Original Article

# The value of cardiopulmonary exercise testing in the diagnosis of pulmonary hypertension

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**Background:** Cardiopulmonary exercise testing (CPET) continuously analyzes the gas exchange of patients during rest, exercise, recovery, and simultaneously records the response of the cardiopulmonary system. This study aimed to observe the characteristics of CPET in patients with pulmonary hypertension (PH) and to explore the cutoff value of CPET variables in detecting PH. The diagnostic value of CPET was also investigated in a subgroup of patients who had an incorrect or missed diagnosis of PH by echocardiography.

**Methods:** Treatment-naïve patients with suspected PH who were admitted to Fuwai Hospital from January 2017 to August 2018 were consecutively enrolled. The gold standard criterion for PH was defined as mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest, measured by right heart catheterization. General clinical materials, echocardiography, hemodynamics, and CPET data of the patients were collected and compared between groups. Logistic regression analyses were performed to explore the CPET variables that were independently associated with PH. To further validate the value of CPET for diagnosing PH, the CPET cutoff values obtained from receiver operating characteristic (ROC) curve analysis were used in patients who had an incorrect or missed diagnosis by echocardiography.

**Results:** Five hundred and fifty-nine patients were included in the study. Among them, patients with PH had significantly poorer CPET variables. Multivariate logistic regression analysis showed that peak work rate (WR), peak oxygen uptake ($VO_2$), and end-tidal carbon dioxide partial pressure ($PetCO_2$) at the anaerobic threshold (AT) were independently associated with PH after adjustment for age, sex, and body mass index. The above three CPET variables were all negatively correlated with mPAP. The combined CPET variable including peak WR, peak $VO_2$ and $PetCO_2$ at AT had the largest area under the ROC curve for the diagnosis of PH (0.890, 95% CI: 0.852–0.927, P<0.001). The cutoff value was 0.86, and the sensitivity and specificity were 81.8% and 86.5%, respectively. Using this cutoff value, 83.7% of patients who were misdiagnosed and 67.9% of patients who had a missed diagnosis by echocardiography were identified.

**Conclusions:** PH patients have decreased cardiopulmonary reserve, lower exercise tolerance, and increased ineffective ventilation. The combination of peak WR, peak$VO_2$, and $PetCO_2$ at AT had increased sensitivity and specificity for the diagnosis of PH, and increased the specificity for identifying patients who had been misdiagnosed as PH by echocardiography.

**Keywords:** Cardiopulmonary exercise testing (CPET); pulmonary hypertension (PH); cutoff value; echocardiography

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## Introduction

Pulmonary hypertension (PH) refers to a group of pathophysiological syndromes of multiple etiologies. It is characterized by pulmonary vascular remodeling, which causes pulmonary vascular resistance to progressively increase, leading to right heart failure and death (1). Patients with PH usually complain of dyspnea on exertion-a none specific symptom that easily leads to missed diagnosis and misdiagnosis. At diagnosis, 85% of high-risk PH patients are already at an advanced stage of the disease (2,3). Therefore, the screening and timely identification of suspected PH patients are imperative. Right heart catheterization (RHC) is the gold standard for the diagnosis of PH, but it can also cause complications.

Echocardiography is the most commonly used screening method for PH in the clinical settings. However, it often leads to the overestimation and underestimation of pulmonary artery systolic pressure (4). Held *et al.* (5) retrospectively analyzed the echocardiographic data of 42 patients with chronic thromboembolic pulmonary hypertension (CTEPH) and showed that echocardiography detected CTEPH in 29 patients (69%), while the other 13 patients (31%) went undiagnosed. The European Society of Cardiology proposed that echocardiography was not suitable for screening patients with mild asymptomatic PH (6). Therefore, more accurate screening methods need to be found. CPET may improve diagnostic specificity in patients with echocardiography-suspected PH.

In recent years, several studies have confirmed the important role of cardiopulmonary exercise testing (CPET) in PH diagnosis. Woods *et al.* (7) compared the CPET data of 40 PH patients and 25 healthy controls, and found significantly lower end-tidal carbon dioxide partial pressure ($PetCO_2$) and higher minute ventilation (VE)/carbon dioxide output ($VCO_2$) in the PH patients. Meanwhile, the levels of $PetCO_2$ and $VE/VCO_2$ were found to be correlated with the severity of PH. Nishio *et al.* (8) demonstrated that PH patients had a decreased peak oxygen uptake ($VO_2$) and an increased $VE/VCO_2$ slope compared with chronic heart failure patients. CPET variables were also shown to be associated with hemodynamic parameters. Thirapatarapong *et al.* (9) reviewed and analyzed the data on pulmonary function, RHC, and CPET in 98 patients with severe chronic obstructive pulmonary disease. They observed that chronic obstructive pulmonary disease patients with PH had a significantly reduced peak work rate (WR), peak $VO_2$, and peak oxygen pulse ($O_2$ pulse). Moreover, peak $VO_2$ was negatively correlated with mean pulmonary artery pressure (mPAP). Accordingly, CPET is expected to serve as a noninvasive but effective means of identifying pulmonary vasculopathy in PH. In this study, we aimed to explore the value of CPET in the diagnosis of PH.

