

Prognostic value of end-tidal CO₂ pressure during exercise in patients with left ventricular dysfunction

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Abstract We compared the prognostic power of end-tidal CO₂ pressure (PETCO₂) during exercise, an index of arterial CO₂ pressure, with those of established respiratory gas indexes during exercise testing in patients with left ventricular dysfunction. Seventy-eight consecutive patients with a left ventricular ejection fraction (LVEF) $\leq 40\%$ were enrolled in the study. All the patients performed a symptom-limited incremental exercise test with respiratory gas measurements. PETCO₂ at peak exercise, peak O₂ uptake ($\dot{V}O_2$), the ratio of the increase in ventilation to the increase in CO₂ output ($\dot{V}E/\dot{V}CO_2$ slope), and the ratio of the increase in $\dot{V}O_2$ to the increase in work rate ($\Delta\dot{V}O_2/\Delta WR$) were measured. PETCO₂ at peak exercise was significantly correlated with peak $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope and $\Delta\dot{V}O_2/\Delta WR$. During a prospective follow-up period of 992 ± 570 days, 14 cardiac deaths occurred. As compared to survivors, non-survivors had a significantly lower LVEF, lower PETCO₂ at peak exercise, lower peak $\dot{V}O_2$, lower $\Delta\dot{V}O_2/\Delta WR$ and a higher $\dot{V}E/\dot{V}CO_2$ slope. Among these indexes, only PETCO₂ at peak exercise was found to be an independent predictor for cardiac death. PETCO₂ at peak exercise is useful in predicting poor prognosis in patients with left ventricular systolic dysfunction.

Keywords End-tidal CO₂ pressure · Peak $\dot{V}O_2$ · Exercise testing

Introduction

Parameters obtained from cardiopulmonary exercise testing reflect the severity of heart disease and the activities of daily living in cardiac patients [1]. Among these, the peak O₂ uptake ($\dot{V}O_2$) has traditionally been considered a gold standard for identifying patients with a poor prognosis and selecting candidates for cardiac transplantation [2]. The ratio of the increase in ventilation ($\dot{V}E$) to the increase in CO₂ output ($\dot{V}CO_2$) during exercise ($\dot{V}E/\dot{V}CO_2$ slope) also strongly reflects the severity of heart failure and has been found to be an independent prognostic marker in cardiac patients [3].

End-tidal CO₂ pressure (PETCO₂) is one of the parameters obtained from respiratory gas analysis [4]. PETCO₂ generally reflects arterial PCO₂ (PaCO₂) both at rest and during exercise in healthy subjects [5]. It has been demonstrated that PETCO₂ becomes low in pulmonary vascular occlusive disease because of a lack of perfusion of ventilated lungs [5, 6]. It has also been shown that cardiac patients have an abnormally low PETCO₂ during exercise, in accordance with a decreased peak $\dot{V}O_2$ [4, 7, 8]. In patients with previous myocardial infarction, it has been noted that physical training increases PETCO₂ not at rest, but during exercise, in accordance with an improved response of cardiac output during exercise [9]. Thus, it has been speculated that PETCO₂ during exercise has strong associations with cardiopulmonary function during exercise and cardiac reserve. Although very few studies have suggested the prognostic value of PETCO₂ during exercise [10], it has not been established whether the measurement

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of PETCO_2 during exercise is useful in predicting future cardiac events.

During incremental exercise, PETCO_2 usually remains constant or slightly increases from rest to moderate exercise. Thereafter, it generally declines. The point at which PETCO_2 starts to decline is called the respiratory compensation point [11]. In our experience, this point may not always be identified in cardiac patients. Therefore, we focused simply on PETCO_2 at peak exercise. In the present study, we hypothesized that a low PETCO_2 at peak exercise is related to a worse prognosis, especially cardiac death due to worsening of heart failure, and that its prognostic power might be superior to the established respiratory gas indexes during exercise in cardiac patients. In order to test this hypothesis, we compared the prognostic power of PETCO_2 at peak exercise with those of the left ventricular ejection fraction (LVEF) measured at rest and respiratory gas indexes obtained during exercise testing in patients with left ventricular dysfunction, focusing on their cardiac mortality.

