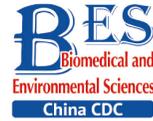


## Original Article



## Effect of Maximal Oxygen Pulse on Patients with Chronic Obstructive Pulmonary Disease\*

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### Abstract

**Objective** This study evaluated the effect of maximal oxygen pulse ( $O_2P_{max}$ ) on patients with chronic obstructive pulmonary disease (COPD) and confirmed the predictive effect on acute exacerbations of COPD (AECOPD).

**Methods** This retrospective study included 91 participants who underwent cardiopulmonary exercise testing (CPET), lung function testing, a dyspnea scale assessment, and a 3-year follow-up. The participants were divided into two groups according to the  $O_2P_{max}$  value. Exercise capacity, ventilatory conditions, gas exchange efficiency, and dyspnea symptoms were compared, and the correlations between  $O_2P_{max}$  and these indices were evaluated. The ability of  $O_2P_{max}$  to predict AECOPD was examined.

**Results** Exercise capacity, ventilatory conditions, and gas exchange efficiency were lower, and dyspnea symptom scores were higher in the impaired  $O_2P_{max}$  group ( $P < 0.05$ ).  $O_2P_{max}$  was positively correlated with forced vital capacity (FVC)%, forced expiratory volume in 1 sec ( $FEV_1$ )%,  $FEV_1/FVC$ %, anaerobic threshold (AT), work rate (WR)%, aximal oxygen uptake ( $VO_{2max}$ )%,  $VO_2/kg_{max}$ ,  $VO_2/kg_{max}$ %,  $WR_{AT}$ ,  $WR_{max}$ ,  $VO_{2AT}$ ,  $VO_{2max}$ , and  $V_{Emax}$ , and was negatively correlated with  $EqCO_{2AT}$ , and  $EqCO_{2max}$  ( $P < 0.05$ ). Most importantly,  $O_2P_{max}$  could be used to predict AECOPD, and the best cut-off value was 89.5% (area under the curve, 0.739; 95% CI, 0.609–0.869).

**Conclusion**  $O_2P_{max}$  reflected exercise capacity, ventilation capacity, gas exchange capacity, and dyspnea symptoms in patients with COPD and may be an independent predictor of AECOPD.

**Key words:** Oxygen pulse; Chronic obstructive pulmonary disease; Cardiopulmonary exercise test; Acute exacerbation

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### INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent airflow limitation. The chronic airflow limitation progressively traps gas during expiration, resulting in hyperinflation, increased dyspnea, and

limitations in exercise capacity. Acute exacerbation of COPD (AECOPD) is defined as an acute worsening of respiratory symptoms necessitating additional therapy. The severity of AECOPD and its increasing frequency is associated with a higher risk of death<sup>[1]</sup>. However, there is a lack of effective indicators to predict AECOPD. A deteriorating airflow limitation is associated with an increasing prevalence of

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exacerbations<sup>[2]</sup>. Forced expiratory volume in 1 sec ( $FEV_1$ ) is an indicator of airflow limitation, but it lacks sufficient precision to be used clinically as a predictor of exacerbation or mortality in patients with COPD<sup>[3]</sup>. Only a weak correlation is observed between  $FEV_1$ , symptoms, and impaired health status of patients<sup>[4]</sup>. Thus, it is important to explore other effective indicators for predicting AECOPD.

Exercise capacity is limited in COPD patients and is significantly correlated with overall survival<sup>[5]</sup>. The probable mechanisms include impaired oxygen delivery to skeletal muscle and ventilatory limitations<sup>[6]</sup>. Cardiopulmonary exercise testing (CPET) is used to assess exercise tolerance and evaluate the pathophysiological mechanism(s) of dyspnea and exercise limitation in patients with COPD<sup>[7]</sup>. Oxygen pulse ( $O_2P$ ), an important CPET variable, is a noninvasive and reliable method used to estimate stroke volume and cardiac function<sup>[8]</sup> with the exclusion of coexisting diseases, but it has rarely been used to evaluate the severity of COPD.  $O_2P$  is defined as oxygen uptake ( $VO_2$ ) divided by heart rate (HR). One study showed that  $O_2P$  is impaired during exercise in patients with COPD, and this is partly related to lung hyperinflation<sup>[9]</sup>. Miniati et al.<sup>[10]</sup> reported that peak  $O_2P$  is significantly lower in patients with moderate to severe emphysema than in those with no or mild emphysema. Thus,  $O_2P$  may be an important indicator for differentiating COPD severity.  $O_2P_{max}$  represents the  $O_2P$  at maximal exercise and reflects the maximal aerobic metabolic function.  $O_2P_{max}$  is extensively used for testing patients with cardiovascular diseases, but it has limited use in those with COPD. Furthermore, increased hyperinflation and gas trapping occur during an exacerbation, with reduced expiratory flow<sup>[11]</sup>. A worsening of gas exchange can also result in hypoxemia<sup>[12]</sup>.  $O_2P$  is directly related to hyperinflation and reflects gas exchange, so  $O_2P$  may be a better predictor of AECOPD. Accordingly, we hypothesized that  $O_2P_{max}$  has a role in COPD and may be related to AECOPD.

In this study, we examined the relationship between  $O_2P_{max}$  and exercise capacity, ventilatory conditions, gas exchange efficiency, and health-related quality of life (HRQL). We also estimated the predictive value of  $O_2P_{max}$  for AECOPD and determined the cut-off value.

## MATERIALS AND METHODS

### Study Design

This retrospective analysis involved patients with

COPD who underwent incremental cardiopulmonary exercise in our exercise laboratory at Beijing Friendship Hospital, Capital Medical University (Beijing, China) from 1 January 2017 to 31 December 2020. This study was conducted in compliance with the Declaration of Helsinki. The Institutional Ethics Committee of Beijing Friendship Hospital of Capital Medical University approved this study (no. 2021-P2-334-01).

### Participants

All participants were men and women aged  $\geq 40$  years with a body mass index of  $18\text{--}32\text{ kg/m}^2$  and no episodes of AECOPD within the previous 6 weeks. All of the participants had been diagnosed with COPD and a grade I, II, III, or IV airflow limitation according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and underwent CPET in our clinic. After enrollment, the participants' smoking history, comorbidities (hypertension, coronary heart disease, type 2 diabetes, and hypercholesterolemia), medications used for COPD, and medications used for cardiovascular disease were recorded. The patients were followed up outside of the hospital by telephone. AECOPD was classified as mild (treated with short-acting bronchodilators only), moderate (treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids), or severe (required hospitalization or visits to the emergency room)<sup>[13]</sup>. The exclusion criteria were respiratory diseases other than COPD, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, orthopedic problems, neurologic problems, and hemopathy.

