Evaluating exercise limitation, gas exchange inefficiency and recurrence risk in PE patients by cardiopulmonary exercise testing

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Abstract

Background

Pulmonary embolism (PE) which is a form of venous thromboembolism (VTE) can induce acute symptoms and post-PE syndrome. Cardiopulmonary exercise testing (CPET) can evaluate exercise responses of multiple systems, including respiratory, cardiovascular, hematopoietic and skeletal muscle systems.

Methods

We retrospectively collected 103 subjects' data of demographics, hematologics, CT pulmonary angiogram (CTPA), pulmonary function test (PFT) and CPET at Shanghai Pulmonary Hospital from March 2015 to October 2021. The 103 subjects were composed of 10 healthy people as control, 25 patients who had been diagnosed with PE and 68 patients who were diagnosed with PE. The CPET performance differences of the three groups of subjects and subgroups of PE patients divided according to CTPA were analyzed. Spearman correlation test was performed to analyze the correlation between CPET and Blood test parameters of the enrolled subjects. Univariate logistic regression analysis, multivariable cox regression analysis and Kaplan–Meier cumulative survival analysis was used to find CPET parameters for predicting the risk of PE recurrence.

Results

The exercise tolerance (load @ peak), metabolic capacity (VO_2 @ AT, VO_2 @ Peak), ventilatory efficiency (VE/VCO_2 @ AT, VE/VCO_2 @ Peak, OUEP, LOWEST VE/VCO_2), gas exchange ($PETCO_2$ @ AT, $PETCO_2$ @ Peak, $PETO_2$ @ AT), and cardiovascular response (VO_2/HR) of healthy people, Post-PE and PE subjects were different. The ventilatory efficiency (VE/VO_2 , VE/VCO_2 , LOWEST VE/VCO_2 , OUEP, VE/VCO_2 slope), gas exchange ($PETO_2$, $PETCO_2$) of PE subgroups divided according to CTPA were also different. VO_2 @ AT (% pred) can be used to predict the risk of PE recurrence.

Conclusion

CPET is an effective and responsible method for the assessment of pulmonary embolism.

Background

PE is the most serious form of VTE and can be life-threatening. The acute symptoms induced by emboli include dyspnea, chest pain, syncope and shock[1]. Survivors of PE may develop long-term sequelae called post-PE syndrome. Post-PE syndrome is characterized by persistent dyspnea, exercise limitation, decreased quality of life and even chronic thromboembolic pulmonary hypertension (CTEPH)[2].

CPET is a kind of exercise test that can measure subjects' exercise ability and evaluate the respiratory, circulatory and skeletal muscle systems. It is widely applied in the evaluation of exercise intolerance, unexplained dyspnea, cardiovascular disease, respiratory disease, pulmonary rehabilitation and preoperative evaluation. It has attracted great attention in clinical and scientific research work for its unique excellence[3].

Thus, in this study we used a combination of CTPA and CPET methods to evaluate PE patients. It aimed to explore whether CPET is an effective and responsible method for the assessment of PE.

Methods

Patients

This study retrospectively enrolled 103 subjects who were referred to Shanghai Pulmonary Hospital from March 2015 to October 2021. Among them, 10 subjects were healthy people, 25 patients had been diagnosed with PE within one year but with normal CTPA now (Post-PE) and 68 patients were diagnosed with PE with abnormal CTPA now (PE). The diagnosis of PE in this study was referred to the 2019 ESC guidelines. Patients were excluded from study if they had any evidence of the following: serious heart, lung, circulatory disease or history of pulmonary malignant tumor surgery. Enrolled subjects' data including demographics, hematologics, CTPA, PFT and CPET were collected.

Ethical approval by the medical ethics committee of Shanghai Pulmonary Hospital was obtained. The study protocol was reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital. Written informed consent was obtained from each patient for inclusion into the study prior to the performance of any study-related procedures. All methods including CPET, PFT, CTPA and blood test were carried out in accordance with relevant guidelines and regulations.

CPET

CPET was performed on an electromagnetically braked cycle ergometer (Master Screen CPX, Jaeger corp, Hoechstberg, Germany) to record gas exchange data over 10-s intervals by using a breath-by-breath system. The protocol was consisted of the rest phase of 3 minutes, the unloaded phase of 3 minutes, the incremental phase, and the recovery phase of 5 minutes. The patients were instructed to pedal at 55-60 revolutions/min in the unloaded and the incremental phase, and once they reached their limit, entered the recovery phase. Patients could quit at any time if they developed fatigue, dyspnea, chest tightness or any

other discomfort during the process. There were three ramp increments models that we used in the incremental phase: 10 W/min, 15 W/min and 20 W/min. We would choose an appropriate model according to the patient's clinical condition and PFT result.

