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ORIGINAL RESEARCH

Unraveling the Role of Oxygen Pulse Variability in Endurance Exercise Training in Individuals with COPD: A Novel Approach to Response of Oxygen Pulse and Quality of Life in Pulmonary Rehabilitation

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Background: Chronic obstructive pulmonary disease (COPD) is characterized by airway inflammation, airflow limitation, reduced health-related quality of life (HRQL), and exercise intolerance. Pulmonary rehabilitation (PR) is essential for COPD management, but outcomes may be influenced by individual physiological factors. Cardiopulmonary exercise testing (CPET) measures oxygen pulse (O2P), an indicator of stroke volume, yet the impact of baseline O2P on PR effectiveness remains unclear.
Methods: This retrospective study included 97 participants with COPD who had received PR, of whom 48 were classified as Group 1 (normal O2P) and 49 as Group 2 (low O2P). PR involved 12 weeks of hospital-based endurance training on a bike, performed twice a week. Participants were assessed before and after PR using spirometry, respiratory muscle strength measurements, CPET, and HRQL evaluation with the St. George's Respiratory Questionnaire (SGRQ).
Results: PR significantly improved exercise capacity (peak work rate and oxygen consumption), dyspnea score, and all domains of the SGRQ, maximum expiratory pressure, ventilatory equivalent, respiratory rate, and mean blood pressure at rest in both groups ($p < 0.05$). However, improvements in O2P, maximal inspiratory pressure, and tidal volume at rest were observed only in Group 2 but not in Group 1.
Conclusion: PR improves exercise capacity, HRQL and specific respiratory function in participants with COPD, regardless of baseline O2P levels. Individuals with lower baseline O2P experience more benefits from PR, including a significant increase in O2P.
Keywords: Chronic obstructive pulmonary disease, COPD, Oxygen pulse, Pulmonary rehabilitation

Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating lung disease and a prevalent respiratory condition worldwide, and ranks among the top ten leading causes of death worldwide,[1] making it a major global health concern. COPD is characterized by chronic airway and lung inflammation in response to inhaled stimuli, leading to persistent airflow limitation and lung tissue destruction.[2] Individuals with COPD frequently exhibit exercise intolerance and impaired health-related quality of life (HRQL).[3] Despite recent advances in COPD treatment, those diagnosed with

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the disease continue to experience prominent symptoms like cough and dyspnea, as well as a significant impact on their well-being, even under standard treatment.

Cardiovascular dysfunction is common in individuals with COPD, with prevalence ranging from 20% to 60%.[4] The common evaluation of cardiovascular function includes echocardiography.[5] However, resting echocardiography alone is often insufficient for comprehensive assessment.[5] Stress echocardiography serves as a valuable tool, offering a more complete evaluation of cardiovascular function and revealing potential impairments that may not be evident at rest.[5] However, it is highly dependent on operator expertise, as accurate interpretation requires skill and experience.[5] Cardiopulmonary exercise testing (CPET) is an effective tool for assessing cardiovascular function, providing valuable insights into the cardiac ability to respond to physical stress.[6] In addition, CPET evaluates cardiac and respiratory function concurrently during exercise, which helps identify limitations in exercise capacity, as well as cardiopulmonary function, offering a comprehensive assessment of individuals with COPD.[6]

A key parameter of CPET is oxygen pulse (O2P), which is defined as the amount of oxygen consumption (VO2) per heartbeat.[7] O2P serves as an indirect and non-invasive indicator of stroke volume.[7] A low O2P, particularly at peak exercise, is indicative of poor cardiovascular efficiency and has been associated with worse outcomes in individuals with COPD.[7] O2P provides insight into the severity of cardiovascular impairment in individuals with COPD.[7] Previous findings suggest that individuals with COPD who exhibit low O2P demonstrate reduced exercise capacity, poor HRQL, impaired ventilatory and circulatory functions and more frequent hospitalization.[8] Therefore, O2P appears to be an important parameter in COPD.

The components of a pulmonary rehabilitation (PR) program include education, exercise training, airway clearance, nutritional support, and psychosocial support.[9] Exercise training is an essential component of PR.[9] Numerous studies have demonstrated that exercise training significantly improves exercise capacity, dyspnea, daily activities, and overall health.[9-11] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines also indicate that PR benefits all severity levels of COPD, leading to improvements in HRQL, exercise endurance, and overall health status.[10] In addition, PR is also known to improve cardiovascular function in individual with COPD.[12] Our previous research demonstrated that PR enhanced heart rate variability in participants with COPD.[13] O2P, one key indicator of cardiovascular function, is closely associated with the cardiovascular ability to deliver oxygenated blood to tissues. However, it remains unclear whether O2P influences the effects of PR or if PR improves O2P.

