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End-tidal oxygen partial pressure is a strong prognostic predictive factor in patients with cardiac disease

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Short title: End-tidal oxygen partial pressure as prognostic predictor

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Abstract

Background

Cardiopulmonary exercise testing (CPET) variables represent central and peripheral factors and combined factors in the pathology of patients with cardiac disease. The difference in end-tidal oxygen partial pressure from resting to anaerobic threshold (ΔPETO_2) may represent predominantly peripheral factors. This study aimed to verify the prognostic significance of ΔPETO_2 for major adverse cardiac and cerebrovascular events (MACCE) in cardiac patients, including comparison with the minute ventilation-carbon dioxide production relationship ($\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope) and peak oxygen uptake ($\dot{V}\text{O}_2$).

Methods

In total, 185 patients with cardiac disease who underwent CPET were consecutively enrolled in this retrospective study. The primary endpoint was 3-year MACCE. The ability of ΔPETO_2 , $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope, and peak $\dot{V}\text{O}_2$ to predict MACCE was examined.

Results: Optimal cut-off values for predicting MACCE were 2.0 mmHg for ΔPETO_2 (area under the curve [AUC]: 0.829), 29.8 for $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope (AUC: 0.734), and 19.0 mL/min/kg for peak $\dot{V}\text{O}_2$ (AUC: 0.755). The AUC of ΔPETO_2 was higher than those of $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope and peak $\dot{V}\text{O}_2$. The MACCE-free survival rate was significantly lower in the $\Delta\text{PETO}_2 \leq 2.0$ group than in the $\Delta\text{PETO}_2 > 2.0$ group (44.4% vs. 91.2%, P

<0.001). $\Delta\text{PETO}_2 \leq 2.0$ was an independent predictor of MACCE after adjustment for age and $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope (hazard ratio [HR], 7.28; $P < 0.001$) and after adjustment for age and peak $\dot{V}\text{O}_2$ (HR, 6.52; $P < 0.001$).

Conclusion

ΔPETO_2 was a strong predictor of MACCE independent of and superior to $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope and peak $\dot{V}\text{O}_2$ in patients with cardiac disease.

Keywords: End-tidal oxygen partial pressure, Major adverse cardiac and cerebrovascular events, Cardiac disease, Cardiopulmonary exercise testing, Prognostic predictive factor

1. Introduction

Several variables obtained by cardiopulmonary exercise testing (CPET) have been firmly established as prognostic indicators used to stratify prognosis for patients with cardiac disease (Myers et al., 2015; Paolillo et al., 2017; Corrà et al., 2018; Poggio et al., 2020). Various studies have reported on the superiority or inferiority of each variable's prognostic power. Among them, oxygen uptake (peak $\dot{V}O_2$) and the minute ventilation-carbon dioxide production relationship ($\dot{V}E/\dot{V}CO_2$ slope) are major prognostic indicators. These are generally used as comparison values in studies of the predictive power of other CPET variables (Guazzi, 2014; Shafiq et al., 2016; Coeckelberghs et al., 2016). Peak $\dot{V}O_2$ represents exercise tolerance and reflects central (cardiovascular and/or pulmonary) and peripheral (skeletal muscle) function (Guazzi et al., 2012, 2017). The $\dot{V}E/\dot{V}CO_2$ slope represents ventilatory efficiency and reflects pulmonary and cardiac dysfunction and skeletal muscle metabolic disorders (Guazzi et al., 2012; Myers et al., 2015; Paolillo et al., 2017). Thus, these two variables reflect both central and peripheral function. In addition, other prognostic variables such as oxygen uptake efficiency slope, exercise oscillatory ventilation, end-tidal carbon dioxide partial pressure, and oxygen pulse have been reported. These variables also relate to both central and peripheral function or mainly to central function (Guazzi et al., 2012; Coeckelberghs et al., 2016). In this study, we focused on the fact that there are currently

few reports on the relationship between CPET variables, which mainly represent peripheral function, and prognosis. We reported on Δ end-tidal oxygen partial pressure (P_{ETO_2}), i.e., the difference between resting P_{ETO_2} and P_{ETO_2} at anaerobic threshold (AT), as a CPET variable associated with peripheral function. We showed that ΔP_{ETO_2} reflects renal dysfunction, diabetes mellitus (DM), and hypertension (Ogura et al., 2021, 2022). Although these diseases have pathologies that adversely affect the prognosis of patients with cardiac disease (Bavry et al., 2013; Rushton et al., 2015; Schefold et al., 2016), these diseases have also been shown to cause deterioration of peripheral function (Lahera et al., 2017; Gamboa et al., 2020; Wood et al., 2021).