Measurements including load, minute ventilation (VE), carbon dioxide output (VCO₂), oxygen uptake (VO₂), oxygen pulse (VO₂/HR), end-tidal partial pressure for carbon dioxide (PETCO₂), end-tidal partial pressure for oxygen (PETO₂), heart rate (HR), respiratory exchange ratio (RER) and breathing frequency (BF) were recorded and calculated. Anaerobic threshold (AT) which represents the beginning of anaerobic metabolism was determined by the V-slope method and was independently defined by two experienced investigators who have been engaged in clinical and scientific research on CPET for several years. VE/VCO₂ slope was obtained by linear regression analysis of the relation between VE and VCO₂. Oxygen uptake efficiency slope (OUES) was computed by linear square regression from the oxygen uptake on the logarithm of the minute ventilation according to the following equation: $VO_2 = a \cdot \lg VE + b$. Constant "a" is called the OUES. Oxygen uptake efficiency plateau (OUEP) was at 90 seconds of the highest consecutive values for VO₂ (mL/min)/VE (L/min).

PFT

Spirometry and body plethysmography were performed on each patient using standard equipment (Masterscreen-PFT, Jaeger corp, Hoechberg, Germany; Masterscreen-plethysmography, Jaeger corp, Hoechberg, Germany). Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), residual volume (RV), total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLCO) were determined by standard procedures. For each patient, data were presented in absolute terms and normalized to percentage of normal predicted (% Pred). All measurements were calculated using accepted equations for Chinese adults.

CTPA image analysis

CTPA images were assessed by two experienced radiologists who have been engaged in clinical and scientific research on CTPA for several years. Divergent opinions concerning the emboli in the specific arteries were settled by inviting a third party. The emboli were assessed by the Mastora and Qanadli scoring systems to calculate the obstruction index[4, 5]. The emboli position was also assessed as two types: central type and peripheral type.

Statistical analysis

Data were analyzed by using SPSS 22.0 and GraphPad Prism 6. The data were presented as mean ± SD, median (interquartile range), or n. Unpaired t test, Mann-Whitney U test, one-way ANOVA test, Kruskal-Wallis test, chi-square test, spearman correlation test, univariate logistic regression analysis, multivariable Cox regression analysis and Kaplan–Meier cumulative survival analysis were used according to the corresponding situation. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Characteristics of the subjects

10 healthy people and 93 patients were involved in the study. 93 patients were divided into "PE" and "Post-PE" group according to the CTPA results: 25 patients had been diagnosed with PE within one year but with normal CTPA now (Post-PE) and 68 patients were diagnosed with PE with abnormal CTPA now (PE). The characteristics of all groups were summarized in Table 1. Some blood test parameters and PFT parameters were statistically different between "PE" and "Post-PE" group.

Table 1
Characteristics of the enrolled subjects.

Variables	Control	Post-PE	PE	P
<i>Clinical characteristics</i>				
Age (years)	56.7 ± 10.7	57.2 ± 13.4	57.1 ± 14.4	0.995
Sex, n (female/male)	10(6/4)	25(14/11)	68(32/36)	0.611
Body mass index (kg/m ²)	25.5 ± 3.2	24.9 ± 3.44	26.3 ± 3.5	0.084
<i>Blood test parameters</i>				
NT-ProBNP (pg/mL)		64.4 (27.9, 119.7)	69.0 (34.4, 115.7)	0.677
DD (ng/mL)		237.8(121.0, 363.1)	320.0(176.8, 730.3)	0.047
Plt (x10 ⁹ /L)		206.0 (180.0, 237.0)	213.5 (177.0, 273.3)	0.378
MPV (fL)		10.9 (10.5,11.5)	10.2 (9.8,11.2)	0.012
PDW (%)		13.1 (11.6,14.3)	11.9 (11.1,13.4)	0.080
Pct (%)		0.23 (0.20, 0.26)	0.23 (0.18, 0.27)	0.923
PLCR (%)		26.5 (23.3, 33.5)	31.3 (28, 37.3)	0.030
<i>PFT parameters</i>				
FVC (L)		3.0 ± 0.9	3.0 ± 0.9	0.774
FVC (% Pred)		92.5 ± 17.6	84.7 ± 13.7	0.028
FEV1 (L)		2.5 ± 0.8	2.4 ± 0.7	0.463
FEV1 (% Pred)		94.8 ± 17.0	84.5 ± 14.0	0.004
FEV1/FVC (%)		83.3 ± 7.6	80.6 ± 6.1	0.083
RV (L)		2.2 ± 0.6	2.3 ± 0.7	0.582
RV (% Pred)		117.7 ± 24.4	115.1 ± 27.0	0.674
TLC (L)		5.1 ± 1.2	5.2 ± 1.3	0.695
TLC (% Pred)		99.9 ± 15.5	96.0 ± 14.2	0.261
RV/TLC (%)		43.3 ± 9.0	43.7 ± 9.6	0.850
SB DLCO (% Pred)		92.9 ± 16.6	89.2 ± 18.8	0.389
<i>CTPA parameters</i>				
Central type (n)			40	
Peripheral type (n)			28	
Qanadli (%)			16.40 ± 14.08	
Mastora (%)			14.37 ± 13.88	
PA diameter (cm)			3.19 ± 0.49	
The data are presented as mean ± SD, median (interquartile range), or n. Statistical analysis of characteristics of "Post-PE", "PE" and "Control" was analyzed with One-way ANOVA test, Kruskal-Wallis test or chi-square test, and was presented as "P". PE = pulmonary embolism; BNP = brain natriuretic peptide; DD = D-dimer; Plt = platelet; MPV = mean platelet volume; PDW = platelet distribution width; Pct = plateletcrit; PLCR = platelet-larger cell ratio; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1s; RV = residual volume; TLC = total lung capacity; SB DLCO = carbon monoxide diffusing capacity; mRVd/mLvd = the ratio of right to left ventricular transverse diameter; mRVa/mLVa = the ratio of right ventricular area to that of left ventricular area; PA diameter = pulmonary artery diameter.				

