomyopathy, $n=38$; valvular disease, $n=37$; hypertensive heart disease, $n=33$; others, $n=18$) who underwent cardiopulmonary exercise testing to determine the $\dot{V}_E/\dot{V}_{CO_2}$ slope. Patients were divided into 2 groups according to the $\dot{V}_E/\dot{V}_{CO_2}$ slope and were followed-up for 3 years. Forty-eight cardiac events (6 deaths, 42 re-hospitalizations) occurred during the observation period. Patients with a $\dot{V}_E/\dot{V}_{CO_2}$ slope >34 had a significantly higher 3-year cardiac event rate (32.1%) than patients with $\dot{V}_E/\dot{V}_{CO_2}$ slope <34 (18.9%, $p<0.05$). When patients were selected with relatively preserved peak oxygen uptake values ($>16 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), patients with $\dot{V}_E/\dot{V}_{CO_2}$ slope >34 still demonstrated a significantly higher cardiac event rate than other patients (35.0% vs 13.3%, $p<0.01$).

Conclusion The $\dot{V}_E/\dot{V}_{CO_2}$ slope may be a prognostic indicator of cardiac events in a heterogeneous group of patients with heart disease, independent of exercise tolerance. (Circ J 2006; 70: 1332–1336)

Key Words: Exercise tolerance; Heart disease; Prognosis; Ventilatory efficiency

There are several parameters that can be used to predict cardiac events, mortality, or both, in patients with heart disease and of these peak oxygen uptake ($\dot{V}O_2$),¹ plasma norepinephrine concentration² and brain natriuretic peptide (BNP)³ are considered to be the most important. Specifically, peak $\dot{V}O_2$ is recognized as an indicator for heart transplantation because it is the strongest predictor of cardiac events in patients with heart failure.¹ However, peak $\dot{V}O_2$ is not always the same as maximal $\dot{V}O_2$ because some subjects are poorly motivated or uncooperative.^{4,5} As well, peak exercise is sometimes risky for heart disease patients.

Recently, the slope of the relationship between carbon-dioxide output ($\dot{V}_{CO_2}$) and minute ventilation ($\dot{V}_E$) (ie, $\dot{V}_E/\dot{V}_{CO_2}$ slope) was investigated as a marker of the severity of heart failure.^{6–8} Increased ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching is one of the principal mechanisms by which the $\dot{V}_E/\dot{V}_{CO_2}$ slope steepened.^{9–11} Because deteriorated alveolar hypoventilation rarely occurs in patients with heart failure, the cause of the augmented $\dot{V}/\dot{Q}$ mismatching is usually due to lack of stroke volume increase and impaired pulmonary arterial dilatation during exercise. Cardiac function and vascular endothelial cell function is related to mortality,¹² so the $\dot{V}_E/\dot{V}_{CO_2}$ slope is a good indicator of

cardiac function. Moreover, the $\dot{V}_E/\dot{V}_{CO_2}$ slope correlates positively with central chemosensitivity to carbon dioxide, which suggests that the $\dot{V}_E/\dot{V}_{CO_2}$ slope is related to chemoreceptor sensitivity¹³ and thus influenced by sympathetic nervous activity.¹⁴ It is known that a hypersensitive central chemoreceptor and increased plasma norepinephrine are related to prognosis,^{2,15} which also explains why the $\dot{V}_E/\dot{V}_{CO_2}$ slope is associated with prognosis in heart disease.

Patients with preserved exercise tolerance do not always show a low $\dot{V}_E/\dot{V}_{CO_2}$ slope, as peak $\dot{V}O_2$ has a weak negative correlation with the $\dot{V}_E/\dot{V}_{CO_2}$ slope.¹⁶ It also is not known whether the $\dot{V}_E/\dot{V}_{CO_2}$ slope is a prognostic marker of cardiac events in Japanese patients with preserved exercise tolerance. Therefore, the aim of this study was to determine whether the $\dot{V}_E/\dot{V}_{CO_2}$ slope is a prognostic marker in Japanese heart disease patients with preserved exercise tolerance.

