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ORIGINAL RESEARCH

Understanding the Impact of Pulmonary Rehabilitation on Airway Resistance in Patients with Severe COPD: A Single-Center Retrospective Study

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Purpose: We investigated the effect of pulmonary rehabilitation (PR) on airway resistance in chronic obstructive pulmonary disease (COPD) patients with severe airway obstruction and hyperinflation.

Patients and Methods: This retrospective cohort study was conducted with data from severe COPD cases with those who underwent an 8-week PR program. Main inclusion criteria were having severe airflow obstruction (defined as a forced expiratory volume in one second (FEV_1) <50%) and plethysmographic evaluation findings being compatible with hyperinflation supporting the diagnosis of emphysema (presence of hyperinflation defined as functional residual capacity ratio of residual volume to total lung capacity (RV/TLC) >120%). Primary outcomes were airway resistance (R_{aw}) and airway conductance (G_{aw}) which were measured by body plethysmography, and other measurements were performed, including 6-minute walk test (6-MWT), modified Medical Research Council dyspnea scale (mMRC) and COPD assessment test (CAT).

Results: Twenty-six severe and very severe COPD patients (FEV_1, 35.0 ± 13.1%; RV/TLC, 163.5 ± 29.4) were included in the analyses, mean age 62.6 ± 5.8 years and 88.5% males. Following rehabilitation, significant improvements in total specific airway resistance percentage (sR_{awtot}%, p = 0.040) and total specific airway conductance percentage (sG_{awtot}%; p = 0.010) were observed. The post-rehabilitation mMRC scores and CAT values were significantly decreased compared to baseline results (p < 0.001 and p < 0.001, respectively). Although there were significant improvements in 6-MWT value (p < 0.001), exercise desaturation (ΔSaO_2, p = 0.026), the changes in measured lung capacity and volume values were not significant.

Conclusion: We concluded that PR may have a positive effect on airway resistance and airway conductance in COPD patients with severe airflow obstruction.

Keywords: airway resistance, body plethysmography, airflow limitation, emphysema, lung mechanics

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation caused by a combination of many factors,[1] including increased airway resistance, impaired airway-parenchymal tethering due to emphysema, and lumen narrowing due to mucus occlusion and bronchoconstriction.[2–5] Among the conditions referred to as COPD, patients with emphysema have highest airway resistance.[6] In patients with emphysema, peripheral airway resistance may be increased by four to 40-fold.[7]

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Although activity limitation in COPD is multifactorial (reduced cardiac function, hypoperfusion of the working muscle, limb muscle dysfunction and impaired neural regulation),[8] therapies aimed at partially reversing pulmonary hyperinflation represent the first step in improving dyspnea and exercise capacity.

Various pharmacological and non-pharmacological interventions have been shown to reduce hyperinflation and delay the onset of airflow restriction in patients with COPD.[4] For instance, bronchodilators reduce expiratory airflow resistance by increasing the diameter of the airways, emptying of peripheral airways with trapped air is facilitated, thus reducing hyperinflation and improving breathing mechanics.[9] Previous studies showed that inhaled long-acting bronchodilators (LABA/LAMA combination) have been proven to be able to reduce hyperinflation and therefore to improve dyspnea and tolerance to physical activity.[10] Inhaled low-dose short-acting β-agonists (SABAs) have been demonstrated to reduce lung hyperinflation despite no change in forced expiratory volume within one second (FEV_1) in patients with advanced emphysema.[5,11–13]

Pulmonary rehabilitation (PR) is the most effective non-pharmacological therapy that has emerged as a standard of care for patients with COPD.[14] PR reduces ventilatory requirements and improves breathing efficiency, thereby reducing hyperinflation and improving exertional dyspnea.[5] Although there is a limited data to draw a firm conclusion as to the mechanism by which this PR effect occurs, it may be attributable to the multifactorial effects of the rich PR content.[15]

To date, the benefit of PR in COPD patients has been mostly evaluated by investigating effects on exercise capacity, dyspnea and health-related quality of life.[16] Due to variabilities in perceptions and interpretations, assessing benefit based solely on symptoms and clinical response may lead to incomplete or inaccurate outcomes. Moreover, the relationship of improvements in the degree of hyperinflation, which is attributed to the effect of PR on respiratory mechanics in patients with COPD,[15] with intra-alveolar pressure and airway conductance has not been elucidated yet. Previous investigations have shown that body plethysmography can potentially provide additional insights into the respiratory mechanics of COPD patients.[17]

