

Correlation Between Diaphragmatic Excursion and Exercise Tolerance Improvement Following Pulmonary Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease-Obstructive Sleep Apnea Overlap Syndrome

Honghua Shen^{1,2}, Yiming Xu², Yin Zhang², Lei Ren², Rui Chen¹

¹Department of Respiratory Medicine, the Second Affiliated Hospital of Soochow University, Suzhou, 215004, People's Republic of China;

²Department of Respiratory Rehabilitation, the Fourth Rehabilitation Hospital of Shanghai, Shanghai, 200040, People's Republic of China

Correspondence: Rui Chen, Department of Respiratory Medicine, the Second Affiliated Hospital of Soochow University, Suzhou, 215004, People's Republic of China, Email chenrui000@126.com

Purpose: We assess the predictive value of diaphragm excursion (DE) in enhancing exercise tolerance following pulmonary rehabilitation (PR) among patients with COPD-OA overlap syndrome.

Material and Methods: This prospective cohort study enrolled 63 patients diagnosed with COPD-OA overlap syndrome who actively participated in a PR program from January 2021 to May 2023. Among these, 58 patients successfully completed the 20-week PR program, with exercise tolerance assessed through the measurement of six-minute walk distance (6MWD), and DE evaluated by ultrasonography. The responder to PR in terms of exercise ability was defined as a patient who showed an increase of >30m in 6MWD. The cutoff value for predicting PR response based on DE was determined using receiver operating characteristic (ROC) curves.

Results: Following the PR program, significant improvements were observed in mMRC, 6MWD, DE during deep breathing, and diaphragm thickness fraction (DTF). Of the participants, 33 patients (57%) were classified as responders, while 25 patients (43%) were considered non-responders. Baseline values of FEV₁% predicted, 6MWD, DE during deep breathing, DTF, and PaO₂ exhibited a significant elevation in responders as compared to non-responders. The changes of 6MWD were positively associated with the baseline values of DTF and DE during deep breathing, FEV₁% predicted and PaO₂, while negatively correlated with baseline value of mMRC. The predictive performance in terms of the area under the ROC curve for determining responder's DTF was found to be 0.769, accompanied by a sensitivity of 85% and specificity of 68%, using a cutoff value at 17.26%. Moreover, it was observed that DE during deep breathing could predict the area under the ROC curve for responders to be 0.753, with a sensitivity of 91% and specificity of 56% at a cutoff value of 3.61cm.

Conclusion: Diaphragm excursion serves as a valuable predictor for determining the enhancement of exercise tolerance following PR in patients with COPD-OA overlap syndrome.

Trial Registration: ChiCTR1800020257, www.chictr.org.cn/index.aspx.

Keywords: pulmonary rehabilitation, COPD-OA overlap syndrome, diaphragm excursion, diaphragm thickness fraction, six-minute walk distance

Background

Overlap syndrome¹ denotes the coexistence of Chronic Obstructive Pulmonary Disease (COPD) and Obstructive Sleep Apnea (OSA), which is anticipated to manifest in approximately 0.5% of adults aged over 40 years, and is associated with substantial morbidity and mortality.² In China, the prevalence of coexisting COPD with OSA was determined to be 66.0% based on Apnea-Hypopnea Index (AHI) of ≥ 5 events/h, with 23% exhibiting an AHI ≥ 15 events/h.³ COPD is a prevalent and preventable

condition characterized by persistent airflow limitation that exhibits limited reversibility.⁴ The occurrence of OSA is characterized by recurrent upper airway closure during sleep and is frequently observed in individuals with COPD. The overlap syndrome presents poorer outcomes than OSA or COPD alone, and its management differs from that of either condition. Therefore, the identification of concurrent OSA in individuals diagnosed with COPD gives significant clinical ramifications.

The overlap syndrome exerts a more profound detrimental impact on the quality of life in individuals with COPD, leading to reduced daily activity attributed to dyspnea. The coexistence of COPD and OSA leads to more severe nocturnal hypoxemia and hypercapnia effects than either condition alone, due to their similar pathophysiological effects, particularly in terms of hypoxia and systemic inflammation.^{5–7} Additionally, overlap syndrome is associated with a decrease in daytime oxygen saturation and quality of life scores, as well as an increase in the frequency of acute exacerbations, comorbidities, and economic burden linked to COPD.^{8,9}

Although there is limited literature on rehabilitation interventions for OSA, there is substantial evidence supporting pulmonary rehabilitation (PR) as the standard of care for patients with COPD.¹⁰ The implementation of PR has been documented to enhance dyspnoea, exercise capacity, and quality of life among patients diagnosed with COPD.¹¹ Studies by Boutou et al¹² and Costi et al¹³ demonstrated that patients with better exercise capacity and health-related quality of life likelihood of successfully completing PR. Conversely, van Ranst et al reported inconclusive findings, indicating that status and extensive utilization of health-care services may encounter challenges in effectively completing PR.¹⁴