Methods

Patients

From January 1997 to October 1999, 215 patients with cardiac disease and New York Heart Association (NYHA) class I or II were recruited. The cohort consisted of 172 men and 43 women with an average age of 59 ± 12 years. The spectrum of heart disease included ischemic heart disease in 89 patients, idiopathic dilated cardiomyopathy in 38, valvular heart disease in 37, hypertensive heart disease in 33, and other heart diseases in 18. Subjects were excluded from the study if they had musculoskeletal abnormalities or pain that would affect their ability to exercise,

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Table 1 Comparison of Anthropometric Data and Exercise Test Results From Group H-V and Group L-V

	Group H-V (n=56)	Group L-V (n=159)	p value
Body height (cm)	162.9±9.6	163.7±8.6	NS
Body weight (kg)	62.4±13.1	62.7±12.1	NS
Body mass index	23.3±3.3	23.1±3.0	NS
Age (years)	59.4±10.3	58.8±10.9	NS
AT $\dot{V}O_2$ (ml·min ⁻¹ ·kg ⁻¹)	13.4±3.2	14.6±4.9	0.05
Peak $\dot{V}O_2$ (ml·min ⁻¹ ·kg ⁻¹)	18.3±3.9	20.7±5.4	0.01

Group H-V, patients with a minute ventilation ($\dot{V}E$)/carbon-dioxide output ($\dot{V}CO_2$) slope >34; Group L-V, patients with a $\dot{V}E/\dot{V}CO_2$ slope <34; AT, anaerobic threshold; $\dot{V}O_2$, oxygen consumption.

Data are mean ± SD.

Table 2 Comparison of Anthropometric Data and Exercise Test Results From Subgroups H-V and L-V of Group H-EC

	Group H-V (n=40)	Group L-V (n=120)	p value
Body height (cm)	162.1±8.6	163.9±8.4	NS
Body weight (kg)	63.5±12.5	62.5±12.2	NS
Body mass index	23.2±3.0	23.3±3.1	NS
Age (years)	58.8±11.2	57.6±10.1	NS
AT $\dot{V}O_2$ (ml·min ⁻¹ ·kg ⁻¹)	13.9±2.5	14.8±3.6	NS
Peak $\dot{V}O_2$ (ml·min ⁻¹ ·kg ⁻¹)	20.0±2.9	22.3±4.7	0.01

Group H-EC, patients with a peak $\dot{V}O_2$ >16 ml·min⁻¹·kg⁻¹. Other abbreviations see in Table 1.

Data are mean ± SD.

significant pulmonary disease, or a history of cerebral vascular disease. The hospital's ethics committee granted approval for the study.

Exercise Testing

All patients performed a symptom-limited exercise tests on an electronically controlled upright cycle ergometer (CPE2000, MedGraphics, St Paul, MN, USA) as previously described^{17,18} The work rate was increased continuously at a rate of 10 W/min (ramp protocol) after 3 min of unloaded pedaling (0 W). The test was terminated if the subject failed to maintain the required speed, or became breathless and/or had muscle fatigue and unable to continue the exercise. We excluded patients who had significant ST segment depression or chest pain during the exercise. The ramp protocol was performed until exhaustion (ie, Borg score >17), so we confirmed that all patients reached their maximal effort.

Gas Exchange Measurements

Peak $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ were measured on a breath-by-breath basis using a gas analyzer (MINATO 280S, Minato Ikagaku, Osaka, Japan). The $\dot{V}E/\dot{V}CO_2$ slope was calculated by linear regression analysis. Because the relationship between $\dot{V}E$ and $\dot{V}CO_2$ during incremental exercise changes above the respiratory compensation point, the $\dot{V}E/\dot{V}CO_2$ slope was calculated below that point.

Data Analysis

We regarded more than 130% normal as abnormal, reported by Kleber et al⁹ and because the average value of the $\dot{V}E/\dot{V}CO_2$ slope in normal subjects in the hospital was 26.5, a value >34 was determined as abnormal. The patients were divided into 2 groups according to the $\dot{V}E/\dot{V}CO_2$ slope:^{20,21} the high $\dot{V}E/\dot{V}CO_2$ slope group (Group H-V) in-

Fig 1. Event-free survival for all patients.

Fig 2. Kaplan-Meier life-table analysis for high minute ventilation/carbon-dioxide output ($\dot{V}E/\dot{V}CO_2$) slope group (Group H-V) vs low $\dot{V}E/\dot{V}CO_2$ slope group (Group L-V). Group H-V patients had a significantly higher 3-year cardiac event-free rate than Group L-V patients.

cluded patients with a $\dot{V}E/\dot{V}CO_2$ slope >34 and the low $\dot{V}E/\dot{V}CO_2$ slope group (Group L-V) included those with a $\dot{V}E/\dot{V}CO_2$ slope <34. We also divided the patients into 2 groups according to their exercise capacity:^{22,23} high-exercise capacity (Group H-EC) was a peak $\dot{V}O_2$ >16 ml·kg⁻¹·min⁻¹ and low-exercise capacity (Group L-EC) was a $\dot{V}O_2$ <16 ml·kg⁻¹·min⁻¹. We focused on the patients who had a high $\dot{V}E/\dot{V}CO_2$ slope and a high exercise capacity; that is, the subgroup H-V in the group H-EC.

