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Effect of pre-discharge cardiopulmonary fitness on outcomes in patients with ST-elevation myocardial infarction after percutaneous coronary intervention

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Abstract

Background: The purpose of this study was to analyze cardiopulmonary fitness in Phase I cardiac rehabilitation on the prognosis of patients with ST-Elevation Myocardial Infarction (STEMI) after percutaneous coronary intervention (PCI).

Methods: The study enrolled a total of 499 STEMI patients treated with PCI between January 2015 and December 2015. Patients were assigned to individualized exercise prescriptions (IEP) group and non-individualized exercise prescriptions (NIEP) group according to whether they accept or refuse individualized exercise prescriptions. We compared the incidence of major cardiovascular events between the two groups. IEP group were further divided into two subgroups based on prognosis status, namely good prognosis (GP) group and poor prognosis (PP) group. Key cardio-pulmonary exercise testing (CPX) variables that may affect the prognosis of patients were identified through comparison of the cardio-respiratory fitness (CRF).

Results: There is no significant difference in the incidence of cardio-genetic death, re-hospitalization, heart failure, stroke, or atrial fibrillation between the IEP and the NIEP group. But the incidence of total major adverse cardiac events (MACE) was significantly lower in the IEP group than in the NIEP group ($P = 0.039$). The oxygen consumption (VO_2) at ventilation threshold (VT), minute CO_2 ventilation (E-VCO_2), margin of minute ventilation carbon dioxide production ($^{\Delta}CO_2$), rest partial pressure of end-tidal carbon dioxide(R-$P_{ET}CO_2$), exercise partial pressure of end-tidal carbon dioxide(E-$P_{ET}CO_2$) and margin of partial pressure of end-tidal carbon dioxide($^{\Delta}P_{ET}CO_2$) were significantly higher in the GP subgroup than in the PP subgroup; and the slope for minute ventilation/carbon dioxide production (V_E/VCO_2) was significantly lower in GP subgroup than in PP subgroup ($P = 0.010$). The VO_2 at VT, V_E/VCO_2 slope, E-VCO_2, $^{\Delta}CO_2$, R-$P_{ET}CO_2$, E-$P_{ET}CO_2$ and margin of partial pressure of end-tidal carbon dioxide CO_2 ($^{\Delta}P_{ET}CO_2$) were predictive of adverse events. The VO_2 at VT was an independent risk factor for cardiovascular disease prognosis.

Conclusions: Individualized exercise prescription of Phase I cardiac rehabilitation reduced the incidence of cardiovascular events in patients with STEMI after PCI. VO_2 at VT is an independent risk factor for cardiovascular disease prognosis, and could be used as an important evaluating indicator for Phase I cardiac rehabilitation.

Keywords: Percutaneous coronary intervention, Cardio-pulmonary exercise, Cardiac rehabilitation, ST-segment elevation myocardial infarction

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Background

Acute STEMI is a leading cause of mortality and morbidity globally. STEMI leads to fatal conditions such as heart failure and sudden cardiac death, and results in an enormous psychological and financial burden on patients and the society [1]. Medication, coronary artery bypass grafting, and percutaneous coronary intervention (PCI) can reduce the morbidity and mortality in patients with STEMI [2, 3]. Medication is a basic treatment for patients before/after PCI. Compared with coronary artery bypass grafting, PCI provides an effective treatment for coronary artery stenosis. However, PCI operation may lead to coronary spasm, endothelial cell injury, and even restenosis or thrombus; moreover, a poor prognosis may still exist in patient with STEMI after PCI [4].

Cardiac rehabilitation (CR) has been found to improve the prognosis for patients with STEMI after PCI [5]. CR includes nutritional therapies, weight loss programs, management of lipid abnormalities with diet and medication, blood pressure control, diabetes management, stress management and physical exercise, and can help the recovery of physical function in patients with cardiac disease or recent cardiac surgeries. Therefore, PCI associated with CR have been recognised internationally as the preferred treatment of STEMI, now PCI combined with CR has become the internationally recognized effective treatment for patients with STEMI. Exercise training is an important part of CR, which not only improves cardiopulmonary fitness and physical activity, but also reduces the morbidity and mortality in patients with STEMI. However, as physical exercise intensifies, it also comes with certain risk. Currently, there is no specific aim for cardiopulmonary fitness in Phase I cardiac rehabilitation according to the American Heart Association (AHA) guidelines [6, 7]. The purpose of this study is to analyze cardiopulmonary fitness in Phase I cardiac rehabilitation on the prognosis of patients with STEMI after PCI, we reviewed all the information and CPX results of STEMI patients after PCI before the discharge and analyze long term prognosis of STEMI patients based on the exercise tolerance.

Methods

Patients

This retrospective study included a total of 586 STEMI patients treated with PCI in the Department of Cardiology at the First Hospital of Jilin University, between January 2015 and December 2015. After excluding 46 patients who were lost to follow-up and 41 patients who were not administrated with exercise prescription (Table 1), data from 499 STEMI patients were used in the final analyses. The study protocol was approved by the Institutional Review Board of each hospital.