Methods

Study patients

We prospectively evaluated 78 cardiac patients who performed exercise testing with a respiratory gas analysis at the Cardiovascular Institute between February 2001 and August 2003 and whose LVEF was equal to or less than 40% by echocardiography (mean LVEF = $28.6 \pm 7.7\%$). The etiology of heart diseases was coronary artery disease in 43, valvular heart disease in 18 and idiopathic dilated cardiomyopathy in 17 patients. Among the 43 patients with coronary artery disease, 38 had previous myocardial infarction. Coronary artery disease was diagnosed by the presence of significant coronary stenosis defined as a $\geq 75\%$ reduction in the luminal diameter of coronary vessels or the presence of myocardial infarction diagnosed according to the World Health Organization criteria [12]. The protocol was approved by the human subjects committee of the Cardiovascular Institute. Its purposes and risks were explained to the patients, and informed consent was obtained from each.

Follow-up

Patients were prospectively followed up at the outpatient clinic of the Cardiovascular Institute. The endpoint was defined as cardiac death. Causes of cardiac deaths were categorized into progressive heart failure, acute myocardial infarction and sudden cardiac death. Sudden cardiac death was diagnosed according to published criteria [13].

Cardiopulmonary exercise testing

An incremental symptom-limited exercise test was performed using an upright, electromagnetically-braked cycle ergometer (Corival 400, Lode, Holland). Exercise began with a 4-min warm-up at 0 W or 20 W at 60 rpm, and the load was then increased incrementally by 1 W every 6 s (10 W/min). The work rate of the warm-up exercise was selected as 0 W in 34 patients whose daily activity was assumed to be very low. In the remaining 44 patients, 20 W was used. Through a rubber mask attached to the subject's face, breath-by-breath $\dot{V}\text{O}_2$, $\dot{V}\text{CO}_2$, $\dot{V}\text{E}$, and PETCO_2 were measured during the test using an Aeromonitor AE-300S (Minato Medical Science, Osaka, Japan) [8, 14]. The Aeromonitor AE-300S consists of a microcomputer, a hot wire flowmeter, and a gas analyzer, which contains a sampling tube, filter, suction pump, O_2 analyzer made by a paramagnetic oxygen transducer, and an infrared CO_2 analyzer. Gas was sampled through a filter by a suction pump through the gas analyzers at a rate of 170 ml/min. The system was carefully calibrated before each study.

Data analysis

Prior to any calculation of the parameters from the respiratory gas analysis, a five-point moving average of the breath-by-breath data was performed. The peak $\dot{V}\text{O}_2$ and PETCO_2 at peak exercise were defined as the average values obtained during the last 15 s of incremental exercise. The ratio of the increase in $\dot{V}\text{O}_2$ to the increase in work rate ($\Delta\dot{V}\text{O}_2/\Delta\text{WR}$) was calculated by a least-squares linear regression from the data recorded between 30 s after the start of incremental exercise to 30 s before the end of the exercise [15]. The $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope was calculated from the start of incremental exercise to the respiratory compensation point by the least-squares linear regression [15]. The respiratory compensation point was determined using the following criteria: (1) the ratio of $\dot{V}\text{E}$ to $\dot{V}\text{CO}_2$ starts to increase after a period of decrease or stasis; and (2) the PETCO_2 starts to decrease after a period of stasis. When the respiratory compensation point could not be clearly identified, the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope was calculated from the data recorded between the start of incremental exercise to the end of the exercise [15]. PETCO_2 at rest was also determined as the average of the value obtained as the subject sat on the ergometer over a 4-min period before the start of the exercise test.

