The predictive value of minute ventilation versus carbon dioxide production in pulmonary hypertension associated with left heart disease

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Background: The aim of the present study was to investigate the role of key cardiopulmonary exercise testing (CPET) parameters in the identification of pre-capillary components in patients with pulmonary hypertension associated with left heart disease (PH-LHD), and to evaluate their correlations with hemodynamic parameters.

Methods: Ninety patients with PH-LHD underwent right-heart catheterization, echocardiography, and CPET. The differences in related indexes between a combined post- and pre-capillary PH (Cpc-PH) group (n=47) and an isolated post-capillary PH (Ipc-PH) group (n=43) were compared. Correlation analysis was performed. Logistic regression and receiver operator characteristic (ROC) analyses were performed to assess the ability of CPET variables to distinguish patients with Cpc-PH from those with Ipc-PH.

Results: The hemodynamics, hyperventilation and right ventricular function of Cpc-PH group were worse than those of Ipc-PH group. The parameters related to minute ventilation versus carbon dioxide production (VE/VCO2) played a significant role in the differentiation of Cpc-PH and Ipc-PH, and had a moderate positive correlation with pulmonary vascular resistance (PVR). Univariate and multivariate logistic analyses showed that lowest percentage of VE/VCO2 in predicted value (VE/VCO2%pred) was the single best predictor of Cpc-PH, and the area under ROC curve also confirmed that lowest VE/VCO2%pred (≥137%) could serve as a novel diagnostic marker for Cpc-PH. On the basis of this lowest VE/VCO2%pred threshold, patients were divided into two groups. Most hemodynamic parameters were worse in patients with a lowest VE/VCO2%pred ≥137%.

Conclusions: VE/VCO2-related parameters are powerful prognosticators for the presence of pre-capillary components in patients with PH-LHD, especially lowest VE/VCO2%pred.

Keywords: Pulmonary hypertension associated with left heart disease; combined post- and pre-capillary pulmonary hypertension; cardiopulmonary exercise testing (CPET); minute ventilation versus carbon dioxide production

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**Introduction**

Pulmonary hypertension (PH) is a common complication of left heart disease (LHD), with patients with LHD accounting for 65–80% of PH cases (1). PH associated with LHD (PH-LHD) is associated with poor prognosis and low exercise tolerance (2). PH-LHD is divided into combined post- and pre-capillary PH (Cpc-PH) and isolated post-capillary PH (Ipc-PH). Cpc-PH represent the presence of pre-capillary components in patients with PH-LHD. The best way to describe the presence of pre-capillary components in post-capillary PH is still controversial; all hemodynamic variables used to describe PH-LHD are not unlimited. Recent guidelines have revised the distinction between Cpc-PH and Ipc-PH. In the previous guidelines, Cpc-PH was referred to as reactive PH (3), and the transpulmonary gradient (TPG) was used as the distinguishing standard. At the 5th World Symposium on Pulmonary Hypotension (WSPH) in 2013, the combination (4,5) of pulmonary vascular resistance (PVR) and diastolic pulmonary pressure gradient (DPG) was presented as a diagnostic marker for distinguishing Cpc-PH and Ipc-PH. Recent guidelines have proposed PVR alone to be a suitable marker (6). Although hemodynamics is the gold standard currently, there are still some limitations in its clinical application. Therefore, further study of noninvasive methods for early diagnosis of Cpc-PH is worthy of attention. Furthermore, cardiopulmonary exercise testing (CPET) can be used assess the exercise capacity of patients with PH-LHD, but it is unclear whether it can distinguish between those with Ipc-PH and those with Cpc-PH.

Modern CPET systems allow analysis of gas exchange during rest, exercise, and recovery, and measurement of oxygen uptake (VO₂), carbon dioxide output (VCO₂), and ventilation (VE). CPET is the gold standard for evaluating cardiopulmonary function (7,8), and it may have important diagnostic utility for PH-LHD (9-11). Exercise-induced hyperventilation occurs in patients with Ipc-PH, while patients with Cpc-PH have even higher hyperventilation (10). Hyperventilation was characterized by an increase in VE versus VCO₂ (VE/VCO₂) in the few studies on CPET in patients with PH-LHD (9-11), VE/VCO₂ relationship is most often expressed as VE/VCO₂ slope, lowest VE/VCO₂, and peak VE/VCO₂. Except PH-LHD, pulmonary arterial hypertension (PAH) is a common type of PH. The end-tidal CO₂ (P₄₃CO₂), as an index of hyperventilation, may be valuable in the differential diagnosis of PAH (12). Cpc-PH is associated with decreased exercise capacity and is similar to PAH phenotype (10). Therefore, we hypothesized that a pre-capillary component in PH-LHD might be identified by the gas exchange parameters derived from CPET. In the current study, we investigated the differences in CPET parameters between patients with Ipc-PH and patients with Cpc-PH, and evaluated their correlations with hemodynamic diagnostic indicators, so as to identify reliable predictors of CPET for the diagnosis of Cpc-PH.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-21-366).