Table 1 The reason of not administering exercise prescriptions for the 41 patients

	Number of patients
Herpes zoster	1
Multiple serous cavity effusion	1
Hepatic renal failure	2
Acute onset of chronic obstructive pulmonary disease	2
Cerebral infarction sequelae	8
Uremia	1
Ankylosing spondylitis	1
Diabetic ketosis	1
Diabetic foot	1
Systemic lupus erythematosus	1
Gastrointestinal ulcer	1
Cardio genic shock	1
Severe arrhythmia	8
Right intercalf venous thrombosis (acute phase)	2
Tumours	7
After aortic stent implantation	1
Second degree scald of left thigh	1
Left ventricular apical thrombosis	1
Total	41

Patients data including age, sex, cardiac function and test indices were collected, including white blood cell (WBC), hemoglobin (HGB), creatinine (Cr), glutamic pyruvic transaminase (AST), glutamic pyruvic aminotransferase (ALT), total cholesterol (TC); high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). All 499 patients had no contraindication of cardiopulmonary exercise testing. Depending on whether patients accepted or refused individualized exercise prescriptions based on cardiopulmonary exercise testing (CPX) in Phase I cardiac rehabilitation, they were assigned to the individualized exercise prescriptions (IEP) group ($n = 118$) or the non-individualized exercise prescriptions (NIEP) group ($n = 381$). In the IEP group, the intensity of exercise was formulated base on each patient's cardio-respiratory fitness (CRF) from CPX data [7]. In the NIEP group, the intensity of exercise was limited to Borg 11–13 by subjective sensation [7]. We compared the incidence of major cardiovascular events (MACE) between the two groups. IEP group were further divided into two subgroups based on prognosis status, namely the good prognosis (GP) group ($n = 88$) and the poor prognosis (PP) group ($n = 30$). By comparing the CRF between the two groups, we identify key CPX variables that may affect the prognosis of patients.

Quantification of CRF

To accurately quantify CRF, we used CPX which is a widely accepted evaluation tool in both the United States (US) and Europe[8, 9]. The measurement of ventilatory gas exchange was used for function-based prognostic stratification [9–11]. In the IEP group, oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (V_E), partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$), and respiratory exchange ratio (RER) were measured in standard exercise testing using Cardio-respiratory instrumentation Medisoft (MS, made in Belgium, SN:130619–05-1470, Model: E100000011000001). The exercise tolerance was estimated from bicycle cycle ergometer work rate. The use of CPX during progressive exercise (10 watts per minute) is based on measurement of exercise gas exchange. The exercise test was terminated if any of the following occurred: abnormal hemodynamic or ECG exercise response or other reasons (i.e., lower extremity muscle fatigue, angina and dyspnoea).

Clinical follow-up

Major adverse cardiac events (MACE) included cardiogenic death, re-hospitalization, heart failure, stroke, and atrial fibrillation. Follow-up data were collected through hospital records and telephone interviews which was conducted every 3 months after discharge until death or December 1, 2017, whichever came first. Mortality data for patients who were lost to telephone follow up were obtained from the population registry bureau. The average follow-up time was 2.5 years.

Statistical analysis

For continuous variables, depending on whether a variable follows a normal distribution, the mean or median was reported and the t-test or nonparametric Wilcoxon's rank sum test was applied for group comparison. The Chi-square tests were used for categorical variables. Multivariable logistic regression, in which we included age, cardiac function, test indices and variables showing a p-value< 0.05 in the univariate analysis, was used to identify independent risk factors for prognosis. The ROC curve was used to evaluate the predictive value of the model for MACE. All statistical analyses were done using SPSS 19 software (IBM Corp., Armonk, NY, USA).

Results

Incidence of major cardiovascular events

The patients' clinical data are shown in Table 2. No significant difference in demographics was found between the IEP group and the NIEP group.

The results of adverse events are shown in Table 3. There was no significant difference in the incidence of cardio-genetic death (3 vs. 18, $P = 0.442$), re-hospitalization (27 vs. 109, $P = 0.270$), heart failure (3 vs. 13, $P = 0.865$), stroke (1 vs. 10, $P = 0.429$), or atrial fibrillation (0 vs. 2, $P = 1.000$) between the IEP and the NIEP groups. But the incidence of total MACE was significantly lower in the IEP group than in the NIEP group (34 vs. 152, $P = 0.039$; Fig. 1).

The key CPX variables affecting prognosis

The clinical data of the patients in the IEP group are summarized in Table 4. No significant difference was found between the GP subgroup and the PP subgroup.

Table 2 Clinical data of the two study groups

	IEP group ($n = 118$)	NIEP group ($n = 381$)	P
Age, median (IQR)	57.0 (50.0, 62.3)	58.0 (51.0, 64.0)	0.363
Sex, male (%)	96 (81.4%)	291 (76.4%)	0.310
Extensive anterior wall MI (%)	27 (22.9%)	93 (24.4%)	0.830
Killip class ≥II (%)	17 (14.4%)	64 (18.6%)	0.640
Stenotic vessels ≥2 (%)	97 (82.2%)	337 (88.5%)	0.120
WBC (10^9/L), median (IQR)	9.2 (7.7, 11.0)	9.5 (7.3, 12.3)	0.396
HGB (g/L), median (IQR)	148.0 (137.3, 158.0)	144.0 (133.0, 154.0)	0.082
Cr (umol/L), median (IQR)	75.5 (64.3, 84.8)	72.6 (61.5, 86.7)	0.306
AST (U/L), median (IQR)	60.5 (28.5, 132.4)	66.1 (29.5, 147.7)	0.413
ALT (U/L), median (IQR)	38.2 (23.2, 59.1)	37.2 (22.8, 54.0)	0.393
TC (mmol/L), median (IQR)	4.5 (3.9, 5.0)	4.5 (3.8, 5.1)	0.915
HDL-C (mmol/L), median (IQR)	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)	0.054
LDL-C (mmol/L), median (IQR)	2.9 (2.4, 3.4)	2.8 (2.3, 3.3)	0.249
Fasting blood sugar (mmol/L), median (IQR)	6.1 (5.1, 7.3)	6.1 (5.1, 7.6)	0.526