On the basis of the above, we hypothesized that ΔP_{ETO_2} would be a predictor of prognosis in cardiac patients. Therefore, the purpose of this study was to clarify the prognostic significance of ΔP_{ETO_2} for major adverse cardiac and cerebrovascular events (MACCE) in cardiac patients, including comparison with peak $\dot{V}O_2$ and the $\dot{V}E/\dot{V}CO_2$ slope.

2. Methods

2.1. Study design and patients

This was a retrospective, single-centre, observational study in which 185 patients with cardiac disease (defined as myocardial infarction, angina, and heart failure) who

underwent CPET in our institution from April 2016 to July 2019 were consecutively enrolled. Exclusion criteria included patients with a resting respiratory exchange ratio (RER) ≥ 1.00 to reduce the affect of resting hyperventilation and abnormal breathing, peak RER < 1.10 during CPET (Balady et al., 2010; Pescatello, 2014), AT that was impossible to determine, and no laboratory data. Patients' characteristics and clinical parameters including age, sex, body mass index, left ventricular ejection fraction (LVEF), medical history, laboratory data (estimated glomerular filtration rate [eGFR (mL/min/1.73 m²), haemoglobin [Hb (g/dL)]), medications, and the results of CPET were obtained from the patients' electronic medical records by two physical therapists. Laboratory data at CPET were extracted within 2 weeks around the date of CPET. Prognostic values were MACCE, cardiac death, and all-cause death.

This study complied with the Declaration of Helsinki with respect to investigation in humans and was approved by the Ethics Committee of Sanda City Hospital (approval number: 2022008). Written informed consent was obtained from each patient.

2.2. Cardiopulmonary exercise testing

All patients underwent symptom-limited maximal CPET using a cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan) with a 10 or 20 watt/min continuous ramp exercise protocol after an initial 3-min rest period and a 4-

min warm-up period. The warm-up wattage was chosen to be 0 watts or 20 watts in consideration of each patient's age, sex, cardiac function, and exercise habits. During CPET, analysis of expired gas was performed with an AE-310S analyzer (Minato Medical Science, Osaka, Japan). The patients were encouraged to perform a maximal or near maximal effort by monitoring the RER at ≥ 1.10 (Pescatello. 2014). Peak $\dot{V}O_2$ was defined as the mean value of $\dot{V}O_2$ during the last 15 s of the test, and %peak $\dot{V}O_2$ was also calculated. AT was determined using the V-slope, ventilatory equivalents, and end-tidal pressure methods based on the statement from the American Heart Association (Balady et al., 2010) by at least two experts in CPET. Resting PETO₂ was determined as the mean value during the last 30 s of rest, and AT PETO₂ was the PETO₂ at AT. Peak oxygen pulse (peak O₂ pulse), $\dot{V}E/\dot{V}CO_2$ slope, and minimum $\dot{V}E/\dot{V}CO_2$ were also obtained. Peak work rate was defined as the work rate at peak $\dot{V}O_2$.

2.3. Primary endpoint and follow-up

The primary endpoint was MACCE, which included acute coronary syndrome (defined as unstable angina pectoris or non-ST-segment elevation or ST-segment elevation myocardial infarction), revascularization with percutaneous coronary intervention for angina (excluding stenoses present before CPET and in-stent restenosis), hospitalization for heart failure, and stroke. These diagnoses were based on the guideline of the

Japanese Circulation Society (Kimura et al., 2019).

All patients were followed for 3 years after CPET. Follow-up data were obtained through hospital records review and telephonic contact. Patients lost to follow-up were excluded.

2.4. Statistical analysis

A time-dependent receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off values of ΔPETO_2 , $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope, and peak $\dot{V}\text{O}_2$ to predict MACCE. Each area under the curve (AUC) was also calculated. Patients were divided into two groups based on the cut-off value of ΔPETO_2 , the low ΔPETO_2 group and high ΔPETO_2 group, and were compared using the Student *t*-test, Mann-Whitney test, χ -square test, and Fisher's exact test, as appropriate. Data are expressed as mean values $\pm$ standard deviation (SD). Normality of distribution was verified using the Shapiro-Wilk test. Kaplan-Meier analysis with log-rank test was conducted to compare the MACCE-free survival within 3 years using each cut-off value. Cox regression analysis was used to determine the ability of ΔPETO_2 , $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope, and peak $\dot{V}\text{O}_2$ to predict MACCE. In addition, analyses were adjusted for age and heart failure, and each parameter was added. A *P*-value of <0.05 was considered to indicate statistical significance. The statistical analyses were performed with EZR (Saitama Medical

Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Of the 185 patients with cardiac disease who underwent CPET, 32 patients were excluded because of resting RER ≥ 1.00 ($n = 5$), peak RER < 1.10 ($n = 20$), judgement of AT impossible ($n = 4$), and no laboratory data ($n = 3$). Thus, 153 patients were subject to follow-up, but after exclusion of 6 patients lost to follow-up (3.9%), 147 patients were finally enrolled in the analyses (Figure 1). As a result of the ROC analyses, the optimal cut-off values for predicting MACCE were 2.0 mmHg for ΔPETO_2 (AUC: 0.829), 29.8 for the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope (AUC: 0.732), and 19.0 mL/min/kg for peak $\dot{V}\text{O}_2$ (AUC: 0.753). The AUC of ΔPETO_2 was higher than those of the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope and peak $\dot{V}\text{O}_2$ (Figure 2). Patient characteristics and CPET parameters in the $\Delta\text{PETO}_2 \leq 2.0$ group can be compared with those in the $\Delta\text{PETO}_2 > 2.0$ group in Table 1. The patients in the $\Delta\text{PETO}_2 \leq 2.0$ group were older and had a higher proportion of chronic heart failure and lower values of LVEF, eGFR, and Hb.

MACCE occurred more frequently in the $\Delta\text{PETO}_2 \leq 2.0$ group than in the $\Delta\text{PETO}_2 > 2.0$ group (55.6% vs. 8.8%, $P < 0.001$). Similarly, the incidence of MACCE was significantly higher in the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope ≥ 29.8 group than in the < 29.8 group

(34.2% vs. 10.3%, $P = 0.001$) and in the peak $\dot{V}O_2 \leq 19.0$ group than in the > 19.0 group (41.4% vs. 11.2%, $P < 0.001$). Regarding cardiac mortality and all-cause mortality, both were significantly higher in the $\Delta PETO_2 \leq 2.0$ group than in the $\Delta PETO_2 > 2.0$ group (8.9% vs 1.0%, $P = 0.031$ and 13.3% vs 2.9%, $P = 0.024$, respectively). In contrast, only all-cause mortality was significantly higher in the $\dot{V}E/\dot{V}CO_2$ slope ≥ 29.8 group than in the < 29.8 group (11.4% vs. 0%, $P = 0.004$).

The Kaplan-Meier analysis for MACCE with a $\Delta PETO_2$ cut-off of 2.0, $\dot{V}E/\dot{V}CO_2$ slope cut-off of 29.8, and peak $\dot{V}O_2$ cut-off of 19.0 is shown in Figure 3. The Kaplan-Meier curves indicated that the cumulative MACCE-free survival rate was significantly lower in the $\Delta PETO_2 \leq 2.0$ group than in the $\Delta PETO_2 > 2.0$ group (44.4% vs. 91.2%, $P < 0.001$), in the $\dot{V}E/\dot{V}CO_2$ slope ≥ 29.8 group than in the < 29.8 group (65.8% vs. 89.7%, $P < 0.001$), and in the peak $\dot{V}O_2 \leq 19.0$ group than in the > 19.0 group (58.6% vs. 88.8%, $P < 0.001$). More than half of the patients with $\Delta PETO_2 \leq 2.0$ suffered from MACCE within 3 years.

Figure 4 shows the results of univariable and multivariable Cox regression analyses and forest plot for MACCE. $\Delta PETO_2 \leq 2.0$ was an independent predictor of MACCE even after adjustment for age and $\dot{V}E/\dot{V}CO_2$ slope ≥ 29.8 (hazard ratio [HR], 7.28; 95% confidence interval [CI], 3.15–16.79; $P < 0.001$), and after adjustment for age and peak $\dot{V}O_2 \leq 19.0$ (HR, 6.52; 95% CI, 2.63–16.17; $P < 0.001$). $\dot{V}E/\dot{V}CO_2$ slope ≥ 29.8 was

also an independent predictor of MACCE even after adjustment for age and $\Delta\text{PETO}_2 \leq 2.0$ (HR, 2.41; 95% CI, 1.01–5.75; $P = 0.048$) and after adjustment for age and peak $\dot{\text{V}}\text{O}_2 \leq 19.0$ (HR, 2.40; 95% CI, 0.99–5.82; $P = 0.054$). However, peak $\dot{\text{V}}\text{O}_2 \leq 19.0$ was a predictor of MACCE after adjustment for age and $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope ≥ 29.8 (HR, 3.04; 95% CI, 1.35–6.84; $P = 0.007$) but not for age and ΔPETO_2 . All variables were independent predictors of MACCE after adjusting for age and HF ($\Delta\text{PETO}_2 \leq 2.0$: HR, 8.45; 95% CI, 3.64–19.60; $P < 0.001$ / $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope ≥ 29.8 : HR, 3.42; 95% CI, 1.45–8.06; $P = 0.005$ / peak $\dot{\text{V}}\text{O}_2 \leq 19.0$: HR, 3.80; 95% CI, 1.72–8.37; $P < 0.001$).