**Methods**

**Study design and patient population**

Patients with LHD who underwent in-hospital assessment for PH between May 2015 and May 2020 at Shanghai Pulmonary Hospital Affiliated to Tongji University School of Medicine were retrospectively included in the study. Clinical and laboratory tests were conducted to assess the World Health Organization functional class (WHO FC), N-terminal pro-B type natriuretic peptide (NT-pro-BNP) and 6-minute walk distance (6MWD) of all patients. Right heart catheterization (RHC) was performed on all patients. PH was defined as mean pulmonary artery pressure (PAP) >20 mmHg and pulmonary artery wedge pressure (PAWP) >15 mmHg at rest (6,13). Cpc-PH and Ipc-PH were further defined as PVR ≥3 Wood units (WU) and PVR <3 WU, respectively (6,13).

The inclusion criteria were: patients confirmed as PH-LHD by RHC, including those with PH due to heart failure with preserved left ventricular ejection fraction (LVEF) (HFpEF), those with PH due to heart failure with reduced LVEF (HFrEF), those with valvular heart disease, and those with congenital/acquired cardiovascular conditions leading to post-capillary PH. Patients also needed to have CPET data, with complete hemodynamic data by 2-dimensional echocardiography within 7 days of RHC. Patients were excluded if they could not perform a valid baseline exercise test or presented with any of the following clinical conditions: acute decompensated heart failure; severe cardiogenic shock requiring inotropic support or urgent mechanical circulatory support; signs of ischemia during CPET; or any other comorbidity with a life expectancy of <1 year. Patients with pulmonary arterial hypertension (PAH) or PH resulting from other diseases were excluded. All procedures performed in this...
study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital (K16-317). Individual consent for this retrospective analysis was waived.

RHC

RHC was conducted using the Swan-Ganz catheter (7- or 7.5-Fr; Edwards Lifesciences LLC, Irvine, CA), and the PAP and PAWP tracings were recorded. Cardiac output (CO) was measured using the thermodilution method with cold saline. PAWP was measured by digitized mean. DPG = diastolic PAP-PAWP, TPG = mean PAP-PAWP, PVR in WU was calculated as: (mean PAP-PAWP)/CO, total pulmonary resistance (TPR) = mean PAP/CO.

Transsthoracic echocardiography

Transthoracic echocardiography was performed according to the recommendations from the latest guidelines published by the American Society of Echocardiography (14). Tricuspid regurgitation was quantified by Doppler in accordance with current recommendations (15). Right ventricular (RV) end-diastolic transverse dimension (RVEDTD), right atrial transverse dimension (RATD), and end-systolic-stage eccentricity index (ENDSEI) were measured to evaluate the presence of right heart enlargement. Pulmonary artery systolic pressure (PASP) was measured by tricuspid regurgitation velocity (TRV) (14). RV function was assessed using tricuspid annular plane systolic excursion (TAPSE) (14). LVEF was measured using M-mode in the parasternal long-axis view.

CPET

CPET was performed on an electromagnetically braked cycle ergometer (Master Screen CPET, Jaeger Crop., Hoechberg, Germany), and gas exchange data were recorded over 10-second intervals via a breath-by-breath system. A test was terminated if any of the following conditions were observed: fatigued, dyspnea, chest tightness, or any other uncomfortable feeling reported by the patient. Measurements included heart rate (HR), O₂ uptake (VO₂), oxygen pulse (O₂ pulse), PET CO₂, VE/VCO₂, VO₂/VE, oxygen uptake efficiency plateau (OUEP), and oxygen uptake efficiency slope (OUES).

The HR, VO₂, PET CO₂, VE/VCO₂, VO₂/VE, and O₂ pulse values at peak exercise were measured according to the highest 30-second averaged value obtained during peak exercise. The lowest VE/VCO₂ was calculated by averaging the 9 lowest consecutive 10-second-averaged data points of VE/VCO₂. The VE/VCO₂ slope was obtained from linear regression analysis of the relationship of VE with VCO₂. The lowest VE/VCO₂ and VE/VCO₂ slope predicted values depends on age, sex, and size (16). percentage of predicted value (%pred) = Measured value/predicted value × 100%. The OUEP was the highest consecutive values for VO₂ (mL/min)/VE (L/min) at 90 seconds (17). Using linear square regression, we computed the OUES according to the following equation: VO₂ = a × lgVE + b (‘a’ is OUES) (17).