Despite a more unfavorable prognosis, there is a critical need for clinical attention to rehabilitation, and objective evaluation of therapeutic effects is necessary for individuals with COPD-OSA overlap syndrome. Currently, there is no universally accepted standardized approach for accessing diaphragm excursion in patients with overlap syndrome both pre- and post-PR. Although computed tomography (CT) and dynamic magnetic resonance imaging (MRI) have been used in previous studies to measure diaphragm movement, the utilization of these methodologies incurs substantial expenses and exposes individuals to heightened levels of radiation.^{15–17} In contrast, ultrasound (US) imaging, a cost-effective and widely available technique devoid of ionizing radiation risks, is not commonly used to assess diaphragm dysfunction associated with COPD-OSA overlap syndrome. Relevant investigations have been conducted to explore the thickness and motion of the diaphragm in individuals with COPD, and similar studies on diaphragm using ultrasonography have been conducted.^{18,19} Given the pivotal role of dynamic lung hyperinflation (DLH) in the pathogenesis of dyspnea and impaired exercise capacity among patients with COPD, employing objective measures that accurately reflect the extent of DLH could facilitate the identification of individuals who are likely to respond favorably to PR. Shiraishi et al²⁰ reported that ultrasonography can effectively predict the improvement in exercise tolerance after PR in patients with COPD by measuring the maximum level of DE. However, there is a lack of previous investigation on the US characteristics of the diaphragm for COPD-OSA overlap syndrome. Therefore, it is crucial to accurately identify patients who are more likely to derive greater benefits from a PR program, especially for these patients. The primary objective of this study is to elucidate the role of diaphragmatic excursions in predicting the enhancement in exercise tolerance following PR in individuals with COPD-OSA overlap syndrome.

Methods

Materials and Methods

Study Design and Subjects

This present study is a prospective cohort study with a parallel group design and a 20-week follow-up period. It was conducted at the Department of Respiratory Rehabilitation, The Fourth Rehabilitation Hospital of Shanghai, China, from January 2021 to May 2023, following the principles of good clinical practice.

The study was granted approval by the Ethics Committee of The Fourth Rehabilitation Hospital of Shanghai (SP202002), and written informed consent was obtained from all participants.

The inclusion criteria with both COPD and OSA were defined as follows:

1. The diagnosis of stable COPD is established by integrating clinical history, physical examination findings, chest radiography results, and pulmonary function tests in accordance with the diagnostic and severity criteria for COPD outlined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD);²¹

2. Inpatients or outpatients diagnosed with stable COPD and exhibiting peripheral oxygen saturation (SpO_2) $\geq 92\%$ during calm breathing;
3. Absence of acute exacerbation for a minimum duration of 4 weeks and self-reported the history of OSA.
4. No clinically significant respiratory, neuromuscular, or other disorders causing hypercapnia;
5. Ability to undergo all-night polysomnographic (PSG) testing. The severity of OSA was categorized as mild if the AHI ranged from $\geq 5/\text{h}$ to $<15/\text{h}$, moderate if it ranged from $\geq 15/\text{h}$ to $<30/\text{h}$, and severe if it was $\geq 30/\text{h}$.

The exclusion criteria in this study were as follows:

1. Patients presenting with gas exchange abnormalities resulting from alternative etiologies and restrictive pulmonary conditions. (eg, bronchiectasis, interstitial fibrosis, diaphragmatic paralysis, and kyphoscoliosis) were excluded;
2. Concurrent administration of anxiolytics, analeptic, or treatment for other comorbid respiratory conditions;
3. The diseases exerted negative effects on the diaphragm by affecting small vessels and inducing neuropathy were excluded. Furthermore, patients with cognitive or psychiatric disorders, speech disorders, wound healing disorders, as well as other orthopedic and neurological disorders that restrict movement from the scope of patient recruitment were also excluded.

Patients provided informed consent prior to participation, and the protocols adhered to international ethical standards.

Measurements

Demographic and clinical data, including age, gender, GOLD stage, and Body Mass Index (BMI) at the initiation of PR, as well as results of pulmonary function tests and frequency of COPD exacerbations were extracted from the medical records. Two time points for evaluations were conducted at baseline and after 20 weeks of PR.

Ultrasonography Study

Ultrasonography (SONIMAGE HS1, Konica Minolta, Tokyo, Japan) was conducted to assess diaphragm excursion (DE) and diaphragm thickness in all participants. A convex array probe with a frequency range of 1 to 5 MHz and a linear array probe with a frequency range of 8 to 10 MHz were employed. Diaphragm excursion was the vertical distance between the position of the diaphragm raised at the end of expiration and the position of the diaphragm lowered at the end of inspiration (Figure 1B2 and C2). Under the B-mode, the diaphragm was seen as a single echogenic line (Figure 1B1 and C1), moving towards the probe during inhalation and away from the probe during exhalation. The convex array probe was positioned between the mid-clavicular and mid-axillary lines below the right costal margin, and the right hemidiaphragm was measured with the liver as the acoustic window at a frequency of 3.5-MHz.^{22,23} The probe was placed medially, cranially, and dorsally, so that the ultrasound beam could be perpendicular to the right hemi-diaphragmatic dome. The convex array probe visualized the right hemi-diaphragm in B-mode, and the diaphragm excursion was quantified using images acquired during calm breathing and deep breathing in M mode. The highest value obtained from three measurements was utilized.