Whether O2P levels are influenced by the efficacy of PR remains unclear. Previous studies have not specifically examined the influence of PR in individuals with decreased O2P, nor have they explored potential differential responses based on initial O2P levels.[9–13] Understanding these differences may be crucial in tailoring interventions to meet the needs of all individuals with COPD. Therefore, this study aimed to investigate the effects of PR on HRQL, cardiopulmonary response, and exercise capacity in participants with varying baseline O2P levels.

Materials and Methods

Participant Enrollment

This retrospective cohort study analyzed the data of individuals with physician-diagnosed COPD who completed the PR program. A total of 108 participants with COPD were initially recommended for PR. However, 11 participants either declined to participate or withdrew from the program due to the inconvenience of traveling to the hospital for the PR programs. No participants withdrew due to cardiovascular or other adverse events. Consequently, 97 participants who successfully completed PR were included in the analysis. The diagnosis of COPD was defined by a post-bronchodilator forced expiratory volume in the first second (FEV1)/ forced vital capacity (FVC) ratio of less than 70%, in accordance with GOLD guidelines.[10] The inclusion criteria of the current study were as follows: stable condition for three months, ability to perform exercise tests and exercise training, and willingness to complete exercise training programs. Exclusion criteria included acute exacerbation within the past three months, inability to perform CPET due to severe joint disease, and unwillingness to participate in PR programs.

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of Taipei Tzu-Chi Hospital, ensuring that the research procedures adhered to appropriate ethical standards. All participants provided signed informed consent, in accordance with the Declaration of Helsinki.

Pulmonary Function Test

Participants underwent pulmonary function assessments in accordance with the established guidelines of the American Thoracic Society, employing a spirometer device produced by the Medical Graphics Corporation (St. Paul, Minnesota, USA.[14] FVC and FEV1 measurements were included. The severity of airflow obstruction was assessed by evaluating the FEV1 percentage (FEV1%).[10] The severity is classified into four stages: mild (GOLD 1), where FEV1 is ≥80% of the predicted value; moderate (GOLD 2), where FEV1 is between 50% and 80% of the predicted value; severe (GOLD 3), where FEV1 is between 30% and 50% of the predicted value; and very severe (GOLD 4), where FEV1 is less than 30% of the predicted value.[10]

Cardiopulmonary Exercise Test

All study participants completed a CPET on a bicycle ergometer system manufactured by Lode Corival (Netherlands) following a standard protocol.[7] The CPET protocol uses a progressive incremental approach. During the exercise test, exhaled air was continuously analyzed using a sophisticated breath-by-breath gas analysis system (Breeze Suite 6.1; Medical Graphics Corporation, St. Paul, Minnesota, USA). This system allows measurement and monitoring of physiological parameters, including oxygen consumption (VO2), carbon dioxide output (VCO2), oxygen saturation (SpO2), end-tidal partial pressure of carbon dioxide (PETCO2), respiratory rate (RR) and tidal volume (VT), blood pressure (BP) and heart rate (HR) both at rest and during exercise.

Oxygen pulse (O2P) is determined as the ratio of VO2 to HR.[7] According to the Fick principle, VO2 can be calculated as the product of cardiac output (CO) and the difference between arterial oxygen content (CaO2) and venous oxygen content (CvO2). Therefore, VO2 can be expressed as VO2 = CO × (CaO2 - CvO2). This can be further broken down as HR × stroke volume (SV) × (CaO2 − CvO2). Therefore, O2P = VO2/HR = SV × (CaO2 − CvO2). Because the difference between arterial and venous oxygen content (CaO2–CvO2) is assumed to remain relatively constant during maximal exercise, peak O2P is considered a non-invasive indicator of SV,because peak O2P reflects the maximal amount of oxygen extracted by the peripheral tissues per heartbeat, which is primarily determined by the ability of the circulatory system to deliver oxygen to the muscles during exercise. Peak O2P provides valuable insights into an individual's cardiovascular function.[7] An O2P at peak exercise below 80% of the predicted value is defined as poor.[7]

VO2 at the anaerobic threshold (AT) was identified by analyzing the relationship between VO2 and VCO2, commonly depicted in a VO2 versus VCO2 graph.[7] The represents The AT point during incremental exercise where the body transitions from predominantly aerobic to anaerobic metabolism. VO2 at the anaerobic threshold that is below 40% of the predicted maximum VO2 is generally considered a poor value.