We present the following article in accordance with the STARD reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1061b).

## Methods

This single center study was conducted at Fuwai Hospital, National Center for Cardiovascular Diseases in Beijing, China. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Committee Board of the Fuwai Hospital. Informed consent was given by all patients.

### *Study sample*

Untreated patients with suspected PH who were admitted to Fuwai Hospital between January 2017 and August 2018 were consecutively included in this study. Patients with any of the following conditions were considered to be suspected PH cases: (I) exertional dyspnea as the chief complaint; (II) P2 enhancement and pathological third heart sound during physical examination; (III) elevated levels of plasma B-type natriuretic peptide or N-terminal prohormone of brain natriuretic peptide (NT-proBNP); (IV) electrocardiogram manifestations, such as right axis deviation, right bundle branch block, and other phenomena, reflecting an increased right heart load; (V) protruding pulmonary artery segment and expanded right heart image from chest X-ray; (VI) reduced pulmonary diffusion capacity; (VII) suspected PH by echocardiography, including tricuspid regurgitation velocity (TRV) >2.8 m/s, a widened pulmonary artery, a dilated right heart, and a widened inferior vena cava, etc.; (VIII) patients at high-risk of PH.

All patients were over the age of 18. Patients with any of the following conditions were excluded: (I) recurrent syncope or massive hemoptysis; (II) neuromuscular disease affecting the 6-minute walk test and CPET; (III) severe arrhythmia requiring intervention; (IV) severe liver and kidney dysfunction; (V) severe anemia (hemoglobin <90 g/L). Patients who had recently received exercise rehabilitation training were also excluded.

### *Echocardiography and RHC*

Patients' echocardiographic and hemodynamic parameters were collected in addition to their age, sex, body mass index (BMI), 6-minute walking distance (6-MWD), World Health Organization functional class (WHO FC), and plasma levels of NT-proBNP. As a screening tool for PH, echocardiography was performed on each patient on the day of admission. Patients who had a TRV >2.8 m/s and other echocardiographic signs such as a widened pulmonary artery, dilated right heart, and widened inferior vena cava were considered to have PH (10). The diastolic left ventricle diameter was measured in the left ventricular long-axis view, and the diastolic right ventricle diameter was measured in the apical four-chamber view. Ejection fraction was assessed using the Simpson biplane method.

The diagnosis of PH in each patient was confirmed by RHC. As the gold standard for PH diagnosis, RHC was conducted by experienced pulmonary vascular physicians. The hemodynamic parameters obtained by RHC included right atrial pressure, mPAP, total pulmonary resistance, cardiac index, and mixed venous oxygen saturation. As assessed by RHC, mPAP $\geqslant$ 25 mmHg at rest was defined as PH (11). Physicians who conducted RHC were blind to the CPET information of the participants.

### *CPET*

Before RHC, each suspected PH patient enrolled in this study underwent symptom-limited CPET using the COSMED Quark CPET system. The performers of CPET were blind to the RHC information of the enrolled patients. The following four phases were completed on a cycle ergometer: (I) 3 minutes of rest; (II) 3 minutes of unloaded pedaling at an approximate speed of 60 rpm; (III) WR-incremental exercise to achieve maximal tolerance; (IV) 5 minutes of recovery. VE, $VO_2$, and $VCO_2$ were measured breath-by-breath and were averaged every 10 seconds during the entire process. Meanwhile, the responses of the cardiovascular system including blood pressure, heart rate (HR), and a 12-lead electrocardiogram were recorded.

Peak $VO_2$ was defined as the highest 30-second average value of $VO_2$ during the final minute of exercise. The anaerobic threshold (AT) was the maximal $VO_2$ before the onset of lactic acidosis, which was determined using the V-slope method. The peak $O_2$ pulse was the ratio of peak $VO_2$ to peak HR. The $VE/VCO_2$ slope was the linear regression slope of the relation of VE to $VCO_2$ over the whole exercise period. The oxygen uptake efficiency slope (OUES) was the slope in the following equation: $VO_2 = OUES \times VE + B$. The peak respiratory exchange ratio (RER) was defined as the ratio of peak $VCO_2$ to peak $VO_2$. Heart rate recovery (HRR) was considered as the maximum HR minus the HR at 2 minutes after peak exercise. Peak circulatory power was defined as the product of peak $VO_2$ and peak systolic blood pressure (SBP). Peak ventilatory power was defined as peak SBP divided by the $VE/VCO_2$ slope (12). Ventilation efficiency was assessed according to the $VE/VCO_2$ ratio, $VE/VCO_2$ slope, and $PetCO_2$.