For diaphragm thickness assessment, the patient was positioned in a supine posture, and the high-frequency linear array probe was placed along the mid-clavicle line, extending towards the midpoint of the front axillary line until reaching the junction between the seventh and eighth costal cartilage. The thickness of the diaphragm, which exhibited hyperechoic characteristics on both sides and hypoechoic characteristics internally, was measured and recorded at the termination of inspiratory and expiratory phases (Figure 1A). The average value was determined through three measurements. The diaphragm thickness fraction (DTF) was computed as (diaphragmatic thickness at the end of inspiration, DTei) - (diaphragmatic thickness at the end of expiration, DTee)/ $\text{DTee} \times 100\%$.

Pulmonary Function Tests

The spirometry and plethysmography were performed using a Master Screen device (Care Fusion Germany 234 GmbH, Germany) by proficient personnel in a quiet environment. Three trials were conducted for each test, and the optimal

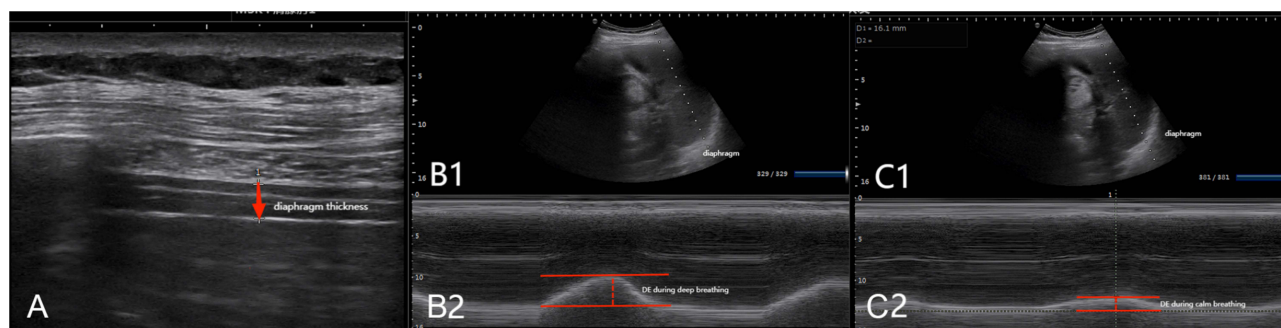


Figure 1 Using the liver as an acoustic window. **(A)** Represents the diaphragm thickness. **(B)** Represents the diaphragm excursion during deep breathing. **(C)** Represents the diaphragm excursion during calm breathing.

outcomes were recorded to determine forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and the FEV_1 /FVC ratio.

PSG Study

All participants underwent a single night of PSG study, lasting at least 8 hr, at the sleep laboratory within our department. Overnight sleep polysomnography (SOMNO check 2; Weinmann; Germany) included electroencephalography, electrooculography, submental electromyography, electrocardiography, bilateral anterior tibialis electromyography, nasal airflow measurement, oxygen saturation assessment, thoracoabdominal movement monitoring, body position tracking, and snoring. The sleep parameters were manually scored in accordance with the American Academy of Sleep Medicine (AASM) Manual v2.3 2016.²⁴ Respiratory sleep patterns were examined following the recommendations provided by AASM.²⁵ Apnea was defined as the cessation of airflow for a minimum duration of 10 s, accompanied by respiratory effort, while hypopnea was characterized by a reduction in airflow of at least 30% lasting for at least 10 s and associated with either a decrease in oxygen saturation of $\geq 3\%$ or arousal. TS90 referred to the percentage of time spent during sleep with oxygen saturation levels $< 90\%$. The AHI was calculated to assess severity, referred to as the average number of apnea and hypopnea events per hour. Individuals with an $AHI \geq 5$ were classified as having OSA, whereas those with an AHI of < 5 were categorized as primary snorers.

Assessment of Other Parameters

Arterial blood gases, including pH, PaO_2 , and $PaCO_2$, were evaluated through supine resting arterial blood gas analysis upon waking in the morning.