Work efficiency (WE) represents the slope of the relationship between oxygen consumption (VO2) and work rate (WR) during exercise, which is determined by linear regression analysis.[7] This parameter provides insight into the efficiency of oxygen utilization and energy expenditure during physical activity. The normal reference range for the WE slope is reported to be 8.6 and 10.1 milliliters of oxygen consumed per minute per watt of work (mL/min/W).[7] Values below the lower limit of 8.6 mL/min/watt are generally considered to indicate poor or impaired WE.

Of the 97 participants with COPD, 48 had a normal O2P (≥ 80% of the predicted value) at baseline and were classified as Group 1 (Gr 1), while the remaining 49 had a low O2P (< 80% of the predicted value) and were classified as Group 2 (Gr 2).

Respiratory Muscle Strength Assessment

Respiratory muscle strength was evaluated by assessing maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP). These measurements were conducted using a specialized pressure gauge device (Respiratory Pressure Meter, Micro Medical Corp., UK). To assess MIP, the participants first exhaled fully to their residual volume and then executed a forced maximal inhalation effort.[11] This maneuver allowed for the measurement of the maximum negative pressure generated by the inspiratory muscles during inhalation. To measure MEP, participants first fully inhaled their total lung capacity and then exhaled with maximal force. This procedure captured the maximum positive pressure generated by the expiratory muscles during exhalation. The measurements were repeated five times, and the highest readings for both the MIP and MEP were recorded.[11]

Health-Related Quality of Life

The health status of the participants was evaluated using the Chinese version of St. George's Respiratory Questionnaire (SGRQ) in Chinese version.[15] The SGRQ evaluates four main domains: symptoms, activity, impacts on daily life, and total score. All domains are scored on a scale from 0 to 100, where a higher score indicates a worse HRQL.[15] The symptom domain assesses the frequency and severity of respiratory symptoms. The activity domain evaluates activity limitations through patient-reported outcomes collected via a questionnaire. The impact domain focuses on the psychosocial and social consequences of respiratory conditions on an individual's daily life. The total score provided an overall assessment of the patient's HRQL.[15]

CPET, PFTs, respiratory muscle strength, and SGRQ were evaluated at baseline (within one week before PR) and after PR (within one week after PR).

PR Program

All participants received education on COPD management, including medication use, inhaler techniques, smoking cessation, breathing exercise and limbs exercise, as well as strategies for managing symptoms, dyspnea, and exacerbations. Lower limb exercise training was conducted using a bicycle ergometer. Participants took part in a supervised, hospital-based exercise training program, completing 12 weeks of bi-weekly PR sessions. Each session lasted 40 minutes, with a training intensity of 60–80% of the maximum workload.[16] During exercise training in the present study, respiratory therapists continuously monitored HR and SpO2. BP, RR, and symptoms, including dyspnea and leg fatigue, which were assessed at 10-minute intervals throughout the session. The PR program did not include strength training.

Statistical Analysis

The study data are presented as the mean and standard deviation. Baseline comparisons between groups for categorical variables (COPD stage, smoking status, and gender) were analyzed using the Chi-square test. An independent samples *t*-test was used to compare the changes in parameters between the study groups before and after PR. Within the same group, a paired *t*-test was used to evaluate changes in the parameters before and after the PR program. All statistical analyses were conducted using SPSS software (version 24.0; SPSS, Inc., Chicago, IL, USA).

Results

Demographic and Clinical Features

Table 1 summarizes the baseline characteristics of the study participants. No significant differences were observed between the groups in terms of age, sex, height, weight, BMI, mean blood pressure (MBP), HR, SpO2, PETCO2 or smoking status (all $p>0.05$). However, the distribution of COPD stages was significantly different ($p < 0.001$), with more stages III and IV in Gr 2.

Exercise Capacity Before and After Pulmonary Rehabilitation

Table 2 shows the effect of PR on exercise capacity by comparing the two groups. Overall, PR led to significant improvements in the peak VO2 and WR (all $p<0.05$). Both Gr 1 and 2 showed significant increases in peak VO2 and WR after the exercise training (all $p<0.05$). No statistically significant differences were found in the changes in peak VO2 and WR after PR between the two groups (all $p > 0.05$).