Cardiac Events

We defined death from heart failure and re-hospitalization as the cardiac events. Only worsening of heart failure was considered as the cause of hospitalization.

Statistical Analysis

All data are expressed as mean ± standard deviation. To compare prognostic parameters, linear and logistic regression analyses were performed. Follow-up data for 3 years were analyzed by Kaplan-Meier cumulative mortality curves. Survival curves were compared by Cox proportional-hazards analysis. A value of $p < 0.05$ was considered as significant.

Fig 3. Kaplan-Meier life-table analysis for Group high-exercise capacity (H-EC) vs Group low-exercise capacity (L-EC). Group L-EC patients had a significantly higher 3-year cardiac event-free rate than Group H-EC patients.

Fig 4. Event-free survival in Group high-exercise capacity (H-EC) patients. Patients with a minute ventilation/carbon-dioxide output slope >34 had a significantly lower cardiac event-free rate than the others (35.0% vs 13.3%, $p<0.001$).

Results

There were 48 cardiac events in the 3-year follow up period: 42 re-hospitalizations and 6 deaths.

Comparison of the anthropometric data and exercise capacity of Groups H-V and L-V are shown in Table 1. There were no statistical differences between the 2 groups with regard to the anthropometric data. Group H-V showed lower exercise tolerance than Group L-V. Comparisons of the anthropometric data and exercise capacity of the subgroups H-V and L-V from Group H-EC are shown in Table 2. There were no statistical differences between the 2 groups with regard to the anthropometric data. Again, Group H-V showed lower exercise tolerance than Group L-V.

The event-free survival rate for all patients was 77.7% for 36 months (Fig 1). As shown in Fig 2, Group L-V had a higher event-free rate (81.1%) than Group H-V (67.9%; $p<0.05$).

The event-free survival rates for the 2 groups stratified by peak $\dot{V}O_2$ are shown in Fig 3. Group H-EC had a better event-free rate (81.9%) than Group L-EC (65.3%; $p<0.01$).

Within Group H-EC, the subgroup L-V had a better

cardiac event-free survival rate (86.7%) than subgroup H-V (65.0%; $p<0.01$) (Fig 4).

Fig 5 shows the weak, but significant negative correlation between $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$ in these patients ($r=-0.28$, $p<0.01$). There are several subjects with preserved peak $\dot{V}O_2$ but high $\dot{V}E/\dot{V}CO_2$ slope. Subjects who died during the study period are had a $\dot{V}E/\dot{V}CO_2$ slope >34 , although their peak $\dot{V}O_2$ ranged above and below the cut-off point of $16 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. In this case, the specificity of the $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$ was 79.6% and 79.3%, respectively, and the sensitivity was 37.5% and 41.7%, respectively. If we determined the cut-off values as 30 and $20 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the specificity is 52.1% and 55.1%, respectively, and the sensitivity is 79.2% and 77.1%, respectively. At 40 and $14 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the specificity is 97.6% and 95.8%, respectively, and the sensitivity is 22.9% and 33.3%, respectively. When we analyze the event-free rate using this cut-off value, there was no significant difference between the 2 groups.

Discussion

Our results confirm that the $\dot{V}E/\dot{V}CO_2$ slope is an impor-

Fig 5. Relationship between minute ventilation/carbon-dioxide output ($\dot{V}E/\dot{V}CO_2$) slope and peak oxygen uptake for all patients. (○) Patients who were re-hospitalized, (□) patients who died during follow up.

tant prognostic marker in a heterogeneous group of patients with cardiovascular disease, both with and without preserved exercise tolerance.

Recently, the $\dot{V}E/\dot{V}CO_2$ slope was proposed as a marker of disease severity in patients with heart failure⁶⁻⁸ The finding that the $\dot{V}E/\dot{V}CO_2$ slope is a powerful prognostic marker independent of peak $\dot{V}O_2$ is of great value in the prognostic paradigm for patients with congestive heart failure.

Kleber et al¹⁹ observed that heart failure patients (mean NYHA class 2.6, mean peak $\dot{V}O_2$ 15.3 ml·kg⁻¹·min⁻¹, ejection fraction 27%) with a $\dot{V}E/\dot{V}CO_2$ slope <130% of age- and gender-adjusted normal values had a significantly better 1-year event-free survival rate than those with a $\dot{V}E/\dot{V}CO_2$ slope >130% of normal. This suggests that the $\dot{V}E/\dot{V}CO_2$ slope is an important predictor of prognosis in patients with mild to severe heart failure. In the clinical setting, we sometime have patients with heart failure who have a poor prognosis despite preserved exercise tolerance. Therefore, in the present study we selected patients with peak $\dot{V}O_2$ >16 ml·kg⁻¹·min⁻¹, corresponding to a Weber Janicki classification of class A and B^{24,25} In this subgroup, a similar result was obtained for up to 3 years.