Statistical analysis

Data were analyzed using SPSS 19.0 (SPSS Inc.; Chicago, IL, USA). Characteristics of patients in the two groups (Ipc-PH and Cpc-PH) were compared using the independent-samples t-test and the Mann-Whitney U test for parametric and nonparametric data, respectively. Differences in categorical variables between groups were assessed using the χ² test. Correlations between CPET parameters and PVR, DPG, and TPG were assessed using Pearson’s correlation coefficient. Univariate and multivariate logistic regression analyses were used to evaluate the diagnostic value of CPET for Cpc-PH. Further, the ability of CPET parameters to identify Cpc-PH was assessed through receiver operating characteristic (ROC) curve analysis. Patients were subdivided into two groups according to the cutoff value of the CPET parameter with the highest diagnostic value, and hemodynamic differences were compared between the groups. For all analyses, statistical significance was indicated by a 2-sided P value of P<0.05.

Results

Patient characteristics

A total of 90 patients with PH-LHD were included in this study. These patients were further classified into two groups according to their PVR measured by RHC: the Cpc-PH group (n=47) and the Ipc-PH group (n=43). Sixteen patients with Cpc-PH had DPG ≥ 7 mmHg, and all patients with Ipc-PH had DPG <7 mmHg. The patients had an average age of 64.0 (56.5, 72.3) years, and 36 patients (40%) were male. There were no significant differences in age, sex, body mass index (BMI), WHO FC, PH-LHD classification, or
comorbidities between the two groups. The mean 6MWD was shorter in the Ipc-PH and Cpc-PH groups than in the non-PH group, and the NT-pro-BNP was higher. Key baseline characteristics are listed in Table 1.

**Comparison of echocardiographic and hemodynamic parameters between Cpc-PH and Ipc-PH**

As Table 1 shows, the Cpc-PH group had more significant enlargement of the RV (P<0.05) (Figure 1), a significantly higher occurrence of ENDSEI (P<0.05), and significantly higher PASP (P<0.01) than the Ipc-PH group (Figure 1). Further, the right atrium was also more enlarged in the Cpc-PH group than in the Ipc-PH group, although the difference was not statistically significant (P>0.05). The TAPSE and LVEF showed no difference between the Cpc-PH and Ipc-PH groups.

Table 1 also shows the main hemodynamic parameters of all patients. Systolic PAP, diastolic PAP, mean PAP, PVR, DPG, and TPG in the Cpc-PH group were significantly higher than those in the Ipc-PH group (P<0.001). TPR was also higher (P<0.05), whereas CO was lower (P<0.01) in Cpc-PH group. There was no significant difference in PAWP between the two groups (P>0.05).

**Comparison of CPET parameters between the Cpc-PH and Ipc-PH groups**

Compared with the Ipc-PH patients, Cpc-PH patients showed greater abnormalities in CPET results (Table 2). The lowest VE/VCO₂, lowest VE/VCO₂ % pred, VE/VCO₂ slope, VE/VCO₂ slope % pred, and peak VE/VCO₂ values of the Cpc-PH patients were significantly higher than those in the Ipc-PH group (P<0.001), and the VE/VCO₂ slope value was also higher (P<0.01). However, in Cpc-PH group, the OUEP was significantly lower (P<0.001), and the peak PET CO₂ and peak VO₂/VE values were also lower than those in the Ipc-PH group (P<0.01). In Cpc-PH patients, peak VO₂ was significantly decreased (P<0.05). The peak O₂ pulse and work load values were lower, but the difference was not statistically significant (P>0.05). Meanwhile, the resting HR and peak HR values were higher, but this difference was also without statistical significance (P>0.05).

**Correlations between CPET parameters and PVR, DPG, and TPG**

Table 3 illustrates the correlation between CPET parameters and three hemodynamic parameters used to identify Cpc-PH in PH-LHD patients. Lowest VE/VCO₂, lowest VE/VCO₂ % pred, VE/VCO₂ slope, VE/VCO₂ slope % pred, and peak VE/VCO₂ showed a moderate positive correlation with PVR (r=0.5, P<0.001). VE/VCO₂-related parameters had a stronger correlation with PVR than with DPG and TPG, and their correlations with PVR, DPG, and TPG were stronger than those with other CPET parameters. It could also be seen that the main echocardiographic indexes had weaker correlations with PVR, DPG, and TPG than with CPET parameters. Furthermore, RATD was more closely related to DPG, whereas PASP was more closely related to TPG.

As shown in Figure 2, there was a strong positive correlation between lowest VE/VCO₂ and peak VE/VCO₂ (r=0.939, P<0.0001). Moreover, there were moderate positive correlations between peak VE/VCO₂ and VE/VCO₂ slope (r=0.766, P<0.0001), between lowest VE/VCO₂ and VE/VCO₂ slope (r=0.693, P<0.0001), and between lowest VE/VCO₂ % pred and VE/VCO₂ slope % pred (r=0.758, P<0.0001).