### *Statistical analysis*

Continuous variables are presented as the mean ± standard deviation or median (interquartile range), and categorical variables are presented as counts or percentages. To compare the differences between groups, an independent sample *t*-test was used for continuous variables with normal distribution, a non-parametric Kruskal-Wallis test was used for continuous variables with non-normal distribution, and the chi-square test was used for categorical variables. Univariate and multivariate logistic regression analyses were carried out to identify the CPET variables that were independently associated with PH. Furthermore, linear correlation analysis between CPET variables and mPAP was performed. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff values, sensitivity, and specificity of CPET variables for diagnosing PH. Missing data are processed using weights. $P<0.05$ was defined as statistically significant. All statistical analyses were carried out with SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA).

## Results

In total, 559 suspected PH patients without treatment were recruited. Of them, 485 patients were confirmed as PH by RHC, including 136 patients with congenital heart disease-associated pulmonary arterial hypertension, 117 with idiopathic pulmonary arterial hypertension, 86 with CTEPH, 35 with connective tissue disease-associated pulmonary arterial hypertension, 19 with hypoxia-associated PH, 16 with PH due to pulmonary vasculitis, 12 with left heart disease-associated PH, 8 with heritable pulmonary arterial hypertension, 7 with pulmonary veno-occlusive disease, and 49 with other subtypes of PH. The participant enrollment and exclusion processes are detailed in *Figure 1*.

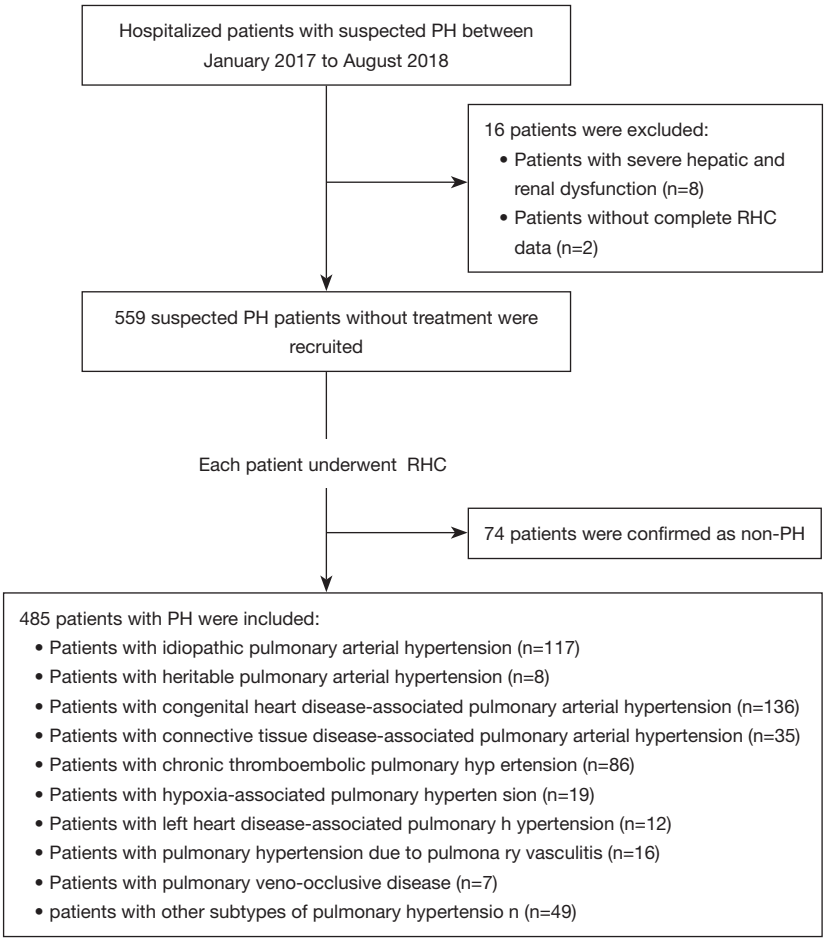


**Figure 1** Flow diagram of participant enrollment and exclusion. PH, pulmonary hypertension; RHC, right heart catheterization.

### *Baseline characteristics of patients*

Baseline characteristics were compared between patients with and without PH. PH patients were younger (42±14 *vs.* 50±14 years, P<0.001) and had a lower BMI (22.6±3.9 *vs.* 23.8±3.6 $kg{\cdot}m^{-2}$, P=0.005), a shorter 6-MWD (401±100 *vs.* 459±104 m, P<0.001), a higher NT-proBNP [903.5 (238.8–2189.3) *vs.* 112.1 (44.6–234.7), P<0.001], and a poorer WHO FC (P<0.001). The echocardiographic and hemodynamic parameters of the two groups were also statistically significantly different. The details are displayed in *Table 1*.