Statistics

Data are presented as the mean \pm SD. Linear regression analysis was used to correlate the PETCO_2 at peak exercise and the CPX parameters. Intergroup differences for

variables were compared using the unpaired *t* test or Fisher's exact test, where appropriate. A Cox proportional hazards model was used to measure the impact of cardiopulmonary variables on event-free survival time. The optimal threshold value of PETCO₂ at peak exercise for cardiac death was determined by receiver operating characteristics (ROC) curve analysis. The difference in survival between two groups divided on the basis of the optimal threshold value was detected by the Kaplan–Meier method, and compared using the logrank test. For all comparisons, *P* < 0.05 was considered statistically significant.

Results

As shown in Fig. 1, PETCO₂ at peak exercise showed significant positive correlations with peak $\dot{V}O_2$ (*r* = 0.60, *P* < 0.0001) and $\Delta\dot{V}O_2/\Delta WR$ (*r* = 0.56, *P* < 0.0001), and a negative correlation with the $\dot{V}E/\dot{V}CO_2$ slope (*r* = -0.79, *P* < 0.0001).

During the follow-up period of 992 ± 570 days, no patients underwent cardiac transplantation, but three patients received implantation of a cardioverter defibrillator. Among the 43 patients with coronary artery disease, four patients underwent coronary artery bypass graft surgery and two patients received percutaneous coronary intervention during the follow-up period. Among the 18 patients with valvular disease, four patients underwent replacements and/or repairs of cardiac valves during this period.

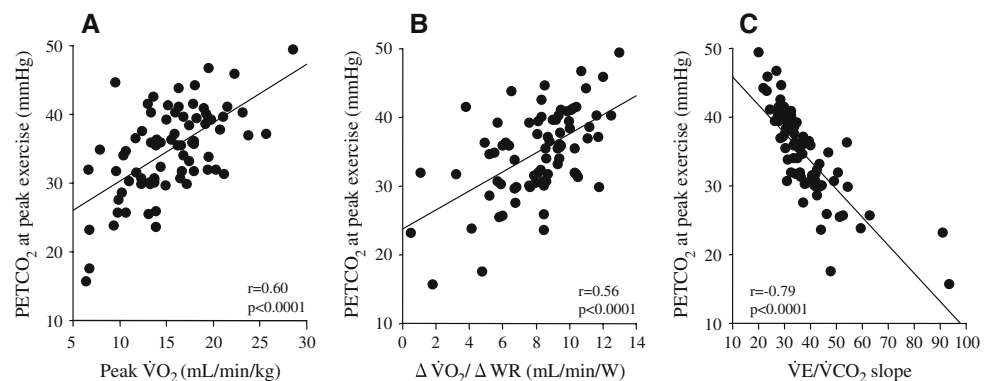
By the end of the study, 14 cardiac deaths occurred. Of these, seven patients died of progressive heart failure (five patients with coronary artery disease, one patient with valvular disease and one patient with idiopathic dilated cardiomyopathy), six patients had a sudden cardiac death (four patients with coronary artery disease and two patients with valvular disease) and one patient with coronary artery disease died of acute myocardial infarction. LVEF at rest was 24.7 ± 8.0% in non-survivors, which was lower than that of survivors (29.4 ± 7.5%, *P* = 0.04). As compared to survivors, non-survivors had lower heart rate and systolic

blood pressure at peak exercise. Non-survivors had a lower PETCO₂ both at rest (28.4 ± 5.2 vs. 33.4 ± 4.1 mmHg, *P* = 0.0002) and at peak exercise (28.7 ± 6.7 vs. 35.9 ± 5.6 mmHg, *P* < 0.0001) than survivors. Non-survivors achieved a lower peak $\dot{V}O_2$ than survivors (12.1 ± 3.5 vs. 15.9 ± 4.4 ml/min/kg, *P* = 0.004). $\Delta\dot{V}O_2/\Delta WR$ in non-survivors was 6.5 ± 1.9 ml/min/W, which was significantly lower than that in survivors (8.3 ± 2.6 ml/min/W, *P* = 0.01). The $\dot{V}E/\dot{V}CO_2$ slope was significantly higher in non-survivors than in survivors (44.5 ± 16.1 vs. 35.7 ± 11.2, *P* = 0.02).