**Diagnostic value of CPET parameters for Cpc-PH**

Logistic regression was used to investigate the value of the candidate CPET parameters in the diagnosis of Cpc-PH (Table 4). In the univariate analysis, peak VO₂, peak VE/VCO₂, lowest VE/VCO₂, lowest VE/VCO₂ % pred, VE/VCO₂ slope, VE/VCO₂ slope % pred, peak PET CO₂, peak VO₂/VE, and OUEP were significant predictors of Cpc-PH. Subsequently, age, BMI, and all factors with a P value ≤0.05 were included in the multivariate logistic regression (forward) analysis, which revealed that only lowest VE/VCO₂ % was a significant independent predictor of Cpc-PH (odds ratio 0.957, 95% CI: 0.934–0.981; P<0.001).

ROC curve analysis was then performed to evaluate the independent predictors of Cpc-PH (Figure 3). Lowest VE/VCO₂ % pred was the best predictor for Cpc-PH, as demonstrated by an area under the curve (AUC) of 0.77. Lowest VE/VCO₂ % pred ≥137.0% was considered to be the best cutoff value for predicting Cpc-PH, with a sensitivity of 63.8% and a specificity of 86.0%.

**Effects of independent predictors on hemodynamics**

The patients were divided into two groups using the best cutoff value for lowest VE/VCO₂ % pred (≥137%) as the threshold (Table 5). Systolic PAP, diastolic PAP, mean PAP,
Table 1 Patient baseline characteristics, and echocardiographic and hemodynamic parameters

| Variable                      | Cpc-PH (n=47) | Ipc-PH (n=43) | P value |
|-------------------------------|---------------|---------------|---------|
| Age, years                    | 63.0 (51.0, 69.0) | 67.0 (60.0, 74.0) | 0.053   |
| Males, n (%)                  | 21 (44.7)     | 15 (34.9)     | 0.343   |
| BMI, kg/m²                    | 23.4 (20.7, 27.3) | 23.5 (21.8, 27.4) | 0.526   |
| WHO FC, n (%)                 |               |               | 0.802   |
| I–II                          | 12 (25.5)     | 10 (23.3)     | 0.351   |
| III–IV                        | 35 (74.5)     | 33 (76.7)     |         |
| 6MWD, m                       | 340.0 (250.0, 423.8) | 412.5 (350.0, 467.5) | 0.010   |
| NT-pro-BNP, pg/mL             | 1,575.0 (539.5, 2,657.5) | 903.0 (345.5, 1,698.8) | 0.034   |
| HFReF, n (%)                  | 3 (6.4)       | 1 (2.3)       | 0.059   |
| VHD, n (%)                    | 14 (29.8)     | 19 (44.2)     | 0.157   |
| Comorbidities, n (%)          |               |               | 0.915   |
| COPD                          | 18 (38.3)     | 16 (37.2)     |         |
| AF                            | 11 (23.4)     | 16 (37.2)     | 0.153   |
| Hypertension                  | 18 (38.3)     | 19 (44.2)     | 0.571   |
| Diabetes                      | 5 (10.6)      | 10 (23.3)     | 0.109   |
| Renal insufficiency           | 6 (12.8)      | 4 (9.3)       | 0.601   |
| Echocardiography              |               |               |         |
| RVEDTD, cm                    | 3.7 (3.2, 4.1) | 3.3 (2.8, 3.8) | 0.040   |
| RATD, cm                      | 4.3 (4.0, 5.4) | 4.2 (3.8, 5.1) | 0.099   |
| ENDSEI-yes, n (%)             | 15 (31.9)     | 6 (14.0)      | 0.044   |
| LVEF (%)                      | 68.1±12.2     | 66.9±9.1      | 0.609   |
| TAPSE, mm                     | 1.8 (1.6, 2.1) | 1.8 (1.6, 2.2) | 0.580   |
| PASP, mmHg                    | 62.5±19.8     | 49.3±17.9     | 0.003   |
| Pulmonary hemodynamics        |               |               |         |
| Systolic PAP, mmHg            | 70.0 (60.0, 89.0) | 46.0 (40.0, 51.0) | <0.001 |
| Diastolic PAP, mmHg           | 24.0 (20.0, 29.0) | 15.0 (12.0, 18.0) | <0.001 |
| Mean PAP, mmHg                | 43.0 (36.0, 49.0) | 28.0 (25.0, 32.0) | <0.001 |
| PAWP, mmHg                    | 19.0 (16.0, 23.0) | 18.0 (16.0, 19.0) | 0.087   |
| PVR, Wood U                   | 4.9 (3.7, 6.3) | 2.0 (1.5, 2.5) | <0.001 |
| DPG, mmHg                     | 3.0 (0.0, 8.0)  | −3.0 (−6.0, −1.0) | <0.001 |
| TPG, mmHg                     | 20.0 (17.0, 31.0) | 10.0 (8.0, 13.0) | <0.001 |
| CO, L/min                     | 4.7 (4.0, 5.4) | 5.4 (4.6, 6.2) | 0.005   |
| TPR, Wood U                   | 9.0 (7.9, 11.9) | 5.2 (4.4, 6.5) | 0.030   |