### Pulmonary Function Testing

All participants underwent static spirometry (MasterScreen Body; CareFusion, San Diego, CA, USA), including measurements of  $FEV_1$ , forced vital capacity (FVC), vital capacity (VC), peak expiratory flow, and maximal mid-expiratory flow rate 75/25. Body plethysmography was performed to measure the residual volume (RV), total lung capacity (TLC), and the transfer factor of the lungs for carbon monoxide/alveolar volume. All pulmonary function tests were performed according to the American Thoracic Society/European Respiratory Society guidelines<sup>[14]</sup>.

### CPET

CPET was performed according to the American Thoracic Society/European Respiratory Society guidelines<sup>[15]</sup>. All patients rested for 3 min,

performed unloaded pedaling for 3 min, and then underwent an incremental, symptom-limited exercise test using an electronically braked cycle ergometer (ViaSprint, CareFusion, Hoechst, Germany) at a pedaling rate of 40–70 rpm (approximately 60 rpm). The work rate (WR) was set to 5–20 W/min and was gradually increased by 5–15 W/min (5 W/min if  $FEV_1 < 1.0$  L and 10 W/min if  $FEV_1 \geq 1.0$  L). The test ended when the cadence fell below 40 rpm and did not return with an exhortation, the patients requested termination, or the technician terminated the test for safety<sup>[16]</sup>. The limiting symptom was defined as the inability to maintain pedaling frequency or the development of intolerable shortness of breath. Chest pain (suggesting myocardial ischemia), ventricular tachycardia, and blood pressure (BP)  $\geq 240/130$  mmHg also prevented further exercise. The  $O_2P_{max}$  was defined as  $VO_{2max}/HR$ . According to the current guidelines<sup>[17]</sup>,  $O_2P_{max}$  values  $\geq 80\%$  of the predicted value were considered normal, whereas  $O_2P_{max} < 80\%$  of the predicted value was considered pathological. Accordingly, Group 1 was defined as patients with impaired  $O_2P_{max}$  ( $< 80\%$  predicted), and Group N was defined as patients with normal  $O_2P_{max}$  ( $\geq 80\%$  predicted).  $VO_2$ , carbon dioxide production ( $VCO_2$ ), minute ventilation ( $V_E$ ), breathing reserve (BR), and 12-lead electrocardiography were measured continuously. BP was measured at the end of every 2 min. Load was reported at maximum exertion.  $VO_2/kg$ , the ventilatory equivalent for carbon dioxide ( $EqCO_2$ ), and HR recovery after 1 min of rest ( $HRR_1$ ) were calculated automatically. The anaerobic threshold (AT) was identified using the modified V-slope method.

### **Dyspnea and Symptom Assessment**

The COPD Assessment Test (CAT) and the St. George's Respiratory Questionnaire (SGRQ) were used to measure the impaired health status of patients with COPD. The SGRQ includes four categories, such as symptoms, physical activities, psychosocial impacts, and the total score. The CAT total score ranges from 0 to 40, and the SGRQ total score ranges from 0 to 100. An SGRQ score  $\geq 25$  was used as the threshold for breathlessness, and the equivalent cut-off point for the CAT was 10<sup>[13]</sup>. The modified British Medical Research Council Questionnaire (mMRC) was used to assess dyspnea severity. The mMRC score ranges from 0 to 5, and  $\geq 2$  was considered the threshold for separating "less breathlessness" from "more breathlessness."

Because our patients were using mouthpieces and could not conveniently answer the doctors' questions during exercise, the dyspnea level and leg muscle fatigue were scored using Borg's 10-point category-ratio scale (Borg CR10 scale) after the patients finished exercising. A Borg CR10 scale score of 4–6 indicated moderate to severe symptoms.

### **AECOPD Follow-up**

Fifty-seven patients (63%) completed the 3-year follow-up. AECOPD was tracked during the next 3 years. Telephone calls were made to the patients every 4 months to determine whether they had experienced any exacerbations, had taken any short-acting bronchodilators, antibiotics, or oral corticosteroids, or had been hospitalized. According to the GOLD<sup>[13]</sup>, patients with AECOPD (AE2 group) developed more than one acute exacerbation episode within 1 year. Patients without AECOPD (AE1 group) had developed no or only one acute exacerbation episode within the year.

### **Statistical Analysis**

Continuous data were expressed as mean  $\pm$  standard deviation, number, and percentage, or median (IQR), while categorical data were expressed as frequencies and percentages. Continuous data were compared using the *t*-test or Mann-Whitney test, and categorical data were compared using the chi-square test. A *P*-value  $< 0.05$  was considered significant.

Pearson's correlation coefficient (*r*) was used to assess the correlations between the static lung function variables ( $FEV_1/FVC\%$ ,  $FEV_1\%$ ,  $FVC\%$ , and VC) and the CPET variables (AT%,  $WR_{AT}$ ,  $WR_{max}$ , WR%,  $VO_{2AT}$ ,  $VO_{2max}$ ,  $VO_2\%$ ,  $VO_2/kg_{max}$ ,  $VO_2/kg\%$ ,  $V_{Emax}$ ,  $V_E\%$ ,  $BR_{AT}$ ,  $BR_{max}$ ,  $EqCO_{2AT}$ ,  $EqCO_{2max}$ , and  $HRR_1$ ) and  $O_2P_{max}$ .

Univariate logistic regression analysis was performed to assess the efficiency of  $O_2P_{max}$  for predicting AECOPD. Static lung function and CPET variables that were significantly different between the AE2 and AE1 groups were assessed to identify risk factors for AECOPD using multivariate logistic regression analysis. Wald's test was used to obtain the logistic regression parameters.

The discriminative ability of  $O_2P_{max}$  in predicting AECOPD was evaluated by receiver operating characteristic (ROC) analysis. The area under the ROC curve (AUC) and the 95% confidence interval (CI) were calculated. The best cut-off value was determined.