The "PE" group had the higher value of DD (ng/mL) (320.0 (176.8, 730.3)) when compared with the "Post-PE" group (237.8 (121.0, 363.1)). The values of MPV (fL) and PLCR (%) of "PE" and "Post-PE" group were statistically different (10.2 (9.8,11.2) vs. 10.9 (10.5,11.5); $P=0.012$) (31.3 (28, 37.3) vs. 26.5 (23.3, 33.5); $P=0.030$).

Additionally, the values of FVC (% Pred) and FEV1 (% Pred) of the "PE" and "Post-PE" group were also statistically different (84.7 ± 13.7 vs. 92.5 ± 17.6; $P=0.028$) (84.5 ± 14.0 vs. 94.8 ± 17.0; $P=0.004$).

CPET performance differences in the subjects

15 parameters were found to be statistically different between “PE”, “Post-PE” and “Control” group. They were listed as followed : load @ AT (W), load @ peak (W), VO₂ @ AT (mL/kg/min), VO₂ @ peak (mL/kg/min), VO₂ @ AT (% pred), VO₂ @ peak (% pred), VO₂/HR @ AT (mL), VE/VCO₂ @ AT, VE/VCO₂ @ peak, VE/VO₂ @ AT, PETCO₂ @ AT (mm Hg), PETCO₂ @ peak (mm Hg), PETO₂ @ AT (mm Hg), OUEP (mL/L) and LOWEST VE/VCO₂. Details were listed in Table 2. The “PE” group were further divided into subgroups according to the emboli position, mastroa index and PA diameter (Table 4).

Table 2
Comparison of the CPET parameters of the enrolled subjects.