Respiratory Parameters Before and After Pulmonary Rehabilitation

Table 3 shows the PR of the respiratory parameters by comparing the two groups. Overall, PR led to significant improvements in MIP, MEP, RR at rest, and ventilatory equivalent (Veq) (all $p <0.05$). In Gr 1, PR led to significant changes in MEP, RR at

Table 1 Clinical and Demographic Characteristics

	All (N=97)	Gr1 (N=48)	Gr2 (N=49)	p value
Age	70±9	71±9	69±9	0.257
Sex (male/female)	82/15	38/10	44/5	0.148
BH (cm)	162±8	161±8	163±8	0.096
BW (kg)	60.7±13.0	60.4±14.3	61.0±11.6	0.835
BMI (kg/m²)	23.0±4.1	22.3±4.4	22.9±3.8	0.615
MBP rest (mmHg)	88.1±11.4	85.8±12.3	90.3±10.0	0.055
HR rest (BPM)	86.9±12.8	85.0±13.3	88.8±12.1	0.142
SpO2 rest (%)	96.0±2.0	96.3±1.8	95.7±2.1	0.137
PETCO2 rest (mmHg)	34.9±5.8	35.4±5.5	34.5±6.0	0.331
COPD stage				<0.001
I (n, %)	12 (12.48%)	9 (18.8%)	3 (6.1%)	
II (n, %)	38 (39.2%)	26 (54.2%)	12 (24.5%)	
III (n, %)	37 (38.1%)	13 (27.0%)	24 (49%)	
IV (n, %)	10 (10.3%)	0 (0%)	10 (20.8%)	
Smoking				0.290
Non-smoking (n, %)	16 (16.5%)	10 (20.8%)	6 (12.2%)	
Current smoking (n, %)	35 (36.1%)	14 (29.2%)	21 (42.9%)	
Ex-smoking (n, %)	46 (47.4%)	24 (50.0%)	22 (44.9%)	

Abbreviations: Gr1, group 1 (normal oxygen pulse); Gr2, group 2 (low oxygen pulse); BH, body height; BW, body weight; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MBP: mean blood pressure; HR, heart rate; BPM: beats per minute; SpO2: oxygen saturation; PETCO, partial pressure of end-tidal carbon dioxide.

rest, and Veq ($p < 0.05$). In Gr 2, PR led to significant changes in MIP, MEP, Veq, RR, and VT at rest ($p < 0.05$). Non-significant changes were observed in FEV1/FVC, FVC, FEV1, VE at rest and exercise in both the groups ($p>0.05$). However, FVC (%) showed greater improvement in Gr 2 (2.4±11.8%) compared to Gr 1 (0.8±11.4%, $p = 0.006$).

Circulatory Parameters Before and After Pulmonary Rehabilitation

Table 4 shows the effects of PR on circulatory parameters by comparing the two groups. Overall, PR led to significant improvements in O2P and MBP at rest (both $p<0.05$). However, in Gr 1, no significant changes in O2P, AT, or WE were observed (all $p>0.05$). After PR, MBP at rest decreased significantly ($p<0.05$). In Gr 2, O2P increased significantly ($p<0.05$), whereas AT and WE did not show significant changes ($p>0.05$). MBP at rest also decreased significantly after PR ($p<0.05$). No significant differences were found in the changes of AT, WE, MBP, and HR at rest after PR between the two groups ($p > 0.05$). However, O2P increased more in Gr 2 than in group 1 ($p<0.05$).

Gas Exchanges Before and After Pulmonary Rehabilitation

Table 5 shows the effects of PR on gas exchange by comparing the two groups. No prominent changes were noted in SpO2 and PETCO2 after PR in the overall population or in either group (all $p>0.05$). No significant differences were noted between the two groups in the changes of SpO2 and PETCO2 after PR ($p > 0.05$).

HRQL Before and After Pulmonary Rehabilitation

Table 6 shows the effects of PR on HRQL by comparing the two groups. The dyspnea score was evaluated at rest and peak exercise during CPET using a 10-point Borg scale. Overall, PR led to significant decreases in dyspnea both at rest