## RESULTS

### Patient Demographics and Characteristics

Table 1 shows the patient demographics and baseline characteristics. Ninety-one patients with COPD were divided into Group 1 ( $n = 27$ ) and Group N ( $n = 64$ ) according to their  $O_2P_{max}$  value. No significant differences in age, sex, body height, body mass index, smoking history, comorbidities, or medications were observed between the two groups. However, significant differences in body weight and classification of the airflow limitation were detected between the two groups ( $P < 0.05$ ). The airflow limitation was more severe in Group 1 than in Group N.

### Differences in Static Lung Function

Table 2 shows the static lung function parameters. Patients with a lower  $O_2P_{max}$  had lower FVC%, VC%, FEV<sub>1</sub>%, and FEV<sub>1</sub>/FVC% values ( $P < 0.05$ ).

### Differences in CPET

Table 3 shows the CPET variables. AT, WR,  $VO_2$ ,  $VO_2/kg$ , HR, systolic BP, diastolic BP,  $V_E$ , BR, and EqCO<sub>2</sub> were measured at the AT and maximum exercise during CPET. HRR<sub>1</sub> was calculated after the exercise. Significant differences in AT, WR%,  $VO_2$ %,  $VO_2/kg$ %,  $V_E$ %, EqCO<sub>2AT</sub>, and EqCO<sub>2max</sub> were observed between the two groups ( $P < 0.05$ ). Among these variables, EqCO<sub>2AT</sub> and EqCO<sub>2max</sub> were higher in patients with impaired  $O_2P_{max}$ , whereas the other variables were lower. Significant differences were also detected in HRR<sub>1</sub> ( $P < 0.05$ ), which was regarded as a circulatory parameter.

### Disease-specific Health Status Questionnaires

Table 4 shows the CAT, mMRC, Borg CR10 scale, and SGRQ scores. The Borg CR10 scale, SGRQ total, SGRQ symptom, and SGRQ activity scores were significantly higher in Group 1 than those in Group N ( $P < 0.05$ ).

### Correlation between $O_2P_{max}$ and FEV<sub>1</sub>/FVC%, FEV<sub>1</sub>%, and FVC%

Figure 1 shows the correlation coefficients between  $O_2P_{max}$  and FEV<sub>1</sub>/FVC%, FEV<sub>1</sub>%, and FVC%, which were regarded as lung ventilation function variables.  $O_2P_{max}$  was slightly but significantly correlated with FEV<sub>1</sub>/FVC% ( $r = 0.207$ ,  $P < 0.05$ ), FEV<sub>1</sub>% ( $r = 0.267$ ,  $P < 0.05$ ), and FVC% ( $r = 0.288$ ,  $P < 0.01$ ).

### CPET Variables

Figure 2 shows the correlation coefficients between  $O_2P_{max}$  and the CPET variables.  $O_2P_{max}$  was positively correlated with AT ( $r = 0.623$ ,  $P < 0.001$ ), WR% ( $r = 0.613$ ,  $P < 0.001$ ),  $VO_{2max}$ % ( $r = 0.681$ ,  $P < 0.001$ ),  $VO_2/kg_{max}$ % ( $r = 0.707$ ,  $P < 0.001$ ), and  $V_{Emax}$ % ( $r = 0.399$ ,  $P < 0.001$ ), but negatively correlated with EqCO<sub>2AT</sub> ( $r = -0.302$ ,  $P < 0.01$ ) and EqCO<sub>2max</sub> ( $r = -0.214$ ,  $P < 0.05$ ).

### Comparison between the AE1 and AE2 Groups

Table 5 shows that FVC%, FEV<sub>1</sub>%,  $O_2P_{max}$ %, WR<sub>max</sub>, and  $VO_{2max}$  were significantly lower in the AE2 group than in the AE1 group ( $P < 0.05$ ).

### Logistic Regression Analysis

The univariate logistic regression confirmed that  $O_2P_{max}$  was an independent predictor of AECOPD [odds ratio (OR), 1.068; 95% CI, 1.023–1.116;  $P = 0.003$ ]. Five variables (FVC%, FEV<sub>1</sub>%,  $O_2P_{max}$ , WR<sub>max</sub>, and  $VO_{2max}$ ) were used to build a logistic regression model to predict AECOPD in a multivariate analysis (Tables 6–7). Only  $O_2P_{max}$  was a predictor of AECOPD (OR = 1.062, 95% CI = 1.012–1.114,  $P = 0.015$ ). ROC curve analysis was applied to categorize the optimal cut-off value of  $O_2P_{max}$  for exacerbation (Figure 3). The AUC was 0.739 (95% CI = 0.609–0.869,  $P = 0.002$ ). The cut-off value was 89.5%, with a sensitivity of 63.30% and a specificity of 77.80%.

## DISCUSSION

The main finding of the present study was that impaired  $O_2P_{max}$  in patients with COPD indicated an impaired ventilatory condition, gas exchange efficiency, exercise capacity, and HRQL. The correlation analysis showed that  $O_2P_{max}$  was correlated with FEV<sub>1</sub>/FVC%, FEV<sub>1</sub>%, FVC%, WR, AT,  $VO_2$ ,  $VO_2/kg$ ,  $V_E$ , and EqCO<sub>2</sub>. Moreover,  $O_2P_{max}$  was significantly different between the AE2 and AE1 groups, which was a new finding. The univariate and multivariate logistic regression analyses demonstrated for the first time that  $O_2P_{max}$  predicted AECOPD (OR 1.068, 95% CI = 1.023–1.116). The optimal  $O_2P_{max}$  cut-off value was 89.5%. The AUC was 0.739 (0.609–0.869) with a sensitivity of 0.633 and a specificity of 0.778.