### *CPET characteristics of patients with PH*

The time interval between CPET and RHC was less than 7 days. No adverse events resulted from performing both of them. *Table 2* compares the CPET variables between patients with and without PH. Besides peak VE, peak SBP, peak diastolic blood pressure (DBP), and HRR, the other CPET variables were statistically different. Patients with PH had decreased exercise tolerance, which was mainly reflected by a significant decrease in peak WR (72±30 *vs.* 103±43 W, P<0.001), AT [10.0 (8.6–12.2) *vs.* 12.5 (10.9–14.3) $mL{\cdot}kg^{-1}{\cdot}min^{-1}$, P<0.001], peak $VO_2$ (13.8±6.0 *vs.* 18.5±5.4 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$, P<0.001), and OUES (1,025.2±463.0 *vs.* 1,539.4±458.0, P<0.001). PH patients also showed poor circulatory response, which was supported by significant decreases in peak HR (134±23 *vs.* 140±24 $min^{-1}$, P=0.038), $O_2$ pulse (6.1±2.1 *vs.* 8.5±2.7 $mL{\cdot}min^{-1}{\cdot}beat^{-1}$, P<0.001), and peak circulatory power [1,776.0 (1,341.2–2,293.2) *vs.* 2,447.3 (1,833.7–3,251.4) $mmHg{\cdot}mL^{-1}{\cdot}kg^{-1}{\cdot}min^{-1}$, P<0.001]. In addition, ineffective ventilation was increased in PH patients, which was reflected by significant decreases in $PetCO_2$ at AT (29±7 *vs.* 38±7mmHg, P<0.001) and peak ventilatory power

 

**Table 1** Basic characteristics of all participants

| Variables | Patients with PH (n=485) | Patients without PH (n=74) | P value |
|---|---|---|---|
| Age, years | 42±14 | 50±14 | <0.001 |
| Female, n (%) | 324 (66.8) | 55 (74.3) | 0.230 |
| BMI, $kg·m^{-2}$ | 22.6±3.9 | 23.8±3.6 | 0.005 |
| WHO FC I/II/III/IV, n | 26/226/205/28 | 36/32/5/1 | <0.001 |
| 6-MWD, m | 401±100 | 459±104 | <0.001 |
| NT-proBNP, $pg·mL^{-1}$ | 903.5 (238.8–2,189.3) | 112.1 (44.6–234.7) | <0.001 |
| Subtypes of PH, n (%) | | | |
| Idiopathic pulmonary arterial hypertension | 117 (24.2) | – | – |
| Heritable pulmonary arterial hypertension | 8 (1.6) | – | – |
| Congenital heart disease-associated pulmonary arterial hypertension | 136 (28.1) | – | – |
| Connective tissue disease-associated pulmonary arterial hypertension | 35 (7.2) | – | – |
| CTEPH | 86 (17.7) | – | – |
| PH due to lung diseases and/or hypoxia | 19 (3.9) | – | – |
| PH due to left heart disease | 12 (2.5) | – | – |
| Pulmonary vasculitis | 16 (3.3) | – | – |
| Pulmonary veno-occlusive disease | 7 (1.4) | – | – |
| Others | 49 (10.1) | – | – |
| Echocardiographic parameters | | | |
| Diastolic left ventricle diameter, mm | 40±8 | 45±5 | <0.001 |
| Diastolic right ventricle diameter, mm | 33±7 | 25±5 | <0.001 |
| Diastolic right ventricle/left ventricle diameter ratio | 0.79 (0.64–1.03) | 0.55 (0.48–0.62) | <0.001 |
| Ejection fraction, % | 62±7 | 64±6 | 0.009 |
| TRV, $m·s^{-1}$ | 4.4±0.7 | 3.0±0.5 | <0.001 |
| Hemodynamic parameters | | | |
| Right atrial pressure, mmHg | 5 (3–8) | 3 (1–5) | <0.001 |
| MPAP, mmHg | 54±17 | 16±4 | <0.001 |
| Total pulmonary resistance, $dyn·s·cm^{-5}$ | 882.2 (584.3–1,185.7) | 209.0 (159.9–269.7) | <0.001 |
| Cardiac index, $L·min^{-1}·m^{-2}$ | 3.2±1.0 | 3.9±0.9 | <0.001 |
| Mixed venous oxygen saturation, % | 70.2±7.6 | 76.8±4.9 | <0.001 |

Continuous variables are presented as mean ± SD or median (interquartile range). Categorical variables are given as counts or percent. P<0.05 represents statistical difference. PH, pulmonary hypertension; BMI, body mass index; WHO FC, World Health Organization functional class; 6-MWD, six minutes walking distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; CTEPH, chronic thromboembolic pulmonary hypertension; TRV, tricuspid regurgitation velocity; MRAP, mean pulmonary arterial pressure.

