Original Article

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/VCO_2) 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/VCO_2 in predicted value (VE/VCO_2%pred) was the single best predictor of Cpc-PH, and the area under ROC curve also confirmed that lowest VE/VCO_2%pred (≥137%) could serve as a novel diagnostic marker for Cpc-PH. On the basis of this lowest VE/VCO_2%pred threshold, patients were divided into two groups. Most hemodynamic parameters were worse in patients with a lowest VE/VCO_2%pred ≥137%.

Conclusions: VE/VCO_2-related parameters are powerful prognosticators for the presence of pre-capillary components in patients with PH-LHD, especially lowest VE/VCO_2%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 (VO_2), carbon dioxide output (VCO_2), 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 VCO_2 (VE/VCO_2) in the few studies on CPET in patients with PH-LHD (9-11), VE/VCO_2 relationship is most often expressed as VE/VCO_2 slope, lowest VE/VCO_2 and peak VE/VCO_2. Except PH-LHD, pulmonary arterial hypertension (PAH) is a common type of PH. The end-tidal CO_2 ($P_{ET}CO_2$), 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.

Transthoracic 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), O_2 uptake (VO_2), oxygen pulse (O_2 pulse), PET CO_2, VE/VCO_2, VO_2/ VE, oxygen uptake efficiency plateau (OUEP), and oxygen uptake efficiency slope (OUES).

The HR, VO_2, PET CO_2, VE/VCO_2, VO_2/VE, and O_2 pulse values at peak exercise were measured according to the highest 30-second averaged value obtained during peak exercise. The lowest VE/VCO_2 was calculated by averaging the 9 lowest consecutive 10-second-averaged data points of VE/VCO_2. The VE/VCO_2 slope was obtained from linear regression analysis of the relationship of VE with VCO_2. The lowest VE/VCO_2 and VE/VCO_2 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 VO_2 (mL/min)/VE (L/min) at 90 seconds (17). Using linear square regression, we computed the OUES according to the following equation: $VO_2 = a \times lgVE + b$ ('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 χ^2 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/VCO_2, lowest VE/VCO_2%pred, VE/VCO_2 slope % pred, and peak VE/VCO_2 values of the Cpc-PH patients were significantly higher than those in the Ipc-PH group (P<0.001), and the VE/VCO_2 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 CO_2 and peak VO_2/VE values were also lower than those in the Ipc-PH group (P<0.01). In Cpc-PH patients, peak VO_2 was significantly decreased (P<0.05). The peak O_2 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/VCO_2, lowest VE/VCO_2% pred, VE/VCO_2 slope, VE/VCO_2 slope% pred, and peak VE/VCO_2 showed a moderate positive correlation with PVR (r>0.5, P<0.001). VE/VCO_2-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/VCO_2 and peak VE/VCO_2 (r=0.939, P<0.0001). Moreover, there were moderate positive correlations between peak VE/VCO_2 and VE/VCO_2 slope (r=0.766, P<0.0001), between lowest VE/VCO_2 and VE/VCO_2 slope (r=0.693, P<0.0001), and between lowest VE/VCO_2%pred and VE/VCO_2 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 VO_2, peak VE/VCO_2, lowest VE/VCO_2, lowest VE/VCO_2%pred, VE/VCO_2 slope, VE/VCO_2 slope %pred, peak $PETCO_2$, peak VO_2/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/VCO_2% 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/VCO_2%pred was the best predictor for Cpc-PH, as demonstrated by an area under the curve (AUC) of 0.77. Lowest VE/VCO_2%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/VCO_2% 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/m^2	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)	
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)	0.351
VHD, n (%)	14 (29.8)	19 (44.2)	0.157
Comorbidities, n (%)			
COPD	18 (38.3)	16 (37.2)	0.915
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.