$VO_2$  represents metabolic efficiency, and WR represents exercise capacity. The AT represents a transition point from aerobic to anaerobic metabolism, and a lower AT indicates reduced oxygen delivery to muscle cells. Declines in AT%, WR,

**Table 1.** Baseline characteristics of Group 1 ( $O_2P_{max} < 80\%$  predicted) and Group N ( $O_2P_{max} \geq 80\%$  predicted)

Item	Group 1 (n = 27)	Group N (n = 64)	All (n = 91)	P-value
Demographic				
Age (years)	65.1 ± 7.6	64.4 ± 7.3	64.6 ± 7.4	0.682
Male/Female (n)	23/4	52/12	75/16	0.652
Height (cm)	169.5 ± 5.4	167.4 ± 6.9	168.0 ± 6.5	0.167
Weight (kg)	73.9 ± 13.3	66.7 ± 9.3	68.9 ± 11.0	<b>0.015</b>
BMI (kg/m <sup>2</sup> )	24.8 ± 3.6	23.8 ± 3.1	24.1 ± 3.3	0.160
Smoking (n)				0.292
Non-smoker	4 (15%)	6 (9%)	10 (11%)	
Current smoker	20 (74%)	42 (66%)	62 (68%)	
Ex-smoker	3 (11%)	16 (25%)	19 (21%)	
GOLD (n)	n (27)	n (64)		<b>0.014</b>
I	1 (4%)	8 (13%)	9 (10%)	
II	14 (52%)	43 (67%)	57 (63%)	
III	9 (33%)	13 (20%)	22 (24%)	
IV	3 (11%)	0 (0%)	3 (3%)	
Comorbidities (n)	n (22)	n (53)		0.398
Hypertension	8	28	36	
CHD	4	6	10	
Type 2 diabetes	9	14	23	
Hypercholesterolemia	1	5	6	
Medications for COPD (n)	n (27)	n (64)		0.716
None	16	37	53	
LABA	1	2		
LAMA	1	7		
LABA + LAMA	0	1		
LABA + ICS	2	7		
LABA + LAMA + ICS	7	10		
Medications for CVD (n)	n (13)	n (45)		0.680
Beta-blockers	3	14		
Aspirin	1	6		
ACEI	1	1		
CCB	3	12		
ARBs	3	4		
Statin	2	8		

**Note.** Data are presented as mean ± standard deviation or numbers (percentage). All demographic data except sex were compared using the *t*-test. Other data were compared using the chi-square test. Bold numbers indicate a significant difference ( $P < 0.05$ ) between the two groups. Abbreviations: BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CHD, coronary heart disease; LABA, long-acting beta 2 agonist; LAMA, long-acting antimuscarinic antagonist; ICS, inhaled corticosteroid; CVD, cardiovascular disease; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ARB, angiotensin receptor blocker.

and  $\dot{V}O_2$  contribute to exercise intolerance<sup>[18]</sup>. The present study indicated that AT, WR%,  $\dot{V}O_2\%$ ,  $\dot{V}O_2/\text{kg}\%$ , and  $\dot{V}_E\%$  were lower in Group 2 than those in Group 1 (impaired  $O_2P_{\text{max}}$  group). This finding

**Table 2.** Differences in the static lung function test parameters between Group 1 ( $O_2P_{\text{max}} < 80\%$  predicted) and Group N ( $O_2P_{\text{max}} \geq 80\%$  predicted)

Item	Group 1 (n = 27)	Group N (n = 64)	All (n = 91)	P-value
FVC (% predicted)	75.00 ± 16.67	86.80 ± 16.57	83.30 ± 1.82	<b>0.003</b>
VC (% predicted)	72.55 ± 16.34	84.45 ± 16.29	80.92 ± 1.79	<b>0.003</b>
FEV <sub>1</sub> (% predicted)	51.49 ± 20.33	63.79 ± 16.15	60.14 ± 1.92	<b>0.003</b>
FEV <sub>1</sub> /FVC (%)	52.25 ± 13.07	58.34 ± 10.46	56.53 ± 1.21	<b>0.038</b>
RV/ TLC (%)	0.57 ± 0.11	0.55 ± 0.17	0.56 ± 0.02	0.618
PEF (% predicted)	60.81 ± 24.02	69.80 ± 21.70	67.14 ± 2.37	0.084
MMEF <sub>75/25</sub> (% predicted)	20.03 ± 11.40	24.01 ± 11.00	22.83 ± 1.17	0.121
TL <sub>CO</sub> /VA (% predicted)	73.41 ± 26.16	81.11 ± 21.56	78.83 ± 2.43	0.148

**Note.** Data are presented as mean ± standard deviation. Data were compared using the *t*-test. Bold numbers indicate a significant difference ( $P < 0.05$ ) between the two groups. Abbreviations: FVC, forced vital capacity; VC, vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; RV, residual volume; TLC, total lung capacity; PEF, peak expiratory flow; MMEF<sub>75/25</sub>, maximal mid-expiratory flow rate 75/25; TL<sub>CO</sub>/VA, transfer factor of the lungs for carbon monoxide/alveolar volume.

**Table 3.** Differences in the CPET parameters between Group 1 ( $O_2P_{\text{max}} < 80\%$  predicted) and Group N ( $O_2P_{\text{max}} \geq 80\%$  predicted)

Item	Group 1 (n = 27)	Group N (n = 64)	All (n = 91)	P-value
AT (%)	37.92 ± 9.34	54.51 ± 11.85	49.59 ± 13.47	<b>&lt; 0.001</b>
WR (% predicted)	57.67 ± 15.07	90.84 ± 22.92	81.00 ± 25.80	<b>&lt; 0.001</b>
$\dot{V}O_2$ (% predicted)	55.37 ± 8.21	77.86 ± 13.37	71.19 ± 15.85	<b>&lt; 0.001</b>
$\dot{V}O_2/\text{kg}$ (% predicted)	54.78 ± 8.37	77.63 ± 12.18	70.85 ± 15.31	<b>&lt; 0.001</b>
HR <sub>AT</sub> (beats/min)	106.70 ± 12.14	106.83 ± 14.06	106.79 ± 13.45	0.968
HR <sub>max</sub> (beats/min)	130.59 ± 16.70	130.86 ± 18.80	130.78 ± 13.11	0.949
SBP <sub>AT</sub> (mmHg)	140.96 ± 24.68	137.53 ± 23.47	138.55 ± 23.75	0.542
SBP <sub>max</sub> (mmHg)	167.63 ± 23.07	161.31 ± 31.08	163.19 ± 28.95	0.345
DBP <sub>AT</sub> (mmHg)	81.19 ± 12.57	83.77 ± 18.98	83.00 ± 17.30	0.519
DBP <sub>max</sub> (mmHg)	90.41 ± 17.47	94.94 ± 29.50	93.58 ± 26.45	0.460
$\dot{V}_E$ (% predicted)	47.26 ± 11.73	62.83 ± 14.02	58.21 ± 15.12	<b>&lt; 0.001</b>
BR <sub>AT</sub> (mL/min)	42.56 ± 18.74	50.94 ± 14.03	48.45 ± 15.94	<b>0.043</b>
BR (% predicted)	71.11 ± 70.12	73.14 ± 64.31	72.54 ± 65.70	0.894
EqCO <sub>2AT</sub>	35.65 ± 6.05	32.33 ± 4.94	33.31 ± 5.48	<b>0.007</b>
EqCO <sub>2max</sub>	34.10 ± 6.93	30.93 ± 5.86	31.87 ± 6.32	<b>0.028</b>
HRR <sub>1</sub> (beats/min)	14.78 ± 7.66	19.28 ± 9.66	17.95 ± 9.30	<b>0.034</b>