Variables	Rest				AT				Peak		
	Control	Post-PE	PE	<i>P</i>	Control	Post-PE	PE	<i>P</i>	Control	Post-PE	PE
Load (W)					70.5 (46,84)	48 (39,66)	48 (36,54)	0.015	116.3 (101.5,173)	99.3 (71.7,115.7)	86.33 (71.33,119.9)
HR	75.7 ± 8.3	77.7 ± 12.1	79.5 ± 10.2	0.481	105.5 ± 15.4	106.8 ± 19.3	103.3 ± 15.3	0.643	146.2 ± 19.6	136.6 ± 26.2	127.9 ± 24.6
VO ₂ (mL/kg/min)	4.1 ± 0.6	4.1 ± 0.8	4.0 ± 0.7	0.947	14.4 ± 2.8	11.4 ± 2.5	10.6 ± 2.4	< 0.001	21.7 ± 4.7	17.2 ± 4.4	15.5 ± 4.0
VO ₂ (% pred)	17.0 ± 5.7	16.1 ± 4.6	15.1 ± 3.7	0.320	59.8 ± 18.2	45.2 ± 13.3	39.7 ± 9.7	< 0.001	87.5 ± 19.5	66.3 ± 15.2	57.5 ± 13.9
VO ₂ /HR (mL)	3.8 ± 1.0	3.5 ± 1.0	3.7 ± 0.8	0.652	9.7 ± 2.2	7.2 ± 1.8	7.5 ± 1.8	0.001	10.6 ± 3.3	8.4 ± 2.5	8.9 ± 2.4
VE (L/min)	10.7 ± 2.5	10.2 ± 3.0	11.5 ± 2.6	0.113	28.7 ± 6.7	23.5 ± 5.9	25.6 ± 6.2	0.077	58.2 ± 17.1	42.5 ± 12.2	44.6 ± 15.1
RER	0.84 ± 0.07	0.84 ± 0.08	0.86 ± 0.08	0.498	0.88 ± 0.06	0.92 ± 0.06	0.92 ± 0.07	0.139	1.22 ± 0.12	1.17 ± 0.13	1.13 ± 0.13
VE/VCO ₂	45.2 ± 6.4	45.3 ± 5.3	46.8 ± 6.1	0.463	32.8 ± 3.4	34.5 ± 5.1	37.0 ± 5.1	0.012	31.5 ± 3.3	32.8 ± 4.8	35.7 ± 5.6
VE/VO ₂	38.0 ± 6.3	38.3 ± 5.9	40.4 ± 6.0	0.231	28.7 ± 4.0	31.8 ± 5.5	34.1 ± 6.0	0.012	38.4 ± 5.0	38.2 ± 6.9	40.2 ± 7.7
PETCO ₂ (mm Hg)	32.9 ± 4.8	32.5 ± 2.8	31.3 ± 3.2	0.181	39.5 ± 5.6	38.5 ± 4.7	35.4 ± 4.3	0.002	38.7 ± 5.6	37.6 ± 5.1	35.0 ± 4.8
PETO ₂ (mm Hg)	112.5 ± 4.6	112.7 ± 4.4	114.9 ± 4.6	0.068	106.9 ± 6.2	108.4 ± 6.4	112.0 ± 5.9	0.007	117.5 ± 3.7	116.3 ± 6.0	117.7 ± 6.0
	Control	PEH	PE	<i>P</i>							
OUES(L/min/log(L/min))	1.9 ± 0.4	1.6 ± 0.4	1.7 ± 0.4	0.222							
OUEP (mL/L)	35.9 ± 4.3	32.5 ± 4.7	31.2 ± 4.7	0.012							
VE/VCO ₂ slope	28.7 ± 3.8	29.5 ± 5.6	31.7 ± 5.5	0.091							
LOWEST VE/VCO ₂	30.6 ± 3.3	32.0 ± 4.6	34.5 ± 4.6	0.007							
The data are presented as mean ± SD, median (interquartile range), or n. Statistical analysis of characteristics of “PEH”, “PE” and “Control” was analyzed with way ANOVA test, Kruskal-Wallis test or chi-square test, and was presented as “ <i>P</i> ”. PE = pulmonary embolism; VO ₂ = oxygen uptake; HR = heart rate; VE = minut ventilation; BR = breathing reserve; RER = respiratory exchange ratio; VCO ₂ = carbon dioxide output; PETCO ₂ = end-tidal partial pressure for carbon dioxide; PETO ₂ = end-tidal partial pressure for oxygen; OUES = oxygen uptake efficiency slope; OUEP = oxygen uptake efficiency plateau.											

Table 3
Correlation analysis between CPET and Blood test parameters of the Post-PE and PE subjects.

Variables	NT-proBNP (pg/mL)		DD (ng/mL)		MPV (fL)		PLCR (%)	
	r	P	r	P	r	P	r	P
VO ₂ @ Rest (% pred)					0.207	0.047		
VE/VCO ₂ @ Rest (mm Hg)	0.250	0.016						
VE/VO ₂ @ Rest (mm Hg)	0.252	0.015	0.209	0.044				
PETCO ₂ @ Rest (mm Hg)	-0.351	0.001						
PETO ₂ @ Rest (mm Hg)	0.300	0.003	0.205	0.049				
VE @ AT (L/min)	0.280	0.007						
VO ₂ @ AT (% pred)					0.304	0.003	0.290	0.005
VE/VCO ₂ @ AT (mm Hg)	0.475	< 0.001	0.213	0.041				
VE/VO ₂ @ AT (mm Hg)	0.408	< 0.001						
PETCO ₂ @ AT (mm Hg)	-0.426	< 0.001	-0.277	0.007				
PETO ₂ @ AT (mm Hg)	0.389	< 0.001						
VE @ Peak (L/min)			0.222	0.032				
VE/VCO ₂ @ Peak (mm Hg)	0.479	< 0.001	0.364	< 0.001				
VE/VO ₂ @ Peak (mm Hg)	0.289	0.005	0.413	< 0.001				
PETCO ₂ @ Peak (mm Hg)	-0.406	< 0.001	-0.370	< 0.001				
PETO ₂ @ Peak (mm Hg)	0.297	0.004	0.292	0.005				
OUPE (mL/L)	-0.359	< 0.001						
VE/VCO ₂ slope	0.551	< 0.001	0.287	0.005				
LOWEST VE/VCO ₂	0.502	< 0.001	0.247	0.017				
Statistical analysis of the correlation between CPET parameters and Blood test parameters was analyzed with Spearman rank correlation, and was presented as "r" and "P". PE = pulmonary embolism; BNP = brain natriuretic peptide; DD = D-dimer; MPV = mean platelet volume; VO ₂ = oxygen uptake; VE = minute ventilation; VCO ₂ = carbon dioxide output; PETCO ₂ = end-tidal partial pressure for carbon dioxide; PETO ₂ = end-tidal partial pressure for oxygen; OUPE = oxygen uptake efficiency plateau.								