IEP group Individualized exercise prescriptions group, *NIEP group* Non-individualized exercise prescriptions group, *extensive anterior wall MI* Extensive anterior wall myocardial infarction, *WBC* White blood cell, *HGB* Hemoglobin, *Cr* Creatinine, *AST* Glutamic pyruvic transaminase, *ALT* Glutamic pyruvic aminotransferase, *TC* Total cholesterol, *HDL-C* High density lipoprotein cholesterol, *LDL-C* Low density lipoprotein cholesterol, *IQR* Interquartile range

Table 3 Comparison of two groups of MACE (2 years)

	IEP group ($n = 118$)	NIEP group ($n = 381$)	P
Cardiogenic death, n (%)	3 (2.5%)	18 (4.7%)	0.442
Rehospitalization, n (%)	27 (22.9%)	109 (28.6%)	0.270
Heart failure, n (%)	3 (2.5%)	13 (3.4%)	0.865
Stroke, n (%)	1 (0.9%)	10 (2.6%)	0.429
Atrial fibrillation, n (%)	0 (0.0%)	2 (0.5%)	1.000
MACE, n (%)	34 (28.8%)	152 (39.9%)	0.039

IEP group Individualized exercise prescriptions group, *NIEP group* Non-individualized exercise prescriptions group, *MACE* Major cardiac events

The VO_2 at VT, E-VCO_2, $^{\triangle}CO_2$, R-$_{PET}CO_2$, E-$_{PET}CO_2$ and $^{\triangle}{}_{PET}CO_2$ were significantly higher in the GP subgroup than in the PP subgroup ($P = 0.006$, $P = 0.017$, $P = 0.018$, $P = 0.045$, $P = 0.005$ and $P = 0.022$, respectively; Table 5). The VE/VCO2 slope was significantly lower in the GP subgroup than in the PP subgroup ($P = 0.010$). There were no statistically significant differences in other parameters.

We found that VO_2 at VT, V_E/VCO_2 slope, E-VCO_2, $^{\triangle}CO_2$, R-$P_{ET}CO_2$, E-PETCO$_2$ and $^{\triangle}$PETCO$_2$ to be predictive of adverse events (the areas under the curve being 0.666, 0.658, 0.646, 0.636, 0.623, 0.670 and 0.638, respectively), and the optimal cut-off point was 10.5 ml/kg/min, 33.4, 0.635 L/min, 0.345 L/min, 30.5 mmHg, 32.5 mmHg, and 2.5 mmHg, respectively (Figs. 2 and 3, Table 6). The VO_2 at VT was an independent risk factor for cardiovascular disease prognosis (OR = 0.732, 95% CI: 0.541–0.988, $P = 0.042$; Table 7). The incidence of cardiogenetic death (0 vs. 3, $P = 0.037$), re-hospitalization (11 vs. 16, $P = 0.033$), and total MACE (13 vs. 21, $P = 0.005$) was significantly lower when the VO_2 at VT was greater than 10.5 ml/kg/min (Table 8, Fig. 4).

Discussion

This study found that individualized exercise prescription of Phase I cardiac rehabilitation reduced the incidence of cardiovascular events in patients with STEMI after PCI. The key CPX variables, including VO_2 at VT, V_E/VCO_2 slope, E-VCO_2, $^{\triangle}CO_2$, R-$_{PET}CO_2$, E- $_{PET}CO_2$ and $^{\triangle}{}_{PET}CO_2$ were predictive of these adverse events. Furthermore, the VO_2 at VT was an independent risk factor for prognosis of cardiovascular disease.

Cardiac rehabilitation is a comprehensive treatment program that includes multiple components such as drug therapy, smoking cessation, exercise, psychology and nutrition. Phase I cardiac rehabilitation is in-hospital rehabilitation, which involves educating patients to recognize disease, prevent disease, and self-management. It can improve the

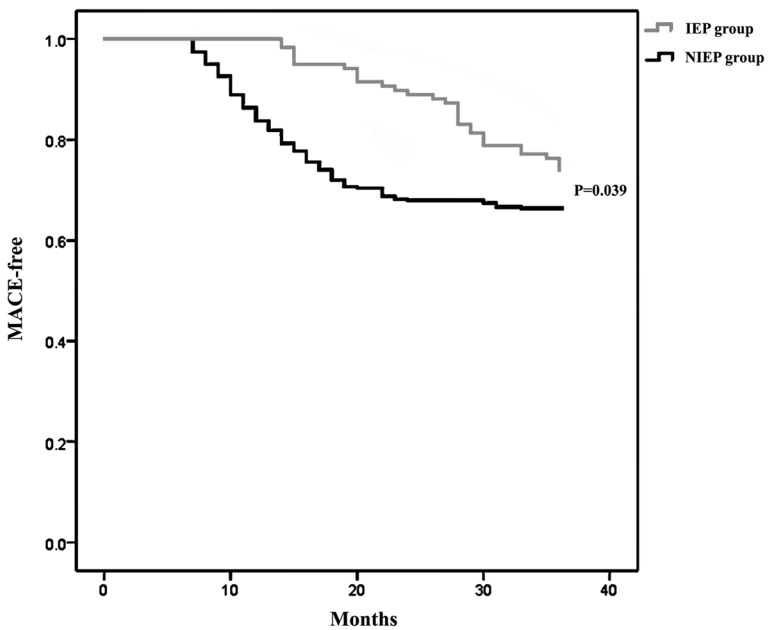

Fig. 1 The Kaplan-Mayer curves of MACE-free survival. IEP group: individualized exercise prescriptions group; NIEP group: non-individualized exercise prescriptions group; MACE: major cardiac events