Body plethysmography is an integrative diagnostic procedure in respiratory medicine for comprehensive pulmonary function testing to evaluate static lung volumes and airway resistance (R_{aw}), as well as specific airway conductance (sG_{aw}).[18–20] R_{aw} reflects changes in alveolar pressure over changes in flow, representing true resistance of the airways. In this context, it may be a good parameter for the diagnosis of airflow obstruction.[21,22] In contrast, sR_{aw} can be interpreted as the work to be performed to establish this flow rate; Raw is calculated as the ratio of sR_{aw} to FRC;[23] sG_{aw} is the inverse of sR_{aw} and therefore reflects the conductance of the airways independent of lung volumes.[23] In obstructive lung diseases, the R_{aw} value is higher and the sG_{aw} value is lower than both healthy controls and non-obstructive respiratory diseases.[18] Furthermore, some authors have suggested that sG_{aw} is more sensitive to changes in airway resistance than FEV_1.[24]

The use of different functional markers to evaluate the effectiveness of PR in COPD may provide a better understanding of its effects on lung mechanics. Assessment of airway resistance is, therefore, important to characterize respiratory mechanisms that contribute to improved exercise capacity after PR in patients adopting different breathing strategies during exercise. To the best of our knowledge, no previous studies have addressed the effects of PR on airway resistance and specific airway conductance in patients with COPD. Accordingly, the primary aim of this study was to examine the effects of PR on airway resistance in patients with advanced COPD who had clinical and physiological features of emphysema, and secondarily, to assess whether airway resistance tests could be used as a physiological biomarker for PR.

Patients and Methods

Study Design and Patient Selection

This observational study involved a retrospective analysis of COPD patients admitted to the PR outpatient clinic of a tertiary-level training and research hospital, between December 2012 and June 2019. The study protocol was approved by the ethics committee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Approval Number: 2020–27; September 17, 2020). Written informed consent was obtained from all participants before PR. This study complied with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Records of 154 COPD patients with predominant pathology to emphysema who had attended an 8-week outpatient PR program were reviewed. The criteria for inclusion into the study for all participants were 1) having completed the 8-week outpatient PR program; 2) having a post-bronchodilator ratio of forced expiratory volume per second to forced vital capacity (FEV_1 / FVC) less than 0.7 to qualify for the definition of COPD;[25] 3) having severe airflow obstruction (defined as a FEV_1 less than 50% of the predicted value); 4) presence of hyperinflation defined as functional residual capacity (FRC) ≥120% and/or RV/TLC >120% of the predicted value;[26] 5) having undergone a body plethysmography test, including measures of lung volumes, airway resistance (R_{aw}) and specific airway conductance (sG_{aw}), and 6) no change in dose or use of bronchodilator treatment, prior to, and throughout the duration of the PR program. Patients were excluded in the presence of 1) patients who only participated in a home-based pulmonary rehabilitation program, even if having severe or very severe COPD; 2) patients whose data is missing from their file; 3) patients who could not complete the eight-week PR program due to various reasons; 4) patients whose COPD treatment was changed for an attack and/or other reason during the PR program; 5) patients whose body plethysmography test measurement was discordant; 6) those who have another chronic obstructive pulmonary disease (chronic bronchitis, asthma, bronchiectasis, etc.) other than emphysema, and 7) significant diseases other than COPD that could contribute to dyspnea and exercise limitation (interstitial lung disease, advanced heart disease, anemia, thyroid dysfunction).

Baseline data included age, sex, body mass index (BMI), smoking status, pulmonary function tests (PFTs), and comorbid diseases. The outcome measures were body plethysmography test, 6-minute walk test (6-MWT), modified Medical Research Council (mMRC) dyspnea scale, and COPD Assessment Test (CAT). Disease classification was made according to the GOLD staging.[25]