In Fig. 2, ROC curve for PETCO₂ at peak exercise is illustrated for cardiac death. The optimal threshold value for PETCO₂ at peak exercise was 30.9 mmHg (ROC area = 0.81, 95% confidence interval = 0.68 – 0.94, *P* < 0.001, Sensitivity = 83%, Specificity = 79%). Table 1 shows a comparison of clinical characteristics between patients with PETCO₂ ≥ 30.9 mmHg (*n* = 56) and those with PETCO₂ < 30.9 mmHg (*n* = 22). As compared to patients with PETCO₂ ≥ 30.9 mmHg, those with PETCO₂ < 30.9 mmHg had lower systolic blood pressure at peak exercise. Patients with PETCO₂ < 30.9 mmHg had a lower PETCO₂ both at rest and at peak exercise than those with PETCO₂ ≥ 30.9 mmHg. Patients with PETCO₂ < 30.9 mmHg achieved a lower peak $\dot{V}O_2$ and $\Delta\dot{V}O_2/\Delta WR$ and a higher $\dot{V}E/\dot{V}CO_2$ slope.

Table 2 shows the univariate and multivariate Cox proportional hazards analyses of the association between cardiopulmonary indexes and cardiac deaths. By the univariate analysis, LVEF, heart rate and systolic blood pressure at peak exercise, PETCO₂ both at rest and at peak exercise, peak $\dot{V}O_2$, $\Delta\dot{V}O_2/\Delta WR$, and the $\dot{V}E/\dot{V}CO_2$ slope were all found to be significant indexes for survival. When these indexes were entered all together, only PETCO₂ at peak exercise (*P* = 0.030) was found to be an independent predictor for cardiac death. Figure 3 shows the Kaplan–Meier survival in each group of subjects divided on the basis of the optimal threshold value for PETCO₂ at peak exercise. Kaplan–Meier survival curves demonstrate a significantly lower survival rate in patients with PETCO₂

Fig. 1 Relationships of PETCO₂ at peak exercise with peak $\dot{V}O_2$ (panel A), $\Delta\dot{V}O_2/\Delta WR$ (panel B) and $\dot{V}E/\dot{V}CO_2$ slope (panel C)



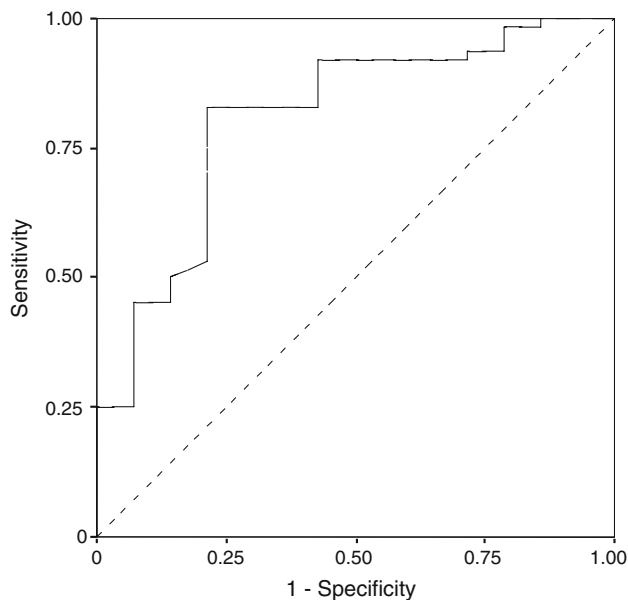


Fig. 2 Receiver operating characteristics (ROC) curve analysis for PETCO₂ at peak exercise on cardiac death. From this analysis, the optimal threshold value for PETCO₂ at peak exercise was determined as 30.9 mmHg

<30.9 mmHg than that seen in those with PETCO₂ ≥30.9 mmHg ($P < 0.0001$).