4. Discussion

To the best of our knowledge, this is the first study to investigate the relationship between ΔPETO_2 and MACCE in patients with cardiac disease. This study showed that (1) patients with $\Delta\text{PETO}_2 \leq 2.0$ had a higher incidence of 3-year MACCE than patients with $\Delta\text{PETO}_2 > 2.0$ (55.6% vs. 8.8%); (2) $\Delta\text{PETO}_2 \leq 2.0$ was a predictor of MACCE independently of the $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope and peak $\dot{\text{V}}\text{O}_2$ in patients with cardiac disease; and (3) ΔPETO_2 is involved in the development of MACCE through a mechanism different from that of exercise tolerance and ventilation efficiency, and this mechanism may be closely related to the development of MACCE.

Although there is debate about the superiority and inferiority of prognostic power, it is generally recognized that peak $\dot{V}O_2$ and the $\dot{V}E/\dot{V}CO_2$ slope are useful tools for predicting the prognosis of patients with heart failure and coronary artery disease (Forman et al., 2012; Myers et al., 2015; Paolillo & Agostoni, 2017; Corrà et al., 2018; Heidenreich et al., 2022). However, the present study clarified that the prognostic power of $\Delta PETO_2$ surpasses that of peak $\dot{V}O_2$ and the $\dot{V}E/\dot{V}CO_2$ slope. The HR for MACCE with $\Delta PETO_2 \leq 2.0$ was always over 7.0-6.5 after each adjustment, which was ~~extremely~~ much higher than not only the HR of peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope in the present study but also in previous studies that examined cardiovascular events for 3 years (Arena et al., 2007; Shafiq et al., 2016). In particular, peak $\dot{V}O_2$ was no longer a predictor of MACCE when adjusted for $\Delta PETO_2$.

The present study showed that the prognostic power of peak $\dot{V}O_2$ for MACCE is influenced by $\Delta PETO_2$ and that $\Delta PETO_2$ is more useful as a predictor of MACCE than is peak $\dot{V}O_2$. The disadvantage of peak $\dot{V}O_2$ as a prognostic factor is that its predictability is reduced if maximal load cannot be achieved (Arena et al., 2004; Sarullo et al., 2010). This issue has been pointed out before, but negative findings were also reported in this regard (Chase et al., 2013). They reported that the prognostic value of peak $\dot{V}O_2$ does not decrease even if the peak RER is low as long as maximum physiological exercise is performed. However, they also pointed out that it is difficult to

determine whether maximum physiological exercise was performed. As ΔPETO_2 can be calculated by the load up to AT, it is not affected by whether maximum physiological exercise is possible. As a result, ΔPETO_2 may contribute to the higher predictive power compared to peak $\dot{\text{V}}\text{O}_2$.

The present study also found that $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope was an independent predictor of MACCE even after adjustment with ΔPETO_2 or peak $\dot{\text{V}}\text{O}_2$. The $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope reflects both peripheral and central components as prognostic indicators, similar to peak $\dot{\text{V}}\text{O}_2$. The predominant view is that the $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope is a more powerful predictor than peak $\dot{\text{V}}\text{O}_2$ because it better reflects the cardiac output and is less susceptible to patient effort (Arena et al., 2004; Forman et al., 2012). Nevertheless, in the present study, the AUC of the ROC curve was significantly higher for ΔPETO_2 than for $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope, indicating that ΔPETO_2 would appear to have better prognostic power than that of $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope. The cut-off value for MACCE of the $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope in the present study was ~~30.8~~29.8, which was not an abnormal value and was slightly lower than that in previous reports (Arena et al., 2004; Sarullo et al., 2010; Guazzi et al., 2012). Therefore, in the present study, the impairment of ventilatory efficiency was mild, and this may explain why the predictive power of MACCE was less than that of ΔPETO_2 . This result may be characteristic of the population in this study with a low VE/VCO_2 slope.

Of particular note is that ΔPETO_2 was a predictor of MACCE occurrence independent of peak $\dot{V}\text{O}_2$ and $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope. This suggests that ΔPETO_2 is involved in the development of MACCE through a mechanism different from that of exercise tolerance and ventilation efficiency and that this mechanism may be closely related to the development of MACCE.

One of the factors possibly responsible for the significantly stronger prognostic power of ΔPETO_2 compared with peak $\dot{V}\text{O}_2$ and $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope is its strong association with renal dysfunction, DM, and hypertension, which influence prognosis in patients with cardiac disease (Bavry et al., 2013; Rushton et al., 2015; Schefold et al., 2016; Ogura et al., 2021, 2022). More importantly, these diseases cause deterioration of peripheral factors (Lahera et al., 2017; Gamboa et al., 2020; Wood et al., 2021).