Table 4
Comparison of the CPET and Blood test parameters of the PE subjects.

Variables	Emboli position			Mastora index			PA diameter		
	Central	Peripheral	<i>P</i>	Grade 1	Grade 2/3	<i>P</i>	Normal	Abnormal	<i>P</i>
Number	40	28		54	11/3		21	47	
NT-ProBNP (pg/mL)				58.8 (30.0,100.4)	110.8 (79.3,192.2)	0.010	47 (28.7,85.5)	83 (41,143)	0.039
DD (ng/mL)				272.5 (172.7,520.9)	769.6 (188.8,2077)	0.033			
VO ₂ @ Rest (mL/kg/min)							4.3 ± 0.8	3.9 ± 0.7	0.015
VE/VCO ₂ @ Rest (mm Hg)	49.0 ± 5.9	43.7 ± 5.1	<0.001						
VE/VO ₂ @ Rest (mm Hg)	42.2 ± 6.1	37.7 ± 5.0	0.002						
PETCO ₂ @ Rest (mm Hg)	30.7 ± 3.5	32.3 ± 2.4	0.025						
VE/VCO ₂ @ AT (mm Hg)				36.1 ± 4.0	40.4 ± 7.3	0.005			
VE/VO ₂ @ AT (mm Hg)				33.3 ± 5.0	37.4 ± 8.0	0.020	32.6 ± 6.8	34.8 ± 5.5	0.043
PETCO ₂ @ AT (mm Hg)				36.2 ± 3.8	32.6 ± 5.0	0.004			
PETO ₂ @ AT (mm Hg)				111.1 ± 5.5	115.2 ± 6.4	0.019	109.7 ± 6.3	113.0 ± 5.5	0.035
VE/VCO ₂ @ Peak (mm Hg)	36.8 ± 6.4	34.0 ± 3.7	0.028	34.4 ± 3.7	40.4 ± 8.5	<0.001			
VE/VO ₂ @ Peak (mm Hg)				38.9 ± 6.1	45.0 ± 11.1	0.025			
PETCO ₂ @ Peak (mm Hg)	33.8 ± 5.3	36.8 ± 3.2	0.005	36.1 ± 3.9	30.9 ± 5.6	<0.001			
PETO ₂ @ Peak (mm Hg)				116.8 ± 5.7	121.4 ± 5.6	0.008			
OUEP (mL/L)				31.8 ± 4.2	28.9 ± 6.3	0.040			
VE/VCO ₂ slope				30.8 ± 4.8	35.4 ± 6.3	0.004			
LOWEST VE/VCO ₂	35.5 ± 5.1	33.2 ± 3.7	0.046	33.6 ± 3.5	38.2 ± 6.5	0.022			
The data are presented as mean ± SD or n. Statistical analysis of characteristics of the subjects was analyzed with Student's t test or Mann-Whitney U test, and was presented as " <i>P</i> ". For Mastora index, 0–24% was divided into grade 1, 25–49% was divided into grade 2, 50–74% was divided into grade 3; 75–99% was divided into grade 4; 100% was divided into grade 5. For PA diameter, < 3 cm was divided into normal, > 3 cm was divided into abnormal. PE = pulmonary embolism; BNP = brain natriuretic peptide; DD = D-dimer; PA diameter = pulmonary artery diameter; VO ₂ = oxygen uptake; VE = minute ventilation; VCO ₂ = carbon dioxide output; PETCO ₂ = end-tidal partial pressure for carbon dioxide; PETO ₂ = end-tidal partial pressure for oxygen; OUEP = oxygen uptake efficiency plateau.									

The "Central" group compared with the "Peripheral" group had the higher value of VE/VCO₂ @ Rest (mm Hg), VE/VO₂ @ Rest (mm Hg), VE/VCO₂ @ Peak (mm Hg) and LOWEST VE/VCO₂, while had lower value of PETCO₂ @ Rest (mm Hg) and PETCO₂ @ Peak (mm Hg) (Table 4, Supplement Table 1, Supplement Table 2).

The value of VE/VCO₂ @ AT (mm Hg), VE/VO₂ @ AT (mm Hg), PETCO₂ @ AT (mm Hg), PETO₂ @ AT (mm Hg), VE/VCO₂ @ Peak (mm Hg), VE/VO₂ @ Peak (mm Hg), PETCO₂ @ Peak (mm Hg), PETO₂ @ Peak (mm Hg), OUEP (mL/L), VE/VCO₂ slope and LOWEST VE/VCO₂ was statistically different between PE patients with different obstruction index determined by CTPA (Table 4, Supplement Table 3, Supplement Table 4).