Discussion

Until 1980s, risk stratification of chronic heart disease was primarily based on the functional assessment by the New York Heart Association functional classifications 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 [2, 16]. Hence, cardiopulmonary exercise testing has become indispensable in stratifying patients with heart failure and singling out those with poor prognosis. In the present study, we found that among patients with left ventricular systolic dysfunction, those with a relatively low PETCO₂ at peak exercise have a significantly lower survival rate than those with a relatively high PETCO₂ at peak exercise. By the multivariate Cox proportional hazards analysis including peak $\dot{V}O_2$, $\Delta\dot{V}O_2/\Delta WR$, and $\dot{V}E/\dot{V}CO_2$ slope, only PETCO₂ at peak exercise was found to be an independent predictor for cardiac deaths.

Parameters obtained from cardiopulmonary exercise testing

Given that $\dot{V}O_2$ is the product of cardiac output and the difference in the arterial and mixed venous blood O₂ content, peak $\dot{V}O_2$ in cardiac patients reflects maximal

cardiac output, i.e., the heart's pumping reserve, along with the O₂ uptake capacity in the skeletal muscle. $\Delta\dot{V}O_2/\Delta WR$, which reflects the rate of the increase in cardiac output during incremental exercise, is known to be approximately 10 ml/min/W in healthy subjects [17]. The lower $\Delta\dot{V}O_2/\Delta WR$ in non-survivors suggests an insufficient cardiac reserve. The $\dot{V}E/\dot{V}CO_2$ slope, which ranges from approximately 24 to 34 in healthy subjects, becomes steeper in cardiac patients, according to the severity of heart failure [3, 18]. Theoretically, a steep $\dot{V}E/\dot{V}CO_2$ slope is assumed to relate to an increased ratio of pulmonary dead space to tidal volume (VD/VT) or to a decrease in the regulatory set point for PaCO₂. During incremental exercise, lactic acidosis develops. This development occurs at lower intensity exercise as the heart disease worsens, and increases ventilation through stimulation of carotid bodies. Therefore, a steeper $\dot{V}E/\dot{V}CO_2$ slope is also related to the increase in the blood lactate level itself. It is assumed that a higher $\dot{V}E/\dot{V}CO_2$ slope leads to a worse prognosis by these mechanisms determining the $\dot{V}E/\dot{V}CO_2$ slope.

It has been reported that the values of PETCO₂ at rest and at peak exercise are, on average, 34 and 40 mmHg, respectively, in healthy subjects of approximately 60 years of age [19]. Thus, PETCO₂ at rest and at peak exercise in non-survivors of the present study are considerably lower than those reported in healthy subjects. The arterial–end-tidal PCO₂ difference is known to reflect a ventilation–perfusion (V/Q) mismatch. In patients with left ventricular dysfunction, the failure of pulmonary blood flow (cardiac output) to increase appropriately during exercise aggravates the V/Q mismatch (high ventilation/perfusion) and the pulmonary dead space, leading to a greater arterial–end-tidal PCO₂ difference. This greater difference attributes to the lower PETCO₂ and becomes much greater with the increasing severity of heart failure [4, 7, 20]. Also during exercise, patients with heart failure have a lower PaCO₂ as compared to healthy subjects because of their lactic acidosis-induced hyperventilation [21]. Thus, a lower PETCO₂ during exercise which is determined by V/Q mismatch and degree of lactic acidosis would be tightly related to insufficient cardiac reserve. Probably by this reason, PETCO₂ at peak exercise was found as a powerful prognostic index for cardiac mortality in patients with left ventricular dysfunction in whom the main cause of death was the worsening of heart failure.