Table 2 Exercise Capacity Before and After Pulmonary Rehabilitation

	All	All	All	P value Pre-PR vs post PR	Gr1	Gr1	Gr1	P value Pre-PR vs post PR	Gr2	Gr2	Gr2	p value Pre-PR vs post PR	p value Difference between Gr 1 and 2
	Pre-PR	**Post-PR**	**Difference**		**Pre-PR**	**Post-PR**	**Difference**		**Pre-PR**	**Post-PR**	**Difference**		
VO2 peak (mL/min)	942.5±305.7	1003.2±328.3	60.7±136.0	<0.001	1107.5±295.4	1152.1±330.6	44.5±147.7	0.042	780.8±217.4	857.3±254.4	76.5±123.0	<0.001	0.249
VO2 peak (%)	66.7±18.5	71.0±20.4	4.3±9.7	<0.001	80.9±13.3	84.5±18.4	3.6±11.3	0.033	52.8±10.4	57.8±12.1	6.0±1.3	<0.001	0.474
WR (watt)	64.1±27.6	72.2±28.9	8.1±11.8	<0.001	76.8±25.6	84.5±28.1	7.7±14.1	<0.001	51.6±23.7	60.2±24.4	8.6±9.2	<0.001	0.702
WR (%)	71.4±27.9	81.3±29.2	10.0±14.8	<0.001	89.5±21.0	99.1±22.9	9.7±17.8	<0.001	53.6±21.8	63.9±23.9	10.2±11.4	<0.001	0.849

Abbreviations: Gr1, group 1 (normal oxygen pulse); Gr2, group 2 (low oxygen pulse); VO2 peak, peak oxygen uptake; WR, work rate.

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Table 3 Respiratory Parameters Before and After Pulmonary Rehabilitation

	All Pre-PR	All Post-PR	All difference	P value Pre-PR vs post PR	Gr1 Pre-PR	Gr1 Post-PR	Gr1 difference	P value Pre-PR vs post PR	Gr2 Pre-PR	Gr2 Post-PR	Gr2 difference	p value Pre-PR vs post PR	p value Difference between Gr 1 and 2
FVC (L)	2.18±0.70	2.20±0.66	0.03±0.30	0.366	2.23±0.73	2.24±0.71	0.01±0.28	0.796	2.13±0.68	2.17±0.62	0.04±0.32	0.366	0.579
FVC (%)	79.3±19.2	80.9±19.9	1.6±11.6	0.176	83.7±18.6	84.5±18.8	0.8±11.4	0.616	75.1±19.1	77.4±20.5	2.4±11.8	0.169	0.006
FEV1 (L/min)	1.14±0.49	1.16±0.52	0.02±0.21	0.281	1.30±0.53	1.32±0.53	0.02±0.20	0.540	0.99±0.40	1.02±0.47	0.02±0.10	0.373	0.819
FEV1 (%)	53.2±19.9	54.6±22.2	1.4±10.4	0.180	61.9±19.1	63.0±19.4	1.1±10.5	0.452	44.7±16.9	46.4±21.8	0.2±10.4	0.260	0.795
FEV1/FVC	53.3±16.6	53.4±17.4	0.0±10.0	0.965	58.7±14.0	59.4±14.8	0.7±9.1	0.606	48.1±17.5	47.5±16.9	5.9±10.9	0.707	0.534
MIP (cmH2O)	67.2±26.3	71.9±26.6	0.47±17.5	0.009	69.0±25.3	73.2±26.5	4.1±18.3	0.124	65.4±27.4	70.7±26.9	5.2±16.8	0.034	0.759
MEP (cmH2O)	111.1±39.0	117.8±36.5	6.7±27.1	0.017	110.8±29.0	118.3±32.6	7.6±29.3	<0.001	111.5±47	117.3±40.3	5.8±24.9	0.017	0.755
VE rest (L/min)	11.9±3.1	11.3±3.2	−0.6±3.4	0.085	12.1±3.1	11.4±3.5	−0.8±3.5	0.128	11.7±3.2	11.2±3.0	−0.4±3.3	0.378	0.611
VE exercise (L/min)	33.5±11.5	34.3±10.0	0.7±7.7	0.346	37.7±11.8	37.1±10.8	−0.6±6.7	0.537	29.4±9.6	31.5±10.5	2.1±8.5	0.094	0.089
RR rest (BPM)	19.3±5.9	17.4±4.8	−1.9±5.3	0.001	19.3±4.3	17.8±4.2	−1.5±5.0	0.042	19.2±7.1	17.0±5.4	−2.3±5.7	0.007	0.472
RR exercise (BPM)	32.9±8.0	33.0±7.9	0.1±5.4	0.852	34.2±7.2	33.8±6.4	−0.3±4.8	0.635	31.6±8.5	32.1±9.0	0.5±6.0	0.539	0.437
V_T rest (mL)	644.3±169.2	673.3±189.7	29.0±180.6	0.117	644.7±155.3	650.1±182.8	−5.4±189.3	0.843	643.9±183.4	696.0±195.4	52.1±170.5	0.038	0.205
V_T exercise (mL)	1048.7±338.0	1068.5±335.5	19.8±154.1	0.208	1137.3±365.1	1137.8±379.8	−0.4±165.7	0.986	961.8±286.9	1000.7±272.7	38.9±140.9	0.059	0.221
Veq	36.7±6.4	34.9±6.7	−1.8±5.3	0.001	35.1±6.1	33.5±6.2	−1.6±5.5	0.049	38.2±6.4	36.3±7.0	−2.0±5.2	0.011	0.754

Abbreviations: Gr1, group 1 (normal oxygen pulse); Gr2, group 2 (low oxygen pulse); FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; VE, minute ventilation; RR, respiratory rate; VT, tidal volume; Veq, ventilatory equivalent; BPM, breaths per minute.

