CLINICAL INVESTIGATIONS

Cardiopulmonary exercise testing improves diagnostic specificity in patients with echocardiography-suspected pulmonary hypertension

Qin-Hua Zhao¹ | Lan Wang¹ | Bigyan Pudasaini¹ | Rong Jiang¹ | Ping Yuan¹ |
Su-Gang Gong¹ | Jian Guo² | Qiang Xiao¹ | Hui Liu¹ | Cheng Wu³ | Zhi-Cheng Jing⁴ |
Jin-Ming Liu^{1,2}

¹Department of Pulmonary Circulation, Shanghai Pulmonary Hospital, Tongji University, School of Medicine, Shanghai, China

²Department of Pulmonary Function, Shanghai Pulmonary Hospital, Tongji University, School of Medicine, Shanghai, China

³Department of Statistics, the Second Military Medical University, Shanghai, China

⁴State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, Peking Union Medical College and Chinese Academy of Medical Science, Beijing, China

Corresponding Author: Jin-Ming Liu, MD, Department of Pulmonary Circulation, Shanghai Pulmonary Hospital, Tongji University, School of Medicine, 507 Zhengmin Road, Shanghai, 200433, China (jinmingliu2007@163.com).

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Shanghai Pulmonary Hospital Research Project (fk1409), Shanghai, China.

Background: Doppler echocardiography is usually the first diagnostic investigation for patients suspected with pulmonary hypertension (PH), but it is often inaccurate when used alone, especially in mild PH.

Hypothesis: Cardiopulmonary exercise testing (CPET) may serve as a complementary tool to improve diagnostic accuracy in echocardiography-suspected “PH possible” patients.

Methods: Eighty-eight consecutive patients with suspected PH (referred to as “PH possible” hereafter) based on echocardiography were included in the study. CPET was assessed subsequently and PH was confirmed by right-heart catheterization in all subjects. We analyzed CPET data from patients and derived a CPET prediction rule to hemodynamically differentiate PH.

Results: Eighty-eight patients (27 patients with confirmed PH, and PH ruled out in 61 patients) were included in the study. Compared with non-PH patients, the PH subjects had lower peak oxygen uptake (VO_2), aerobic capacity (AT), peak partial pressure of end-tidal CO_2 (P_{ETCO_2}), oxygen uptake efficiency plateau (OUEP), and oxygen uptake efficiency slope (OUES), along with higher minute ventilation (VE)/carbon dioxide output (VCO_2) slope and lowest VE/VCO_2 ($P < 0.001$). VE/VCO_2 slope and AT were independent predictors of PH derived from multivariate logistic regression adjusted for age and body mass index. A score combining VE/VCO_2 slope and AT reached a high area under the curve value of 0.98. A score ≥ 0.5 had 95% specificity and 92.6% sensitivity for diagnosis of PH.

Conclusions: A score combining VE/VCO_2 slope and AT provides high specificity in screening out PH from a pool of echocardiography-suspected PH patients.

KEYWORDS

cardiopulmonary exercise testing, Pulmonary hypertension, Imaging, echocardiography, diagnostic procedures

1 | INTRODUCTION

Pulmonary hypertension (PH) is a severe clinical condition, characterized by increased pulmonary vascular resistance and remodeling, leading to right heart failure.^{1,2} Current guidelines recommend transthoracic Doppler echocardiography (DE) as the first noninvasive diagnostic tool in patients with suspected PH.^{1,3,4} Subjects with DE-

estimated pulmonary artery systolic pressure (PASP) of ≥ 50 mm Hg are labeled as “PH likely” and right-sided heart catheterization (RHC) is recommended; whereas subjects with DE-estimated PASP of 37 to 50 mm Hg or PASP < 36 mm Hg with presence of additional echocardiographic variables suggestive of PH are diagnosed as “PH possible” and RHC is recommended.¹ However, DE-estimated PASP differ significantly from those determined by invasive measurements, with a

tendency to both overestimate and underestimate, especially in patients with mild PH.⁵⁻⁹ Although RHC is an invasive procedure and has its complications, it is the gold standard for final diagnosis.¹⁰ Thus, a complementary noninvasive method to increase diagnostic accuracy in a "PH possible" cohort would prove very useful clinically.