Study limitations

During incremental exercise, PETCO₂ usually remains constant or slightly increases from rest to moderate exercise, and then declines during heavy exercise. Since the respiratory compensation point, i.e., the point at which PETCO₂ starts to decline may not always be clear, we

Table 1 Clinical characteristics of the subjects

Characteristics	All patients (n = 78)	PETCO ₂ at peak exercise ≥30.9 mmHg (n = 56)	PETCO ₂ at peak exercise <30.9 mmHg (n = 22)	P value
Age (years)	63.5 ± 10.6	62.8 ± 10.7	65.2 ± 10.5	NS
Male/female gender, No.	70/8	50/6	20/2	NS
Etiology				
Coronary artery disease	43 (55.1)	29 (51.8)	14 (63.6)	NS
Valvular disease	18 (23.1)	12 (21.4)	6 (27.3)	NS
Idiopathic dilated cardiomyopathy	17 (21.8)	15 (26.8)	2 (9.1)	NS
Medication				
Diuretics	54 (69.2)	35 (62.5)	19 (86.4)	NS
Nitrates	39 (50.0)	26 (46.4)	13 (59.1)	NS
β-blockers	31 (39.7)	23 (41.1)	8 (36.4)	NS
Angiotensin receptor blockers	29 (37.2)	23 (41.1)	6 (27.3)	NS
Calcium-channel blockers	19 (24.4)	16 (28.6)	3 (13.6)	NS
Angiotensin-converting enzyme inhibitors	17 (21.8)	12 (21.4)	5 (22.7)	NS
Digitalis	17 (21.8)	11 (19.6)	6 (27.3)	NS
LVEF (%)	28.6 ± 7.7	28.8 ± 7.8	27.9 ± 7.8	NS
Heart rate at rest	80.1 ± 13.4	79.9 ± 13.3	80.6 ± 14.2	NS
Systolic blood pressure at rest	118.7 ± 17.1	120.7 ± 16.4	113.8 ± 18.5	NS
Heart rate at peak exercise	124.2 ± 22.3	125.7 ± 21.8	120.4 ± 23.6	NS
Systolic blood pressure at peak exercise	161.9 ± 30.7	168.1 ± 29.9	146.2 ± 27.5	0.004
Respiratory exchange ratio at rest	0.89 ± 0.05	0.89 ± 0.04	0.90 ± 0.08	NS
Respiratory exchange ratio at peak exercise	1.09 ± 0.10	1.09 ± 0.10	1.10 ± 0.10	NS
PETCO ₂ at rest (mmHg)	32.5 ± 4.7	34.5 ± 3.3	27.4 ± 3.7	<0.0001
PETCO ₂ at peak exercise (mmHg)	34.6 ± 6.4	37.6 ± 4.3	27.0 ± 4.3	<0.0001
Peak $\dot{V}O_2$ (ml/min/kg)	15.2 ± 4.5	16.6 ± 4.3	11.7 ± 3.0	<0.0001
$\Delta\dot{V}O_2/\Delta WR$ (ml/min/W)	8.0 ± 2.6	8.6 ± 2.3	6.4 ± 2.5	0.0007
$\dot{V}E/\dot{V}CO_2$ slope	37.2 ± 12.5	32.6 ± 6.6	49.5 ± 15.9	<0.0001

Data are presented as mean ± SD or No. (%) of patients unless otherwise indicated
 NS not significant