Ponikowski et al¹⁵ reported that the prognosis of heart failure patients with higher $\dot{V}E/\dot{V}CO_2$ slope was diminished even if their peak $\dot{V}O_2$ was preserved¹⁵ and we also obtained similar results. However, they calculated the $\dot{V}E/\dot{V}CO_2$ slope from the beginning of its peak. The $\dot{V}E/\dot{V}CO_2$ slope becomes nonlinear after the onset of respiratory compensation for metabolic acidosis. Therefore, we calculated the $\dot{V}E/\dot{V}CO_2$ slope from data from the beginning of exercise to the respiratory compensation point.

The number of subjects who died during the study period was smaller than in the studies by Francis et al²⁴ and Ponikowski et al¹⁵ most likely because the present patients had better exercise tolerance. In addition, mortality rates for heart failure in Japan are relatively lower than in Europe and America²⁵

Peak $\dot{V}O_2$ has been reported as the strongest predictor of cardiac events in patients with heart failure. In particular, the landmark study of Mancini et al¹ demonstrated that patients with a peak $\dot{V}O_2$ <14 ml·kg⁻¹·min⁻¹ had a significantly lower survival rate. This value has evolved to become the standard for listing patients for heart transplantation.

However, our data revealed that, although peak $\dot{V}O_2$ is preserved, the $\dot{V}E/\dot{V}CO_2$ slope still has prognostic power. The reason why the $\dot{V}E/\dot{V}CO_2$ slope had prognostic power independent of peak $\dot{V}O_2$ may be related to the different mechanisms that regulate these 2 parameters. One of the major mechanisms regulating the $\dot{V}E/\dot{V}CO_2$ slope is a high $\dot{V}_D/\dot{V}_T$ and ventilation/pulmonary blood flow ($\dot{V}/\dot{Q}$) mismatching⁹⁻¹¹ In heart failure, pulmonary blood flow often is inadequate during exercise because both cardiac function and endothelial cell function are impaired. Increased sympathetic nervous activity, diminished nitric oxide production^{26,27} and enhanced endothelin-1²⁸ production restrict pulmonary vascular distensibility. In contrast, for peak $\dot{V}O_2$, $\dot{V}/\dot{Q}$ mismatching is not a major factor determining the peak $\dot{V}O_2$. As shown in Fig 5 there is only a weak correlation between peak $\dot{V}O_2$ and the $\dot{V}E/\dot{V}CO_2$ slope, which means there are not a few patients who had a high $\dot{V}E/\dot{V}CO_2$ slope with preserved exercise tolerance.

Another important mechanism underlying the increased $\dot{V}E/\dot{V}CO_2$ slope might be augmented central and/or peripheral chemosensitivity¹³ When sensitivity to the partial pressure of CO₂ (PaCO₂) is augmented, $\dot{V}E$ increases,

steepening the $\dot{V}E/\dot{V}CO_2$ slope. The mechanism for the correlation between central chemosensitivity and the severity of heart failure has not been elucidated. However, Narkiewicz et al postulated that sympathetic nervous activity correlates with central chemosensitivity¹⁴ It has been reported that there is an accentuation of sympathetic activity in patients with CHF and hypertension. Therefore, augmented chemosensitivity is suggested as one of the regulatory determinants of $\dot{V}E/\dot{V}CO_2$ slope, although there are no data that prove that increases in the PaCO₂, by which the activity of chemoreceptors is modulated, occur during exercise. In addition, Chua et al suggested that hyperventilation is caused by excessive muscle ergoreceptor activation in patients with CHF. This mechanism also seems to increase only the $\dot{V}E/\dot{V}CO_2$ slope¹³ In the present study, we considered 34 and 16 ml·kg⁻¹·min⁻¹ as the respective cut-off values for the $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$ because they have been used in previous studies^{19,20} Their specificity was more than 75%, and the sensitivity was approximately 40.

When we divided the subjects into 2 groups using 14 ml·kg⁻¹·min⁻¹, which is the benchmark for consideration of heart transplantation, the specificity became greater, although the sensitivity became lower. When we analyzed the cumulative 3-year event-free survival curves in each case, there were no significant differences, which may be related to an imbalance in the number of subjects. The $\dot{V}E/\dot{V}CO_2$ slope of the dead subjects was >40 without exception and when we used 40 as the cut off value, the specificity increased and the sensitivity diminished.

As for the clinical implication, it can be difficult to infer a patient's prognosis from only 1 marker, so the combination of $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$ should be a useful prognostic indicator of cardiac events in patients with preserved peak $\dot{V}O_2$.

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