Table 4 Circulatory Parameters Before and After Pulmonary Rehabilitation

	All Pre-PR	All Post-PR	All difference	P value Pre-PR vs post PR	Gr1 Pre-PR	Gr1 Post-PR	Gr1 difference	P value Pre-PR vs post PR	Gr2 Pre-PR	Gr2 Post-PR	Gr2 difference	p value Pre-PR vs post PR	p value Difference between Gr 1 and 2
O2P (mL/beat)	7.5±2.2	7.7±2.2	0.2±1.2	0.034	8.8±2.0	8.8±2.3	0.0±1.3	0.818	6.2±1.4	6.7±1.7	0.5±0.9	<0.001	0.012
O2P (%)	79.5±19.3	82.2±20.5	2.7±12.4	0.033	96.1±10.3	96.2±19.2	0.1±14.9	0.987	63.1±9.4	68.5±9.5	5.3±8.6	<0.001	0.036
AT (mL/min)	633.8±144.4	639.1±132.4	5.4±84.4	0.541	687.9±140.4	680.5±134.5	−7.4±84.8	0.548	576.0±126.3	595.0±116.1	19.0±82.6	0.130	0.132
AT (%)	45.0±10.6	45.5±10.6	0.5±6.0	0.413	51.1±10.0	50.8±11.1	−2.5±6.5	0.793	38.6±6.7	39.9±6.3	1.3±5.4	0.107	0.210
WE (mL/min/watt)	8.3±19.3	8.5±18.6	0.2±1.6	0.227	9.0±1.8	9.2±1.7	0.2±1.6	0.472	7.6±1.8	7.8±1.7	0.2±1.6	0.329	0.864
MBP rest (mmHg)	88.1±11.4	84.8±10.4	−3.3±8.6	<0.001	85.8±12.3	82.4±11.9	−3.5±9.3	0.013	90.3±10.0	87.2±8.2	−3.1±7.9	0.010	0.825
MBP exercise (mmHg)	106.3±15.4	106.3±16.2	0.0±12.9	0.996	106.4±15.5	106.2±17.7	−0.1±12.0	0.940	106.2±15.5	106.3±14.9	0.1±13.8	0.954	0.925
HR rest (BPM)	86.9±12.8	85.3±12.5	−1.6±9.1	0.077	85.0±13.3	82.9±12.1	−2.1±8.6	0.104	88.8±12.1	87.6±12.7	1.2±9.6	0.369	0.660
HR exercise (BPM)	125.8±17.3	129.0±17.5	3.1±13.6	0.025	125.4±17.3	131.6±19.2	6.2±14.0	0.004	126.2±17.4	126.4±15.5	0.2±12.6	0.919	0.030

Abbreviations: Gr1, group 1 (normal oxygen pulse); Gr2, group 2 (low oxygen pulse); O2P, oxygen pulse; AT, anaerobic threshold; WE, work efficiency; MBP, mean blood pressure; BPM, beats per minute.

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Table 5 Gas Exchanges Before and After Pulmonary Rehabilitation

	All Pre-PR	All Post-PR	All difference	P value Pre-PR vs post PR	Gr1 Pre-PR	Gr1 Post-PR	Gr1 difference	P value Pre-PR vs post PR	Gr2 Pre-PR	Gr2 Post-PR	Gr2 difference	p value Pre-PR vs post PR	p value Difference between Gr 1 and 2
SpO2 rest (%)	96.0±2.0	95.9±2.2	−0.1	0.474	96.3±1.8	96.3±1.7	0.1±1.3	0.193	95.7±2.1	95.6±2.4	−0.2±2.2	0.567	0.789
SpO2 exercise (%)	93.2±3.6	93.0±3.6	−0.2	0.559	93.8±3.2	93.8±2.9	−0.1±2.7	0.397	92.6±3.8	92.3±4.2	−0.3±3.5	0.539	0.702
PETCO2 rest (mmHg)	34.9±5.8	35.1±6.6	0.2±6.6	0.795	35.4±5.5	35.8±6.4	0.4±7.7	0.709	34.5±6.0	34.5±6.7	0.1±5.5	0.938	0.725
PETCO2 exercise (mmHg)	40.0±7.7	41.3±8.8	1.3±7.5	0.092	40.2±7.8	42.4±8.6	2.1±8.8	0.098	39.7±7.6	40.2±9.0	0.5±5.8	0.591	0.267

Abbreviations: Gr1, group 1 (normal oxygen pulse); Gr2, group 2 (low oxygen pulse); O2P, oxygen pulse; SpO2, oxygen saturation; PETCO2, partial pressure of end-tidal carbon dioxide.

