Cardiopulmonary Exercise Testing and Pulmonary Function Testing for Predicting Aggravation of CTEPH

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Abstract

Background

Cardiopulmonary exercise testing (CPET) and pulmonary function testing (PFT) are noninvasive methods to evaluate the respiratory and circulatory systems. This research aimed to evaluate and monitor chronic thromboembolic pulmonary hypertension (CTEPH) noninvasively and effectively. At the same time assess the predictive value of CPET and PFT parameters for the aggravation of CTEPH.

Methods

We used data from 86 CTEPH patients (55 for test set, and 31 for validation set) at the Shanghai Pulmonary Hospital Affiliated to Tongji University. The clinical, PFT and CPET parameters of mild, moderate and severe CPET patients classified according to PAP (mm Hg) were compared. Logistic regression analysis was performed to appraise the predictive value of each potential predictor for severe CTEPH. The performance of PFT and CPET parameters for predicting severe CTEPH was determined by receiver operating characteristic (ROC) curves and calibration curves.

Results

Data showed that Load @ Peak (W), FEV1/FVC (%), and VE @ AT (L/min) were independent risk factors for severe CTEPH classified according to PAP (mm Hg). Additionally, the efficacy of the use of Load @ Peak (W), FEV1/FVC (%) and VE @ AT (L/min) in identifying severe CTEPH was found to be moderate with area under the curve (AUC) of ROC curves of 0.736, 0.696 and 0.769, respectively. Furthermore, combination with Load @ Peak (W), FEV1/FVC (%) and VE @ AT (L/min) had a moderate utility value in identifying severe CTEPH with an AUC of 0.897.

Conclusion

Our data suggests that PFT and CPET parameters can noninvasively and effectively evaluate, monitor and predict the aggravation of CTEPH.

Background

Cardiopulmonary exercise testing (CPET) provides a unique and comprehensive evaluation of respiratory and circulatory systems by detecting the gas exchange and exercise load during exercise[1]. It is considered to be a gold standard noninvasive measure of cardiorespiratory fitness and exercise capacity[2]. CPET has been widely carried out in patients with pulmonary hypertension (PH), heart failure (HF), chronic obstructive lung disease (COPD), asthma, etc.[3-5]. It has been reported to be of significance in disease diagnosis, assessing efficacy of therapeutic interventions, and evaluation of prognosis. However, due to the variety of parameters, makes it difficult for clinicians to correctly interpret CPET parameters under different situations.

CTEPH's pathological characteristics are organized thrombus and vascular remodeling ultimately leading to right ventricular failure[6]. Pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA) and PH-targeted medical therapy are the main therapies of CTEPH[6]. The diagnosis of CTEPH can be achieved by right heart catheterization (RHC), ventilation/perfusion scan (V/Q) and CT pulmonary angiography (CTPA)[7, 8].

Since CTEPH is a kind of progressive disease, it is imperative to assess risk that affects disease progression appropriately and accurately for appropriate timely intervention. It has already been reported that CPET may be used to estimate the severity of PH[9]. Abnormalities noted during CPET were consistent, characteristic and correlated well with primary pulmonary hypertension (PPH) patients' NYHA class[10, 11]. Stepping on these, we set this study to examine the difference of CPET performance between patients' with mild-moderate and severe CTEPH.

Methods

Ethical approval

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 and prior to the performance of any study-related procedures.

All methods including CPET, PFT, RHC and blood test were carried out in accordance with relevant guidelines and regulations.

Patients

This study retrospectively enrolled 86 inpatients with CTEPH who were referred to Shanghai Pulmonary Hospital from November 2015 to December 2019. All patients were definitely diagnosed by RHC. Patients with mean pulmonary artery pressure (mPAP) ≥ 25 (mmHg) and pulmonary arterial wedge pressure (PAWP) ≤ 15 (mmHg) were considered to have CTEPH. They also should had performance of ventilation/perfusion scan or pulmonary angiogram which were consistent with thromboembolic disease. Patients were excluded from study if they had any evidence of the following: right-to-left cardiac shunt, coexisting lung diseases (identified clinically or on CT scan), FEV1/FVC% $< 65\%$ and undergone pulmonary endarterectomy. Enrolled patients' data including demographics, medication, NT-pro BNP, hemodynamics, PFT and CPET were collected. Ethical approval by the medical ethics committee of Shanghai pulmonary hospital was obtained.