Table 4 Clinical data of the patients in the PP and GP group

	PP group ($n = 30$)	GP group ($n = 88$)	P
Age (years)	57.9 ± 8.7	56.2 ± 9.8	0.379
Sex, male (%)	22 (73.3%)	75 (85.2%)	0.232
Extensive anterior wall MI(n)	9 (30.0%)	18 (20.5%)	0.410
Killip class ≥II (n)	6 (20.0%)	11 (12.5%)	0.478
Stenotic vessels ≥2 (n)	24 (80.0%)	73 (83.0%)	0.929
WBC(10^9/L), median (IQR)	8.8 (7.5, 12.0)	9.4 (7.8, 10.9)	0.800
HGB(g/L)	139.9 ± 20.7	147.4 ± 16.1	0.080
Cr (umol/L), median (IQR)	77.1 (69.7, 85.5)	75.4 (63.3, 85.0)	0.636
AST(U/L), median (IQR)	58.3 (26.6, 156.1)	60.5 (28.8, 113.2)	0.858
ALT(U/L), median (IQR)	41.3 (22.4, 64.1)	37.5 (22.6, 58.4)	0.807
TC (mmol/L), median (IQR)	4.5 (4.1, 4.7)	4.5 (3.9, 5.1)	0.961
HDL-C (mmol/L), median (IQR)	1.1 (0.9, 1.2)	1.0 (0.9, 1.3)	0.683
LDL-C (mmol/L), median (IQR)	2.7 (2.4, 3.1)	3.0 (2.4, 3.5)	0.232
Fasting blood sugar (mmol/L), median (IQR)	6.0 (5.0, 7.3)	6.1 (5.2, 7.6)	0.663

PP group Poor prognosis group, *GP group* Good prognosis group, *Extensive anterior wall MI* Extensive anterior wall myocardial infarction, *WBC* White blood cell, *HGB* Hemoglobin, *Cr* Creatinine, *AST* Glutamic pyruvic transaminase, *ALT* Glutamic pyruvic aminotransferase, *TC* Total cholesterol, *HDL-C* High density lipoprotein cholesterol, *LDL-C* Low density lipoprotein cholesterol, *IQR* Interquartile range

Table 5 Comparison of cardiopulmonary exercise test results of patients with different prognosis

	PP group ($n = 30$)	GP group ($n = 88$)	P
VO_2 at VT (ml/kg/min)	10.0 (8.8, 12.0)	12.0 (10.0, 14.0)	0.006
Ve/VCO_2 slope	36.0 (32.3, 43.9)	33.0 (30.2, 38.1)	0.010
R-HR (bpm)	74.5 (63.0, 89.0)	73.5 (68.0, 81.8)	0.889
R-VCO_2(L/min)	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)	0.602
R-Ve(L/min)	12.2 ± 2.3	12.2 ± 2.1	0.862
E-HR (bpm)	90.0 (80.8, 111.5)	95.0 (86.3, 103.8)	0.899
E-VCO_2(L/min)	0.6 ± 0.2	0.7 ± 0.2	0.017
E-Ve(L/min)	26.2 ± 6.1	27.2 ± 5.1	0.421
▵Ve(L/min)	14.0 (11.1, 15.8)	14.4 (11.9, 18.6)	0.311
R-$P_{ET}CO_2$ (mm Hg)	29.0 (26.0, 31.3)	31.0 (28.3, 33.0)	0.045
E-$P_{ET}CO_2$ (mm Hg)	32.0 (29.0, 35.0)	35.0 (32.0, 37.0)	0.005
▵PETCO2(mm Hg)	3.0 (2.0, 5.0)	4.0 (3.0, 6.0)	0.022
E-Ve/M (%)	26.0 (21.8, 28.3)	25.0 (22.3, 30.0)	0.843
▵CO2(L/min)	0.4 ± 0.1	0.5 ± 0.2	0.018

PP group Poor prognosis group, *GP group* Good prognosis group, *VO_2 at VT* Oxygen consumption per kilogram of weight per minute at anaerobic threshold, *Ve/VCO_2 slope* Minute ventilation/ Carbon dioxide production slope, *R-HR* Rest heart rate, *R-VCO_2* Rest carbon dioxide production, *R-Ve* Rest minute ventilation, *E-HR* Exercise heart rate, *E-VCO_2* Exercise carbon dioxide production, *E-Ve* Exercise minute ventilation, *▵Ve* Margin of minute ventilation, *R-$P_{ET}CO_2$* Rest partial pressure of end-tidal carbon dioxide, *E-$P_{ET}CO_2$* Exercise partial pressure of end-tidal carbon dioxide, *▵$P_{ET}CO_2$* Margin of partial pressure of end-tidal carbon dioxide, *E-Ve/M* Ratio of exercise minute ventilation to the maximum expected value, *▵CO_2* Margin of Minute ventilation carbon dioxide production