**Table 2** The characteristics of CPET variables in patients with and without PH

| Variables | Patients with PH (n=485) | Patients without PH (n=74) | P value |
|---|---|---|---|
| Peak WR, W | 72±30 | 103±43 | <0.001 |
| AT, mL·kg$^{-1}$·min$^{-1}$ | 10.0 (8.6–12.2) | 12.5 (10.9–14.3) | <0.001 |
| Peak $VO_2$, mL·kg$^{-1}$·min$^{-1}$ | 13.8±6.0 | 18.5±5.4 | <0.001 |
| Peak RER | 1.09±0.10 | 1.14±0.13 | <0.001 |
| Peak VE, mL·min$^{-1}$ | 41.7±14.2 | 43.9±19.1 | 0.729 |
| Peak HR, min$^{-1}$ | 134±23 | 140±24 | 0.038 |
| Peak $O_2$ pulse, mL·min$^{-1}$·beat$^{-1}$ | 6.1±2.1 | 8.5±2.7 | <0.001 |
| Peak SBP, mmHg | 136±31 | 144±34 | 0.056 |
| Peak DBP, mmHg | 86±24 | 88±23 | 0.468 |
| $PetCO_2$ at AT, mmHg | 29±7 | 38±7 | <0.001 |
| $VE/VCO_2$ at AT | 43.6±10.4 | 31.6±5.7 | <0.001 |
| $VE/VCO_2$ slope | 44.0±18.1 | 28.6±7.3 | <0.001 |
| OUES | 1,025.2±463.0 | 1,539.4±458.0 | <0.001 |
| HRR, min$^{-1}$ | 28 (15-45) | 29 (21-38) | 0.790 |
| Peak circulatory power, mmHg·mL$^{-1}$·kg$^{-1}$·min$^{-1}$ | 1,776.0 (1,341.2–2,293.2) | 2,447.3 (1,833.7–3,251.4) | <0.001 |
| Peak ventilatory power, mmHg | 3.5±1.6 | 5.3±1.9 | <0.001 |

Continuous variables are presented as mean ± SD or median (interquartile range). P<0.05 represents statistical difference. CPET, cardiopulmonary exercise testing; PH, pulmonary hypertension; WR, work rate; AT, anaerobic threshold; $VO_2$, oxygen uptake; RER, respiratory exchange ratio; VE, minute ventilation; HR, heart rate; $O_2$ pulse, oxygen pulse; SBP, systolic blood pressure; DBP, diastolic blood pressure; $PetCO_2$, end-tidal carbon dioxide partial pressure; $VCO_2$, carbon dioxide output; OUES, oxygen uptake efficiency slope; HRR, heart rate recovery.

(3.5±1.6 *vs.* 5.3±1.9 mmHg, P<0.001), along with significant increases in $VE/VCO_2$ at AT (43.6±10.4 *vs.* 31.6±5.7, P<0.001) and the $VE/VCO_2$ slope (44.0±18.1 *vs.* 28.6±7.3, P<0.001).

### *CPET variables independently associated with PH*

As shown in *Table 3*, univariate logistic regression analysis revealed that age, BMI, and CPET variables except for AT and peak HR were associated with PH (all P<0.001). Age, sex, BMI, peak WR, peak $VO_2$, peak RER, $O_2$ pulse, $PetCO_2$ at AT, the $VE/VCO_2$ at AT, $VE/VCO_2$ slope, peak circulatory power and peak ventilatory power were subsequently included in multivariate logistic regression analysis. After adjustment for age, sex and BMI, CPET variables including peak WR, peak $VO_2$, and $PetCO_2$ at AT were independently associated with PH (*Table 4*). In addition, the above three CPET variables were significantly correlated with the mPAP measured by RHC, the lower the peak WR, peak $VO_2$ and $PetCO_2$ at AT, the higher the mPAP value (*Figure 2*).

### *ROC curve analysis of CPET variables in PH diagnosis*

The ROC curve analysis of CPET variables in the diagnosis of PH was performed using the gold standard mentioned previously. The sensitivity, specificity, and the area under the receiver operator characteristic curve (AUC) of CPET variables in PH diagnosis are shown in *Table 5*. A regression equation was obtained from multivariate ROC curve analysis as follows: Y=9.294 – 0.0048 × peak WR – 0.0173 × peak $VO_2$ – 0.0752 × $PetCO_2$ at AT. Combining with the above three CPET variables, this model had the highest AUC [0.890 (0.852–0.927), P<0.001] and high sensitivity (81.8%) and specificity (86.5%) for diagnosing PH, as shown in *Figure 3*.