Cardiopulmonary exercise testing (CPET) is a well-established assessment tool for evaluation of disease severity in PH patients.¹¹⁻¹³ Pinkstaff et al go even further by making class recommendations CPET for diagnostic evaluation (level B, class IIa), prognostication (level B, class IIb), and determining therapeutic efficiency (level C, class IIb).¹⁴ Among patients with unexplained exertional dyspnea, a minute ventilation/carbon dioxide output (VE/VCO_2) ≥ 60 and peak partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) < 20 mm Hg at ventilatory threshold are highly suggestive of PH.¹⁵ CPET is also a useful noninvasive diagnostic tool for detection of chronic thromboembolic pulmonary hypertension (CTEPH) in patients with a normal echocardiogram.¹⁶ VE/VCO_2 slope ≥ 36.0 was considered as a best predictor of a PASP ≥ 40 mm Hg for the detection of left heart-associated PH in heart failure.¹⁷ Yet, we still lack studies employing echocardiography and CPET for screening PH. We aimed to determine the role of CPET as a complementary tool for screening out PH in patients labeled as "PH possible" after an initial echocardiography.

2 | METHODS

2.1 | Study population

We retrospectively enrolled suspected PH patients referred to Shanghai Pulmonary Hospital between January 2013 and January 2016. All patients routinely undergo blood and immunology tests, an electrocardiogram (ECG), pulmonary function testing, chest X-rays, high-resolution chest CT scans and/or pulmonary ventilation perfusion scans, echocardiography, CPET, and finally confirmed by RHC. Patients with estimated PASP 37 to 50 mm Hg or PASP < 36 mm Hg but presence of additional echocardiographic variables suggestive of PH were defined as "PH possible" and were included.^{1,4} We excluded patients with estimated PASP ≥ 50 mm Hg, as they already had high clinical probability of PH.^{1,4} Patients with the following conditions were excluded: (1) severe chronic heart failure with left ventricular ejection fraction (LVEF) $< 50\%$, valvulopathy, or cardiomyopathy; (2) chronic lung disease in which pulmonary function indicated forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) $< 70\%$ of predicted value and total lung capacity $< 70\%$ predicted value; (3) neuromuscular diseases, severe metabolic diseases, and mental disorders; and (4) hemoglobin < 90 g/L, serious liver dysfunction, or kidney dysfunction. None of the patients had ever been admitted to a physical rehabilitation program.

2.2 | Cardiopulmonary exercise testing

CPET was performed as upright cycling on a stationary cycle ergometer (Ergoselect 100; Ergoline GmbH, Bitz, Germany) using a standardized protocol.¹⁸ Minute ventilation (VE), minute oxygen uptake

(VO_2), carbon dioxide output (VCO_2), heart rate (HR), O_2 uptake vs HR (VO_2/HR), VO_2/VE , VE/VCO_2 , $P_{ET}CO_2$, and the respiratory exchange ratio were averaged every 10 seconds. Peak VO_2 was defined as the highest 30-second average value of oxygen uptake during the last minute of the exercise test. The anaerobic threshold (AT) was determined by the V-slope method in all patients.¹⁹ Other key variables, such as oxygen uptake efficiency plateau (OUEP), lowest VE/VCO_2 , VE/VCO_2 slope, and oxygen uptake efficiency slope (OUES), were calculated and plotted based on standard equations as previously described.²⁰

2.3 | Echocardiography and hemodynamics

Patients underwent a standard transthoracic echocardiographic examination using GE Vivid 7 Ultrasound (GE Vingmed Ultrasound, Horten, Norway). All echocardiographic measurements were performed according to American Society of Echocardiography recommendations.^{4,21}