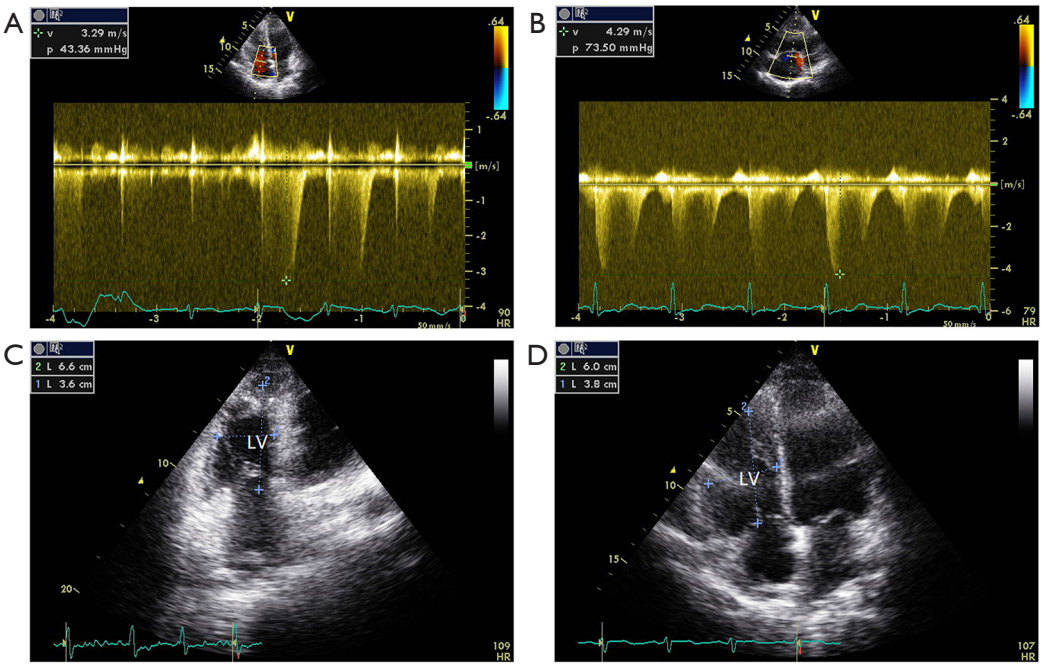

Figure 1 Comparison of echocardiography in patients with Ipc-PH and Cpc-PH. (A) In the patient with Ipc-PH, pulmonary artery systolic pressure is estimated by maximal doppler tricuspid regurgitation velocity as 43.36 mmHg approximately; (B) in the patient with Cpc-PH, pulmonary artery systolic pressure 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/VCO_2-related parameters were moderately correlated with PVR, and played a more significant role in distinguishing Cpc-PH from Ipc-PH. VE/VCO_2-related parameters also showed significant correlation with each other. Lowest VE/VCO_2%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/VCO_2%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 O_2 pulse, mL/beat	5.7 (4.4, 7.2)	6.4 (5.3, 8.2)	0.058
Peak VO_2, mL/min/kg	11.5±3.4	13.0±3.3	0.032
Ventilatory and gas exchange efficiency			
Lowest VE/VCO_2	43.2 (35.2, 49.3)	36.0 (32.4, 39.5)	<0.001
Lowest VE/VCO_2%pred	147.2 (122.1, 165.1)	121.9 (110.6, 131.3)	<0.001
VE/VCO_2 slope	37.1 (30.4, 55.3)	31.9 (27.6, 35.5)	0.002
VE/VCO_2 slope %pred	121.4 (95.2, 166.5)	96.5 (79.7, 107.0)	<0.001
Peak VE/VCO_2	44.0 (35.8, 53.0)	36.7 (33.2, 40.8)	<0.001
Peak P_{ET} CO_2, mmHg	31.2±7.8	35.7±4.3	0.001
Peak VO_2/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; 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; 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/VCO_2, PET CO_2, 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/VCO_2) 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/VCO_2 (peak, lowest, and slope) and lower peak PET CO_2, peak VO_2/VE, and OUEP values than Ipc-PH patients, indicating that gas exchange was worse in patients with Cpc-PH. A lowest VE/VCO_2 of ≥155% predicted was considered to be the single best predictor of mortality in patients with heart failure (26). Compared with the VE/VCO_2 slope, the lowest VE/VCO_2 is considered to be a more stable and labor-saving method of measurement. In this study, peak VE/VCO_2, lowest VE/VCO_2, lowest VE/VCO_2%pred, VE/VCO_2 slope, and VE/VCO_2 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/VCO_2%pred was most the helpful parameter for guiding PH-LHD classification. The lowest VE/VCO_2%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	
	r	P value	r	P value	r	P value
Cardiopulmonary exercise test						
Lowest VE/VCO_2	0.517	<0.001	0.358	0.001	0.420	<0.001
Lowest VE/VCO_2%pred	0.547	<0.001	0.416	<0.001	0.461	<0.001
VE/VCO_2 slope	0.515	<0.001	0.352	0.001	0.464	<0.001
VE/VCO_2 slope %pred	0.546	<0.001	0.393	<0.001	0.487	<0.001
Peak VE/VCO_2	0.521	<0.001	0.382	0.001	0.446	<0.001
Peak $P_{ET}CO_2$, mmHg	–0.405	<0.001	–0.219	0.038	–0.304	0.004
Peak VO_2/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 VO_2, mL/min/kg	–0.312	0.003	–0.240	0.023	–0.256	0.015
Peak O_2 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/VCO_2, minute ventilation/carbon dioxide output; P_{ET} CO_2, end-tidal partial pressure of CO_2; VO_2/VE, oxygen uptake/minute ventilation; OUEP, oxygen uptake efficiency plateau; VO_2, oxygen uptake; OUES, oxygen uptake efficiency slope; HR, heart rate; 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; 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 VO_2 (30), work rate, and O_2 pulse. In the present study, only peak VO_2 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/VCO_2 and lower PET CO_2 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