**Table 3** Factors associated with PH in univariate logistic regression analysis

| Variables | Odd ratio | 95% CI | P value |
|---|---|---|---|
| Age | 0.962 | 0.945–0.979 | <0.001 |
| Female *vs.* male | 0.695 | 0.399–1.211 | 0.199 |
| BMI | 0.930 | 0.876–0.987 | 0.017 |
| Peak WR | 0.976 | 0.969–0.983 | <0.001 |
| AT | 0.999 | 0.992–1.007 | 0.833 |
| Peak $VO_2$ | 0.864 | 0.821–0.909 | <0.001 |
| Peak RER | 0.008 | 0.001–0.077 | <0.001 |
| Peak HR | 0.990 | 0.979–1.001 | 0.065 |
| Peak $O_2$ pulse | 0.690 | 0.623–0.765 | <0.001 |
| $PetCO_2$ at AT | 0.819 | 0.781–0.859 | <0.001 |
| $VE/VCO_2$ at AT | 1.252 | 1.183–1.324 | <0.001 |
| $VE/VCO_2$ slope | 1.102 | 1.067–1.138 | <0.001 |
| OUES | 0.998 | 0.998–0.999 | <0.001 |
| Peak circulatory power | 0.999 | 0.999–1.000 | <0.001 |
| Peak ventilatory power | 0.542 | 0.449–0.653 | <0.001 |

P<0.05 represents statistical difference. PH, pulmonary hypertension; BMI, body mass index; WR, work rate; AT, anaerobic threshold; $VO_2$, oxygen uptake; RER, respiratory exchange ratio; HR, heart rate; $O_2$ pulse, oxygen pulse; $PetCO_2$, end-tidal carbon dioxide partial pressure; VE, minute ventilation; $VCO_2$, carbon dioxide output; OUES, oxygen uptake efficiency slope.

**Table 4** Multivariate logistic regression analysis after adjustment for age, sex and BMI

| Variables | Odd ratio | 95% CI | P value |
|---|---|---|---|
| Peak WR | 0.973 | 0.961–0.986 | <0.001 |
| Peak $VO_2$ | 0.949 | 0.910–0.990 | 0.015 |
| $PetCO_2$ at AT | 0.865 | 0.820–0.913 | <0.001 |

P<0.05 represents statistical difference. BMI, body mass index; WR, work rate; $VO_2$, oxygen uptake; $PetCO_2$, end-tidal carbon dioxide partial pressure; AT, anaerobic threshold.

### *Subgroup analyses of missed diagnosis and misdiagnosis of PH by echocardiography*

Patients with TRV≤2.8 $m{\cdot}s^{-1}$ were not considered to have PH. However, among 59 patients whose TRV≤2.8 $m{\cdot}s^{-1}$, 28 patients were confirmed to have PH by RHC. The cutoff values of CPET variables could identify a subset of patients with normal echocardiography (*Table 6*). Patients with TRV >2.8 $m{\cdot}s^{-1}$ together with other echocardiographic signs were considered to have PH. Forty-three patients screened as PH by echocardiography were confirmed to have a normal mPAP by RHC. The cutoff values of CPET variables could also identify a subset of patients misdiagnosed as PH by echocardiography (*Table 7*).

## Discussion

PH presents similar lesions like wall thickening and luminal narrowing of the pulmonary arterioles are presented regardless of the specific pathogenetic mechanism (13). This pulmonary vascular remodeling leads to an increase in pulmonary vascular resistance and a corresponding increase

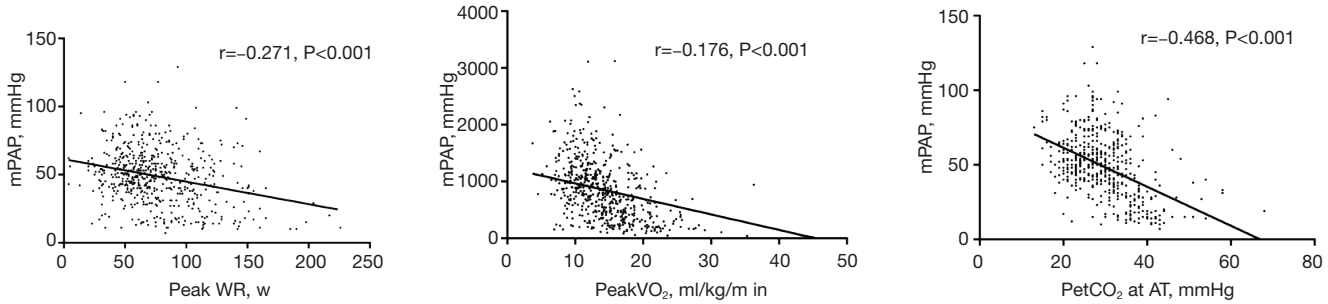


**Figure 2** The relationship between CPET variables and mPAP. CPET, cardiopulmonary exercise testing; MPAP, mean pulmonary arterial pressure; WR, work rate; $VO_2$, oxygen uptake; $PetCO_2$, end-tidal carbon dioxide partial pressure; AT, anaerobic threshold.