Pulmonary Rehabilitation Program

The comprehensive PR program consisted of 1) education (lung anatomy, physiology and pathophysiology etc.) and self-management aimed at improving disease status; 2) training for controlled breathing techniques (slow and deep breathing, pursed-lip breathing, diaphragmatic breathing, and restructuring of breath); 3) teaching effective use of inhaler medication and management of breathing difficulties, both aimed maximizing bronchodilation; 4) at least twice supervised cycle ergometer or treadmill training session (30 min) per a week, the intensity of which was set at 60–80% of maximal workload based on 6-MWT results; 5) supervised upper and lower limb strengthening exercises and inspiratory/expiratory muscle training; 6) psychiatric and social counseling/assistance, and 7) nutritional management (patient counselling and nutritional therapy). All patients underwent a supervised exercise program at the hospital two days per week, for a total of 8 weeks. A home-based program (3 days per week) was also provided, comprising various exercises during the same period. All patients completed a follow-up form for the exercise program.

Functional and Pulmonary Testing

Exercise tolerance was evaluated with the distance covered during a 6-MWT, according to guidelines put forth by the American Thoracic Society (ATS).[27] Before and after the test, oxygen saturation, heart rate, dyspnea, and Borg fatigue scores were recorded, and the distance covered was documented.[25,28] Oxygen desaturation was defined according to the Royal College of Physicians' guidelines as a ≥ 4% reduction between arterial oxygen saturation measured by pulse oximetry pre-test and post-test (ΔSpO_2 ≥4%) and post-test SpO_2 <90%.[29] Patients were introduced to a 10-point Borg category scale.[30] Patients were asked to describe their perception of dyspnea before exercise testing and at the end of tests.

Lung function testing was performed according to current ATS/ERS recommendations with a Sensor Medics model 2400 (Yorba Linda, CA, USA).[31,32] Static, dynamic lung volumes and total specific airway resistances (sR_{awtot}) were assessed by means of an ultrasonic flow measurement plethysmograph (Ganshorn PowerCube Body+, SCHILLER, Germany). The system automatically derived total specific conductance (sG_{awtot}) from the breathing loops and determined total respiratory resistance (R_{awtot}).

Perceived levels of effort dyspnea were assessed through the modified medical research council (mMRC) dyspnea scale which performs evaluations with respect to daily activities.[33] Patient-reported CAT results were obtained to identify COPD impact on health status (ie, cough, sputum and dyspnea).[33]

Statistical Analysis

Statistical analysis was performed using the SPSS software for Windows, version 15.0 (IBM, Armonk, NY, USA). Continuous variables were expressed with minimum–maximum (median) values (for non-normally distributed variables) or with mean ± standard deviation values (for normally distributed variables), while categorical variables were depicted with number (absolute frequency) and percentage (relative frequency). When continuous variables in dependent groups met normal distribution, they were examined using the paired samples *t*-test; otherwise, the Wilcoxon test was utilized. A p value of <0.05 was considered statistically significant.

Results

A total of 26 emphysema patients (88.5% males) with severe airflow limitation (FEV_1, mean ± SD, 35.0 ± 13.15%) and static hyperinflation (RV/TLC, mean ± SD, 163.5 ± 29.4%) were included in the study, mean age 62.6 ± 5.8 year. The number of patients with at least one comorbidity was 10 (38%), diabetes mellitus was the most common (others: hypertension, hypercholesterolemia and osteoporosis). The demographic characteristics and baseline values of the patients are shown in Table 1. Following PR, there were significant improvements in total specific airway resistance percentage (sR_{awtot}%, p = 0.040) and total specific airway conductance percentage (sG_{awtot}%, p = 0.010) (Table 2; Figures 1 and 2). Of note, after PR, some limited improvements in plethysmographic respiratory measurement values [pre-PR vs post-PR, % of pred (IC: inspiratory capacity; 49.0 ± 24.6 vs 49.2 ± 20.7; p = 0.970), (FVC: forced vital capacity; 57.8 ± 17.0 vs 60.4 ± 15.8; p = 0.054), (FRC: functional residual capacity; 133.7 ± 37.2% vs 132.0 ± 39.9%; p = 0.788), (ERV: expiratory reserve volume; 80.8 ± 29.2% vs 88.5 ± 36.6%; p = 0.364)] were identified in our group of patients, especially in RV and RV/TLC [pre-PR vs post-PR, % of pred (169.9 ± 51.3 vs 163.8 ± 67.9) and (163.5 ± 29.4 vs 156.0 ± 42.5)], albeit statistical significance was not achieved (p > 0.05).