VO₂ @ Rest (mL/kg/min), VE/VO₂ @ AT (mm Hg) and PETO₂ @ AT (mm Hg) were the parameters found to be different between "Normal" and "Abnormal" group defined according to PA diameter (Table 4, Supplement Table 5, Supplement Table 6).

Table 5
Univariate logistic regression analysis for the risk of of PE recurrence in the PE subjects.

	Cox-hazard ratio	95% CI	P
Age (years)	1.085	0.998–1.1180	0.057
Sex (male/female)	0.319	0.074–1.366	0.124
FVC (L)	0.290	0.097–0.867	0.027
FEV1 (L)	0.196	0.050–0.760	0.018
FEV1 (% Pred)	0.964	0.912–1.019	0.199
TLC (L)	0.563	0.294–1.079	0.084
RV/TLC (%)	1.079	0.990–1.176	0.084
HR @ Rest	0.950	0.888–1.016	0.133
MPV (fL)	2.040	0.971–4.287	0.060
PDW (%)	1.293	0.972–1.720	0.078
PLCR (%)	1.087	0.995–1.188	0.064
VO ₂ @ Rest (% pred)	1.306	1.051–1.623	0.016
VO ₂ @ AT (% pred)	1.172	1.046–1.312	0.006
VO ₂ @ Peak (% pred)	1.066	1.004–1.131	0.036
OUEP (mL/L)	0.889	0.757–1.045	0.153
PA diameter (cm)	3.023	0.815–11.207	0.098
Parameters were all analyzed with univariate logistic regression analysis, and parameters with <i>P</i> value ≤ 0.2 were presented in the table. Results are expressed as odds ratio (OR) with 95% confidence interval (95% CI). MPV = mean platelet volume; PDW = platelet distribution width; PLCR = platelet-larger cell ratio; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1s; RV = residual volume; TLC = total lung capacity; VO ₂ = oxygen uptake; PA diameter = pulmonary artery diameter.			

Table 6
Final multivariable Cox regression models for the risk of of PE recurrence in the PE subjects.

	Cox-hazard ratio	95% CI	P
Model 1			
VO ₂ @ AT (% pred)	1.094	1.005–1.192	0.038
VO ₂ @ Rest (% pred)	1.081	0.875–1.335	0.470
FEV1 (L)	0.382	0.016–6.778	0.471
FVC (L)	1.960	0.147–26.193	0.611
Model 2			
VO ₂ @ AT (% pred)	1.114	1.024–1.213	0.012
FEV1 (L)	1.087	0.031–37.899	0.963
FVC (L)	0.835	0.054–12.898	0.897
Age (years)	1.050	0.963–1.145	0.270
Model 3			
VO ₂ @ AT (% pred)	1.110	1.013–1.215	0.025
VO ₂ @ Rest (% pred)	1.023	0.832–1.259	0.827
FEV1 (L)	0.914	0.210–3.983	0.905
Age (years)	1.045	0.959–1.139	0.315
Parameters selected by univariate logistic regression analysis were analyzed with multivariable Cox regression. Results are expressed as odds ratio (OR) with 95% confidence interval (95% CI). FVC = forced vital capacity; FEV1 = forced expiratory volume in 1s; VO ₂ = oxygen uptake.			

Correlations between CPET and hematologic parameters in the Post-PE and PE subjects

In order to further verify the relationship between CPET and hematologic parameters in “PE” and “Post-PE” subjects, the correlation analysis of NT-proBNP (pg/mL), DD (ng/mL), MPV (fL) and PLCR (%) with CPET parameters was studied.

Significant correlation was found between CPET and hematologic parameters. Details were listed in Table 3.

Predictive factors for the risk of PE recurrence

To analyze the predictors of the risk of PE recurrence in PE patients, we retrospectively followed up 68 PE patients. The follow-up results were as follows: the shortest follow-up time was 5 months, the longest was 94 months and the median follow-up time was 30.5 months. Among them, 25 patients were lost to follow-up. 34 patients had no obvious PE-related symptoms, were regularly taking or stopping drugs and had no hospitalization records since then, so their condition was considered stable or improved. 10 patients had new thrombosis, the increased obstruction index confirmed by imaging examination, or abnormally elevated DD with PE-related symptoms without other VTE history, so they were considered to have the risk of PE recurrence.

The univariate logistic regression analysis revealed that several CPET-based variables were related to the risk of PE recurrence. These variables included Age (years), sex, FVC (L), FEV1 (L), FEV1 (% Pred), TLC (L), RV/TLC (%), HR @ Rest, MPV (fL), PDW (%), PLCR (%), VO_2 @ Rest (% pred), VO_2 @ AT (% pred), VO_2 @ Peak (% pred), OUEP (mL/L), PA diameter (cm). Details were listed in Table 5. Receiver operating characteristic curve analysis was implemented to analyze the optimal cut-offs for the variables to predict the risk of PE recurrence (Supplement Table 7).