CPET

CPET was performed on an electromagnetically braked cycle ergometer (Master Screen CPX, Jaeger corp, Hoechberg, Germany) by using a breath-by-breath system to record gas exchange data over 10-s intervals. The protocol was consisted of the rest phase of 3 minutes, the unloaded phase of 3 minutes, the

loaded pahse in which the workload increased 10-25W/min, and the recovery phase of 5 minutes. The patients should pedal at 55-60 revolutions/min in the unloaded and loaded phase, and when they reached their maximum tolerance they could enter the recovery phase. Patients could stop at any time when they have fatigue, dyspnea, chest tightness and any other discomfort during the process.

Measurements included 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), breathing reserve (BR), respiratory exchange ratio (RER) and breathing frequency (BF). Anaerobic threshold (AT) which represents the beginning of anaerobic metabolism was determined by the V-slope method. VE/VCO₂ slope was obtained by linear regression analysis of the relation between VE and VCO₂. Oxygen uptake efficiency slope (OUES) was computed by a linear squares 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).

Statistical analysis

Data were analyzed by using SPSS 22.0 and GraphPad Prism 6. The data are presented as mean $\pm$ SD, median (interquartile range), or n. One-way ANOVA test, Kruskal-Wallis test, Tukey's multiple comparisons test, Dunn's multiple comparisons test, Unpaired t test, Mann-Whitney U test, chi-square test, univariate logistic regression analysis and multivariate logistic regression analysis were used according to the corresponding situation. A two-tailed $P < 0.05$ was considered significant.

Results

Characteristics of the CTEPH subjects

55 patients with CTEPH were involved in the test set. They were divided into "Mild", "Moderate" and "Severe" groups according to PAP (mm Hg). Mild: 35>PAP (mm Hg) ≥ 25 ; Moderate: 45>PAP (mm Hg) ≥ 35 ; Severe: PAP (mm Hg) ≥ 45 .

The characteristics of all groups were summarized in Table 1 and Figure 1. The "Severe" group had the highest NT-proBNP (pg/mL) value when compared with the "Mild" and "Moderate" groups (143.0(63.8, 286.7) vs. 648.5(266.3, 2049) vs. 1082(642.0, 2674) pg/mL; $P = 0.001$). The PAP (mm Hg) value of the "Mild", "Moderate" and "Severe" groups were significantly different (28.60 $\pm$ 3.27 vs. 39.50 $\pm$ 3.87 vs. 56.40 $\pm$ 8.03 mm Hg; $P < 0.0001$). Additionally, significant differences in PVR and RAP values among the three groups were noted. PVR (wood u) value for the "Mild", "Moderate" and "Severe" groups (3.7 $\pm$ 1.3 vs. 7.6 $\pm$ 2.4 vs. 10.9 $\pm$ 3.8 wood u; $P < 0.0001$), and for RAP (mm Hg) value of the "Mild", "Moderate" and "Severe" groups (0.5(0.4, 5) vs. 1.0(0.1, 3) vs. 4.0(2.0, 7.0) mm Hg; $P = 0.001$).

CPET and PFT performance differences in subjects with CTEPH

During PFT, we noted FEV1/FVC (%) as the only parameter differing among the "Severe", "Mild" and "Moderate" groups (78.8 $\pm$ 9.3 vs. 81.7 $\pm$ 8.0 vs. 73.4 $\pm$ 8.0 %; $P = 0.013$). Details are listed in Table 1 and Figure 1.

During CPET, several parameters were found to be different among the "Mild", "Moderate" and "Severe" groups. They are listed as followed: Load @ Peak (W), VO₂ @ Peak (mL/Kg/min), VE @ AT (L/min), BR @ Rest (%), BR @ AT (%), VE/VCO₂ @ AT, VE/VCO₂ @ Peak, VO₂/VE @ AT, PETCO₂ @ Rest, PETCO₂ @ AT, PETCO₂ @ Peak, PETO₂ @ Rest, PETO₂ @ AT, PETO₂ @ Peak, VE/VCO₂ slope and LOWEST VE/VCO₂. Details are listed in Table 2, Table 3 and Figure 1.