Data shown as mean ± SD, n (%) or median (quartile range). PH, pulmonary hypertension; Cpc-PH, post- and pre-capillary PH; Ipc-PH, isolated post-capillary PH; BMI, body mass index; WHO-FC, World Health Organization functional class; 6MWD, 6-minute walk distance; HFReF, heart failure with reduced LVEF; VHD, valvular heart disease; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; RVEDTD, right ventricular end-diastolic transverse dimension; RATD, right atrial transverse dimension; ENDSEI, end-systolic-stage eccentricity index; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; DPG, diastolic pulmonary pressure gradient; TPG, transpulmonary gradient; CO, cardiac output; TPR, total pulmonary resistance.
Figure 1 Comparison of echocardiography in patients with Ipc-PH and Cpc-PH. (A) In the patient with Ipc-PH, pulmonary artery systolic pressure is estimated by maximal doppler tricuspid regurgitation velocity as 43.36 mmHg approximately; (B) in the patient with Cpc-PH, pulmonary artery systolic pressure is estimated by maximal doppler tricuspid regurgitation velocity as 73.50 mmHg approximately; (C) in the patient with Ipc-PH, right ventricular diameter at end-diastolic was relatively enlarged; (D) in the patient with Cpc-PH, right ventricular diameter at end-diastolic was larger than that of Ipc-PH patient. Cpc-PH, combined post- and pre-capillary PH; Ipc-PH, isolated post-capillary PH; LV, left ventricle.

PVR, DPG, TPG, and TPR in the above threshold group were significantly higher than those in the below threshold group (P<0.001). However, there was no significant difference in PAWP and CO between the two groups (P>0.05).

Discussion

In this retrospective study, we assessed exercise cardiopulmonary function, hemodynamics, and echocardiographic parameters in patients with Cpc-PH and Ipc-PH, and simultaneously investigated the pathophysiological mechanisms underlying abnormal CPET parameters in PH-LHD. We observed that patients with Cpc-PH had a poorer hemodynamic profile, lower cardiopulmonary exercise capacity, and worse RV dysfunction than patients with Ipc-PH. The DPG did not provide Cpc-PH patients with additional cardiopulmonary capacity information beyond that provided by PVR. VE/VCO₂-related parameters were moderately correlated with PVR, and played a more significant role in distinguishing Cpc-PH from Ipc-PH. VE/VCO₂-related parameters also showed significant correlation with each other. Lowest VE/VCO₂%pred had the best predictive capacity for diagnosing Cpc-PH. On the basis of hemodynamics as the gold standard, CPET appears to be superior to echocardiography as a noninvasive method for identifying Cpc-PH. Hemodynamic differences were obvious between patients with PH-LHD grouped according to the lowest VE/VCO₂%pred value.

Our previous research with a small sample size suggested that DPG does not provide additional cardiopulmonary capacity information for patients with Cpc-PH beyond that provided by PVR (18). After increasing the sample size in the current study, the same results were observed. All but no patients with Cpc-PH had DPG <7 mmHg, while none of the patients with Ipc-PH had DPG ≥7 mmHg; only 34% of patients with Cpc-PH had DPG ≥7 mmHg. CPET parameters were more strongly correlated with PVR than with DPG. The results suggested that it was reasonable...
Table 2 CPET parameters of patients with Cpc-PH and Ipc-PH

| Variable                               | Cpc-PH (n= 47) | Ipc-PH (n=43) | P value |
|----------------------------------------|----------------|---------------|---------|
| **Cardiovascular and exercise capacity** |                |               |         |
| Rest HR, bmp (beats/min)               | 82.0 (72.9, 102.9) | 76.1 (65.8, 91.8) | 0.074   |
| Peak HR, bmp                           | 121.7 (102.0, 132.3) | 117.7 (104.7, 135.3) | 0.768   |
| Work load, watts                       | 52.2±33.6       | 56.9±31.1     | 0.500   |
| Peak O₂ pulse, mL/beat                 | 5.7 (4.4, 7.2)  | 6.4 (5.3, 8.2) | 0.058   |
| Peak VO₂, mL/min/kg                    | 11.5±3.4        | 13.0±3.3      | 0.032   |
| **Ventilatory and gas exchange efficiency** |      |               |         |
| Lowest VE/VCO₂                         | 43.2 (35.2, 49.3) | 36.0 (32.4, 39.5) | <0.001  |
| Lowest VE/VCO₂ %pred                   | 147.2 (122.1, 165.1) | 121.9 (110.6, 131.3) | <0.001  |
| VE/VCO₂ slope                          | 37.1 (30.4, 55.3) | 31.9 (27.6, 35.5) | 0.002   |
| VE/VCO₂ slope %pred                    | 121.4 (95.2, 166.5) | 96.5 (79.7, 107.0) | <0.001  |
| Peak VE/VCO₂                           | 44.0 (35.8, 53.0) | 36.7 (33.2, 40.8) | <0.001  |
| Peak Pₑ₆ CO₂, mmHg                      | 31.2±7.8        | 35.7±4.3      | 0.001   |
| Peak VO₂/VE, mL/L                      | 23.1±6.1        | 26.8±4.4      | 0.001   |
| OUEP, mL/L                             | 26.2±5.2        | 29.9±3.7      | <0.001  |
| OUES                                   | 1.2±0.6         | 1.3±0.4       | 0.353   |