Peripheral factors depend on mitochondrial function, which primarily contributes to the oxygen extraction capacity of skeletal muscle (Guazzi et al., 2017).

Baumbach et al. (2020) revealed that PETO_2 correlates with mitochondrial oxygen intake during exercise. However, in patients with cardiac disease, PETO_2 is affected by abnormal ventilation (Balady et al., 2010). We reported that PETO_2 at AT is affected by abnormal ventilation, whereas ΔPETO_2 from resting to AT may be associated with peripheral factors (Ogura et al., 2021). Because PETO_2 decreases with increasing oxygen extraction in skeletal muscle during gradual exercise up to AT (Binder et al.,

2008; Wasserman, 2012), ΔPETO_2 , which is less susceptible to abnormal ventilation, is suitable for expressing the oxygen extraction capacity of skeletal muscle. As the main component of skeletal muscle oxygen extraction capacity is mitochondrial function (Guazzi et al., 2017), ΔPETO_2 may represent mitochondrial function of skeletal muscle during incremental exercise.

In recent years, the importance of peripheral function in the prognosis of patients with cardiac disease has been drawing attention. Several consensus statements and reviews have been published ~~one after another~~ (Brown et al., 2017; Bonora et al., 2019; Tian et al., 2019; Poznyak et al., 2020). Mitochondrial dysfunction, which has emerged as a main factor in the pathogenesis and progression of cardiac diseases, promotes the excessive production of reactive oxygen species (ROS) and causes cardiovascular disease (Brown et al., 2017). In patients with cardiac disease, ROS is excessively produced not only by the mitochondria of the heart and blood vessels but also by the mitochondria of skeletal muscle (Brown et al., 2017; Tian et al., 2019).-Excessive ROS production promotes the accelerated progression of atherosclerosis, vascular smooth muscle cell proliferation, involvement in apoptosis that promotes cardiovascular damage, and the exacerbation of both hypertension and heart failure (Brown et al., 2017; Bonora et al., 2019; Tian et al., 2019; Poznyak et al., 2020). These pathological conditions eventually induce MACCE. One of the reasons for the remarkably strong

prognostic predictive power of ΔPETO_2 may be that it is a CPET variable representing pathological conditions directly linked to MACCE as described above.

Prevention of MACCE is an important issue for patients with cardiac disease, and risk stratification is important when taking measures to reduce MACCE. ΔPETO_2 offers two main strengths for patient risk stratification. First, it can be calculated with the load up to AT, which makes it possible to predict prognosis even in patients who cannot exercise to a high load. Second, the prognostic power of ΔPETO_2 is superior to that of peak $\dot{V}\text{O}_2$ and the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope. ΔPETO_2 is a CPET variable that may provide important information for the prevention of MACCE.

4.1. Study limitations

This study has several limitations. First, this was a single-centre, retrospective study consisting of a relatively small number of patients. Second, resting PETO_2 is affected by resting ventilation (Wasserman, 2012). To reduce that affect as much as possible, patients with a resting RER > 1.0 were excluded (Balady et al., 2010). Third, as the present subjects had only three types of cardiac disease, in the future it will be necessary to validate our findings based on the type of cardiac disease the patient has. Fourth, the effects of sex, medications, and comorbidities were not examined and need to be investigated in the future. Finally, as the cut-off values were calculated from the ROC

curves based on the data of the subjects in this study, the results may differ in other populations.

5. Conclusion

In patients with cardiac disease, ΔPETO_2 was a strong predictor of MACCE independent of and superior to $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope and peak $\dot{V}\text{O}_2$. ΔPETO_2 appears to be a prognostically significant CPET variable in MACCE risk stratification.

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Disclosures

The authors have no conflict of interest to disclose.

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Figure Legend

Figure 1. Flowchart of patients through the study. CPET, cardiopulmonary exercise testing.

Figure 2. Receiver operating characteristic curve analysis of ΔPETO_2 compared with $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope and peak $\dot{V}\text{O}_2$ in predicting MACCE. AUC, area under the curve; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; PETO_2 , end-tidal oxygen partial pressure; $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope, minute ventilation-carbon dioxide production relationship; $\dot{V}\text{O}_2$, oxygen uptake.

Figure 3. Kaplan-Meier curves of 3-year MACCE based on PETO_2 , $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope, and peak $\dot{V}\text{O}_2$. MACCE, major adverse cardiac and cerebrovascular events; PETO_2 , end-tidal oxygen partial pressure; $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope, minute ventilation-carbon dioxide production relationship; $\dot{V}\text{O}_2$, oxygen uptake.