Predictive value of the CPET and PFT parameters for the severe CTEPH

Furthermore, 55 patients with CTEPH in the test set were re-grouped into "Mild-Moderate" and "Severe" group to analyze predictors for severe CTEPH. All the parameters measured were analyzed with the univariate analysis for the severe CTEPH, and 21 parameters were found to have a $P < 0.05$. They are listed as followed: VE @ AT (L/min), VO₂/VE @ AT, BR @ AT (%), LOWEST VE/VCO₂, VE/VCO₂ @ AT, PETO₂ @ AT, PETCO₂ @ Peak, FEV1/FVC (%), PETCO₂ @ Rest, Load @ Peak (W), VE/VCO₂ @ Peak, BR @ Rest (%), VO₂ @ Peak (mL/Kg/min), VCO₂ @ Peak, VE/VCO₂ slope, FEV1 (% Pred), VE/VCO₂ @ Rest, BMI (kg/m²), NT-proBNP (pg/mL), VO₂/VE @ Peak and RER @ Peak. Considering the sample size, 11 parameters with the minimum P value were fitted into the multivariate analysis, including VE @ AT (L/min) (OR: 1.169, $P = 0.004$), VO₂/VE @ AT (OR: 0.762, $P = 0.004$), BR @ AT (%) (OR: 0.936, $P = 0.006$), LOWEST VE/VCO₂ (OR: 1.129, $P = 0.006$), VE/VCO₂ @ AT (OR: 1.100, $P = 0.008$), PETO₂ @ AT (OR: 1.184, $P = 0.009$), PETCO₂ @ Peak (OR: 0.859, $P = 0.009$), FEV1/FVC (%) (OR: 0.900, $P = 0.010$), PETCO₂ @ Rest (OR: 0.769, $P = 0.011$), Load @ Peak (W) (OR: 0.961, $P = 0.011$) and VE/VCO₂ @ Peak (OR: 1.068, $P = 0.014$). By using multivariate logistic regression analysis, VE @ AT (L/min) (OR: 1.400, $P = 0.048$), FEV1/FVC (%) (OR: 0.756, $P = 0.007$) and Load @ Peak (W) (OR: 0.881, $P = 0.021$) were significant independent predictors for the severe CTEPH. Details are listed in Table 4 and Figure 2.

Combining these three parameters, we got the prediction equation for the severe CTEPH which was $\text{Logit}(P) = 7.397 + 0.205 \cdot \text{VE@AT} - 0.116 \cdot \text{FEV1/FVC} - 0.059 \cdot \text{Load @ Peak}$. To evaluate the ability of the VE @ AT (L/min), FEV1/FVC (%), Load @ Peak (W) and the prediction equation to differentiate severe from mild-moderate CTEPH, ROC curves and calibration curves were performed. Details are listed in Table 5 and Figure 3. It must be noted that the AUC of the prediction equation was better than that for each parameter, indicating that the equation based on three parameters yielded the highest AUC value and could significantly improve the prediction performance for severe CTEPH.

Additionally, we analyzed the prediction equation in the validation datasets to validate the results. Only 4 of 31 patients with CTEPH of the validation set were ambiguous, and the accuracy was 87.10%. Details are listed in Table 6.