**Table 5** ROC curve analysis for CPET variables in PH diagnosis

| Variables | Cutoff value | AUC (95% CI) | Sensitivity/Specificity (%) | P value |
|---|---|---|---|---|
| Peak WR | 82 | 0.734 (0.668–0.799) | 70.3/68.6 | <0.001 |
| $PeakVO_2$ | 14.2 | 0.777 (0.719–0.835) | 82.4/61.4 | <0.001 |
| $PetCO_2$ at AT | 35 | 0.876 (0.830–0.922) | 80.9/86.2 | <0.001 |
| Combined CPET variables | 0.86 | 0.890 (0.852–0.927) | 81.8/86.5 | <0.001 |

P<0.05 represents statistical difference. ROC, receiver operator characteristic; CPET, cardiopulmonary exercise testing; AUC, area under the receiver operator characteristic curve; WR, work rate; $VO_2$, oxygen uptake; $PetCO_2$, end-tidal carbon dioxide partial pressure; AT, anaerobic threshold.

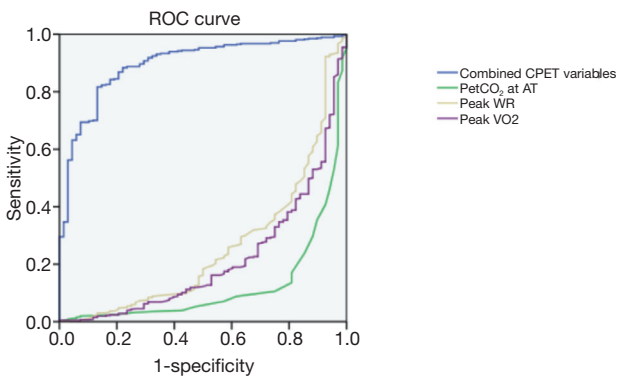


**Figure 3** The ROC curve of CPET variables in PH diagnosis. ROC, receiver operator characteristic; CPET, cardiopulmonary exercise testing; WR, work rate; $VO_2$, oxygen uptake; $PetCO_2$, end-tidal carbon dioxide partial pressure; AT, anaerobic threshold.

in pulmonary artery pressure. Right heart function becomes impaired by the increased right ventricular afterload, and an enlarged right ventricle causes the interventricular septum to shift leftward, which affects left heart filling. Both conditions affect the patient's cardiac output, thus leading to reduced $VO_2$ (14). In addition, pulmonary vascular lesions cause a pulmonary ventilation/ perfusion mismatch and enlargement of a physiological dead space, thus reducing ventilation efficiency (15). Recent studies have found consistent changes in many CPET variables in patients with PH (16-18). In our study, PH patients presented with significantly reduced peak WR, AT, peak $VO_2$, $O_2$ pulse, and $PetCO_2$ at AT, and significantly increased $VE/VCO_2$ at AT and $VE/VCO_2$ slope, compared to non-PH patients. These findings are consistent with the results of previous studies. The value of novel CPET variables including OUES, peak circulatory power and peak ventilatory power were also investigated in this study. Previous research shows that the OUES is significantly lower in patients with heart failure and is also related to the severity of heart failure (19). Borghi-Silva *et al.* (20) analyzed the CPET and echocardiographic data of 86 heart failure patients with reduced ejection fraction. They found a peak ventilatory power to be significantly decreased, reflecting the impaired right heart function and pulmonary hemodynamic deteriorations in these patients. Cohen-Solal *et al.* (21) proposed that, of the many CPET variables, peak circulatory power is the best indicator for predicting adverse clinical outcomes in PH. In this study, we found that the three novel CPET variables were significantly reduced in PH patients, which supports the previous findings.

**Table 6** The value of CPET variables in identification of PH in patients with normal echocardiography

| Variables | Cutoff value | Positive (PH), n (%) |
|---|---|---|
| Peak WR | <82 | 11 (39.3) |
| Peak $VO_2$ | <14.2 | 8 (28.6) |
| $PetCO_2$ at AT | <35 | 21 (75.0) |
| Combined CPET variables | > 0.86 | 19 (67.9) |

Categorical variables are given as counts or percent. CPET, cardiopulmonary exercise testing; PH, pulmonary hypertension; WR, work rate; $VO_2$, oxygen uptake; $PetCO_2$, end-tidal carbon dioxide partial pressure; AT, anaerobic threshold.

**Table 7** The value of CPET variables in identification of non-PH in patients misdiagnosed by echocardiography

| Variables | Cutoff value | Positive (non-PH), n (%) |
|---|---|---|
| Peak WR | ≥82 | 31 (72.1) |
| Peak $VO_2$ | ≥14.2 | 35 (81.4) |
| $PetCO_2$ at AT | ≥35 | 29 (67.4) |
| Combined CPET variables | ≤0.86 | 36 (83.7) |

Categorical variables are given as counts or percent. CPET, cardiopulmonary exercise testing; PH, pulmonary hypertension; WR, work rate; $VO_2$, oxygen uptake; $PetCO_2$, end-tidal carbon dioxide partial pressure; AT, anaerobic threshold.