Data shown as mean ± SD, median (quartile range). HR, heart rate; VO₂, oxygen uptake; VE/VCO₂, minute ventilation/carbon dioxide output; PET CO₂, end-tidal partial pressure of CO₂; VO₂/VE, oxygen uptake/minute ventilation; OUEP, oxygen uptake efficiency plateau; OUES, oxygen uptake efficiency slope. Cpc-PH, combined post- and pre-capillary PH; Ipc-PH, isolated post-capillary PH.

To study the role of CPET between Cpc-PH and Ipc-PH according to the latest PVR standard. Noninvasive measures of pulmonary gas exchange, including VE/VCO₂, PET CO₂, have been shown in previous studies to help in the differentiation of Cpc-PH from Ipc-PH (19,20). Compared with those previous studies, our diagnosis was based only on PVR without DPG, but the results were similar.

CPET is still the gold-standard exercise assessment as well as a standard of care in patients with left-sided heart failure (8,21), and the role of routine CPET in cardiology has been extended to left-sided PH patient populations (22). Our results suggest that CPET seems to have more potential for distinguishing Cpc-PH from Ipc-PH compared with echocardiography, which is worthy of further study.

Ventilatory inefficiency (high VE/VCO₂) is a characteristic abnormality in patients with pulmonary vascular disease (23). Current evidence indicates that ventilatory efficiency may be an important marker for assessing the severity of valvular heart disease, include aortic stenosis (24) and mitral valve disease/dysfunction (25). We found that patients with Cpc-PH displayed higher VE/VCO₂ (peak, lowest, and slope) and lower peak PET CO₂, peak VO₂/VE, and OUEP values than Ipc-PH patients, indicating that gas exchange was worse in patients with Cpc-PH. A lowest VE/VCO₂ of ≥155% predicted was considered to be the single best predictor of mortality in patients with heart failure (26). Compared with the VE/VCO₂ slope, the lowest VE/VCO₂ is considered to be a more stable and labor-saving method of measurement. In this study, peak VE/VCO₂, lowest VE/VCO₂, lowest VE/VCO₂ %pred, VE/VCO₂ slope, and VE/VCO₂ slope %pred were helpful in distinguishing Cpc-PH from Ipc-PH, and there was obvious correlation between them. However, logistic regression and ROC curve analyses showed that lowest VE/VCO₂ %pred was most the helpful parameter for guiding PH-LHD classification. The lowest VE/VCO₂ %pred actually had a better ability to identify Cpc-PH than other CPET parameters.

The typical CPET response in PH (27) and heart
Table 3 Correlation of CPET and echocardiographic parameters with PVR, DPG, and TPG in patients with PH-LHD

| Variable                               | PVR       |          | DPG       |          | TPG       |          |
|----------------------------------------|-----------|----------|-----------|----------|-----------|----------|
| Cardiopulmonary exercise test          |           |          |           |          |           |          |
| Lowest VE/VCO₂                         | 0.517     | <0.001   | 0.358     | 0.001    | 0.420     | <0.001   |
| Lowest VE/VCO₂ %pred                   | 0.547     | <0.001   | 0.416     | <0.001   | 0.461     | <0.001   |
| VE/VCO₂ slope                          | 0.515     | <0.001   | 0.352     | 0.001    | 0.464     | <0.001   |
| VE/VCO₂ slope %pred                    | 0.546     | <0.001   | 0.393     | <0.001   | 0.487     | <0.001   |
| Peak VE/VCO₂                           | 0.521     | <0.001   | 0.382     | 0.001    | 0.446     | <0.001   |
| Peak P₆,CO₂, mmHg                      | –0.405    | <0.001   | –0.219    | 0.038    | –0.304    | 0.004    |
| Peak VO₂/VE, mL/L                      | –0.416    | <0.001   | –0.303    | 0.004    | –0.350    | 0.001    |
| OUEP, mL/L                             | –0.431    | <0.001   | –0.321    | 0.002    | –0.356    | 0.001    |
| Peak VO₂, mL/min/kg                    | –0.312    | 0.003    | –0.240    | 0.023    | –0.256    | 0.015    |
| Peak O₂ pulse, mL/beat                 | –0.245    | 0.020    | –0.242    | 0.022    | –0.212    | 0.044    |
| OUES                                   | –0.239    | 0.029    | –0.170    | 0.125    | –0.220    | 0.046    |
| Work load, watts                       | –0.173    | 0.103    | –0.141    | 0.184    | –0.164    | 0.122    |
| Rest HR                                | 0.123     | 0.247    | 0.161     | 0.130    | 0.117     | 0.271    |
| Peak HR                                | –0.098    | 0.358    | –0.029    | 0.788    | –0.079    | 0.459    |
| Echocardiography                       |           |          |           |          |           |          |
| RVEDTD, cm                             | 0.376     | <0.001   | 0.333     | 0.002    | 0.322     | 0.003    |
| RATD, cm                               | 0.259     | 0.018    | 0.395     | <0.001   | 0.306     | 0.005    |
| LVEF, %                                | 0.292     | 0.007    | 0.148     | 0.183    | 0.335     | 0.002    |
| TAPSE, mm                              | –0.272    | 0.013    | –0.133    | 0.233    | –0.137    | 0.218    |
| PASP, mmHg                             | 0.419     | <0.001   | 0.340     | 0.002    | 0.513     | <0.001   |