**Note.** Data are presented as mean ± standard deviation. Data were compared using the *t*-test. Bold numbers indicate a significant difference ( $P < 0.05$ ) between the two groups. Abbreviations: AT, anaerobic threshold; WR, work rate;  $\dot{V}O_2$ , oxygen uptake;  $\dot{V}O_2/\text{kg}$ , oxygen uptake per kilogram; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure;  $\dot{V}_E$ , minute ventilation; BR, breathing reserve; EqCO<sub>2</sub>, ventilatory equivalent for carbon dioxide; HRR<sub>1</sub>, heart rate recovery after 1 min of rest.

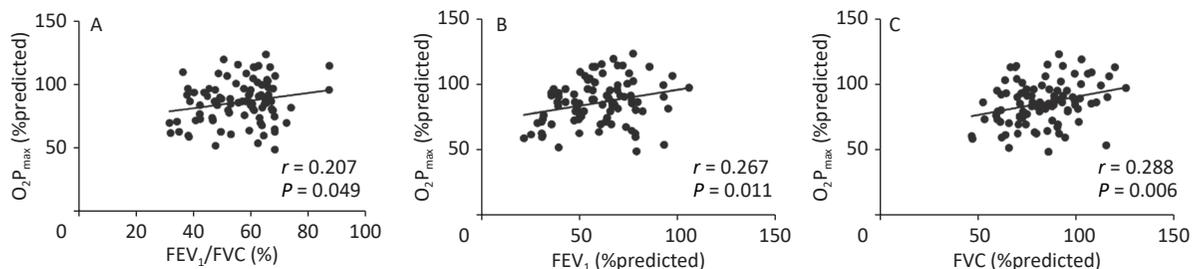
suggests that  $O_2P_{max}$  might be an effective indicator for estimating exercise capacity. Patients with COPD develop dynamic hyperinflation during exercise. Dynamic hyperinflation can reduce left ventricular stroke volume secondary to the increased intrathoracic pressure, which, in turn, decreases preload by reducing venous return and the volume of the left ventricle. This explains why  $O_2P_{max}$  is impaired in patients with COPD. Hyperinflation leads to limited cardiac performance, which occurs when there is a mechanical limitation to an increase in  $V_E$ . Therefore, dynamic hyperinflation in patients with COPD may adversely affect exercise tolerance by reducing  $O_2P_{max}$ . Moreover, lung hyperinflation impairs cardiopulmonary interactions and leads to impaired muscle oxygen availability during exercise. Research has also shown that impaired circulation is not usually a limiting factor for exercise intolerance in patients with COPD<sup>[6]</sup>. Thus,  $O_2P_{max}$  may be a predictor of exercise capacity independent of cardiovascular function. The present study also demonstrated that  $O_2P_{max}$  was highly positively

correlated with AT, WR%,  $VO_{2max}$ %, and  $VO_2/kg\%$ . Montes de Oca et al.<sup>[16]</sup> showed that inspiratory intrathoracic pressure has a direct relationship with  $O_2P$  at peak exercise in patients with severe COPD. Torres-Castro et al.<sup>[19]</sup> reported that  $VO_{2peak}$  and  $W_{max}$  decrease in patients with COPD and pulmonary hypertension, in line with the decrease in  $O_2P$ . An inadequate increase in stroke volume may contribute to the inability of  $VO_2$  to increase. These results explain why  $VO_2$  was positively correlated with  $O_2P_{max}$ . WR and  $O_2P_{max}$  represent exercise capacity; thus, it is easy to understand why  $O_2P_{max}$  was positive correlated with WR. In addition, the circulatory system is responsible for oxygen delivery. When the metabolic demands begin to exceed oxygen delivery to contracting muscles, anaerobic metabolism begins. The AT is the exercise level that reflects the metabolic condition of anaerobic glycolysis<sup>[20]</sup>. A lower AT is observed if a patient's oxygen consumption efficiency is poor. The AT reflects oxygen consumption efficiency, and circulatory function can be used to determine the