Figure 4. Cox regression analyses and forest plot for MACCE. CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; PETO_2 , end-tidal oxygen partial pressure; $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope, minute ventilation-carbon dioxide production relationship; $\dot{V}\text{O}_2$, oxygen uptake.

Table 1. Patient characteristics and CPET parameters.

	$\Delta\text{PETO}_2 \leq 2.0$ n = 45	$\Delta\text{PETO}_2 > 2.0$ n = 102	t or χ - value	P-value
Age, yr	68.3 $\pm$ 10.4	63.3 $\pm$ 10.2	-2.701 [†]	0.008
Male, n (%)	39 (86.7)	92 (90.2)	–	0.570
Body mass index, kg/m ²	22.7 $\pm$ 2.9	23.9 $\pm$ 3.1	2.206 [†]	0.029
MI, n (%)	35 (77.8)	71 (69.6)	0.670	0.413
AP, n (%)	13 (28.9)	26 (25.5)	0.052	0.820
CHF, n (%)	27 (60.0)	34 (33.3)	8.081	0.004
LVEF, %	52.7 $\pm$ 14.3	58.9 $\pm$ 11.0	2.884 [†]	0.005
Hypertension, n (%)	29 (64.4)	72 (70.6)	0.300	0.584
Diabetes, n (%)	19 (46.3)	36 (39.6)	0.292	0.589
Laboratory				
eGFR, mL/min/1.73 m ²	47.1 $\pm$ 18.5	66.7 $\pm$ 13.9	7.064 [†]	<0.001
Haemoglobin, g/dL	13.0 $\pm$ 1.6	13.9 $\pm$ 1.6	3.055 [†]	0.002
Medications				
Beta blockers, n (%)	32 (71.1)	68 (68.0)	0.033	0.857
ACE-I, n (%)	10 (22.2)	35 (34.3)	1.618	0.203
ARB, n (%)	15 (33.3)	39 (38.2)	0.146	0.702
CCB, n (%)	10 (22.2)	17 (16.7)	0.326	0.568
Diuretics, n (%)	20 (44.4)	22 (21.6)	6.925	0.009
Oral diabetic drugs, n (%)	14 (31.1)	30 (29.4)	<0.001	0.991
Statin, n (%)	33 (73.3)	81 (79.4)	0.360	0.549
CPET variables				
Peak $\dot{V}\text{O}_2$, mL/min/kg	17.2 $\pm$ 4.1	21.9 $\pm$ 4.4	6.150 [†]	<0.001
%Peak $\dot{V}\text{O}_2$, %	73.2 $\pm$ 16.5	89.6 $\pm$ 16.9	5.456 [†]	<0.001
AT $\dot{V}\text{O}_2$, mL/min/kg	11.4 $\pm$ 1.9	13.7 $\pm$ 2.6	5.343 [†]	<0.001
Rest RER	0.85 $\pm$ 0.04	0.87 $\pm$ 0.06	1.382 [†]	0.170
AT RER	0.96 $\pm$ 0.03	0.95 $\pm$ 0.04	-2.641	0.010
Peak RER	1.19 $\pm$ 0.06	1.17 $\pm$ 0.05	-2.209 [†]	0.029
Peak WR, watts	88.8 $\pm$ 20.8	117.5 $\pm$ 28.6	6.064 [†]	<0.001
$\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope	33.7 $\pm$ 7.4	29.0 $\pm$ 4.2	-4.866	<0.001
Minimum $\dot{V}\text{E}/\dot{V}\text{CO}_2$	36.7 $\pm$ 6.7	31.8 $\pm$ 4.5	-5.167	<0.001
Peak O ₂ pulse	8.6 $\pm$ 2.1	10.8 $\pm$ 2.5	5.250 [†]	<0.001
$\Delta\dot{V}\text{O}_2/\Delta\text{WR}$	8.2 $\pm$ 1.6	9.3 $\pm$ 1.3	4.196 [†]	<0.001
Rest PETO ₂ , mmHg	107.0 $\pm$ 5.4	107.6 $\pm$ 4.0	0.730 [†]	0.467
AT PETO ₂ , mmHg	106.7 $\pm$ 5.4	102.4 $\pm$ 4.6	-4.946 [†]	<0.001
ΔPETO_2 , mmHg	0.4 $\pm$ 1.6	5.3 $\pm$ 2.6	11.678	<0.001

ACE-I, angiotensin converting enzyme inhibitor; AP, angina pectoris; ARB, angiotensin II receptor blocker, AT, anaerobic threshold; CCB, calcium channel blocker; CHF, chronic heart failure; CPET, cardiopulmonary exercise testing; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; O₂, oxygen; PETO₂, end-tidal oxygen partial pressure; RER, respiratory exchange ratio; $\dot{V}\text{CO}_2$, carbon dioxide output; $\dot{V}\text{E}$, expiratory minute volume; $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope, minute ventilation-carbon dioxide production relationship; $\dot{V}\text{O}_2$, oxygen uptake; WR, work rate.