Table 6 HRQL Before and After Pulmonary Rehabilitation

		All Pre-PR	All Post-PR	All difference	P value Pre-PR vs post PR	Gr1 Pre-PR	Gr1 Post-PR	Gr1 difference	P value Pre-PR vs post PR	Gr2 Pre-PR	Gr2 Post-PR	Gr2 difference	p value Pre-PR vs post PR	p value Difference between Gr 1 and 2
Dyspnea, rest	mean	0.4±0.7	0.2±0.4	−0.2±0.7	0.002	0.3±0.6	0.1±0.3	−0.1±0.606	0.159	0.6±0.7	0.3±0.5	−0.3±0.8	0.006	0.179
Dyspnea, exercise	mean	5.6±1.7	4.7±1.7	0.8±1.7	<0.001	5.6±1.7	4.6±1.8	−1.1±1.5	<0.001	5.5±1.6	4.9±1.7	−0.6±1.9	0.037	0.195
SGRQ, total	mean	49.3±17.4	36.5±18.2	−12.9±14.7	<0.001	45.2±17.2	32.3±20.8	−13.0±14.3	<0.001	53.3±16.7	41.6±19.6	−12.7±15.3	<0.001	0.938
SGRQ, symptom	mean	57.8±22.3	40.9±22.3	−17.0±22.4	<0.001	51.5±20.7	35.9±19.4	−15.5±21.1	<0.001	63.9±22.3	45.4±24.0	−18.4±23.8	<0.001	0.533
SGRQ, activity	mean	62.9±20.2	51.9±19.4	−11.1±17.3	<0.001	56.6±20.5	46.7±17.6	−9.9±17.3	<0.001	69.1±18.0	56.9±20.0	−12.1±17.5	<0.001	0.524
SGRQ, impact	mean	39.3±20.2	27.0±21.8	−12.3±19.3	<0.001	37.0±20.8	23.8±20.4	−13.2±19.9	<0.001	41.6±19.6	30.2±22.8	−11.4±18.8	<0.001	0.645

Abbreviations: Gr1, group 1 (normal oxygen pulse); Gr2, group 2 (low oxygen pulse); SGRQ, St. George's Respiratory Questionnaire.

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and during exercise as well as in all domains of the SGRQ ($p<0.05$). PR led to significant improvements in dyspnea scores in both groups during exercise and in all domains of the SGRQ ($p<0.05$). No significant differences were found between the two groups in the changes of dyspnea scores and SGRQ scores after PR ($p > 0.05$).

Discussion

The present study highlights the impact of PR in individuals with COPD who have different O2P levels, emphasizing benefits tailored to baseline O2P levels. PR significantly improved exercise capacity, HRQL, and specific respiratory parameters in participants from both groups. Notably, a significant increase in O2P was observed only in those with low baseline O2P, underscoring the potential of PR to address specific cardiovascular limitations in this group. These findings reinforce the efficacy of PR in enhancing O2P, an essential cardiovascular parameter.

Exercise training is an important component of PR for improving exercise capacity and health status in individuals with COPD.[17] Strength training alone seems to be as effective as endurance training, while combining strength training with endurance training may lead to even greater improvements in health status.[17] In the present study, only endurance exercise training was performed, which also resulted in significant improvements in exercise capacity and HRQL. In our previous studies,[16,18,19] we found that this type of PR was effective in improving exercise capacity and HRQL in participants with COPD,[18] asthma,[16] or lung cancer.[19] Endurance training is probably the most common exercise modality applied in individuals with COPD.[20] The main objective of endurance training is to improve aerobic exercise capacity as aerobic activities. It has been shown that endurance training also improves peripheral muscle function in individuals with COPD.[20]