A modified British Medical Research Council (mMRC) questionnaire was applied to assess the severity of dyspnea during daily activities.²⁶

The six-minute walk distance (6MWD) was conducted in accordance with a statement from the American Thoracic Society (ATS)/European Respiratory Society (ERS) to assess walking capacity.^{27–29} The 6MWD test was conducted on both pre- and post-PR programs for all participants. Responders to PR in terms of exercise capacity were defined as individuals who exhibited a post-PR increase of more than 30 m in the 6MWD, which was considered the minimal clinically important difference (MCID) for this measure.³⁰

Cardiopulmonary Exercise Testing

In the current study, an incremental exercise test was conducted on a MasterScreen CPX electrically braked cycle ergometer (CareFusion Germany 234 GmbH) with a pedaling cadence of approximately 60 revolutions per minute and terminated upon symptom limitation or in the presence of electrocardiographic changes. After a 3-min rest period followed by 3 min of unloaded pedaling, the work rate was progressively increased (ramp) at a rate of 5–10 Watts per minute, based on the spirometry results of each subject. Upon cessation of exercise, participants were requested to articulate their primary reason for discontinuing physical activity, such as experiencing breathing difficulties or

discomfort in the legs, or any other documented rationale. The intensity of PR was determined through cardiopulmonary exercise testing, specifically targeting a range of 50–70% of peak oxygen uptake, which is defined as moderate-intensity PR exercise. Similar to previous studies, these cutoff values were determined based on the prognostic significance of patients' maximal oxygen uptake.³¹

PR Intervention

Patients diagnosed with COPD-OSA overlap syndrome participated in a standardized multidisciplinary inpatient PR program, encompassing comprehensive health education, psychological support, and tailored aerobic exercise. The provision of psychological support offers patients assistance, guidance, solace, and encouragement while also directing them towards active participation in rehabilitation training. Exercise duration and intensity were adjusted based on individual clinical complaints and cardiopulmonary exercise testing results. All enrolled patients underwent a 20-week course of PR treatment, consistently attending sessions 5 days per week.

The aerobic exercise lasted for 40 min daily, comprising a 10-min pre-exercise warm-up, a 10-min post-exercise relaxation, and a 20-min stationary cycling exercise utilizing the Upper-Lower Limb Coordination Exercise Machine (Jiangsu Tianrui Medical Equipment Co., Ltd., Nanjing, China). The exercise started at 50% of the maximum load achieved during the cardiopulmonary exercise test. If the patient maintained stable heart rate and blood oxygen saturation demonstrating good exercise tolerance, the workload was gradually incremented by 10 W. The electrocardiogram signals and the SpO₂ level were continuously monitored throughout the exercise session and post-exercise period.

Exercise was terminated if the SpO₂ dropped below 85%, blood pressure exceeded 200/100 mmHg, or the heart rate reached 90% of the maximum value during cardiopulmonary exercise testing to ensure patient safety. If a patient experienced severe dyspnea and exhibited subjective intolerance to exercise, the physiotherapist would document the case and provide the patient with a 5-min rest period prior to resuming their training. Patients who exhibited repeated refusal to do aerobic training more than three times or demonstrated poorly cooperative behavior were excluded from this study.

Statistical Analysis

The statistical analyses were conducted using SPSS 22.0 software (IBM, Armonk, NY, USA). Prior to analysis, the normality of continuous data was assessed through the application of both the Kolmogorov–Smirnov test and the Shapiro–Wilk test. The paired *t*-test or the Wilcoxon signed-rank test was employed to assess alterations in parameters pre- and post-implementation of the PR program. Responders and non-responders were compared using appropriate statistical tests, including the *t*-test, the Wilcoxon rank-sum test, or χ^2 test. The Pearson correlation coefficient was employed to examine the association between changes in 6MWD and independent variables. The receiver operating characteristic curve analysis was employed to evaluate the predictive capacity of diaphragm excursion in determining the response. The statistical significance was determined at a significance level of $P < 0.05$ (two-tailed).

Result

Among the 63 patients diagnosed with COPD-OSA overlap syndrome and included in this study, a total of 58 individuals successfully completed the PR program (Figure 2). Three patients terminated their involvement in the PR program owing to poor cooperation, while two patients discontinued their participation due to severe exacerbation of COPD.

Baseline Characteristics of the Participants

Among the patients who underwent PR, 33 individuals demonstrated a significant increase of >30 meters in their 6MWD post-intervention, indicating a positive response rate of 57%. Conversely, 25 patients (43%) were categorized as non-responders. Responders had significantly higher baseline values of FEV₁, FEV₁/FVC, FEV₁%predicted, 6MWD, diaphragm excursion during deep breathing, DTF, and PaO₂, and significantly lower mMRC scores compared to non-responders (all $P < 0.05$) (Table 1). However, no significant differences were observed in gender, age, BMI, GOLD stage, underlying disease, number of positive airway pressure (PAP), and long-term oxygen therapy (LTOT) users, PaCO₂, and diaphragm excursion during calm breathing between responders and non-responders (all $P > 0.05$) (Table 1).