prognosis of patients with unstable angina, acute myocardial infarction and heart failure [10, 11]. A large cohort study found that, in patients with coronary heart disease after revascularization, postoperative cardiac rehabilitations significantly reduced the mortality rate 1–5 years after operation [12]. Our study extends the prior finding by showing that individualized exercise prescription of Phase I cardiac rehabilitation can improve the total MACE of patients than traditional Phase I cardiac rehabilitation. It is somehow disappointing that we did not find significant differences between IEP and NIEP groups, regarding incidence of cardio-genetic death, re-hospitalization, heart failure, stroke, or atrial fibrillation. The reasons are as follows: first, cardiac rehabilitation include patient education, nutrition guidance, medication guidance, smoking cessation and psychological prescription, etc. except for exercise prescription. It shows that other Phase I cardiac rehabilitation parts also plays an important role in cardio-genetic death, re-hospitalization, heart failure, stroke, or atrial fibrillation [13]. Second, our study showed that cardio-genetic death, re-hospitalization, and total MACE decrease significantly when the VO_2 at VT was greater than 10.5 ml/kg/min. Our results showed that pre-discharge cardiopulmonary fitness in Phase I cardiac rehabilitation could improve the long term prognosis of the STEMI patients. In addition, other study [14] also show that individualized exercise could not give any major advantage. These findings, taken together, suggest that individualized exercise prescription based on cardiopulmonary fitness was not only effective but also safe.

Exercise prescription guidance can be based on CPX or 6 min walk test (6MWT) [7]. This study adopted the CPX method, which was well recognized as the gold

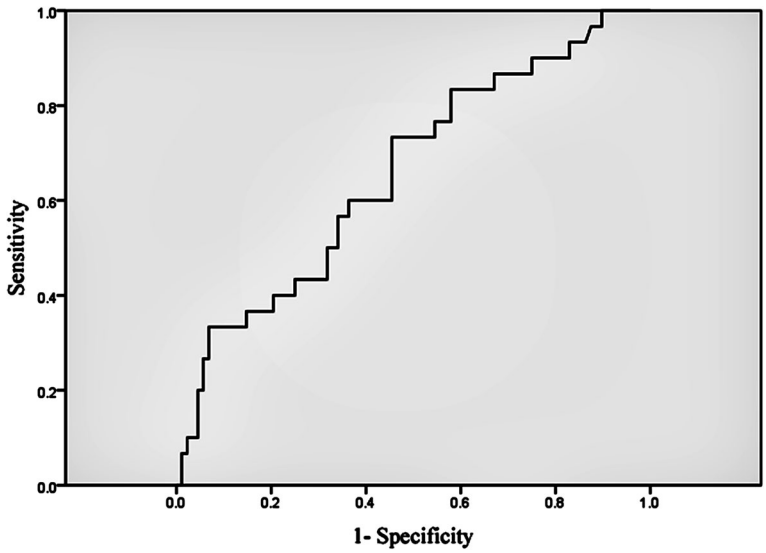

Fig. 2 The ROC curve of Ve/VCO_2 slope. Ve/VCO_2 slope: Slope for minute ventilation/carbon dioxide production

standard aerobic exercise assessment. The use of CRF has many utilizations in clinical, including measuring therapy progress and diagnosis. Although exercise tolerance normally came from the measurement of bicycle cycle ergometer work rate or treadmill, CPX is a more accurate tool to measure CRF. The measurement of CPX depends on the exchange of gases throughout exercise. CPX has got recognition not only it can give accurate measurement of patients with cardiovascular and pulmonary disease, but also it was easier to use because of technological progress, rapid response analyzers and computer-assisted data processing [7]. The 2016 EACPR/AHA scientific statement has indicated that peak VO_2, VO_2 at VT, and the minute ventilation/carbon dioxide production (V_E/VCO_2) relationship (V_E/VCO_2 slope) have prognostic significance [15].

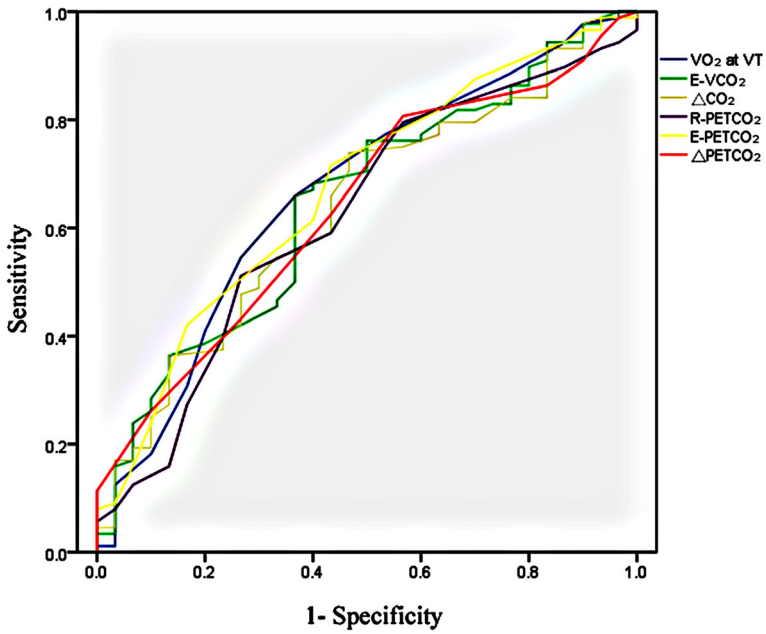

Fig. 3 The ROC curve of VO_2 at VT, E-VCO_2, $^{\triangle}CO_2$, R-$PETCO_2$, E-$PETCO_2$, and $^{\triangle}PETCO_2$. VO_2 at VT: Oxygen consumption per kilogram of weight per minute at anaerobic threshold; E-VCO_2: Exercise carbon dioxide production; $^{\triangle}CO_2$: Margin of Minute ventilation carbon dioxide production; R-$P_{ET}CO_2$: Rest partial pressure of end-tidal carbon dioxide; E-$P_{ET}CO_2$: Exercise partial pressure of end-tidal carbon dioxide; $^{\triangle}P_{ET}CO_2$: Margin of partial pressure of end-tidal carbon dioxide