In line with current recommendations, RHC was performed in all patients during hospitalization. The baseline hemodynamic parameters, including mean right atrium pressure, mean pulmonary atrial pressure (mPAP), and pulmonary arterial wedge pressure, were measured in all patients. Cardiac output was measured in triplicate using the thermodilution technique with ice-cold isotonic sodium chloride solution. Cardiac index was calculated by dividing cardiac output by body surface area. PVR was calculated using the standard method, as described elsewhere.¹

Echocardiography was performed before CPET on almost all occasions. Echocardiography and CPET were performed within 72 hours of the hemodynamic study and before the initiation of pulmonary arterial hypertension (PAH)-specific therapy.

2.4 | Statistical analysis

Categorical data are expressed as the number of patients and proportions, whereas continuous data are presented as mean $\pm$ SD or median (interquartile range), as appropriate. Differences between 2 groups were assessed by independent sample t test or nonparametric test for continuous variables, and Fisher exact test for categorical variables. The primary outcome of interest was whether the hemodynamic criterion for PH was met (mPAP ≥ 25 mm Hg at rest).¹ Logistic regression was used to model the probability of diagnosis of PH. Univariate logistic regression was performed for each CPET predictor with PH as the dependent variable. Then a stepwise forward variable selection procedure was used to find independent predictors of PH. To establish these scores combining multiple CPET parameters, we performed a multivariate discriminant analysis and determined coefficients for multiplying these with the measured values of the CPET parameters. Optimal cutoff points for the combined diagnostic variables were estimated from receiver operating characteristic curves analysis. Statistical analysis was performed using SPSS software version 17.0 (SPSS Inc., Chicago, Illinois). In all cases, a P value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Study population

We retrospectively enrolled 88 patients with an echocardiographic "PH possible" diagnosis who met the inclusion criteria. Patient characteristics are shown in Table 1. Average age was 52 ± 17 years, and 63 (71.5%) were female. They were divided into a PH group and a non-PH group according to the following hemodynamic criteria: mPAP at rest ≥ 25 mm Hg or < 25 mm Hg. Based on RHC results, 27 patients were classified as PH (11 idiopathic PAH, 9 CTEPH, and 7 PAH associated with connective tissue disease) and 61 were classified as non-PH (Table 1).

3.2 | Demographics and clinical characteristics

The PH group included 27 patients (22 females; mean age, 47 ± 17 years) and the non-PH group included 61 patients (41 females; mean age, 54 ± 16 years). Both groups did not differ significantly in terms of age and sex, but the PH group had lower body mass index (BMI). Both groups did not differ significantly in terms of hemoglobin and serum creatinine. The PH group had higher N-terminal brain natriuretic peptide (NT-proBNP) levels than did the non-PH group, but both groups had nearly normal values. The PH group had lower partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide (PaCO_2) compared with the non-PH group.

3.3 | Echocardiography and hemodynamics

In this echocardiography diagnosed "PH possible" cohort, only 30.7% (27/88) were confirmed as PH, whereas 69.3% (61/88) were excluded. The PH group had higher PASP and lower tricuspid annular plane systolic excursion compared with the non-PH group. Left ventricular end-diastolic diameter was larger in the non-PH group than in the PH group. No differences were encountered with other echocardiographic parameters.

Statistically significant differences were found in hemodynamic parameters. The PH group had higher PASP and mean PAP compared with the non-PH group. The PH group had lower cardiac index and higher PVR. There is no difference in pulmonary arterial wedge pressure between the 2 groups (Table 1).

3.4 | Evaluation of the diagnostic value of CPET in suspected PH patients

The measurements of CPET variables in each group are presented in Table 2. Compared with non-PH patients, PH subjects had lower peak VO_2 and AT. PH patients exhibited diminished aerobic capacity. The lowest VE/VCO_2 and VE/VCO_2 slope were higher in the PH group than in the non-PH group. P_{ETCO_2} was also lower in PH patients. Along with significantly lower OUEP and OUES, PH patients also had a steeper HR response for a given change in VO_2 , thereby a lower peak O_2 pulse compared with non-PH subjects.