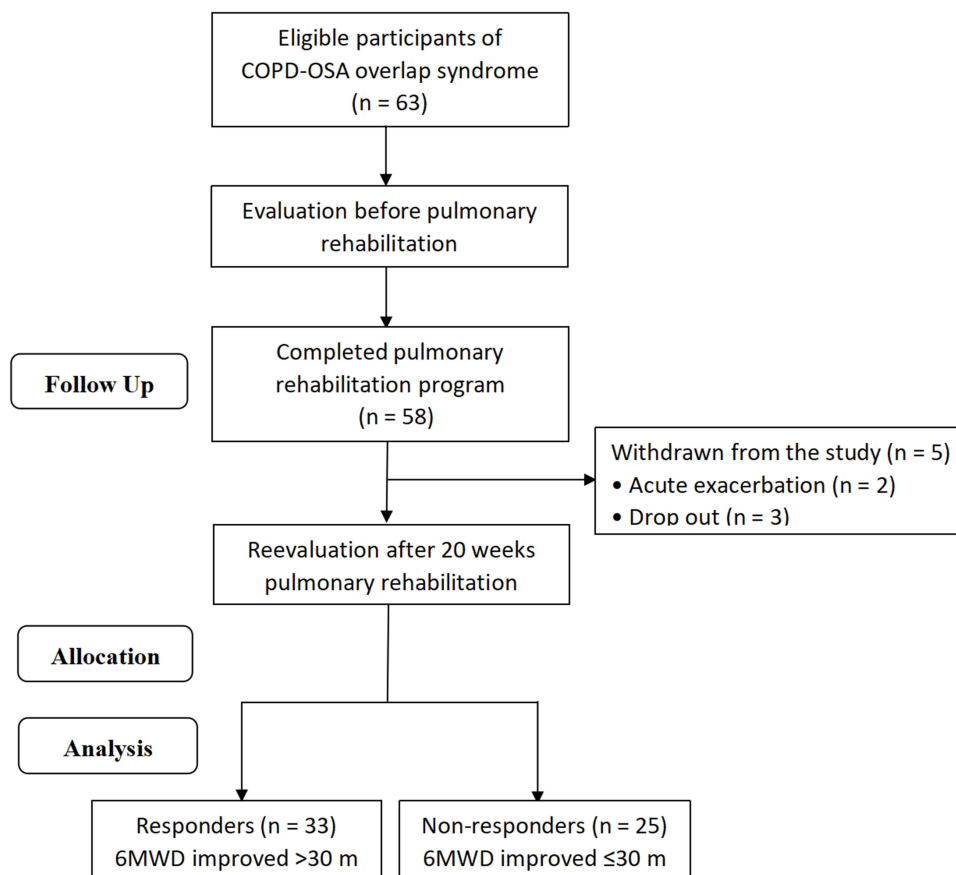


Figure 2 Study flow diagram.

Abbreviation: 6MWD, 6-min walk distance.

Effects of Pulmonary Rehabilitation

After the implementation of PR program, there was a significant improvement observed in all patients regarding 6MWD result, mMRC scores, AHI, diaphragm excursion during deep breathing, and DTF values (all $P < 0.05$) (Table 2).

Table 1 Baseline Characteristics of Study Participants

	All N=58	Responders N=33	Non-Responders N=25	P value
Age, year	66.45±8.21	67.06±6.47	65.64±10.16	0.519
Gender, male/female (%)	33/25 (57/43)	18/15 (55/45)	15/10 (60/40)	0.678
BMI, kg/m ²	24.17±2.42	24.12±2.87	24.24±1.72	0.855
GOLD (II/III) (%)	29/29 (50/50)	20/13 (61/39)	9/16 (36/64)	0.063
PAP users, n (%)	21 (36)	10 (30)	11 (44)	0.282
LTOT users, n (%)	25 (43)	12 (36)	13 (52)	0.234
FEV ₁ (L)	0.95±0.25	1.03±0.25	0.84±0.21	0.004
FEV ₁ %predicted	48.95±5.99	51.09±6.13	46.12±4.52	0.001
FEV ₁ /FVC	0.46±0.08	0.48±0.06	0.43±0.09	0.008
mMRC (0-1-2-3), n	0/12/30/16	0/10/17/6	0/2/13/10	0.018
6MWD, m	298.22±66.75	322.00±48.78	266.84±74.89	0.003
OSA (mild/moderate/ severe) (%)	17/24/17 (29/41/29)	11/14/8 (33/42/24)	6/10/9 (24/40/36)	0.573
AHI (events/h)	21.53±9.82	19.78±8.33	23.85±11.26	0.136

(Continued)

Table 1 (Continued).