The post-rehabilitation mMRC scores and CAT values were significantly decreased compared to the baseline results (p < 0.001 and p < 0.001, respectively) (Table 2 and Figure 1). We observed significant differences between baseline and

Table 1 Patient Characteristics

Gender, n (%)	
Male	23 (88.5)
Female	3 (11.5)
	Mean ± SD
Age, yr	62.6 ± 5.8
Smoking, pack/ yr	46.1 ± 26.2
BMI, kg/m^2	25.4 ± 4.0
BODE-index	5.19 ± 1.83
FVC, % (spirometric)	57.8 ± 17.0
FEV_1, % (spirometric)	35.0 ± 13.1
GOLD grade n (%)	
Severe	11 (42)
Very severe	15 (58)
SaO_2, %	93.4 ± 2.6
Co-morbidities, n (%)	
No	16 (62)
Yes	10 (38)

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; SaO_2, haemoglobin O_2 saturation.

Table 2 Changes in Lung Volumes in Plethysmography Measurements After PR

Variable	Before PR Mean ± SD	After PR Mean ± SD	*p*
$R_{aw\ tot}$ [kPa*s/L]	1.53 ± 1.11	1.32 ± 0.79	0.209
$R_{aw\ tot}$ [% of pred]	506.7 ± 371.1	441.5 ± 262	0.234
$G_{aw\ tot}$ [L/s/ kPa]	0.93 ± 0.56	1.09 ± 0.75	0.054
$G_{aw\ tot}$ [% of pred]	28.3 ± 17.1	32.6 ± 22.4	0.077
$sR_{aw\ tot}$ [kPa*s]	6.76 ± 4.65	6.13 ± 3.99	0.055
$sR_{aw\ tot}$ [% of pred]	609.0 ± 392.5	536.2 ± 341.3	0.040
$sG_{aw\ tot}$ [1/(kPa*s)]	0.22 ± 0.20	0.28 ± 0.25	0.003
$sG_{aw\ tot}$ [% of pred]	25.8 ± 23.4	31.2 ± 29.1	0.010
FEV_1 [L]	1.01 ± 0.41	1.06 ± 0.47	0.065
FEV_1 [% of pred]	35.0 ± 13.1	36.8 ± 14.3	0.080
TLC [L]	6.05 ± 1.47	6.04 ± 1.69	0.983
TLC [% of pred]	97.6 ± 21.3	96.4 ± 22.0	0.767
FRC [L]	4.46 ± 1.38	4.41 ± 1.47	0.820
FRC [% of pred]	133.7 ± 37.2	132.0 ± 39.9	0.788
RV [L]	3.91 ± 1.23	3.81 ± 1.59	0.687
RV [% of pred]	169.9 ± 51.3	163.8 ± 67.9	0.565
RV/TLC	163.5 ± 29.4	156.0 ± 42.5	0.139
mMRC	2.27 ± 0.92	1.73 ± 1.08	< 0.001
CAT	17.6 ± 5.7	11.2 ± 5.3	< 0.001

Note: The p values of < 0.05 was shown in red colour.
Abbreviations: $sR_{aw\ tot}$, total specific resistance of airways; $sG_{aw\ tot}$, total specific conductance of airways; FEV_1, forced expiratory; volume in one second; TLC, total lung capacity; FRC, functional residual; capacity; RV, residual volume; mMRC, modified Medical Research Council; CAT, COPD assessment test.

post-PR measurements in terms of 6-MWT results, including walking distance (Mean ± SD; 307.7 ± 98.3 meters vs 363.7 ± 105.7 meters; $p < 0.001$) and delta of haemoglobin O_2 saturation (ΔSpO_2, difference between rest and maximal exercise values; $p = 0.026$) (Table 3 and Figure 1). In addition, the post-rehabilitation median change in distance (Mean ± SD, 55.9 ± 64.6 meters) observed in the 6-MWT was above the minimal clinically important difference defined for COPD and other chronic respiratory patients.[28] Although an improvement in Borg scores was observed, comparisons did not show significant improvement ($p = 0.314$) (Table 3).

Discussion

The main new finding of this study is that PR may have a positive effect on airway resistance and airway conductivity in COPD patients with severe airway resistance. The present study is the first to demonstrate that the R_{aw} and sG_{aw} plethysmography parameters have the potential to assess the effect of PR on COPD.