Values shown are % (n), mean $\pm$ standard deviation, or median (interquartile range).

[†]t-value.

Table 2. Prognostic values.

	Δ PETO ₂			$\dot{V}E/\dot{V}CO_2$ slope			Peak $\dot{V}O_2$		
	≤ 2.0 n = 45	> 2.0 n = 102	P-value	≥ 29.8 n = 79	< 29.8 n = 68	P-value	≤ 19.0 n = 58	> 19.0 n = 89	P-value
MACCE, n (%)	25 (55.6)	9 (8.8)	<0.001	27 (34.2)	7 (10.3)	0.001	24 (41.4)	10 (11.2)	<0.001
Hospitalization for HF, n (%)	14 (31.1)	2 (2.0)	<0.001	15 (19.0)	1 (1.5)	<0.001	15 (25.9)	1 (1.1)	<0.001
PCI for angina, n (%)	8 (17.8)	5 (4.9)	0.023	8 (10.1)	5 (7.4)	0.765	7 (12.1)	6 (6.7)	0.415
Stroke, n (%)	3 (6.7)	1 (1.0)	0.086	3 (3.8)	1 (1.5)	0.624	2 (3.4)	2 (2.2)	1
ACS, n (%)	0 (0)	1 (1.0)	1	1 (1.3)	0 (0)	1	0 (0)	1 (1.1)	1
Cardiac death, n (%)	4 (8.9)	1 (1.0)	0.031	5 (7.0)	1 (1.2)	0.167	5 (8.6)	0 (0)	0.019
All-cause death, n (%)	6 (13.3)	3 (2.9)	0.024	9 (11.4)	0 (0)	0.004	7 (12.1)	2 (2.2)	0.029

ACS, acute coronary syndrome; HF, heart failure; MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous coronary intervention; PETO₂, end-tidal oxygen partial pressure; VE/VCO₂ slope, minute ventilation-carbon dioxide production relationship; VO₂, oxygen uptake.