Discussion

We retrospectively analyzed the clinical, hematological, PFT and CPET data of 86 patients with CTEPH. Part of the patients were randomly classified into the validation set (a total of 31), and the remaining 55 patients were classified into the test set. Patients with CTEPH were divided into “Mild”, “Moderate” and “Severe” groups according to PAP (mm Hg) detected by RHC. This was used for finding the parameters likely predicting severe CTEPH[12]. Through comparison, we can find that there are differences in the CPET performance of patients with different severity of CTEPH. For example, Load @ Peak (W) and VO_2 @ Peak (mL/Kg/min) decreased with the aggravation of CTEPH. VE (L/min) and BR (%) of patients with different severity of CTEPH differed only at the AT phase. VE/VCO_2 , VO_2/VE , PETCO_2 (mm Hg) and PETO_2 (mm Hg) was different between “Mild” and “Severe” groups. After that, patients with CTEPH were regrouped into “Mild-Moderate” and “Severe” groups. By univariate analysis for analyzing risk factors for severe CTEPH, 21 parameters were found to have a $P < 0.05$. While by multivariate analysis, only Load @ Peak (W), FEV1/FVC (%) and VE @ AT (L/min) were found to have a $P < 0.05$. Combining these three parameters, we got a prediction equation with AUC of 0.897 (Sensitivity: 80.0%, Specificity: 85.0%). ROC curves and calibration curves proved the prediction equation was good in discrimination and calibration. Additionally, its application in the validation set further confirmed the efficiency.

CPET could be used for the detection of CTEPH in patients with suspected PH but normal echocardiography. The number of patients with undiagnosed CTEPH may be significantly higher[13]. Estimates suggest that up to a quarter of patients with CTEPH may have no history of previous pulmonary embolism[14]. Compared with healthy cohorts, patients with CTEPH had higher value of VO_2/VE @ AT, VE/VCO_2 @ AT, $\text{P}(\text{c-ET})\text{CO}_2$ while lower value of PETCO_2 @ AT. $\text{P}(\text{c-ET})\text{CO}_2$ was a diagnostic parameter of CTEPH with the highest sensitivity (85.7%) and specificity (88.2%)[13]. Ventilatory efficiency parameters including $\text{P}(\text{c-ET})\text{CO}_2$, PETCO_2 decrease patterns, VD/VT @ Peak, VE/VCO_2 slope, VE/VCO_2 @ AT, OUEP and OUE @ AT can help to distinguish CTEPH from idiopathic pulmonary arterial hypertension (IPAH)[15-18]. The lowest VE/VCO_2 ratio best predicts CTEPH from the chronic PE patients[19]. Godinas *et al* reported that in distal CTEPH patients, higher VD/VT was associated with lower peak oxygen consumption and worse survival[20]. Qi Jin *et al* reported that after BPA, patients with inoperable CTEPH had significant improvement in CPET and PFT parameters including Load @ Peak, VO_2 @ Peak, OUES, FVC, FEV1 and MVV[21]. As we have seen, CPET can be used for the diagnosis/differential diagnosis, prognostic evaluation and treatment evaluation of CTEPH.

For the first time, we have evaluated the value of CPET in the process of CTEPH aggravation. Despite current evidence not supporting routine screening for CTEPH after pulmonary embolism, it's in the best interest of the up to a quarter of CTEPH patients that have no history of PE at least have a noninvasive test like CPET to better understand disease progression. We hope that CPET can be used for routine monitoring of CTEPH patients in the future, and then the application of this formula can provide value for guiding the further examination and treatment of patients. Our study shows that patients with severe CTEPH, the Load @ Peak (W) and FEV1/FVC (%) value was lower while VE @ AT (L/min) was higher than in patients with mild-moderate CTEPH. The prediction equation $\text{Logit}(P) = 7.397 + 0.205 * \text{VE @ AT} - 0.116 * \text{FEV1/FVC} - 0.059 * \text{Load @ Peak}$ was effective and efficient in discriminating patients with severe CTEPH. Some of the limitations of this study are its patient sample size, non-randomized nature and single-center design and potential selection bias.

Abbreviations

CPET: cardiopulmonary exercise testing; PFT: pulmonary function testing; CTEPH: chronic thromboembolic pulmonary hypertension; PH: pulmonary hypertension; PPH: primary pulmonary hypertension; IPAH: idiopathic pulmonary arterial hypertension; HF: heart failure; COPD: chronic obstructive lung disease; PE: pulmonary embolism; PEA: pulmonary endarterectomy; BPA: balloon pulmonary angioplasty; RHC: right heart catheterization; CTPA: CT pulmonary angiography; V/Q: ventilation/perfusion scan; ROC: receiver operating characteristic curves; AUC: area under the curve; OR: odds ratio; CI: confidence interval; WHO: World Health Organization; BNP: brain natriuretic peptide; PAP: pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; RAP: right atrial pressure; 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; BR: breathing reserve; RER: respiratory exchange ratio; VCO_2 : carbon dioxide output; VD/VT : dead space ventilation as a fraction of tidal volume; 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

All patients in this study were informed at admission that their medical records were likely to be used for clinical studies. Ethical approval by the medical ethics committee of Shanghai pulmonary hospital was obtained.