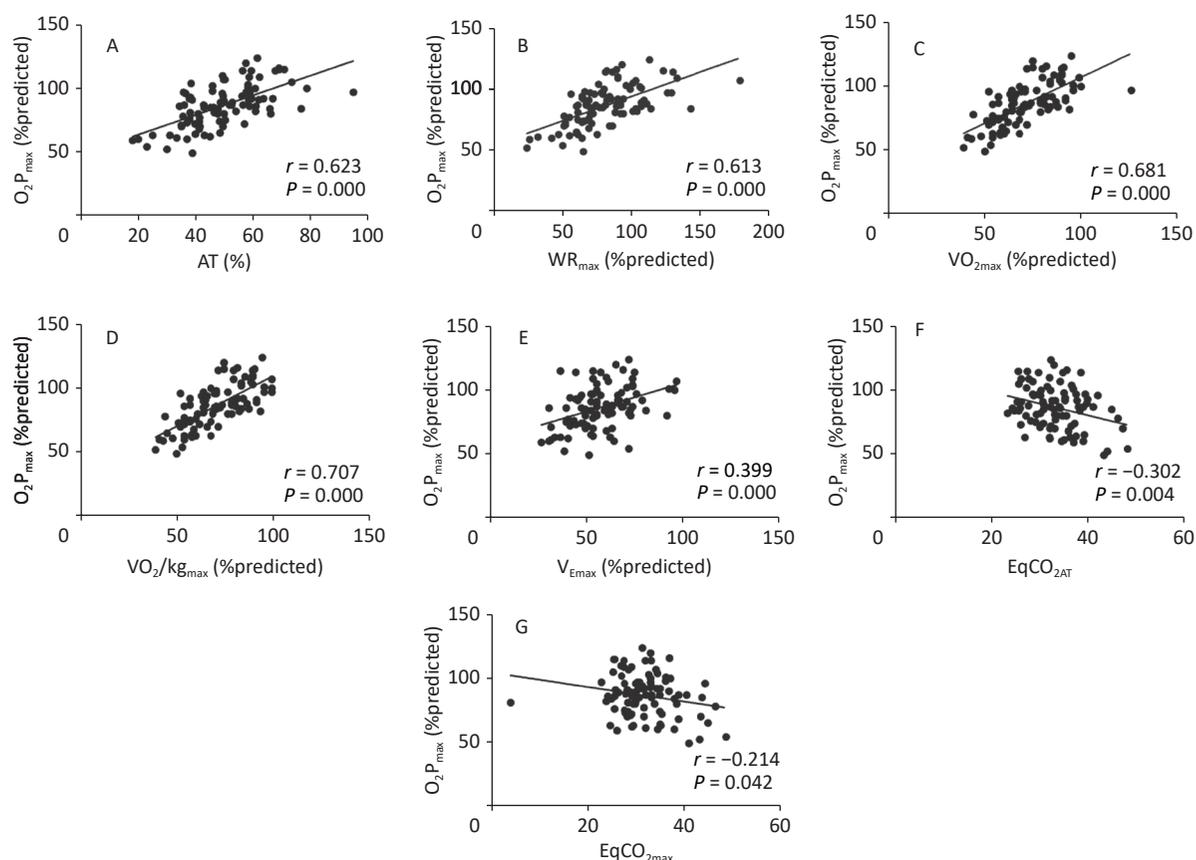
**Table 4.** Differences in the dyspnea scores between Group 1 ( $O_2P_{max} < 80\%$  predicted) and Group N ( $O_2P_{max} \geq 80\%$  predicted)

Item	Group 1 (n = 27)	Group N (n = 64)	All (n = 91)	P-value
CAT (points)	12.50 ± 5.32	9.79 ± 4.01	10.79 ± 4.66	0.084
mMRC (points)	1.71 ± 0.73	1.29 ± 0.76	1.45 ± 0.76	0.099
Borg CR10 (points)	2.64 ± 1.21	1.56 ± 1.45	1.96 ± 1.45	<b>0.025</b>
SGRQ, total (points)	41.78 ± 12.46	25.61 ± 17.15	33.31 ± 16.89	<b>0.024</b>
SGRQ, symptom (points)	54.30 ± 19.34	29.47 ± 17.51	41.29 ± 21.98	<b>0.006</b>
SGRQ, activity (points)	55.89 ± 11.11	35.65 ± 25.67	45.29 ± 22.19	<b>0.032</b>
SGRQ, impact (points)	33.57 ± 15.99	19.66 ± 15.12	26.28 ± 16.73	0.055

**Note.** Data are presented as mean ± standard deviation. Data were compared using the *t*-test. Bold numbers indicate a significant difference ( $P < 0.05$ ) between the two groups. The CAT, mMRC, and SGRQ were evaluated before CPET; the Borg CR10 was evaluated immediately after CPET. Abbreviations: CAT, COPD Assessment Test; mMRC, modified Medical Research Council scale; Borg CR10, Borg's 10-point category-ratio scale; SGRQ, St. George's Respiratory Questionnaire.



**Figure 1.** Correlations between  $O_2P_{max}$  and  $FEV_1/FVC\%$ ,  $FEV_1\%$ , and  $FVC\%$ . Abbreviations:  $O_2P$ , oxygen pulse;  $FEV_1$ , forced expiratory volume in 1 sec;  $FVC$ , forced vital capacity.



**Figure 2.** Correlations between  $O_2P_{max}$  and the CPET parameters. Abbreviations:  $O_2P$ , oxygen pulse; AT, anaerobic threshold; WR, work rate;  $VO_2$ , oxygen uptake;  $VO_2/kg$ , oxygen uptake per kilogram; VE, minute ventilation;  $EqCO_2$ , ventilatory equivalent for carbon dioxide.

**Table 5.** Characteristics, pulmonary function, and CPET data of the patients with COPD grouped in acute exacerbation

Item	AE1 group (n = 30)	AE2 group (n = 27)	P-value
Age (Years)	63.73 ± 8.09	64.30 ± 6.92	0.780
Weight (kg)	69.00 ± 8.60	70.48 ± 13.83	0.625
Smoke (numbers)	27.50 (40.75)	15.00 (30.00)	0.257
Male/Female (n)	25/5	23/4	0.261
FVC (% predicted)	87.08 ± 16.94	76.84 ± 13.88	<b>0.016</b>
FEV <sub>1</sub> (% predicted)	63.52 ± 16.25	51.52 ± 17.78	<b>0.010</b>
FEV <sub>1</sub> /FVC (%)	57.44 ± 9.26	52.12 ± 13.13	0.080
$O_2P_{max}$ (% predicted)	93.23 ± 13.10	79.93 ± 15.41	<b>0.001</b>
$WR_{max}$ (watts)	101.70 ± 21.63	80.48 ± 24.66	<b>0.001</b>
$VO_{2max}$ (mL/min)	1350.23 ± 230.16	1141.15 ± 279.00	<b>0.003</b>

**Note.** Data are presented as mean ± standard deviation, median (IQR), or number. Sex was compared using the chi-square test, smoke was compared using the Mann-Whitney test, and the remaining data were compared using the *t*-test. Bold numbers indicate a significant difference ( $P < 0.05$ ) between the two groups. Abbreviations: AE, acute exacerbation; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s;  $O_2P$ , oxygen pulse; WR, work rate;  $VO_2$ , oxygen uptake.

AT. This explains why  $O_2P_{max}$  was associated with the AT in our study.