Multivariate Cox-regression analyses were performed considering all variables depicted in Table 5 (Table 6). The final models indicated that VO_2 @ AT (% pred) were related to the risk of PE recurrence. Based on the optimal cut-off of VO_2 @ AT (% pred) calculated by ROC curve analysis, we conducted the Kaplan–Meier analysis. There were statistical differences in risk of PE recurrence between the subjects with VO_2 @ AT (% pred) > 40.69 and the subjects with VO_2 @ AT (% pred) < 40.69 (Fig. 1).

Discussion

In the present study, we observed the hematologics, PFT and CPET performance of healthy people, “PE” and “Post-PE” subjects. Their exercise tolerance (load @ peak), metabolic capacity (VO_2 @ AT, VO_2 @ Peak), ventilatory efficiency (VE/VCO_2 @ AT, VE/VCO_2 @ Peak, OUEP, LOWEST VE/VCO_2), gas exchange ($PETCO_2$ @ AT, $PETCO_2$ @ Peak, $PETO_2$ @ AT), and cardiovascular response (VO_2 /HR) were different (Table 2). It provides an explanation for the post-PE syndrome of PE survivors despite the embolism observed on imaging had disappeared, like persistent dyspnea, exercise limitation and decreased quality of life[6, 7]. At the same time, it indicates that it is necessary for PE patients to carry out pulmonary rehabilitation as soon as possible[8].

Our study for the first time evaluate the dynamic cardiopulmonary condition of PE patients by CPET and CTPA. We can observe that the PE patient's exercise tolerance, respiratory and circulatory conditions are significantly limited. Among the variables, the change of VO_2 (% pred) was most obvious compared with healthy people. Past research has suggested that VO_2 (% pred) can broadly reflect physical fitness in healthy people and disease severity in patients with chronic obstructive pulmonary disease, heart failure, pulmonary hypertension and restrictive pulmonary disease[9–14]. Although CTPA results showed that the PE patients involved in the study could be classified as Grade 1/2/3 defined by Mastora index. The VO_2 (% pred) of different severity of PE patients was also different (Supplement Table 4).

Ventilatory inefficiency and worse gas exchange were also the obvious features of PE patients (Table 2). Furthermore, patients of the peripheral pulmonary embolism possessed worse ventilatory efficiency and gas exchange at the rest and exercise phase when compared with the central pulmonary embolism (Table 2). Patients with higher obstruction index also exhibited worse ventilatory efficiency and gas exchange at the exercise phase (Table 2). When PE patients with abnormal PA diameter, they had worse capacity of oxygen utilization (Table 2).

Recent studies have proved that platelets play an important role in the development of atherosclerosis and thrombi[15]. Platelet volume indexes including MPV, PDW and P-LCR were closely related with cardiovascular diseases. It was found that PE patients had higher value of PLCR, probably because larger platelets were metabolically and enzymatically more active in comparison to smaller ones because they contain more alpha granules, produce more thromboxane A2 and feature high expression of adhesive glycoproteins[16, 17]. MPV was considered as independent cardiovascular risk factor[17]. We found PE patients were characterized with lower baseline MPV, which was consistent with previous study[18]. Moreover, platelet volume indexes was proved to have significant correlation with VO_2 @ AT (% pred).

We report for the first time a possible link between PE recurrence rate and CPET parameters. PE patients with VO_2 @ AT (% pred) had a higher risk of PE recurrence. The oxygen consumption above which aerobic energy production is supplemented by anaerobic mechanisms, causing a sustained increase in lactate and metabolic acidosis, is termed the AT[19].

Some of other limitations of this study are its patient sample size, non-randomized nature, single-center design and potential selection bias. Since it's a retrospective study, the follow-up data of patients are not very comprehensive.

Conclusions

In conclusion, our findings suggest that CPET is an effective and responsible method to the assessment of pulmonary embolism symptoms and prognosis.

Abbreviations

CPET: cardiopulmonary exercise testing; PFT: pulmonary function testing; PE: pulmonary embolism; CTPA: CT pulmonary angiography; ROC: receiver operating characteristic curves; AUC: area under the ROC curve; OR: odds ratio; CI: confidence interval; BNP: brain natriuretic peptide; FVC: forced vital capacity; FEV1: forced expiratory volume in 1s; RV: residual volume; TLC: total lung capacity; SB DLCO: carbon monoxide diffusing capacity; VO_2 : oxygen uptake; HR: heart rate; VE: minute ventilation; BF: breathing frequency; RER: respiratory exchange ratio; VCO_2 : carbon dioxide output; $PETCO_2$: end-tidal partial pressure for carbon dioxide; $PETO_2$: end-tidal partial pressure for oxygen; OUES: oxygen uptake efficiency slope; OUEP: oxygen uptake efficiency plateau; VE: ventilation; VCO_2 : carbon dioxide output; AT: anaerobic threshold.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shanghai Pulmonary Hospital. All patients provided written informed consent to participate in the study.