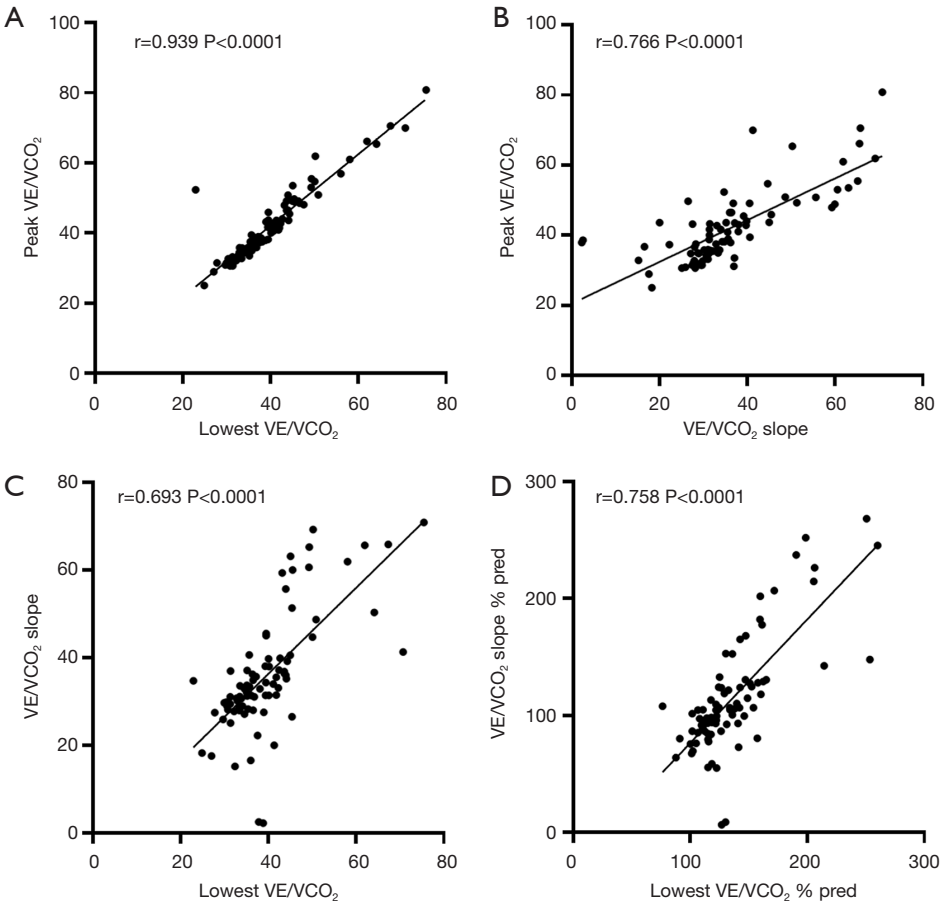

Figure 2 Correlations between VE/VCO_2-related indexes. VE/VCO_2, minute ventilation/carbon dioxide output.