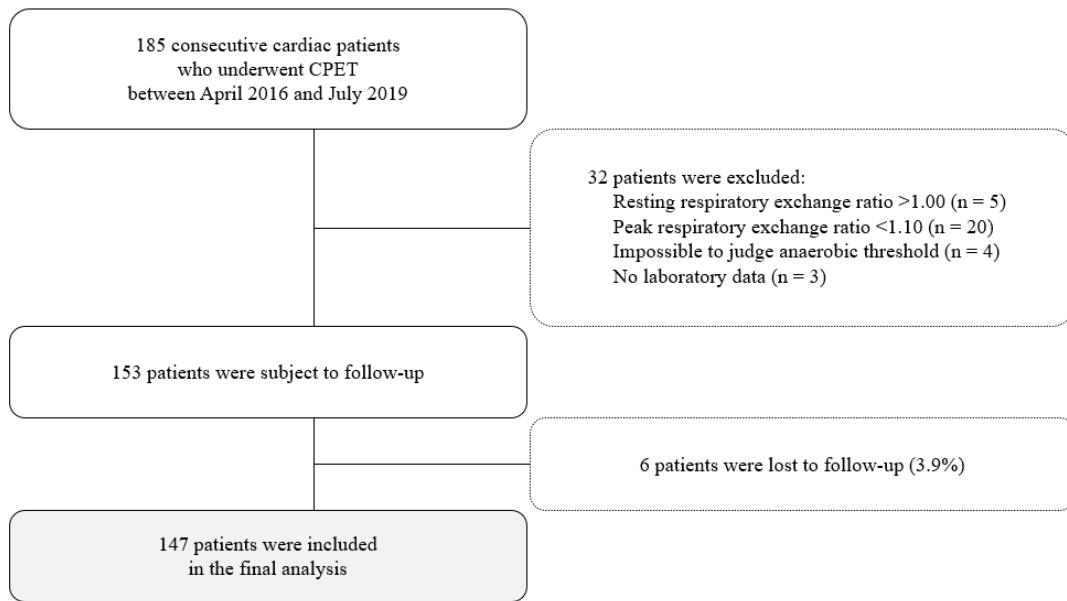


Figure 1

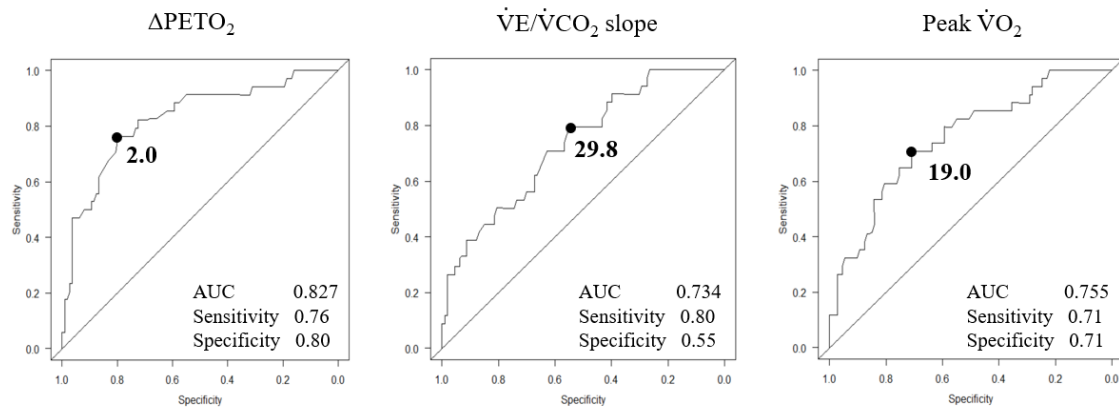


Figure 2

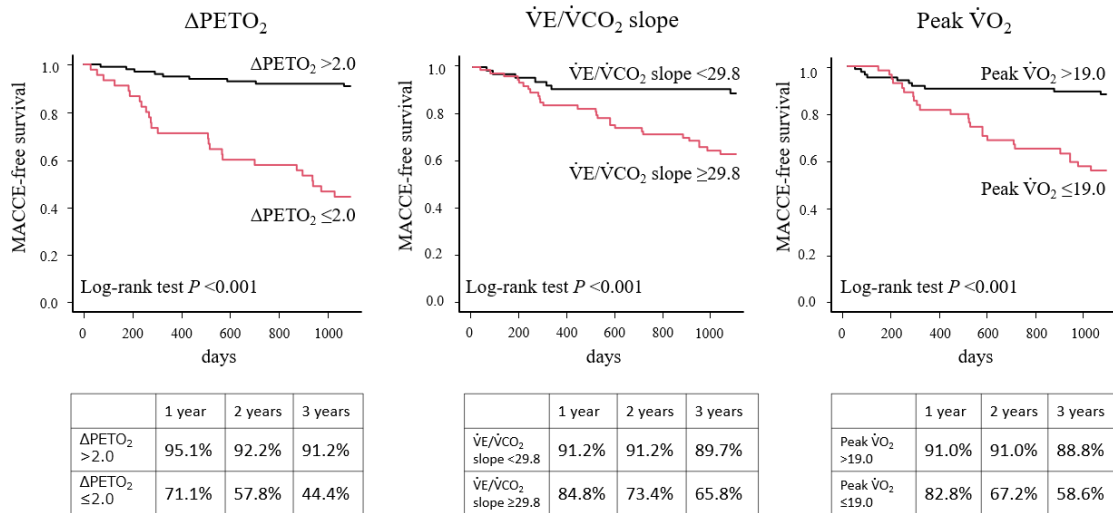


Figure 3

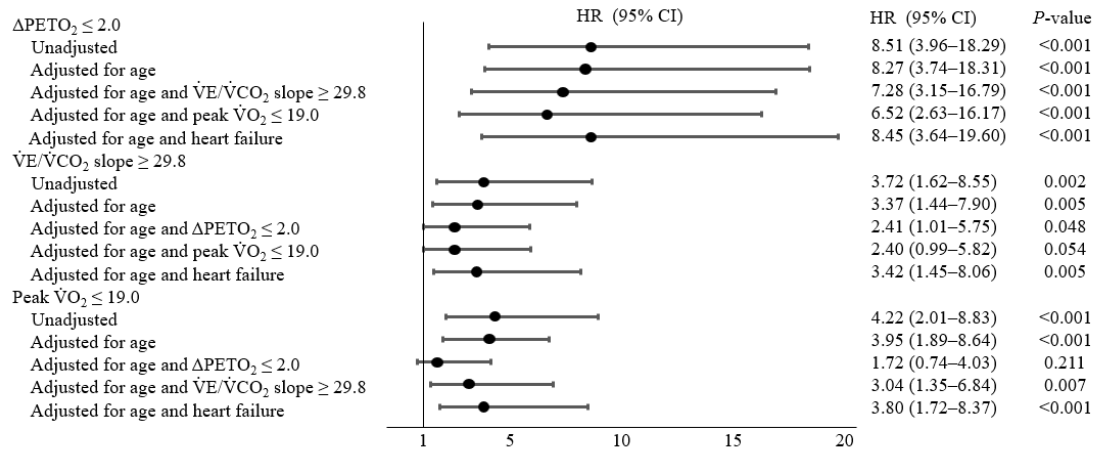


Figure 4