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 LJ GJ.

Performed the experiments: SX CY YW.

Analyzed the data: ZH GJ.

Contributed reagents/materials/analysis tools: ZH SX.

Wrote the paper: ZH SX GJ.

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Tables

Table 1. Characteristics of CTEPH subjects of different severity.

Variables	Total	Mild	Moderate	Severe	<i>P</i>
<i>Clinical characteristics</i>					
Age (years)	61.2±11.2	65.5±9.9	59.8±9.3	60.4±12.0	0.416
Sex, n (female/male)	30/25	4/6	6/4	20/15	0.779
Height (m)	1.6±0.1	1.7±0.1	1.6±0.1	1.6±0.1	0.661
Weight (kg)	63.3±12.9	65.3±12.0	56.6±12.0	64.7±13.1	0.192
Body mass index (kg/m ²)	23.6±3.3	23.8±3.8	20.9±3.4	24.4±2.9	0.010
WHO classification II/III/IV, n	15/39/1	6/4/0	3/6/1	6/29/0	0.026
<i>Blood test</i>					
NT-proBNP (pg/mL)	809.0(296.9,2284)	143.0(63.8,286.7)	648.5 (266.3,2049)	1082(642.0,2674)	0.001
<i>Right heart catheterization parameters</i>					
PAP (mm Hg)	48.27±13.18	28.60±3.27	39.50±3.87	56.40±8.03	<0.0001
PAWP (mm Hg)	7.0(4.0,9.0)	8.5(5.5,10.3)	4.0(3.0,9.3)	7.0(4.0,9.0)	0.250
CO (L/min)	5.0±1.4	5.8±1.7	4.8±1.4	4.9±1.3	0.221
CI (L/min/m ²)	3.0±0.8	3.3±0.8	3.0±0.7	2.9±0.7	0.283
PVR (wood u)	9.0±4.2	3.7±1.3	7.6±2.4	10.9±3.8	<0.0001
RAP (mm Hg)	3.0(1.0,6.0)	0.5(0,4.5)	1.0(0,1.3)	4.0(2.0,7.0)	0.001
<i>Pulmonary function testing parameters</i>					
FVC (L)	2.7±0.9	2.8±0.8	2.8±1.1	2.6±0.8	0.790
FVC (% Pred)	84.4±15.8	88.8±15.6	86.3±24.9	82.6±12.5	0.508
FEV1 (L)	2.1±0.7	2.2±0.5	2.2±0.8	2.0±0.7	0.488
FEV1 (% Pred)	79.5±17.1	85.7±14.0	87.0±23.9	75.6±14.7	0.076
FEV1/FVC (%)	75.9±8.8	78.8±9.3	81.7±8.0	73.4±8.0	0.013
RV (L)	2.4±0.7	2.5±0.9	2.6±0.3	2.3±0.7	0.562
RV (% Pred)	126.8±34.3	122.6±46.1	134.9±27.4	125.7±32.9	0.700
TLC (L)	5.1±1.3	5.3±1.5	5.4±1.2	5.0±1.3	0.629
TLC (% Pred)	100.6±19.0	101.7±26.0	104.7±15.4	99.1±18.0	0.698
RV/TLC (%)	47.3(41.8,53.8)	48.3(39.0,53.8)	49.0(39.4,61.0)	47.2(42.0,56.1)	0.910
SB DLCO (% Pred)	81.8±19.2	81.4±25.2	85.0±28.7	81.0±14.0	0.843