Previous studies have shown that airway resistance and specific conductance have a valuable and potentially important role in the diagnosis of obstructive diseases.[18] In a study including 51 participants with emphysema, the

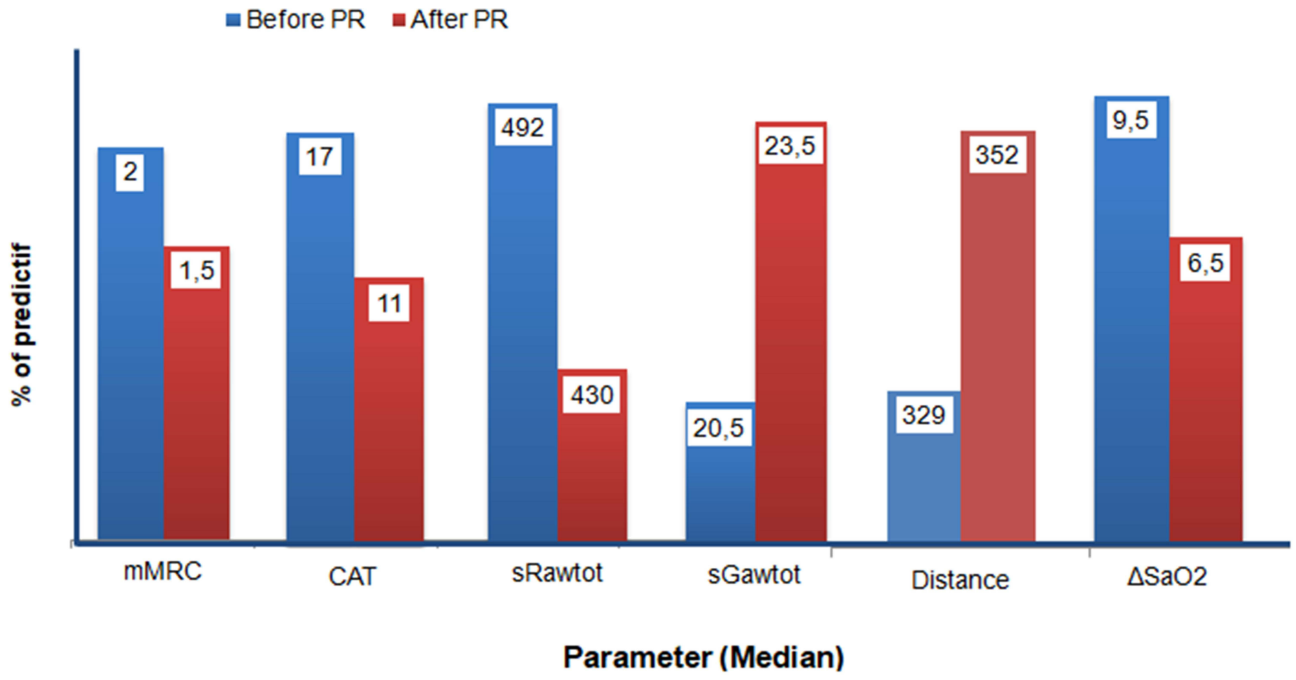

Figure 1 A graph showing the parameters for which statistically significant differences were observed in patients who has participated in an eight-weeks PR program.
Abbreviations: PR, pulmonary rehabilitation; sR_{awtot}, total specific resistance of airways; sG_{awtot}, total specific conductance of airways; ΔSaO_2, delta of haemoglobin O_2 saturation; mMRC, modified Medical Research Council; CAT, COPD assessment test.