In a 2010 review published by Arena *et al.* (22), 19 studies described the reliability of CPET in identifying pulmonary vasculopathy, and its value in diagnosing different PH subtypes. Several studies have demonstrated a significant correlation between CPET variables and hemodynamic parameters. Yasunobu *et al.* (23) found that in PH patients, $PetCO_2$ at rest, at AT and at peak exercise was negatively correlated with mPAP (all $P<0.05$). An article published by Holverda *et al.* (24) indicated that the lowest $VE/VCO_2$ was significantly correlated with mPAP ($r=0.43$, $P<0.05$). Gläser *et al.* (25) investigated patients with pulmonary fibrosis and found that the $VE/VCO_2$ slope ($r=0.77$, $P<0.05$) and peak $VO_2$ ($r=-0.52$, $P<0.05$) was significantly correlated with pulmonary artery systolic pressure in patients who had pulmonary arterial hypertension due to pulmonary fibrosis. As above, our study also found that peak WR, peak $VO_2$, peak RER, peak $O_2$ pulse, $PetCO_2$ at AT, OUES, peak circulatory power, and peak ventilatory power were negatively correlated with mPAP in all included patients with suspected PH, while $VE/VCO_2$ at AT and the $VE/VCO_2$ slope were positively correlated with mPAP (data not shown). Of these, peak WR, peak $VO_2$ and PetCO2 at AT were founded to be independently associated with PH. A study conducted by Zhao *et al.* (26) included 88 patients with echocardiography-suspected PH. The results showed that the combination of the $VE/VCO_2$ slope and AT achieved a sensitivity and specificity of 93% and 95%, respectively, for diagnosing PH with RHC used as the gold standard. In our study, the combination of the CPET variables including peak WR, peak $VO_2$, and $PetCO_2$ at AT also had high sensitivity and specificity in PH diagnosis.

Sciumè *et al.* (27) conducted a follow-up study in patients with primary myelofibrosis and found that patients with normal baseline echocardiography but abnormal CPET developed PH after 12 months of follow-up. Their results demonstrated that CPET was more sensitive and specific than echocardiography in the identification of pulmonary vascular lesions. In the present study, the regression equation $Y=9.294 - 0.0048 \times \text{peak WR} - 0.0173 \times \text{peak } VO_2 - 0.0752 \times PetCO_2$ at AT achieved the highest AUC, which showed improved sensitivity and specificity in diagnosing PH. When Y was >0.86, it supported the PH diagnosis. We conducted subgroup analyses of patients who had a missed diagnosis or misdiagnosis PH by echocardiography. The cutoff value (Y>0.86) of the combined CPET variables including peak WR, peak $VO_2$, and $PetCO_2$ identified 19 out of 28 patients who had a normal echocardiography but who were confirmed as PH by RHC. However, the cutoff value (Y≤0.86) identified 36 out of 49 non-PH patients who were misdiagnosed as PH by echocardiography. Therefore, the negative predictive value of the combined CPET variables for PH diagnosis is higher. This shows that CPET is able to identify patients

who are misdiagnosed as PH by echocardiography, and these patients can therefore be spared from invasive RHC, thus reducing the psychological and financial burden on patients and their families.

### *Limitations*

One significant limitation of the study is the use of sample with suspected PH. Thus, the identified CPET parameters may be more valuable for the identification of PH from suspected PH. Patients with PH in our study had many subtypes due to different etiologies, the degree of $VO_2$ decline and the severity of pulmonary ventilation/ perfusion mismatch might vary. But the PH patients' number in different subtypes had a big difference. Thus, subgroup analyses were not conducted. In future prospective study, the diagnostic value of CPET in each subtype of PH will be explored respectively. In addition, our study investigated only the commonly used clinical CPET variables. The other significant limitation is no external validation sample for testing the external validity of CPET. The accuracy of CPET cutoff values for PH diagnosis needs to be validated in multiple centers.

The authors may consider subgroup analyses according to subtypes of PH. The diagnostic value for PH subtypes is also interesting.

## Conclusions

CPET has significant value as a non-invasive method for the diagnosis of PH. Together with echocardiography, it can reduce the rates of missed diagnosis and misdiagnosis in patients with suspected PH, thus helping clinicians to accurately predict diagnosis and formulate appropriate treatment plans.

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## Footnote

*Reporting Checklist:* The authors have completed the STARD reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-1061b

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-1061b). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by committee board of the Fuwai Hospital (NO.: 2018-BKJ09) and informed consent was taken from all the patients.



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