The present study also illustrated that  $O_2P_{max}$  can be used to assess a ventilation obstruction. FVC%, VC%, FEV<sub>1</sub>%, FEV<sub>1</sub>/FVC%, V<sub>E</sub>%, and BR<sub>AT</sub> were lower, and EqCO<sub>2AT</sub> and EqCO<sub>2max</sub> were higher in patients with impaired  $O_2P_{max}$  than in those without impaired  $O_2P_{max}$ . Additionally,  $O_2P_{max}$  was negatively correlated with EqCO<sub>2AT</sub>, and EqCO<sub>2max</sub> was positively correlated with FEV<sub>1</sub>/FVC%, FEV<sub>1</sub>%, FVC%, and V<sub>Emax</sub>%. Our data corroborate the findings of Frazão et al.<sup>[21]</sup>, who reported that the ability to increase V<sub>E</sub> during aerobic exercise is impaired in patients with COPD because exhalation may not be completed prior to the onset of the next breath, causing an increase in operational lung volume and progressive air retention. EqCO<sub>2</sub> is a measure of ventilatory efficiency and is calculated as V<sub>E</sub> divided by VCO<sub>2</sub>. EqCO<sub>2</sub> symbolizes the capacity to remove carbon dioxide. In patients with COPD who develop impaired  $O_2P_{max}$ , these higher EqCO<sub>2</sub> values may be explained by disproportional reductions in V<sub>E</sub> and perfusion. The decrease in ventilation and perfusion are different<sup>[21]</sup>, and perfusion may have a higher degree of reduction in patients with impaired  $O_2P_{max}$ . The correlations between V<sub>Emax</sub>%, EqCO<sub>2AT</sub>, EqCO<sub>2max</sub>, and  $O_2P_{max}$  can be explained by the fact that airflow limitation impairs cardiac function<sup>[21]</sup>. The increase in inspiratory intrathoracic pressure decreases lung elastic recoil pressure. The combined

effects of decreased lung elastic recoil pressure and increased airway resistance result in reduced V<sub>E</sub> and the development of hyperinflation<sup>[21]</sup>. Improvement in ventilatory mechanics results in improved cardiac function, which manifests as a decrease in HR with improved  $O_2P_{max}$ <sup>[22]</sup>. Lung hyperinflation also causes mechanical constraints on the heart and a reduction in preload<sup>[23]</sup>. These interactions between hyperinflation, ventilation and cardiac function may explain why  $O_2P_{max}$  was positively correlated with V<sub>Emax</sub>%. EqCO<sub>2</sub> was negatively correlated with V<sub>E</sub>, and  $O_2P_{max}$  was negatively correlated with EqCO<sub>2</sub>.

The positive correlations between FEV<sub>1</sub>/FVC%, FEV<sub>1</sub>%, FVC%, and  $O_2P_{max}$  can be explained by the fact that the decreases in FEV<sub>1</sub>/FVC%, FEV<sub>1</sub>%, and FVC% contribute to lung hyperinflation, which, in turn, reduces left ventricular stroke volume. Furthermore,  $O_2P$  is negatively correlated with lung hyperinflation<sup>[24]</sup>, and lung hyperinflation is negatively correlated with FEV<sub>1</sub><sup>[25]</sup>. In addition, Silvestre et al.<sup>[26]</sup> suggested that the association between lung function and exercise capacity may be related to specific abnormalities in cardiopulmonary performance. All of these findings support the relationships between FEV<sub>1</sub>/FVC%, FEV<sub>1</sub>%, FVC%, and  $O_2P_{max}$ . BR reflects the respiratory reserve capacity during extreme exercise, and a lower BR is the main feature of ventilation limitation in patients with pulmonary disease. It is calculated as the maximum ventilatory volume minus V<sub>E</sub>. BR

**Table 6.** Multivariate logistic regression analysis of lung function and the CPET data in patients with AECOPD

Item	$\beta$	P-value	OR	95% CI
FVC (% predicted)	0.012	0.724	1.012	(0.949–1.078)
FEV <sub>1</sub> (% predicted)	0.004	0.898	1.004	(0.946–1.065)
$O_2P_{max}$ (% predicted)	0.060	<b>0.015</b>	1.062	(1.012–1.114)
WR <sub>max</sub> (watts)	0.052	0.215	1.053	(0.970–1.143)
VO <sub>2max</sub> (mL/min)	-0.002	0.608	0.998	(0.992–1.005)

**Note.** Only  $O_2P_{max}$  had a predictive effect for AECOPD (OR = 1.062, 95% CI = 1.012–1.114, P = 0.015). Bold numbers indicate a significant difference (P < 0.05). Abbreviations: FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s;  $O_2P$ , oxygen pulse; WR, work rate; VO<sub>2</sub>, oxygen uptake; OR, odds ratio; CI, confidence interval.

**Table 7.** Univariate logistic regression analysis of  $O_2P_{max}$  in patients with AECOPD

Item	$\beta$	P-value	OR	95% CI
$O_2P_{max}$ (% predicted)	0.066	<b>0.003</b>	1.068	(1.023–1.116)

**Note.**  $O_2P_{max}$  was a predictor of AECOPD (OR = 1.068, 95% CI = 1.023–1.116, P = 0.003). The bold number indicates a significant difference (P < 0.05) between the two groups. Abbreviations: OR, odds ratio; CI, confidence interval.

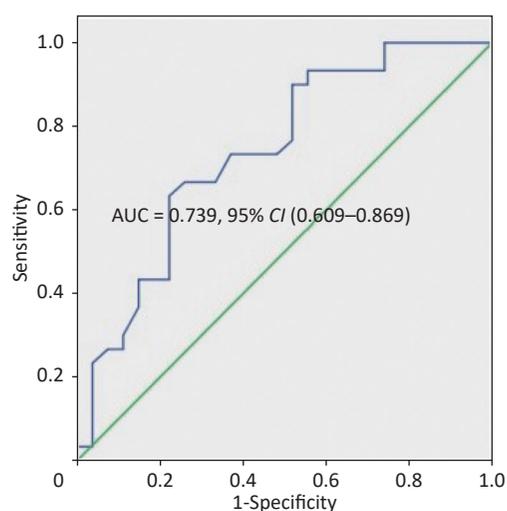
decreases in patients with COPD but increases in those with cardiovascular disease. The present study showed that BR decreased in patients with impaired  $O_2P_{max}$ , whereas no correlation was detected between BR and  $O_2P_{max}$ . This finding could indicate that the decreased  $O_2P_{max}$  in patients with COPD is not only caused by reduced filling of the ventricles but may also be attributable to other mechanisms.