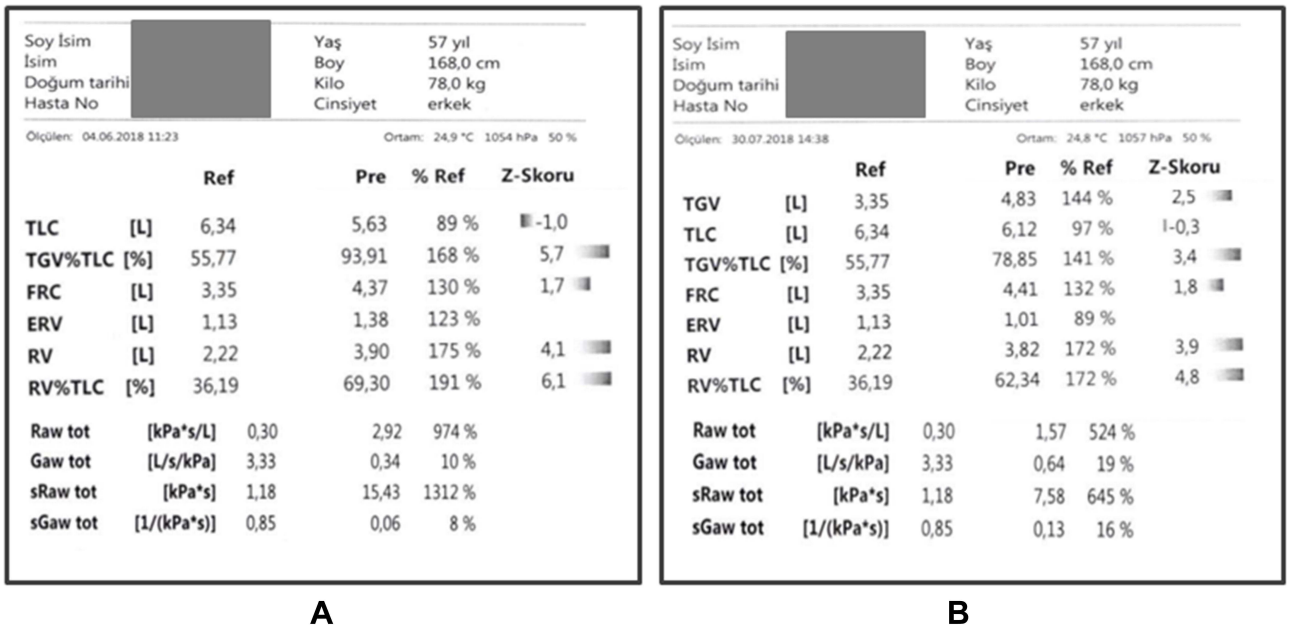

Figure 2 A Body plethysmography data samples of a 57-year-old male patient with a history of smoking 60 pk/year, who has attended sixteen sessions (8 weeks) of PR program; before attending (**A**) and after attending (**B**).

variability and sensitivity of plethysmography and spirometry measurements were compared in order to assess bronchodilation in COPD.[17] The findings of this study demonstrated the high sensitivity of plethysmography in the detection of minor physiological effects, which resulted in improved airway conductance. In COPD, both specific conductance and airway resistance are more sensitive for assessing short-acting bronchodilator effects than FEV_1.[24] Moreover, body

Table 3 Comparison of 6-MWT Data

6-MWT		Mean ± SD	*p*
Desaturation changes, (ΔSaO_2)	Before PR	10.1 ± 6.6	0.029
	After PR	7.8 ± 6.3	
Borg score	Before PR	1.52 ± 1.08	0.314
	After PR	1.33 ± 0.95	
Distance, meter	Before PR	307.7 ± 98.3	< 0.001
	After PR	363.7 ± 105.7	
	Change	55.9 ± 64.6	

Abbreviations: 6-MWT, 6-Minute Walk Test; PR, pulmonary rehabilitation; ΔSaO_2, delta of haemoglobin O_2 saturation.

plethysmography can be a favorable alternative tool in evaluating the effect of PR, especially in elderly patients with COPD who have difficulty in performing spirometry.[34]

The significant decrease in plethysmography-determined airway resistance, the significant increase in airway conductance, and improvements in lung volumes may be attributed to the mechanical effects of PR on respiratory function.[33] We observed limited improvements in the respiratory functions of our cases, as demonstrated by RV and RV/TLC results; however, comparisons did not demonstrate statistical significance ($p > 0.05$) which is similar to the literature on this topic.[35] The changes in R_{aw} and sG_{aw} were also relatively greater compared to the changes in lung volume, and therefore, these parameters are possibly better for the purpose of detecting significant reductions in airflow restriction following PR interventions.