Range for “Mild”: 35>PAP (mm Hg)≥25; range for “Moderate”: 45>PAP (mm Hg) ≥35; range for “Severe”: PAP (mm Hg) ≥45. The data are presented as mean ± SD, median (interquartile range), or n. Statistical analysis of characteristics of “Mild”, “Moderate” and “Severe” was analyzed with One-way ANOVA test, Kruskal-Wallis test or chi-square test, and was presented as “*P*”. WHO=World Health Organization; BNP=brain natriuretic peptide; PAP=pulmonary artery pressure; PAWP=pulmonary arterial wedge pressure; CO=cardiac output; CI=cardiac index; PVR=pulmonary vascular resistance; RAP=right atrial pressure; FVC=forced vital capacity; FEV1=forced expiratory volume in 1s; RV=residual volume; TLC=total lung capacity; SB DLCO=carbon monoxide diffusing capacity.

Table 2. Comparison of the CPET parameters of CTEPH subjects of different severity.

Variables	Rest				AT				Peak	
	Mild	Moderate	Severe	<i>P</i>	Mild	Moderate	Severe	<i>P</i>	Mild	
Load (W)					40.0(35.5,48.5)	36.0(28.0,41.0)	32.0(24.0,42.0)	0.177	74.3(66.4,	
VO ₂ (mL/Kg/min)	17.2(14.6,24.2)	17.5(16.5,23.8)	18.5(15.1,23.6)	0.782	38.9(32.2,57.9)	37.2(32.4,50.3)	37.7(30.8,46.3)	0.897	57.2(52.3,	
VO ₂ (% pred)	38.7±15.3	41.5±11.9	40.4±15.0	0.908	35.1±10.2	33.3±8.0	36.3±10.7	0.700	51.4±13.5	
VO ₂ /HR (mL)	3.2±0.8	3.5±0.8	3.5±0.8	0.527	5.5±1.6	5.0±0.9	5.2±1.3	0.647	6.7±2.1	
VE (L/min)	12.3±2.5	13.1±2.8	14.3±3.2	0.159	26.0±8.0	26.2±4.5	32.2±6.5	0.007	46.5±12.4	
BF (/min)	20.8(16.9,24.7)	18.1(15.3,23.3)	20.1(17.3,23.0)	0.350	26.0(18.8,34.5)	20.0(17.8,31.3)	27.0(23.0,31.0)	0.178	32.0(25.5,	
BR (%)	85.8(84.0,88.3)	85.1(83.0,87.8)	80.0(77.8,85.3)	0.029	68.7(65.9,76.7)	70.0(58.1,77.0)	54.1(42.2,67.3)	0.011	47.9(40.4,	
RER	0.9±0.1	0.9±0.1	0.8±0.1	0.446	1.0±0.1	1.0±0.1	1.0±0.1	0.934	1.1±0.1	
VE/VCO ₂	55.3±9.9	54.7±5.0	60.53±9.1	0.085	46.6±10.9	51.3±8.2	58.9±12.3	0.008	47.0±11.1	
VO ₂ / VE	21.3±2.7	21.5±2.4	20.0±2.6	0.159	23.7±5.5	21.2±3.8	18.4±3.5	0.001	19.5±4.1	
VD/VT	22.1±11.9	22.8±4.2	22.4±6.2	0.980	24.4±8.5	24.3±4.6	23.9±6.9	0.971	24.3±8.0	
PETCO ₂ (mm Hg)	27.7±4.7	25.8±2.1	23.9±3.2	0.009	29.3±5.4	25.2±3.8	22.8±4.4	0.001	28.5±5.8	
PETO ₂ (mm Hg)	119.8±3.2	122.3±3.4	122.9±3.9	0.074	119.9±5.6	125.1±4.7	126.9±4.9	0.001	124.7±4.3	

Range for "Mild": 35>PAP (mm Hg)≥25; range for "Moderate": 45>PAP (mm Hg)≥35; range for "Severe": PAP (mm Hg)≥45. The data are presented as mean ± SD or median (interquartile range). Statistical analysis of characteristics of "Mild", "Moderate" and "Severe" was analyzed with One-way ANOVA test or Kruskal-Wallis test, and was presented as "*P*". VO₂=oxygen uptake; HR=heart rate; VE=minute ventilation; BF=breathing frequency; BR=breathing reserve; RER=respiratory exchange ratio; VCO₂=carbon dioxide output; VD/VT=dead space ventilation as a fraction of tidal volume; PETCO₂=end-tidal partial pressure for carbon dioxide; PETO₂=end-tidal partial pressure for oxygen.