	All N=58	Responders N=33	Non-Responders N=25	P value
L-SaO ₂ (%)	75 (69,81)	73 (69,84)	76 (69,81)	0.625
TS90%	6(4,15)	5(2,14)	7(5,17)	0.061
DE during calm breathing (cm)	2.10±0.41	2.16±0.36	2.02±0.47	0.194
DE during deep breathing (cm)	4.67±1.32	5.12±1.26	4.08±1.19	0.002
DTF (%)	21.06±9.66	24.96±7.97	15.90±9.39	<0.001
PaO ₂ (mmHg)	62.72±8.62	65.58±7.88	58.96±8.24	0.003
PaCO ₂ (mmHg)	48.05±6.39	48.18±6.61	47.88±6.22	0.860
Coronary heart disease, n (%)	9(16)	5(15)	4(16)	0.930
Diabetes mellitus, n (%)	6(10)	3(9)	3(12)	0.719
Hypertension, n (%)	15 (26)	8(24)	7(28)	0.746

Abbreviations: BMI, body mass index; GOLD, Chronic Obstructive Lung Disease; PAP, positive airway pressure; LTOT, long-term oxygen therapy; FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity; mMRC, modified British Medical Research Council; 6MWD, 6-min walk distance; OSA, Obstructive Sleep Apnea; AHI, Apnea Hypopnea Index; L-SaO₂%, lowest nocturnal oxygen saturation; TS90%, percentage of total sleep time with oxygen saturation < 90%; DE, diaphragm excursion; DTF, diaphragm thickness fraction; PaO₂, arterial oxygen partial pressure; PaCO₂, arterial carbon dioxide partial pressure.

Table 2 Effects of Pulmonary Rehabilitation (n = 58)

Variable	Baseline	After PR	P value
mMRC (0-1-2-3)	0/12/30/16	9/28/18/3	<0.001
6MWD, m	298.22±66.75	348.17±88.16	0.001
AHI (event/h)	21.53±9.82	14.26±10.95	<0.001
DE during deep breathing (cm)	4.67±1.32	5.28±1.26	0.013
DTF (%)	21.06±9.66	28.65±7.26	<0.001

Abbreviations: PR, Pulmonary Rehabilitation; mMRC, modified British Medical Research Council; 6MWD, 6-min walk distance; AHI, Apnea Hypopnea Index; DE, diaphragm excursion; DTF, diaphragm thickness fraction.

Associations Between Changes in 6MWD and Baseline Characteristics

The changes in 6MWD were significantly and positively associated with baseline values of DTF, diaphragm excursion during deep breathing, FEV₁, FEV₁/FVC, FEV₁%predicted, and PaO₂(all $P<0.001$). Additionally, they exhibited a negative correlation with baseline values of AHI and mMRC (all $P<0.05$) (Table 3, Figure 3).

ROC Curve Assesses the Predictive Ability of Independent Variables for 6MWD (> 30 m) Following PR

The ROC curve analysis demonstrated that the area under the curve (AUC) values for DE during deep breathing and DTF in predicting positive response individuals were 0.753 and 0.769, respectively, with a sensitivity of 91% and 85%, specificity of 56% and 68%, at the cut-off values of 3.61 cm and 17.26%. Similarly, the AUCs of FEV₁%predicted and PaO₂ for predicting responders were found to be 0.754 and 0.719, respectively, with a sensitivity of 79% for both variables, specificity of 64% and 60%, at the cutoff values of 47.5% and 60.5 mmHg (Figure 4) (Table 4).

Discussion

This study represents the initial demonstration of diaphragm excursion's utility in predicting the effectiveness of a 20-week pulmonary rehabilitation program for patients with COPD-OSA overlap syndrome. Among the participants, 33 patients (57%) were categorized as responders, while 25 patients (43%) were classified as non-responders. The changes in 6MWD exhibited a significant positive correlation with the baseline values of diaphragm excursion during deep breathing and DTF, while displaying a negative correlation with mMRC. Interestingly, no difference was observed in diaphragm excursion during calm breathing between responders and non-responders; however, it increased significantly during exercise. The ROC curve analysis revealed that the AUC of diaphragm excursion during deep breathing in

Table 3 Associations Between Changes in 6MWD and Baseline Characteristics

Independent Variable	Total Patients (n = 58)	
	Pearson Correlation Coefficient (r)	P value
FEV ₁ (L)	0.647	<0.001
FEV ₁ /FVC	0.453	<0.001
FEV ₁ %predicted	0.778	<0.001
PaO ₂ (mmHg)	0.452	<0.001
PaCO ₂ (mmHg)	0.117	0.381
AHI	-0.344	0.008
DE during calm breathing (cm)	0.072	0.592
DE during deep breathing (cm)	0.651	<0.001
DTF (%)	0.758	<0.001
mMRC	-0.255	0.05
6MWD	0.238	0.072
BMI	-0.049	0.717

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity; mMRC, modified British Medical Research Council; 6MWD, 6-min walk distance; AHI, Apnea Hypopnea Index; DE, diaphragm excursion; DTF, diaphragm thickness fraction; PaO₂, arterial oxygen partial pressure; PaCO₂, arterial carbon dioxide partial pressure.

predicting the responders was 0.753, with a sensitivity of 91% and a specificity of 56% at a cutoff value of 3.61cm. Additionally, the AUC of DTF in predicting the responders was 0.769, with a sensitivity of 85% and a specificity of 68% at a cutoff value of 17.26%.