Table 6 Optimal cut-off points and related diagnostic value by ROC analysis

	Cut-off point	Sensitivity	Specificity	AUC	*P*
VO_2 at VT (ml/kg/min)	10.5	0.659	0.633	0.666	0.007
Ve/VCO_2 slope	33.4	0.733	0.545	0.658	0.001
E-VCO_2(L/min)	0.6	0.659	0.633	0.646	0.017
R-$P_{ET}CO_2$ (mm Hg)	30.5	0.511	0.733	0.623	0.046
E-$P_{ET}CO_2$ (mm Hg)	32.5	0.716	0.567	0.67	0.005
$^{\triangle}P_{ET}CO_2$(mm Hg)	2.5	0.807	0.433	0.638	0.024
$^{\triangle}CO_2$(L/min)	0.3	0.739	0.533	0.636	0.027

VO_2 at VT Oxygen consumption per kilogram of weight per minute at anaerobic threshold, *Ve/VCO_2 slope* Minute ventilation/ Carbon dioxide production slope, *E-VCO_2* Exercise carbon dioxide production, *R-$P_{ET}CO_2$* Rest partial pressure of end-tidal carbon dioxide, *E-$P_{ET}CO_2$* Exercise partial pressure of end-tidal carbon dioxide, *$^{\triangle}P_{ET}CO_2$* Margin of partial pressure of end-tidal carbon dioxide, *$^{\triangle}CO_2$* Margin of minute ventilation carbon dioxide production, *AUC* Area under the curve

Table 7 Results of logistic regression

	OR	95% CI	*P*
Age	1.013	0.952–1.077	0.688
Sex, male	2.277	0.302–17.153	0.425
Extensive anterior wall MI	2.300	0.656–8.068	0.193
Killip class ≥II	1.189	0.247–5.730	0.829
Stenotic vessels ≥2	0.605	0.148–2.471	0.484
WBC	0.993	0.813–1.214	0.945
HGB	1.001	0.958–1.046	0.964
Cr	1.000	0.983–1.017	0.988
AST	1.000	0.996–1.005	0.863
ALT	1.002	0.996–1.009	0.489
TC	1.433	0.736–2.787	0.290
HDL-C	0.803	0.385–1.674	0.558
LDL-C	0.487	0.212–1.118	0.090
Fasting blood sugar	0.910	0.702–1.179	0.476
VO_2 at VT	0.732	0.541–0.988	0.042
Ve/VCO_2 slope	0.903	0.744–1.096	0.302
R-HR	0.944	0.878–1.015	0.120
R-VCO_2	1.8E+ 09	0.000–1.3E+ 22	0.158
R-Ve	0.650	0.298–1.417	0.279
E-HR	1.050	0.982–1.122	0.153
E-VCO_2	0.000	0.000–1.9E+ 03	0.221
E-Ve	1.543	0.864–2.755	0.142
R-$P_{ET}CO_2$	0.955	0.634–1.438	0.825
E-$P_{ET}CO_2$	0.922	0.573–1.484	0.739
E-Ve/M	0.936	0.813–1.078	0.359

Extensive anterior wall MI Extensive anterior wall myocardial infarction, *WBC* White blood cell, *HGB* Hemoglobin, *Cr* Creatinine, *AST* Glutamic pyruvic transaminase, *ALT* Glutamic pyruvic aminotransferase, *TC* Total cholesterol, *HDL-C* High density lipoprotein cholesterol, *LDL-C* Low density lipoprotein cholesterol, *VO_2 at VT* Oxygen consumption per kilogram of weight per minute at anaerobic threshold, *Ve/VCO_2 slope* Minute ventilation/ carbon dioxide production slope, *R-HR* Rest heart rate, *R-VCO_2* Rest carbon dioxide production, *R-Ve* Rest minute ventilation, *E-HR* Exercise heart rate, *E-VCO_2* Exercise carbon dioxide production, *E-Ve* Exercise minute ventilation, *R-$P_{ET}CO_2$* Rest partial pressure of end-tidal carbon dioxide, *E-$P_{ET}CO_2$* Exercise partial pressure of end-tidal carbon dioxide, *E-Ve/M* Ratio of exercise minute ventilation to the maximum expected value, *OR* Odds ratio, *CI* Confidence interval

Peak VO2 is defined as the highest O_2 uptake obtained during exercise. Its response is resulting from central and peripheral functions, and widely indicates disease seriousness. Lots of studies have demonstrated that non-invasively determined peak cardiac output was regarded as a separate predictor of outcomes that improves the prognostic benefit of Peak VO_2 [16–19]. Present evidence shows that if predicted peak VO_2 value is below 50%, patients with heart failure (HF) have a poor prognosis in [20]. The prognostic value of VO_2 at VT has been regarded to be a significant prognostic marker when evaluating pre-surgical risk using CPX [21, 22]. Importantly, an accurate and predictable recognition of VO_2 at VT is not always possible which has been shown in patients with HF. If VO_2 at VT is not predictable, the validity of the CPX should be accepted by providing that the subject attempt to reach an acceptable level (i.e., peak respiratory exchange ratio ≥ 1.00). The present study only uses this index to formulate exercise prescriptions. While the 2016 AHA guide pointed out that VO_2 at VT is an independent risk factor for the prognosis of postoperative patients, it did not mention the implication of the index in STEMI patients.