Table 3. Comparison of the CPET parameters of CTEPH subjects of different severity.

Variables	Mild	Moderate	Severe	<i>P</i>
OUES (L/min/log(L/min))	1.3±0.5	1.0±0.3	1.0±0.4	0.067
OUEP (mL/L)	23.4(21.0,27.9)	22.7(21.4,23.8)	21.3(19.1,22.7)	0.078
VE/VCO ₂ slope	40.9(32.3,53.0)	48.4(41.1,68.7)	61.7(49.9,78.5)	0.006
LOWEST VE/VCO ₂	43.7±9.1	48.6±5.8	55.0±10.1	0.004

Range for "Mild": 35>PAP (mm Hg)≥25; range for "Moderate": 45>PAP (mm Hg)≥35; range for "Severe": PAP (mm Hg)≥45. The data are presented as mean ± SD or median (interquartile range). Statistical analysis of characteristics of "Mild", "Moderate" and "Severe" was analyzed with One-way ANOVA test or Kruskal-Wallis test, and was presented as "*P*". OUES=oxygen uptake efficiency slope; OUEP=oxygen uptake efficiency plateau; VE=ventilation; VCO₂=carbon dioxide output.

Table 4. Predictors of of severe CTEPH on univariable and multivariable analysis of CPET and PFT parameters.

Variables	Univariate analysis			Multivariate analysis		
	OR	<i>P</i>	95% CI	OR	<i>P</i>	95% CI
VE @ AT (L/min)	1.169	0.004	1.051-1.300	1.400	0.048	1.004-1.954
VO ₂ / VE @ AT	0.762	0.004	0.632-0.917	1.468	0.406	0.594-3.626
BR @ AT (%)	0.936	0.006	0.892-0.981	1.041	0.504	0.916-1.183
LOWEST VE/VCO ₂	1.129	0.006	1.036-1.230	0.815	0.483	0.460-1.444
VE/VCO ₂ @ AT	1.100	0.008	1.025-1.180	1.354	0.399	0.670-2.735
PETO ₂ @ AT (mm Hg)	1.184	0.009	1.043-1.345	0.673	0.069	0.440-1.032
PETCO ₂ @ Peak (mm Hg)	0.859	0.009	0.767-0.963	0.378	0.056	0.139-1.027
FEV1/FVC (%)	0.900	0.010	0.830-0.975	0.756	0.007	0.616-0.928
PETCO ₂ @ Rest (mm Hg)	0.769	0.011	0.628-0.943	1.050	0.902	0.485-2.273
Load @ Peak (W)	0.961	0.011	0.931-0.991	0.881	0.021	0.790-0.981
VE/VCO ₂ @ Peak	1.068	0.014	1.013-1.126	0.802	0.251	0.551-1.168

Range for "Severe": PAP (mm Hg) ≥ 45 . CPET and PFT parameters were all analyzed with univariate logistic regression analysis, and 11 parameters with minimum *P* value entered in the multivariate logistic regression analysis. Results are expressed as odds ratio (OR) with 95% confidence interval (95% CI). VE=minute ventilation; VO₂=oxygen uptake; BR=breathing reserve; VCO₂=carbon dioxide output; PETO₂=end-tidal partial pressure for oxygen; PETCO₂=end-tidal partial pressure for carbon dioxide; FEV1=forced expiratory volume in 1s; FVC=forced vital capacity.

Table 5. Predictive value of single factor and multiple factors for severe CTEPH.

Variables	AUC	95% CI	<i>P</i>	Cutoff-point value	Sensitivity	Specificity	Youden index
Load @ Peak (W)	0.736	0.600-0.873	0.004	61.0	71.4%	75.0%	0.464
FEV1/FVC (%)	0.696	0.549-0.843	0.016	77.9	71.4%	65.0%	0.364
VE @ AT (L/min)	0.769	0.630-0.908	0.001	29.5	65.7%	85.0%	0.507
Logit(P)	0.897	0.816-0.978	0.000	0.658	80.0%	85.0%	0.650

AUC=area under curve ; CI=confidence interval; FEV1=forced expiratory volume in 1s; FVC=forced vital capacity; VE=minute ventilation.