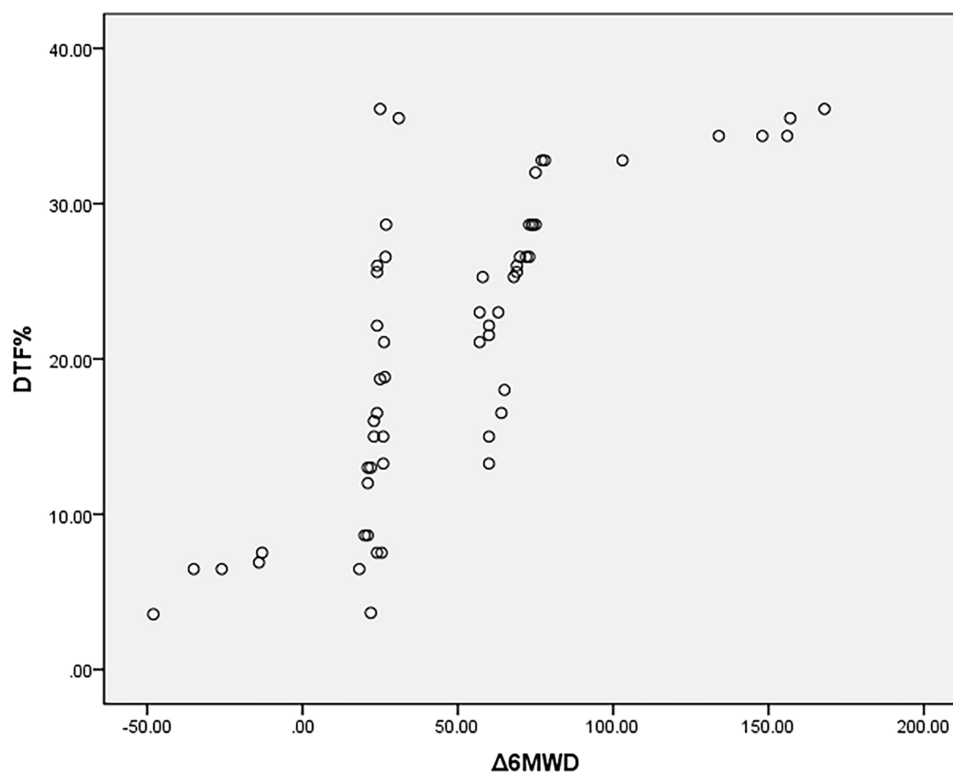


Figure 3 The relationship between DTF (%) and changes in 6MWD after pulmonary rehabilitation was examined. The results showed a significant positive correlation between changes in 6MWD and DTF% ($r = 0.758$; $P < 0.001$).

Abbreviations: DTF, diaphragm thickness fraction; 6MWD, 6-min walk distance.

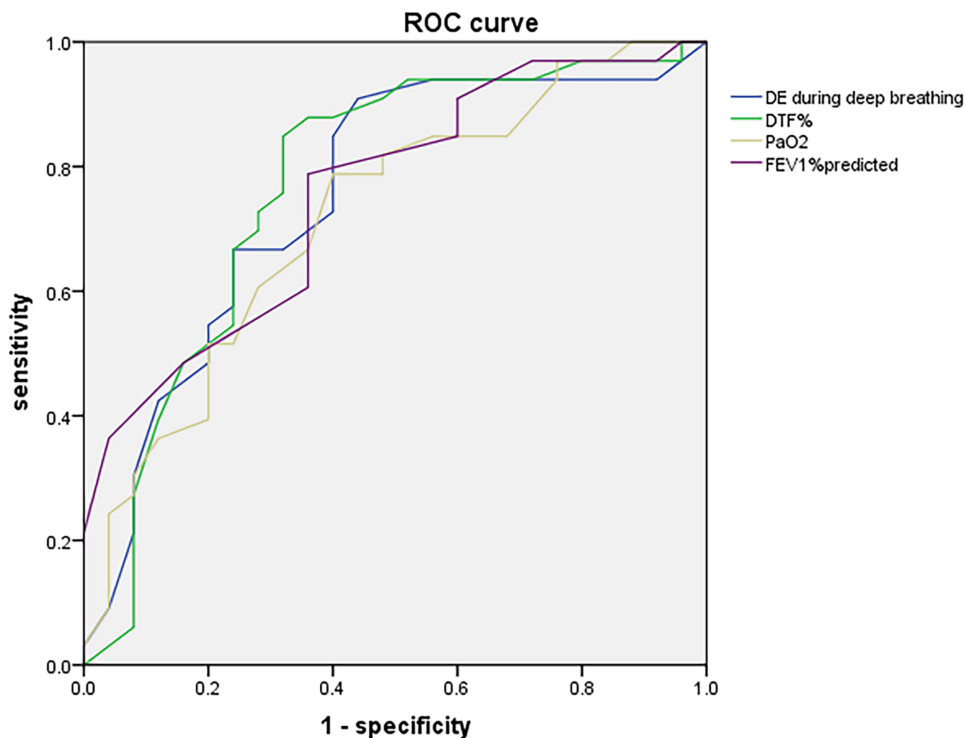


Figure 4 Receiver operating characteristic (ROC) curves were generated to assess the predictive ability of baseline DE during deep breathing, DTF (%), FEV₁%predicted, and PaO₂ for the response to pulmonary rehabilitation.