Individuals diagnosed with COPD often experience compromised cardiovascular function owing to various underlying mechanisms. Chronic inflammation associated with COPD can lead to endothelial dysfunction and increased oxidative stress, contributing to cardiovascular disease.[21] Lung hyperinflation leads to increased intrathoracic pressure, which reduces venous return to the heart. This decrease in venous return impairs heart filling, resulting in reduced SV.[22] The autonomic nervous system imbalance, characterized by increased sympathetic and decreased parasympathetic activity, can further exacerbate cardiovascular complications in individuals with COPD by altering heart rate variability and increasing the risk of arrhythmias.[23] The episodes of hypoxia experienced by individuals with COPD may result in vasoconstriction, increased pulmonary arterial pressure, and impaired cardiac function.[24] Common risk factors, such as smoking and aging, also play a role in the concurrent development of COPD and cardiovascular disease.[25] Evaluation of cardiac function is crucial for the comprehensive management of individuals with COPD and the development of tailored treatments. Given that peak O2P is a parameter that reflects SV, it is essential to identify individuals with COPD who have impaired peak O2P.

To the best of our knowledge, this is the first study to examine the effects of PR on participants with varying O2P levels. We observed that O2P increased after PR, which is consistent with previous studies.[26,27] However, we further discovered that O2P improvement occurred only in participants who had lower O2P at baseline, but not in those with normal baseline O2P.

Understanding the possible mechanisms by which exercise training improves O2P is crucial. Exercise has been shown to improve cardiac contractility and alleviate lung hyperinflation.[27,28] Enhanced cardiac muscle strength and contractility lead to increased SV.[27] This enables more efficient blood circulation and oxygen delivery for individuals with COPD, whose cardiovascular function is often impaired.[27] Exercise training also reduces lung hyperinflation, which, in turn, lowers intrathoracic pressure, enhances venous return, and improves left ventricular filling, ultimately leading to an increase in SV.[22,28] Therefore, the increase in O2P following exercise training may reflect enhanced cardiovascular and respiratory efficiency.

In the present study, PR was observed to improve tidal volume and ventilatory equivalent. Individuals with COPD who experience respiratory muscle weakness often experience more severe dyspnea, reduced exercise capacity, and poorer HRQL.[11] PR enhances respiratory muscle strength, leading to an increased tidal volume and this improvement results in a reduced respiratory rate and alleviates the sensation of dyspnea.[11] Additionally, PR reduces lung hyperinflation in individuals with COPD, which allows for more efficient lung expansion.[29] By decreasing excessive air trapping and lowering intrathoracic pressure, PR helps improve airway patency and lung mechanics.[29] This reduction in hyperinflation facilitates better alveolar ventilation and enhances overall lung function. Other techniques, such as diaphragmatic and pursed-lip breathing, which are incorporated into PR, optimize ventilatory control, increase tidal volume, and lower the ventilatory equivalent.[30,31] The improvements in exercise capacity contribute to enhanced respiratory efficiency, decreased dyspnea, and better HRQL.

Clinical Implications

When PR is incorporated into the standard care regimen for individuals with COPD, exercise training has been shown to significantly enhance exercise capacity, respiratory function, and HRQL, making it a crucial intervention for COPD management. Low O2P has previously been associated with poor stroke volume and may raise concerns regarding the effectiveness of PR in such individuals. Therefore, clinicians should prioritize PR as a component of a comprehensive treatment strategy, especially for individuals diagnosed with COPD who have a lower baseline O2P, to achieve optimal functional outcomes.

Study Limitations

Although the present research highlights many novel and significant aspects of COPD, it has several limitations. First, the lack of a control group in the study design limited our ability to attribute the observed improvements exclusively to PR, as other factors may also play a role. Second, a single-center setting may introduce selection bias and limit generalizability to other locations and study populations. Finally, we focused on short-term outcomes, leaving the long-term effects of exercise training on individuals with unexplored O2P levels. Further prospective studies are needed to address these issues by including diverse populations, incorporating control groups, and investigating long-term effects to gain a more thorough understanding of PR's benefits of PR in COPD management.

Conclusions

Results of the present study highlight the significant benefits of PR across varying baseline O2P levels in individuals diagnosed with COPD. PR effectively enhances exercise capacity, HRQL and specific respiratory parameters, regardless of baseline O2P. However, only individuals with low baseline O2P experience a significant increase in O2P, suggesting the potential of PR to specifically address underlying cardiovascular limitations.

Data Sharing Statement

All data supporting underlying findings are included in the manuscript.

Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the Ethics Committee of Taipei Tzu-Chi Hospital, ensuring that the research procedures adhered to appropriate ethical standards. All participants provided signed informed consent, in accordance with the Declaration of Helsinki.

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Disclosure

All authors have no financial or other potential conflicts of interest to declare.

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