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
		Lower	Higher			Lower	Higher	
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	0.957	0.934	0.981	<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

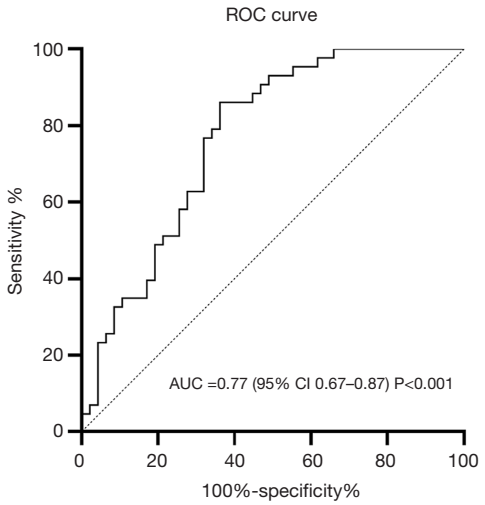

Figure 3 Receiver operating characteristic curves displaying the diagnostic performance of lowest VE/VCO_2%pred in Cpc-PH patients. ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval; VE/VCO_2, minute ventilation/carbon dioxide output; Cpc-PH, combined post- and pre-capillary PH.

function and dimensions by echocardiography showed that the RV condition in patients with left HF was associated with ventilatory inefficiency (33), which is consistent with the concept that RV extension and rigidity increase secondary chemosensitivity (34). Both diastolic stiffness and increased RV afterload in patients with PAH were also found to be related to exercise hyperventilation. RV dilation is the obvious reason for the increase in atrial and RV stretch and stiffness, which are important triggers of chemosensitivity and sympathetic nervous system tone in PAH patients (35). At present, the relationship between ventilatory inefficiency and RV dysfunction in severe LHD patients is consistent with that reported by studies on PAH patients (33). Our data displayed that RV dilation and ventilatory inefficiency were more obvious in Cpc-PH patients than in Ipc-PH patients, while systolic PAP, diastolic PAP, mean PAP, and TPR were obviously higher in patients above the lowest VE/VCO_2%pred threshold. These observations suggest that RV dilation in patients with Cpc-PH may increase ventilation waste, and that increased RV afterload was related to poor ventilatory efficiency in PH-LHD, which

Table 5 Pulmonary hemodynamic parameters of patients according to the optimal cutoff for VE/VCO_2%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/m^2	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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Footnote

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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.

References

1. Rosenkranz S, Gibbs JS, Wachter R, et al. Left ventricular heart failure and pulmonary hypertension. Eur Heart J 2016;37:942-54.
2. Rosenkranz S, Lang IM, Blindt R, et al. Pulmonary hypertension associated with left heart disease: Updated Recommendations of the Cologne Consensus Conference 2018. Int J Cardiol 2018;272S:53-62.
3. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation 2012;126:975-90.
4. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903-75.
5. Naeije R, Gerges M, Vachiery JL, et al. Hemodynamic Phenotyping of Pulmonary Hypertension in Left Heart Failure. Circ Heart Fail 2017;10:e004082.
6. Vachiéry JL, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. Eur Respir J 2019;53:1801897.
7. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation 2012;126:2261-74.
8. Arena R, Ozemek C. Intracardiac multimorbidity: assessing right ventricular function in left-sided heart failure through cardiopulmonary exercise testing. Expert Rev Cardiovasc Ther 2019;17:331-3.
9. Guazzi M, Cahalin LP, Arena R. Cardiopulmonary Exercise Testing as a Diagnostic Tool for the Detection of Left-sided Pulmonary Hypertension in Heart Failure. J Card Fail 2013;19:461-7.
10. Caravita S, Faini A, Deboeck G, et al. Pulmonary hypertension and ventilation during exercise: Role of the pre-capillary component. J Heart Lung Transplant 2017;36:754-62.
11. Lim HS, Theodosiou M. Exercise ventilatory parameters for the diagnosis of reactive pulmonary hypertension in patients with heart failure. J Card Fail 2014;20:650-7.
12. Welch CE, Brittain EL, Newman AL, et al. End-Tidal Carbon Dioxide as a Prognostic Feature in Pulmonary Arterial Hypertension. Ann Am Thorac Soc 2017;14:896-902.
13. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913.
14. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713, quiz 786-8.
15. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.
16. Sun XG, Hansen JE, Garatachea N, et al. Ventilatory efficiency during exercise in healthy subjects. Am J Respir Crit Care Med 2002;166:1443-8.
17. Sun XG, Hansen JE, Stringer WW. Oxygen uptake efficiency plateau (OUEP): physiology and reference value. Eur J Appl Physiol 2012;112:919-28.