Consent for publication

Not applicable.

Availability of data and materials

All the related data are presented in the manuscript.

Competing interests

The authors confirm that there are no conflicts of interest.

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Authors' contributions

Conceived and designed the experiments: ZH GJ.

Performed the experiments: SX CY XJH YW.

Analyzed the data: ZH ZW GJ.

Contributed reagents/materials/analysis tools: ZH ZW.

Wrote the paper: ZH ZW GJ.

All authors have read and approved the manuscript.

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References

1. Righini M, Robert-Ebadi H, Le Gal G. Diagnosis of acute pulmonary embolism. *Journal of thrombosis and haemostasis* : JTH. 2017; 15: 1251-61.
2. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. *Blood reviews*. 2014; 28: 221-6.
3. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010; 122: 191-225.
4. Li Y, Dai Y, Deng L, Yu N, Guo Y. Computer-aided detection for the automated evaluation of pulmonary embolism. *Technology and health care : official journal of the European Society for Engineering and Medicine*. 2017; 25: 135-42.
5. Sun ZT, Hao FE, Guo YM, Liu AS, Zhao L. Assessment of Acute Pulmonary Embolism by Computer-Aided Technique: A Reliability Study. *Medical science monitor : international medical journal of experimental and clinical research*. 2020; 26: e920239.
6. Klok FA, Tijmens JE, Haeck ML, van Kralingen KW, Huisman MV. Persistent dyspnea complaints at long-term follow-up after an episode of acute pulmonary embolism: results of a questionnaire. *European journal of internal medicine*. 2008; 19: 625-9.
7. Tavoly M, Utne KK, Jelsness-Jørgensen LP, Wik HS, Klok FA, Sandset PM, et al. Health-related quality of life after pulmonary embolism: a cross-sectional study. *BMJ open*. 2016; 6: e013086.

8. Haukeland-Parker S, Jervan Ø, Johannessen HH, Gleditsch J, Stavem K, Steine K, et al. Pulmonary rehabilitation to improve physical capacity, dyspnea, and quality of life following pulmonary embolism (the PeRehab study): study protocol for a two-center randomized controlled trial. *Trials*. 2021; 22: 22.
9. Herdy AH, Ritt LE, Stein R, Araújo CG, Milani M, Meneghelo RS, et al. Cardiopulmonary Exercise Test: Background, Applicability and Interpretation. *Arquivos brasileiros de cardiologia*. 2016; 107: 467-81.
10. Piepoli MF, Corrà U, Agostoni PG, Belardinelli R, Cohen-Solal A, Hambrecht R, et al. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation. Part I: definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*. 2006; 13: 150-64.
11. Stringer W, Marciniuk D. The Role of Cardiopulmonary Exercise Testing (CPET) in Pulmonary Rehabilitation (PR) of Chronic Obstructive Pulmonary Disease (COPD) Patients. *Copd*. 2018; 15: 621-31.
12. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary Exercise Testing in Heart Failure. *JACC Heart failure*. 2016; 4: 607-16.
13. Weatherald J, Farina S, Bruno N, Laveneziana P. Cardiopulmonary Exercise Testing in Pulmonary Hypertension. *Annals of the American Thoracic Society*. 2017; 14: S84-S92.
14. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O, et al. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. *Respiration; international review of thoracic diseases*. 2014; 88: 378-88.
15. Vizioli L, Muscari S, Muscari A. The relationship of mean platelet volume with the risk and prognosis of cardiovascular diseases. *International journal of clinical practice*. 2009; 63: 1509-15.
16. Martin JF, Kristensen SD, Mathur A, Grove EL, Choudry FA. The causal role of megakaryocyte–platelet hyperactivity in acute coronary syndromes. *Nature reviews Cardiology*. 2012; 9: 658-70.
17. Batista TR, Figueiredo RC, Rios DRA. Platelets volume indexes and cardiovascular risk factors. *Revista da Associacao Medica Brasileira (1992)*. 2018; 64: 554-9.
18. Llorente-Chávez A, Martín-Nares E, Núñez-Álvarez C, Hernández-Molina G. Thrombosis and thrombocytopenia in antiphospholipid syndrome: their association with mean platelet volume and hematological ratios. *Thrombosis research*. 2021; 203: 12-7.
19. Wasserman K. The anaerobic threshold: definition, physiological significance and identification. *Advances in cardiology*. 1986; 35: 1-23.

Figures

Figure 1

Kaplan–Meier cumulative curves for the risk of of PE recurrence in the PE subjects by $VO_2 @ AT (\% \text{ pred})$.

Kaplan–Meier cumulative curves for the risk of of PE recurrence in the PE subjects by $VO_2 @ AT (\% \text{ pred})$. Cutoffs were determined by ROC curve analysis.

Supplementary Files

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