In this study, we found that VO_2 at VT is positively correlated with the prognosis of STEMI patients such that patients with VO_2 at VT < 10.5 had poor cardiovascular prognosis. Therefore, VO_2 at VT can be used as an important evaluation index of Phase I cardiac rehabilitation. It is safe and effective to formulate exercise prescription according to blood pressure, heart rate and watt under VO_2 at VT. Large-scale randomized controlled trials are needed to confirm this.

V_E/VCO_2 slope represents matching of ventilation and perfusion within the pulmonary system, and broadly reflects disease severity as well as prognosis in several patient populations including HF, hypertrophic cardiomyopathy (HCM), pulmonary arterial hypertension (PAH)/secondary pulmonary hypertension (PH), chronic obstructive pulmonary disease (COPD), and interstitial lung Disease (ILD). A VE/V_{CO2} slope < 30 is considered normal while slight

Table 8 Comparison of MACE by the cut-off points of VO_2 at VT (2 years)

	> 10.5 ml/kg/min (*n* = 69)	≤ 10.5 ml/kg/min (*n* = 49)	*P*
Cardiogenic death, n (%)	0 (0.0%)	3 (6.1%)	0.037
Rehospitalization, n (%)	11 (15.9%)	16 (32.7%)	0.033
Heart failure, n (%)	1 (1.4%)	2 (4.1%)	0.371
Stroke, n (%)	1 (1.4%)	0 (0.0%)	0.397
Atrial fibrillation, n (%)	0 (0.0%)	0 (0.0%)	1.000
MACE, n (%)	13 (18.8%)	21 (42.9%)	0.005

VO_2 at VT Oxygen consumption per kilogram of weight per minute at anaerobic threshold, *MACE* Major cardiac events

increase is possible with advanced age [7]. The index is usually used to assess the efficiency of ventilation, and involves in detecting high pulmonary pressures [23, 24]. Because pulmonary hypertension is often a consequence of left-sided valvular heart disease [25], the estimate of the V_E/VCO_2 slope may be particularly helpful. In many asymptomatic patients with severe aortic stenosis, it was found that elevated V_E/VCO_2 slope could be a significant predictor of decompensated HF or mortality [26]. Studies also showed that measures of ventilator efficiency, specifically the V_E/VCO_2 slope and $P_{ET}CO_2$, may be valuable in patients with HCM as these measures are implicated in increased pulmonary pressures [27, 28]. In this study, we found that V_E/VCO_2 slope was also a predictor of prognosis in STEMI patients after PCI, with a cut-off point value of 33.4, suggesting that patients with VE/VCO_2 slope over 33.4 tended to have poorer prognosis. Impaired cardiac output leads to decreased aerobic metabolism, increased anaerobic metabolism, and decreased VCO_2 emissions, which may result in increased VE/VCO_2 slope.

In all the CPX variables in patients with systolic HF, peak VO_2 and the V_E/VCO_2 slope have been shown stable separate prognostic significance. While V_E/VCO_2 slope is a stronger predictive marker in the univariate model compared with peak VO_2, there is strong evidence that indicates that a multivariate approach may improve prognostic accuracy [7]. With current healthy management strategies, a VE/VCO_2 slope ≥ 45, and a peak VO_2/ kg/ min < 10.0 ml are indicative of poorer prognosis over a 4-year period following CPX [27]. In this study, likely because all the patients had acute STEMI, and most of them did not have respiratory dysfunction, the cut-off point of V_E/VCO_2 slope differed, but the cut-off point of VO_2/kg/min was the same as the study of Arena, R. et al. [27].

As V_E/VCO_2 slope, $P_{ET}CO_2$ widely reflects disease severity in lots of patient with HF, HCM, PAH/secondary PH, COPD, and ILD. Both exercise oscillatory ventilation and $P_{ET}CO_2$ during rest and exercise have been shown to be of prognostic value in patients with systolic