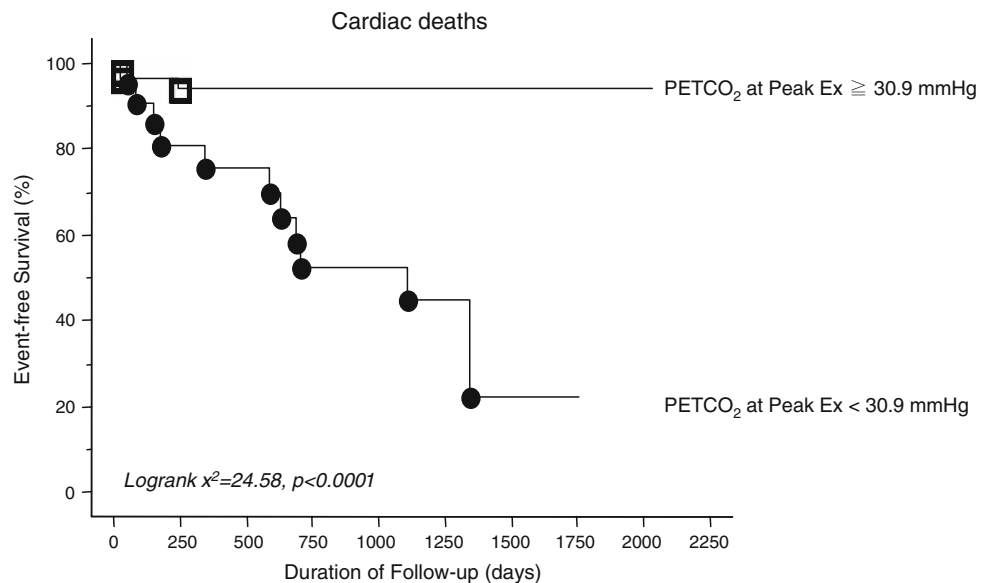
Table 2 Predictors for cardiac death

Variables	Univariate analysis				Multivariate analysis			
	X ²	P value	Hazard ratio	95% CI	X ²	P value	Hazard ratio	95% CI
LVEF	5.73	0.0167	0.924	0.866–0.986	1.95	0.163	0.936	0.852–1.027
Heart rate at peak exercise	6.12	0.0134	0.968	0.943–0.993	2.88	0.090	0.965	0.926–1.006
Systolic blood pressure at peak exercise	7.20	0.0073	0.972	0.952–0.992	0.01	0.936	1.002	0.965–1.040
PETCO ₂ at rest	15.47	<0.0001	0.798	0.713–0.893	0.33	0.566	1.079	0.833–1.397
PETCO ₂ at peak exercise	17.49	<0.0001	0.815	0.740–0.897	4.73	0.030	0.741	0.566–0.971
Peak $\dot{V}O_2$	10.08	0.0015	0.789	0.682–0.913	0.60	0.438	0.878	0.631–1.221
$\Delta\dot{V}O_2/\Delta WR$	8.23	0.0041	0.772	0.647–0.921	0.35	0.552	1.159	0.712–1.888
$\dot{V}E/\dot{V}CO_2$ slope	9.54	0.0020	1.052	1.019–1.086	2.07	0.151	0.943	0.871–1.021

obtained the value at peak exercise. The value of PETCO₂ at peak exercise is influenced by the subjects' motivation and the philosophy of the physician who has the

responsibility to terminate the exercise. Thus, PETCO₂ at the respiratory compensation point or at the anaerobic threshold rather than the point at peak exercise might have

Fig. 3 Kaplan–Meier survival curves for patients stratified into two groups on the basis of the threshold value for PETCO₂ at peak exercise determined from ROC analysis: Patients with a PETCO₂ at peak exercise ≥ 30.9 mmHg ($n = 56$) and those with a PETCO₂ at peak exercise < 30.9 mmHg ($n = 22$). The survival rate in the patients with a lower PETCO₂ at peak exercise was significantly lower than that seen in those with a higher PETCO₂ at peak exercise ($P < 0.0001$)



been better to discriminate cardiac patients with poor prognosis.

Although the prognostic power of the parameters may depend partly on the etiology of heart disease, the number of subjects in the present study was not sufficient to bring out disease-specific characteristics of each prognostic index. Also, the prognostic power of indexes obtained during cardiopulmonary exercise testing must depend on the severity of heart disease. Thus, the results of our present study do not refute the significance of peak $\dot{V}O_2$ in predicting mortality in heart failure patients and in selecting candidates for cardiac transplantation. For the future, it will be ideal to estimate the cardiopulmonary reserve and to identify high risk patients by integrating the indexes of cardiopulmonary exercise testing.

Conclusion

PETCO₂ at peak exercise is useful in predicting poor prognosis in patients with left ventricular systolic dysfunction.

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