Univariate logistic regression models were used to assess whether CPET variables allowed discrimination between PH and non-PH groups. It indicated that peak VO_2 , AT, P_{ETCO_2} , lowest VE/VCO_2 ,

VE/VCO_2 slope, OUEP, OUES, and O_2 pulse all can predict PH. Then, using multivariate logistic forward regression, it indicated that VE/VCO_2 slope (odds ratio: 1.76, 95% confidence interval: 1.24-2.48, $P = 0.001$) and AT (odds ratio: 0.71, 95% confidence interval: 0.52-0.96, $P = 0.03$) were identified as independent predictors of PH adjusted for age and BMI (Table 3). The following new score was constructed:

$$\ln[(p/1-p)] = X = 6.66 + (0.56 \times \text{VE}/\text{VCO}_2 \text{ slope}) - (0.35 \times \text{AT}) - (0.09 \times \text{age}) - (0.75 \times \text{BMI}), \text{ where AT is given in mL/min, age in years, and BMI in kg/m}^2.$$

Combined with these 2 CPET parameters, this model leads to an improved specificity of 95% and sensitivity of 92.6% with a cutoff value 0.5 (area under the curve: 0.98, $P < 0.001$, probability value $\geq$ cutoff = PH; Figure 1).

4 | DISCUSSION

In this study, we demonstrate that combining VE/VCO_2 slope and AT from CPET as a complementary tool to echocardiography increases diagnostic specificity for screening PH in patients with an echocardiographic-alone diagnosis of "PH possible."

Our study enrolled echocardiographic-diagnosed "PH possible" patients (PASP < 50 mm Hg) because echocardiographic-estimated PASP ≥ 50 mm Hg has very high specificity of PH as recommended by European Society of Cardiology guidelines.¹ In our "PH possible" cohort, only 30.7% of patients had confirmed PH, whereas 69.3% were diagnosed as non-PH confirmed by RHC. In 48.9% of cases there were differences ≥ 10 mm Hg between DE-estimated PASP and the invasive measurement, which concurs with results from similar previous studies.⁶ As we enrolled patients whose echocardiographic-estimated PASP was < 50 mm Hg, overestimation by DE led more often to misclassification of the possibility of PH. So in the echocardiography-diagnosed "PH possible" cohort, another complementary tool was necessary to increase diagnostic specificity for detecting PH.

In our study, the PH group and the non-PH group had significant differences in CPET parameters. The main CPET characteristics in PH patients were exercise intolerance and ventilatory inefficiency due to abnormal gas-exchange findings characteristic of a ventilation-perfusion mismatch.¹¹ Subjects with PH had lower peak VO_2 and AT than did non-PH patients, indicating impaired activity endurance and an earlier development of lactic acidosis. There were marked increases in the lowest VE/VCO_2 and VE/VCO_2 slope in the PH group. Compared with the non-PH group, OUEP and OUES were significantly reduced in PH patients. The PH group had lower oxygen pulse than did the non-PH group, which is widely used as an indirect measure of cardiac stroke volume. PH impairs dilatation of affected pulmonary blood vessels, impeding pulmonary blood flow during exercise. As the vasculopathy progresses, the right ventricular reserve fails to meet the increased pulmonary O_2 requirement during exercise, leading to exertional dyspnea, fatigue, and other physical signs of pulmonary hypertension.