VE/VCO₂, minute ventilation/carbon dioxide output; P₆,CO₂, end-tidal partial pressure of CO₂; VO₂/VE, oxygen uptake/minute ventilation; OUEP, oxygen uptake efficiency plateau; VO₂, oxygen uptake; OUES, oxygen uptake efficiency slope; HR, heart rate; RVEDTD, right ventricular end-diastolic transverse dimension; RATD, right atrial transverse dimension; ENDESI, end-systolic-stage eccentricity index; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; DPG, diastolic pulmonary pressure gradient; TPG, transpulmonary gradient.

Disease (28,29) is observed and characterized by a severe reduction in peak VO₂ (30), work rate, and O₂ pulse. In the present study, only peak VO₂ differed significantly between the Cpc-PH and Ipc-PH groups, and it was negatively correlated with PVR; however, its guiding significance was not as good as that of ventilation efficiency-related indicators. We believe that ventilation inefficiency is the main characteristic of CPET in Cpc-PH patients. Many factors are believed to account for hyperventilation induced by excessive exercise, including ventilation/perfusion mismatch with increased dead-space ventilation, pulmonary vascular function, RV function, and nervous reflex. Chemoreflex was also shown by Vicenzi et al. to be effective in PH patients with different hyperventilation patterns, and the increase in chemosensitivity made higher VE/VCO₂ and lower PET CO₂ more likely (31). According to the results of the present study, we consider chemoreflex to be the key factor in the difference in ventilation efficiency between Cpc-PH and Ipc-PH patients.

RV afterload is considered to play an important role in the regulation of ventilation efficiency during exercise (32). In Methvin et al.’s study, the measurement of RV systolic...
Figure 2 Correlations between VE/VCO$_2$-related indexes. VE/VCO$_2$, minute ventilation/carbon dioxide output.

Table 4 Univariate and multivariate logistic regression analyses of CPET for predicting Cpc-PH

| CPET                  | Univariate logistic | Multivariate logistic (forward) |
|-----------------------|---------------------|---------------------------------|
|                       | OR                  | 95%CI                           | P value | OR                  | 95%CI                           | P value |
| Peak VO$_2$            | 1.150               | 1.010                           | 1.311   | 0.029               |
| Peak VE/VCO$_2$        | 0.882               | 0.826                           | 0.943   | <0.001              |
| Lowest VE/VCO$_2$      | 0.866               | 0.801                           | 0.937   | <0.001              |
| Lowest VE/VCO$_2$%pred | 0.954               | 0.931                           | 0.977   | <0.001              |
| VE/VCO$_2$ slope       | 0.921               | 0.877                           | 0.968   | 0.001               |
| VE/VCO$_2$ slope %pred | 0.975               | 0.960                           | 0.990   | 0.001               |
| Peak P$_{ET}$CO$_2$    | 1.126               | 1.042                           | 1.216   | 0.003               |
| Peak VO$_2$/VE         | 1.143               | 1.047                           | 1.248   | 0.003               |
| OUEP                  | 1.201               | 1.079                           | 1.338   | 0.001               |

Data was presented by P value, OR and 95% CI. The value of CPET to predict Cpc-PH was tested using a univariate and multivariate logistic regression model. P value <0.05 was considered statistically significant. HR, heart rate; VO$_2$, oxygen uptake; VE/VCO$_2$, minute ventilation/carbon dioxide output; PET CO$_2$, end-tidal partial pressure of CO$_2$; VO$_2$/VE, oxygen uptake/minute ventilation; OUEP, oxygen uptake efficiency plateau. Cpc-PH, combined post- and pre-capillary PH.
Table 5: Pulmonary hemodynamic parameters of patients according to the optimal cutoff for VE/VCO₂%pred