HRR is a marker of cardiac autonomic function independent of the workload and the change in HR during exercise. A low HRR is a common finding in patients with impaired lung function and is associated with decreased survival in patients with COPD<sup>[27]</sup>. In these patients, autonomic nervous dysfunction contributes to the increased work of breathing, which promotes a wider airway caliber<sup>[27]</sup>.  $HRR_1$  is defined as the decrease from peak HR to 1 min of recovery and is an independent predictor of morbidity and all-cause mortality<sup>[28]</sup>. To our knowledge, no study has explored the correlation between  $HRR_1$  and  $O_2P$  in patients with COPD until now. Our present results indicate that  $HRR_1$  decreased significantly in patients with impaired  $O_2P_{max}$ . This may be attributed to the fact that both parameters are regulated by the autonomic nervous system, and an increase in sympathetic tone and/or a decrease in parasympathetic tone may reduce  $HRR_1$  and contribute to tachyarrhythmia.

COPD is largely characterized by breathlessness. The mMRC is considered adequate for assessing breathlessness symptoms. However, COPD affects patients beyond dyspnea. The SGRQ is the most comprehensive disease-specific health status

questionnaire. The CAT is simpler. The Borg CR10 scale is mainly used to evaluate dyspnea and leg muscle fatigue during maximum exercise<sup>[29]</sup>. Because our patients had instruments in their mouths and could not conveniently answer questions during exercise, we evaluated the patients using the Borg CR10 scale at the end of the exercise. As a result, the Borg CR10 scale score and the SGRQ symptom, activity, and total scores were higher in the  $O_2P_{max}$  impaired group than those in the other groups. Souza et al.<sup>[30]</sup> showed that patients with COPD who had lower activities of daily living exhibit lower  $O_2P$ , which may reflect the presence of a limiting cardiac component. Lan et al.<sup>[31]</sup> indicated that the increased  $O_2P_{max}$  is accompanied by improvements in the SGRQ. Therefore,  $O_2P_{max}$  is a valid indicator of HRQL and should be measured in patients with COPD. This may be attributed to the increase in right ventricular afterload during exercise, impairing stroke volume, which was augmented by increased intrathoracic pressure swings and is related to  $O_2P_{max}$ <sup>[32]</sup>.

AECOPD is associated with an increased risk of death<sup>[33]</sup>. It is defined as an acute worsening of respiratory symptoms that results in additional therapy<sup>[34]</sup>. AECOPD is classified as mild (treated with short-acting bronchodilators only), moderate (treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids), or severe (requires hospitalization or an emergency room visit). No effective indicator has been established to predict AECOPD. History of earlier AECOPD may be a predictor of frequent exacerbations<sup>[35]</sup>. Deteriorating airflow limitation is associated with an increasing prevalence of exacerbations<sup>[2]</sup>, but  $FEV_1$  lacks sufficient precision to be used clinically as a predictor of exacerbations or mortality in patients with COPD<sup>[36]</sup>. A novelty of our study is that  $O_2P_{max}$  was an effective predictor of AECOPD, and, to the best of our knowledge, this is the first study to identify the  $O_2P_{max}$  cut-off value for predicting AECOPD. Wu et al.<sup>[37]</sup> reported that patients with impaired peak  $O_2P$  were hospitalized more frequently during a 1-year follow-up. In the present study, the  $O_2P_{max}$  decreased in the AE2 group. Multivariate and univariate logistic regression analyses showed that  $O_2P_{max}$  predicted AECOPD. We used a ROC curve to determine the best cut-off value of  $O_2P_{max}$  for AECOPD (89.5%). The AUC was 0.739 (0.609–0.869) with a sensitivity of 0.633 and a specificity of 0.778. Our findings indicate moderate accuracy of  $O_2P_{max}$  for predicting AECOPD. Further research is needed to validate whether  $O_2P_{max}$ , in combination with other parameters, would increase



**Figure 3.** ROC curve of  $O_2P_{max}$  as an overall predictor of AECOPD. Abbreviations: AUC, area under the ROC curve; CI, confidence interval.

the accuracy of prediction. Nevertheless, it is important to inform patients of the high risk of acute exacerbations once the CPET reveals an impaired  $O_2P_{max}$  value (< 89.5%). Doctors should choose higher-level treatment strategies for these patients.

Why lower  $O_2P_{max}$  is associated with more frequent AECOPD is not entirely clear. To our knowledge, progressive respiratory failure, cardiovascular disease, and other diseases are the primary cause of death in patients with COPD hospitalized for an exacerbation<sup>[36]</sup>. In addition, deteriorating airflow limitation is associated with an increasing prevalence of exacerbations<sup>[2]</sup>. Hyperinflation and gas trapping increase with the reduced expiratory flow during exacerbations<sup>[11]</sup>. Therefore, the association between impaired  $O_2P_{max}$  and AECOPD may be related to hyperinflation, which can be caused by airflow limitation and is associated with poor cardiac function. A larger scale study is needed to validate the role of  $O_2P_{max}$  in the risk of AECOPD.

This study had several limitations. First, this was a retrospective study, and not all of the patients finished the 3-year follow-up for AECOPD. Additionally, the sample size was small. Second,  $O_2P_{max}$  is an effective indicator of cardiac function and muscle function, but the echocardiographic parameters and stroke volume were not tested. Third, we did not measure dynamic lung hyperinflation parameters, such as the end-expiratory lung volume, inspiratory capacity, or RV using CPET. Thus, the evidence indicating that  $O_2P_{max}$  is related to dynamic lung hyperinflation is insufficient. Fourth, because not all of the enrolled patients underwent hemoglobin concentration and blood gas analyses, we did not consider these factors in the analysis. Hemoglobin is very important for oxygen carrying capacity, and blood gas values reflect disease severity to some extent. Nevertheless, our current study found that an indicator can play a role in the assessment of COPD severity and prognosis.

### CONCLUSION

This present study illustrated that impaired  $O_2P_{max}$  indicates impairments in exercise capacity, ventilatory condition, gas exchange efficiency, and HRQL. The most important finding was that  $O_2P_{max}$  was an independent predictor of AECOPD. This is the first study to identify the  $O_2P_{max}$  cut-off value.

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### AUTHORS' CONTRIBUTIONS

ZHAO Ran Ran and XU Bo designed the study together. LI Yun Xiao drafted the whole manuscript. WANG Jun, WU Bo, and LIN Fang performed the data analyses. TAN Chun Ting, YU Gang Gang, and NIE Shan followed up the patients. ZHAO Ran Ran and XU Bo contributed equally to this work. All authors read and approved the final manuscript.

### COMPETING INTERESTS

The authors declare that they have no competing interests.

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