We additionally found that VE/VCO_2 slope and AT were independent predictors of PH. The gas-exchange abnormalities during

TABLE 1 Baseline characteristics of the patient groups

	All (N = 88)	PH Group, n = 27	Non-PH Group, n = 61	P Value
Age, y	52 ± 17	47 ± 17	54 ± 16	0.08
Sex, M/F	25/63	5/22	20/41	0.207
BMI, kg/m ²	23.60 ± 3.33	22.08 ± 2.44	24.28 ± 3.47	0.004
Diagnosis				
IPAH	—	11	—	
CTD-PAH	—	7	—	
CTEPH	—	9	—	
Biochemical indicators				
Hgb, g/L	130 ± 15	129.04 ± 14.95	130.84 ± 15.53	0.614
NT-proBNP, pg/mL	64 (27–141)	72 (42–213)	61 (25–117)	0.147
sCr, μmol/L	62.63 ± 20.88	64.26 ± 19.77	61.91 ± 21.47	0.629
PaO ₂ , mm Hg	89.53 ± 18.98	81.85 ± 17.76	92.93 ± 18.64	0.011
PaCO ₂ , mm Hg	37.02 ± 3.94	35.47 ± 4.16	37.68 ± 3.67	0.015
Echocardiographic parameters				
PASP, mm Hg	39.1 ± 7.25	44 ± 6	37 ± 7	<0.001
TAPSE, cm	2.10 ± 0.45	1.81 ± 0.35	2.24 ± 0.42	<0.001
RA-t, mm	37.77 ± 7.03	38.3 ± 8.5	37.5 ± 6.3	0.667
RV-t, mm	33.09 ± 4.83	33.7 ± 4.5	32.8 ± 4.9	0.433
LA, mm	32.13 ± 4.82	31.0 ± 3.9	32.6 ± 5.1	0.168
LVEDD, mm	44.64 ± 5.44	42.5 ± 4.4	45.6 ± 5.6	0.017
Pulmonary function testing				
FVC, L, %pred	2.88 ± 0.89 (90.40 ± 15.56)	2.8 ± 0.5 (87.8 ± 10.2)	2.9 ± 1.0 (91.5 ± 17.4)	NS
FEV1, L, %pred	2.38 ± 0.77 (91.83 ± 17.38)	2.3 ± 0.4 (88 ± 11.2)	2.4 ± 0.9 (82.7 ± 6.3)	NS
FEV1/FVC, %pred	82.84 ± 6.43	83.1 ± 6.8	82.7 ± 6.3	NS
DLCO, mL/mm Hg/min, %pred	18.76 ± 7.01 (97.18 ± 26.86)	14.8 ± 3.3 (78.1 ± 16.7)	20.5 ± 7.5 (105.5 ± 26.3)	<0.001
TLC, L, %pred	4.99 ± 1.13 (104.02 ± 29.22)	4.7 ± 0.6 (97.9 ± 10.3)	5.1 ± 1.3 (106.7 ± 34.1)	NS
Hemodynamic parameters				
RAP, mm Hg	3 (1–5)	3 (1–5)	2 (1–4)	0.465
PASP, mm Hg	34 (25–44)	54 (42–64)	28 (22–36)	<0.001
MPAP, mm Hg	20 (14–26.8)	31 (27–38)	17 (13–21)	<0.001
PAWP, mm Hg	7.73 ± 3.33	7.00 ± 3.19	8.09 ± 3.37	0.165
CO, L/min	5.93 ± 1.57	5.00 ± 1.28	6.36 ± 1.51	<0.001
CI, L/min/m ²	3.56 ± 0.81	3.14 ± 0.75	3.76 ± 0.76	<0.001
PVR, Wood units	1.96 (1.09–3.42)	4.84 (3.39–7.76)	1.35 (0.92–2.02)	<0.001
TPR, Wood units	3.44 (2.50–4.89)	5.74 (4.88–9.71)	2.81 (2.14–3.49)	<0.001
SVO ₂ , %	75 (71–78)	69 (65.3–77)	75.8 (73.5–80)	<0.001

Abbreviations: %pred, percent of predicted value; BMI, body mass index; CI, cardiac index; CO, cardiac output; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusion capacity for carbon monoxide; F, female; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; Hgb, hemoglobin; IPAH, idiopathic pulmonary arterial hypertension; IQR, interquartile range; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; M, male; MPAP, mean pulmonary arterial pressure; NS, not significant; NT-proBNP, N-terminal probrain natriuretic peptide; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial oxygen partial pressure; PASP, pulmonary arterial systolic pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrium pressure; RA-t, right atrium transverse diameter; RV-t, right ventricular transverse diameter; sCr, serum creatinine; SD, standard deviation; SvO₂, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TLC, total lung capacity; TPR, total pulmonary resistance.