Table 6. Characteristics of subjects with $P < 0.658$ and $P > 0.658$ calculated by the predication equation in validation set.

Variables	<i>P</i> <0.658	<i>P</i> >0.658	<i>P</i>
Age (years)	53.9±16.0	56.9±12.0	0.552
Sex, n (female/male)	9/4	8/10	0.275
Height (m)	1.6±0.1	1.6±0.1	0.504
Weight (kg)	61.1±11.2	61.7±11.0	0.874
Body mass index (kg/m ²)	23.6±3.4	23.2±2.7	0.743
WHO classification II/III/IV, n	7/6/0	5/12/1	0.273
NT-proBNP (pg/mL)	203.0(44.5,329.5)	858.5(488.3,2182)	0.002
PAP (mm Hg)	38.5±7.6	52.3±8.3	<0.0001
PAWP (mm Hg)	6.2±2.7	8.0±2.7	0.081
CO (L/min)	4.9±1.1	4.2±0.8	0.037
CI (L/min/m ²)	3.0±0.6	2.5±0.5	0.028
PVR (wood u)	6.7±2.0	10.8±3.0	0.0001
RAP (mm Hg)	3.2±2.8	6.6±4.3	0.022
Load @ Peak (W)	74.2±24.5	54.3±24.4	0.033
FEV1/FVC (%)	82.5±8.6	74.9±5.7	0.006
VE @ AT (L/min)	25.7±6.8	32.7±8.5	0.020

The data are presented as mean ± SD, median (interquartile range), or n. Statistical analysis of characteristics of “*P*<0.658” and “*P*>0.658” was analyzed with Unpaired t test, Mann-Whitney U test or chi-square test, and was presented as “*P*”. WHO=World Health Organization; BNP=brain natriuretic peptide; PAP=pulmonary artery pressure; PAWP=pulmonary arterial wedge pressure; CO=cardiac output; CI=cardiac index; PVR=pulmonary vascular resistance; RAP=right atrial pressure; FVC=forced vital capacity; FEV1=forced expiratory volume in 1s; VE=minute ventilation.

Figures

Figure 1

Comparison of the parameters of CTEPH subjects of different severity. Range for “Mild”: $35 > \text{PAP (mm Hg)} \geq 25$; range for “Moderate”: $45 > \text{PAP (mm Hg)} \geq 35$; range for “Severe”: $\text{PAP (mm Hg)} \geq 45$. The data are presented as mean $\pm$ SD or median (interquartile range). Statistical analysis of characteristics of “Mild”, “Moderate” and “Severe” was first analyzed with One-way ANOVA test or Kruskal-Wallis test, and was followed by Tukey’s multiple comparisons test or Dunn’s multiple comparisons test was presented as “*”, “**” or “***”. BNP=brain natriuretic peptide; PVR=pulmonary vascular resistance; RAP=right atrial pressure; FEV1=forced expiratory volume in 1s; FVC=forced vital capacity; VO₂=oxygen uptake; HR=heart rate; VE=minute ventilation; BR=breathing reserve; VC02=carbon dioxide output; PETCO₂=end-tidal partial pressure for carbon dioxide; PEO₂=end-tidal partial pressure for oxygen.

Figure 2

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Predictors of severe CTEPH on multivariable analysis of CPET and PFT parameters. Range for "Severe": PAP (mm Hg)≥45. Results are expressed as odds ratio (OR) with 95% confidence interval (95% CI). FEV1=forced expiratory volume in 1s; FVC=forced vital capacity; VE=minute ventilation.

Figure 3

Performance of CPET and PFT parameters for the prediction of severe CTEPH. A. Receiver operating characteristic (ROC) curves for single factor and multiple factors that predict severe CTEPH. B. Calibration curves for single factor and multiple factors that predict severe CTEPH.