| Variable            | Below cutoff value | Above cutoff value | P value |
|---------------------|-------------------|-------------------|---------|
|                     | <137.0 (n=54)     | ≥137.0 (n=36)     |         |
| Age, years          | 65.0 (58.5, 74.0) | 62.5 (51.5, 70.0) | 0.210   |
| Male, n (%)         | 19 (35.2)         | 17 (47.2)         | 0.253   |
| BMI, kg/m²          | 23.5 (21.6, 27.4) | 23.4 (20.7, 27.3) | 0.604   |
| Systolic PAP, mmHg  | 49.5 (43.8, 63.5) | 66.5 (58.5, 91.3) | <0.001  |
| Diastolic PAP, mmHg | 16.5 (13.8, 22.0) | 23.0 (19.3, 28.8) | <0.001  |
| Mean PAP, mmHg      | 30.0 (26.0, 37.0) | 42 (35.3, 48.8)   | <0.001  |
| PAWP, mmHg          | 18.0 (16.0, 20.3) | 18.0 (16.0, 23.0) | 0.242   |
| PVR, Wood U         | 2.3(1.8, 3.9)     | 4.7 (3.2, 6.9)    | <0.001  |
| DPG, mmHg           | -2.0 (-4.0, 2.3)  | 2.0 (0.0, 9.3)    | <0.001  |
| TPG, mmHg           | 12.0 (8.0, 18.3)  | 20.0 (15.3, 32.0) | <0.001  |
| CO, L/min           | 5.4 (4.1, 6.1)    | 4.9 (4.0, 5.4)    | 0.157   |
| TPR, Wood U         | 6.3 (4.7, 7.8)    | 8.8 (6.9, 12.4)   | <0.001  |

Data shown as n (%) or median (quartile range). PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; DPG, diastolic pulmonary pressure gradient; TPG, transpulmonary gradient; CO, cardiac output; TPR, total pulmonary resistance.
may be related to the increased chemosensitivity.

The alterations in the ventilatory efficiency response to exercise in patients with heart failure also likely result from a reduced blood flow to the pulmonary blood vessels with a consequent increase in the inhomogeneity of ventilation-perfusion matching (36). Hypoperfusion may also affect the stimulation of the peripheral chemoreceptors, leading to an enhanced ventilatory response (37). In the Cpc-PH patients, cardiac output decreased, whereas PVR and TPR increased significantly, which could have had an aggravating effect on hypoperfusion.

A study by Butler et al. (38) showed that impairment of exercise capacity was obvious in patients with elevated PVR, and the degree of exercise abnormalities is related to the severity of PVR. In the present study, peak VO$_2$ in patients with Cpc-PH was reduced, which may have further aggravated ventilation inefficiency. The decreases in the skeletal muscle blood supply and arterial hypoxemia can alter the concentration of CO$_2$ and oxygen in the blood, and stimulate the response of peripheral chemoreceptors to exercise, thus resulting in an enhanced hyperventilation response. Our results showed that peak VO$_2$ was lower in Cpc-PH patients than in Ipc-PH patients, while the peak VO$_2$/VE and OUEP values were significantly lower in Cpc-PH patients, suggesting that VE showed a more significant increase in the Cpc-PH group. Taken together, the other mechanisms underlying exercise-induced hyperventilation might centrally interact with chemoreflex in such a way to increase ventilation inefficiency. Finally, the condition of the Cpc-PH patients was poorer than that of the Ipc-PH patients, with a worse pattern of ventilatory control derangement.

We found a significant correlation between PVR and VE/VCO$_2$, which may indicate a possible association of the presence and range of a pre-capillary component with the degree of exercise-induced hyperventilation. PVR was obviously lower in patients below the lowest VE/VCO$_2$%pred threshold. A decrease in PVR in patients with PH-LHD may reduce the tendency of inefficient ventilation, whereas an increase in PVR may provide obvious physiological stimulation for exercise hyperventilation. Based on our findings, we conclude that careful evaluation of VE/VCO$_2$ may be helpful in identifying subjects with elevated PVR levels in RHC.

Our study is based on the established relationship between abnormal ventilation and poor pulmonary hemodynamics, suggesting that hyperventilation parameters may have diagnostic value in identifying the presence of pre-capillary components in patients with PH-LHD. As the potential treatment methods of PH-LHD patients continue to be explored, an effective noninvasive evaluation method may also guide the treatment intervention.

Our study has some limitations. Firstly, it is a single-center study with a limited sample size, and the study design is retrospective, which may have provided less relevant evidence than randomized controlled trials. A study of a larger population involving multiple clinical centers is required to further assess the validity of our results. Secondly, the study only focused on associations between hemodynamic parameters at rest and CPET. The correlation between hemodynamic indexes under exercise and CPET indexes calls for further study. Thirdly, there was no assessment of patients’ prognoses, which will be accounted for in the design of our future research.

Conclusions

CPET is useful in assisting the evaluation of patients with PH-LHD and can provide information to differentiate between Cpc-PH and Ipc-PH. Our observations suggest that the degree of exercise-induced hyperventilation can indicate the presence of pre-capillary components, and VE/VCO$_2$ may be an acceptable noninvasive marker for the diagnosis of Cpc-PH in future.

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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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital (K16-317). Individual consent for this retrospective analysis was waived.

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