Data are presented as median (IQR), mean ± SD, or n (%), unless otherwise stated.

CPET in patients with PH reflect hypoperfusion of well-ventilated alveoli. Ventilation is high compared with relatively low CO₂ output and reduced end-tidal PCO₂, manifesting as a hypoperfusion of well-ventilated lungs. Dumitrescu et al studied parameters of CPET in patients with scleroderma and found that a high VE/VCO₂ ratio and decreasing P_{ET}-CO₂ at AT identifies the presence of pulmonary vasculopathy.²² P_{ET}-CO₂ was found significantly lower in CTEPH vs idiopathic PAH at rest and during exercise and confirmed the

pronounced ventilatory inefficiency in CTEPH.²³ A score combining VE/VCO₂ slope, P(A-a)O₂, P(c-ET)CO₂, and P_{ET}-CO₂ provides a sensitivity of 83.3% and a specificity of 92.2% to detect CTEPH in patients with normal echocardiography.¹⁶ Lim et al found ventilatory parameters, including VE/VCO₂ slope, change in P_{ET}-CO₂ on exercise, and exercise oscillatory ventilation are associated with reactive PH in patients with HF.²⁴ We also found AT to have a significant role in detecting PH. The AT, which describes the highest VO₂ that the

TABLE 2 CPET parameters between the PH and non-PH groups

	PH Group, n = 27	Non-PH Group, n = 61	P Value
WR, watts	76.71 ± 28.65	105.26 ± 43.27	0.001
WR, %pred	71.21 ± 34.39	97.69 ± 38.19	0.003
Metabolic parameters			
Peak VO ₂ , mL/min	877.22 ± 259.12	1253.99 ± 466.17	<0.001
Peak VO ₂ /kg, mL · min ⁻¹ · kg ⁻¹	15.43 ± 4.33	19.58 ± 6.49	<0.001
AT, mL/min	595.07 ± 161.82	908.00 ± 347.5	<0.001
AT /kg, mL/min/kg	10.42 ± 2.66	14.34 ± 5.65	<0.001
Ventilatory parameters			
VE peak, L/min	43.42 ± 11.54	45.11 ± 16.60	0.634
RER	1.12 ± 0.12	1.11 ± 0.12	0.902
P _{ET} CO ₂ , mm Hg	28.20 ± 7.49	38.16 ± 4.92	<0.001
Lowest VE/VCO ₂	39.01 (33.28–50.99)	32.36 (28.96–34.24)	<0.001
VE/VCO ₂ slope	38.80 (32.80–57.45)	28.98 (26.17–31.03)	<0.001
OUEP	26.83 ± 6.06	34.80 ± 5.29	<0.001
OUES	1.19 ± 0.37	1.90 ± 0.63	<0.001
Cardiovascular parameters			
Peak HR, bpm	140 ± 18	142 ± 30	0.623
Oxygen pulse, (mL/beat)/min ⁻¹	6.21 ± 1.62	8.68 ± 2.43	<0.001

Abbreviations: %pred, percentage of predicted value; AT, anaerobic threshold; CPET, cardiopulmonary exercise testing; OUEP, oxygen uptake efficiency; OUES, oxygen uptake efficiency slope; P_{ET}CO₂, partial pressure of end-tidal carbon dioxide; PH, pulmonary hypertension; RER, respiratory exchange ratio; SD, standard deviation; VCO₂, carbon dioxide output; VE, minute ventilation; VO₂, oxygen uptake; WR, work rate.