In our cases, there was a statistically significant improvement in exercise-induced hypoxaemia levels observed in 6-MWT after PR compared to baseline (Table 3 and Figure 1). We speculate that the improvement in desaturation during exercise following PR may be achieved by both the reduction in the effort required to breath and the decrease in the oxygen demand associated with the improvement of the oxygen utilization in peripheral muscles.[36] In addition, controlled pursed-lip breathing and deeper and longer breaths to decrease the frequency of hyperventilation can reduce the O_2 cost caused by the unit force.[37,38] It was thought that the decrease in R_{aw} would improve hypoxemia, as it would increase air conduction and reduce the O_2 cost caused by the resistant respiratory workload. The clinical equivalent of this was interpreted as an increase in effort capacity and improvement in dyspnea levels in our cases. Although the patients in this study were under optimal pharmacological treatment and there was minimal change in lung function after rehabilitation, improvements in exertional dyspnea and capacity should be mainly attributed to the effect of rehabilitation. This is important as it demonstrates that even patients with advanced emphysema may experience considerable benefit from PR.

In previous studies, the addition of inspiratory muscle training to a PR program for COPD was reported to contribute to improved outcomes.[39,40] However, patients with predominant pathologies such as chronic bronchitis or emphysema were not evaluated separately in these studies, whereas, in emphysematous lungs, the radial traction exerted by the surrounding alveoli to the airway decreases, correlated with the degree of parenchymal destruction.[41] Accordingly, the bronchodilation effect of deep and strong inspiration is not proportional to the severity of emphysema, and may even cause bronchoconstriction.[42] Therefore, in patients with emphysema, it would be more appropriate to focus on PR interventions that affect the expiratory rather than the inspiratory phase of respiratory mechanics, altering the breathing pattern and reducing air trapping.

The impact of PR on airway resistance-related respiratory mechanics cannot be resolved through this study design, but some assumptions are worth testing. The PR interventions that may lead to improved airflow resistance in emphysema may be summarized as follows: 1) breathing training, particularly pursed-lip breathing and controlled breathing techniques, prevent early airway closing, providing enough time to expel trapped air;[37,43] 2) deep inspiration

is established to increase the production of surfactant, which maintains alveolar and airway stability;[44] 3) effective inhalation techniques allow inhaled medications to reach higher concentrations in the airways, facilitating stronger bronchodilation effect; 4) effective coughing and expectoration techniques eliminate secretions that cause airway obstruction and increased resistance;[45] 5) exercise training of leg muscles reduces lactate production and decreases ventilator load.[46] A lower ventilation load allows COPD patients to breathe more slowly during exercise, consequently reducing dynamic hyperinflation.[15,47] We speculate that airway resistance may be significantly reduced by the cumulative effect of PR interventions.[48,49] It is clear that breathing exercises in COPD patients yield complex changes in pulmonary physiology.[39,49] Therefore, body plethysmography can be beneficial in assessing the different aspects of these physiological changes.[24]

Although the expansion of airway diameter achieved by bronchodilator drugs in patients with COPD is smaller than in patients with asthma, the decrease in R_{aw} provides an above-expected resistance reduction in relation to Poiseuille's law (a reduction correlated with the 4th power of airway diameter).[50] In addition, according to our clinical experience, we recommend that severe COPD patients take their short-acting bronchodilator drugs (with a nebulizer if necessary) 15–20 minutes before exercise, thus reducing the level of exercise limitation due to shortness of breath.[51,52] Similarly, it would be more appropriate to focus on reducing airway resistance before respiratory muscle exercises with an incentive spirometry device.[33] Otherwise, in the patient trying to breathe against the high resistance caused by the narrowed airway, the increased respiratory workload may increase O_2 cost and cause more harm than benefit.

There are several limitations to this study. The main limitation is the single-center study design and small sample size. Inclusion of only patients with emphysema was the main reason for the low number of patients, but this was necessary for accurate analysis in this particular population. Another reason that plethysmography tests were expensive and had limited indications (preoperatively or before volume reduction intervention, etc.) in our hospital. We realize that the small size of the group does not allow generalization of results beyond this select group of patients. However, our group represents a fairly homogeneous group of patients with severe COPD and hyperinflation of the lungs, which is an important strength of the study.

In conclusion, our study suggests that the PR is effective in reducing airway resistance in COPD patients with severe hyperinflation. In addition, we believe that R_{aw} and sG_{aw} can be used as physiological biomarkers in the evaluation of PR benefit, especially in a select group of patients with severe airflow obstruction.

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Disclosure

The authors report no conflicts of interest in this study.

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