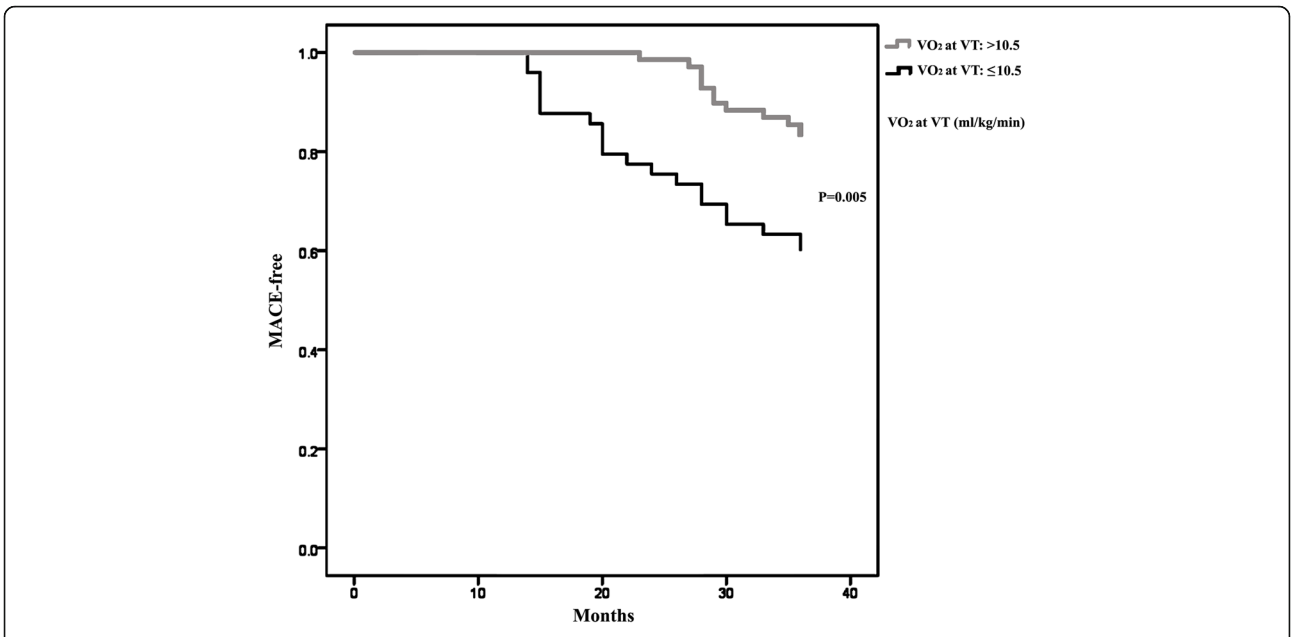

Fig. 4 The Kaplan-Mayer curves of MACE-free survival. VO_2 at VT: Oxygen consumption per kilogram of weight per minute at anaerobic threshold, MACE: major cardiac events

HF [29, 30]. Abnormalities in the V_E/VCO_2 slope and $P_{ET}CO_2$ have been thought to be pulmonary vasculopathy. We found that $P_{ET}CO_2$ was also a predictor of the prognosis of patients with STEMI after PCI, such that increased $P_{ET}CO_2$ was associated with a better prognosis. The difference in the heart function in the quiet/movement and $P_{ET}CO_2$ might be due to difference in infarct area of the patients.

Conclusion

This study found that individualized exercise prescription of Phase I cardiac rehabilitation reduced the incidence of cardiovascular events in patients with STEMI after PCI, and long term prognosis of patients based on their pre-discharge cardiopulmonary fitness. The key CPX variables, including VO_2 at VT, V_E/VCO_2 slope, E-VCO_2, $^{\triangle}CO_2$, R-$P_{ET}CO_2$, E-$P_{ET}CO_2$ and $^{\triangle}P_{ET}CO_2$, are predictive of MACE. VO_2 at VT was an independent risk factor for cardiovascular disease prognosis and could be used as an important evaluating indicator for Phase I cardiac rehabilitation. Future studies with larger sample sizes are warranted to validate these findings.

Abbreviations

$^{\triangle}CO_2$: Margin of minute ventilation carbon dioxide production; $^{\triangle}P_{ET}CO_2$: Margin of partial pressure of end-tidal carbon dioxide; 6MWT: 6 min walk test; AHA: American Heart Association; ALT: Glutamic pyruvic aminotransferase; AST: Glutamic pyruvic transaminase; COPD: Chronic obstructive pulmonary disease; CPX: Cardio-pulmonary exercise testing; CR: Cardiac rehabilitation; Cr: Creatinine; CRF: Cardio-respiratory fitness; E-VCO_2: Exercise carbon dioxide production; GP: Good prognosis; HCM: Hypertrophic cardiomyopathy; HDL-C: High-density lipoprotein cholesterol; HF: Heart failure; HGB: Hemoglobin; IEP: Individualized exercise prescriptions; ILD: Interstitial lung disease; LDL-C: Low-density lipoprotein cholesterol; MACE: Major adverse cardiac events; NIEP: Non-individualized exercise prescriptions; PAH: Pulmonary arterial hypertension; PCI: Percutaneous coronary intervention; $P_{ET}CO_2$: Exercise partial pressure of end-tidal carbon dioxide; $P_{ET}CO_2$: Partial pressure of end-tidal carbon dioxide; $P_{ET}CO_2$: Rest partial pressure of end-tidal carbon dioxide; PH: Pulmonary hypertension; PP: Poor prognosis; RER: Respiratory exchange ratio; STEMI: ST-segment elevation myocardial infarction; TC: Total cholesterol; VCO_2: Carbon dioxide production; V_E: Minute ventilation; V_E/VCO_2 slope: Slope for minute ventilation/carbon dioxide production; VO_2 at VT: Oxygen consumption per kilogram of weight per minute at anaerobic threshold; VO_2: Oxygen consumption; VT: Ventilation threshold; WBC: White blood cell

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Authors' contributions

PC and YZ conceived and designed the study. HC, ZL, XZ, RL, WS, LW and LZ performed the experiments and statistical analysis. HC wrote the paper. PC and YZ reviewed and edited the manuscript. All authors read and approved the manuscript.

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval and consent to participate

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests, and all authors should confirm its accuracy.

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