Values are expressed as mean ± SD and percentage of measured to predicted values (%pred).

patient can sustain without developing a lactic acidosis, appears to be an independent marker of severity in primary PH.¹¹ Oudiz et al reported that O₂ uptake at AT and peak exercise are reduced in relation to disease severity and ventilatory efficiency in PAH.²⁵ Exercise-induced PAH has significantly lower mean aerobic capacity, higher ventilatory equivalents for oxygen at the anaerobic threshold. Thus, CPET is useful in identifying exercise-induced PAH and serves well to diagnose PAH at an early stage.²⁶

We conducted a model combining 2 CPET parameters adjusted for age and BMI, which led to an improved specificity of 95% and

sensitivity of 92.6%. Our study confirms that CPET may be another important tool, along with echocardiography, in evaluating patients with suspected PH by revealing impaired gas exchange and aerobic capacity. This method could prove useful in centers where the service or expertise may be inadequate, avoiding invasive RHC to confirm diagnosis, or when the costs of the services are a concern.

4.1 | Study limitations

The relatively small number of patients and the fact that all data originate from a single PH center is a limitation; thus, the accuracy

TABLE 3 ORs for PH diagnosis derived from univariate logistic regression and results from multivariate backward binary logistic regression, identifying independent predictors of PH

	OR (95% CI)	P Value	β-Coefficient	OR (95% CI)	P Value
Age	0.98 (0.95–1.00)	0.08	−0.09	0.92 (0.85–0.98)	0.012
Sex	2.15 (0.71–6.5)	0.17			
BMI	0.78 (0.66–0.93)	0.006	−0.75	0.47 (0.26–0.85)	0.012
CPET parameters					
VO ₂ peak, mL/min/kg	0.86 (0.77–0.95)	0.005			
AT, mL/min/kg	0.75 (0.61–0.93)	0.008	−0.35	0.71 (0.52–0.96)	0.03
P _{ET} CO ₂ , mm Hg	0.72 (0.62–0.83)	<0.001			
Lowest VE/VCO ₂	1.37 (1.17–1.61)	<0.001			
VE/VCO ₂ slope	1.37 (1.17–1.59)	<0.001	0.56	1.76 (1.24–2.48)	0.001
OUEP	0.74 (0.64–0.85)	<0.001			
OUES					
O ₂ pulse	0.54 (0.39–0.74)	<0.001			

Abbreviations: AT, anaerobic threshold; BMI, body mass index; CI, confidence interval; CPET, cardiopulmonary exercise testing; OR, odds ratio; OUEP, oxygen uptake efficiency; OUES, oxygen uptake efficiency slope; P_{ET}CO₂, partial pressure of end-tidal carbon dioxide; PH, pulmonary hypertension; VE, minute ventilation; VCO₂, carbon dioxide output; VO₂, oxygen uptake.

FIGURE 1 ROC curve for the determination of PH in patients with echocardiographic diagnosis of "PH possible" cohort. Abbreviations: AUC, area under the curve; PH, pulmonary hypertension; ROC, receiver operator characteristic.

of the formula needs further verification by other centers including more patients. CPET measures a broader range of variables related to cardiorespiratory function; our study excluded chronic pulmonary disease, left heart disease, valvular heart disease, cardiomyopathy, and severe metabolic diseases to avoid analyzing the effects of coexistent conditions on exercise responses. Thus, our PH group included only CTEPH and PAH patients, thereby limiting the application of the formula to a very narrow spectrum of diseases. Finally, this equation should be used to derive sensitivity and specificity values to predict PH in a separate validation cohort. We intend to evaluate the value of the equation in the prospective validation cohort in the future.

5 | CONCLUSION

CPET is valuable as a complementary tool to echocardiography in screening out PH in patients with an echocardiographic diagnosis of "PH possible." We have shown that a formula including CPET variables VE/VCO₂ slope and AT, along with echocardiographic evidence, confers higher specificity.

Conflicts of Interest

Z.-C.J. has associations with the drug companies Actelion, Bayer Schering, Pfizer, and United Therapeutics, in addition to being an investigator in trials sponsored by these companies. Associations include consultancy services and membership on scientific advisory boards. The authors declare no other potential conflicts of interest.

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