18. Zhong XJ, Tang J, Zhao QH, et al. Can the diastolic pulmonary pressure gradient provide cardiopulmonary capacity information in patients with pulmonary hypertension and left heart disease? Int J Cardiol 2020;305:138.
19. Correale M, Tricarico L, Ferraretti A, et al. Cardiopulmonary exercise test predicts right heart catheterization. Eur J Clin Invest 2017;47(12).
20. Taylor BJ, Smetana MR, Frantz RP, et al. Submaximal Exercise Pulmonary Gas Exchange in Left Heart Disease Patients with Different Forms of Pulmonary Hypertension. J Card Fail 2015;21:647-55.
21. Guazzi M, Arena R, Halle M, Piepoli MF, et al. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Eur Heart J 2018;39:1144-61.
22. Guazzi M, Bandera F, Ozemek C, et al. Cardiopulmonary Exercise Testing: What Is its Value? J Am Coll Cardiol 2017;70:1618-36.
23. Weatherald J, Farina S, Bruno N, et al. Cardiopulmonary Exercise Testing in Pulmonary Hypertension. Ann Am Thorac Soc 2017;14:S84-S92.
24. Bandera F, Generati G, Pellegrino M, et al. Paradoxical low flow/low gradient aortic stenosis: Can cardiopulmonary exercise test help in identifying it? Int J Cardiol 2016;203:37-9.
25. Izumo M, Suzuki K, Moonen M, et al. Changes in mitral regurgitation and left ventricular geometry during exercise affect exercise capacity in patients with systolic heart failure. Eur J Echocardiogr 2011;12:54-60.
26. Sun XG, Hansen JE, Beshai JF, et al. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. J Am Coll Cardiol 2010;55:1814-23.
27. Paolillo S, Farina S, Bussotti M, et al. Exercise testing in the clinical management of patients affected by pulmonary arterial hypertension. Eur J Prev Cardiol 2012;19:960-71.
28. Malhotra R, Bakken K, D'Elia E, et al. Cardiopulmonary Exercise Testing in Heart Failure. JACC Heart Fail 2016;4:607-16.
29. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: A scientific statement from the American Heart Association. Circulation 2010;122:191-225.
30. Mancini D, LeJemtel T, Aaronson K. Peak VO(2): a simple yet enduring standard. Circulation 2000;101:1080-2.
31. Vicenzi M, Deboeck G, Faoro V, et al. Exercise oscillatory ventilation in heart failure and in pulmonary arterial hypertension. Int J Cardiol 2016;202:736-40.
32. Lewis GD, Shah RV, Pappagianopolas PP, et al. Determinants of ventilatory efficiency in heart failure: the role of right ventricular performance and pulmonary vascular tone. Circ Heart Fail 2008;1:227-33.
33. Methvin AB, Owens AT, Emmi AG, et al. Ventilatory inefficiency reflects right ventricular dysfunction in systolic heart failure. Chest 2011;139:617-25.
34. Farina S, Correale M, Bruno N, et al. The role of cardiopulmonary exercise tests in pulmonary arterial hypertension. Eur Respir Rev 2018;27:170134.
35. Tello K, Dalmer A, Vanderpool R, et al. Impaired right ventricular lusitropy is associated with ventilatory inefficiency in pulmonary arterial hypertension. Eur Respir J 2019;54:1900342.
36. Taylor BJ, Olson TP, Kim CH, et al. Use of Noninvasive Gas Exchange to Track Pulmonary Vascular Responses to Exercise in Heart Failure. Clin Med Insights Circ Respir Pulm Med 2013;7:53-60.
37. Johnson RL Jr. Gas exchange efficiency in congestive heart failure. Circulation 2000;101:2774-6.
38. Butler J, Chomsky DB, Wilson JR. Pulmonary hypertension and exercise intolerance in patients with heart failure. J Am Coll Cardiol 1999;34:1802-6.

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