Abbreviation: DE, diaphragm excursion.

The efficacy of PR has been demonstrated in patients with chronic respiratory diseases, as supported by our previous research³² and confirmed in this study. However, the extent of benefit from PR varies among patients. While ideally PR would be effective for all patients,³³ it has been observed that the response to PR differs significantly between individuals^{34–37}. In this study, responders exhibited significantly higher baseline values of pulmonary ventilation function, 6MWD, diaphragm excursion during deep breathing, DTF, and PaO₂, while significantly lower mMRC scores compared to non-responders. However, there was no statistical difference in AHI and other indicators of OSA. Likewise, no significant differences were observed in BMI, GOLD classification, PAP, LTOT, and diaphragm excursion during calm breathing between the two groups, despite overall improvements noted in AHI, mMRC, 6MWD, diaphragm excursion during deep breathing, and DTF following PR.

Our study revealed an overall FEV₁%predicted value of 48.95±5.99 for the patient cohort, with responders demonstrating a significantly higher value (51.09±6.13) compared to non-responders (46.12±4.52). These results are in line with prior studies, indicating that individuals with elevated initial values of FEV₁ or FEV₁/FVC tend to have substantial enhancements in 6MWD following PR.^{14,38,39} Similarly, patients with milder mMRC scores also showed a better response to PR.³⁴ However, some studies have reported contradictory findings^{12,13,40–42} or failed to identify any

Table 4 ROC Curve Assesses the Predictive Ability of Independent Variables for 6MWD (>30 m) Following PR

Independent Variable	AUC (95% CI)	P value	Sensitivity	Specificity	Cut-off value
FEV ₁ %predicted	0.754 (0.630–0.878)	0.001	0.79	0.64	47.5
PaO ₂ (mmHg)	0.719 (0.586–0.853)	0.004	0.79	0.60	60.5
DTF (%)	0.769 (0.637–0.901)	<0.001	0.85	0.68	17.26
DE during deep breathing (cm)	0.753 (0.621–0.884)	0.001	0.91	0.56	3.61

Abbreviations: PR, Pulmonary Rehabilitation; FEV₁, forced expiratory volume in 1s; PaO₂, arterial oxygen partial pressure; DTF, diaphragm thickness fraction; DE, diaphragm excursion.

significant baseline characteristics for predicting PR response.⁴³ The identification of predictors of response is therefore essential for ensuring the effectiveness and individualization of PR programs for patients diagnosed with COPD-OSA overlap syndrome.

The diaphragm, as the primary skeletal muscle involved in respiration, plays a crucial role by contributing to approximately 75% of the maximal tidal volume.⁴⁴ The diaphragm may experience fatigue in patients with COPD-OSA overlap syndrome when they exert effort against upper airway obstruction, potentially impacting the occurrence of OSA. However, the effects of diaphragm function vary in different stages of the disorder.⁴⁵ Dyspnea and limited exercise capacity are observed due to the impact of chronic obstructive pulmonary disease (COPD) on ventilator workload and inspiratory muscle strength, resulting from dynamic lung hyperinflation caused by diaphragm dysfunction.⁴⁶ Although the pathophysiological mechanisms are complex, the exact contribution of the diaphragm to the pathophysiology of COPD-OSA overlap syndrome remains elusive, and its impact on rehabilitation is also unclear. Therefore, in this study, we employed ultrasound imaging, a relatively inexpensive and readily available technology, as a diagnostic tool to assess diaphragmatic dysfunction associated with COPD-OSA overlap syndrome, which is particularly important for evaluating the efficacy of PR.

A significant finding of this research is that DE during deep breathing and DTF at baseline were crucial predictors for identifying patients who responded positively to PR, specifically in terms of their 6MWD. The strong predictability of diaphragm movement may be attributed to its correlation with dynamic lung hyperinflation and exercise-induced breathlessness, as previously observed in patients with COPD.⁴⁷ In a study by Shiraishi et al,²⁰ DE max, reflecting the degree of dynamic lung hyperinflation and exercise-induced dyspnoea, was shown to be superior to other physiological indices. However, there have been limited studies on diaphragm function and morphology in patients with OSA. Pazarlı et al observed a positive correlation between the severity of OSAS and an augmented diaphragm thickness in patients with OSAS, while finding no significant difference in the thickness ratio compared to individuals without OSAS.⁴⁸ Diaphragmatic exhaustion resulting from the exertion of inhaling against a blocked airway has also been suggested,⁴⁹ in addition to diaphragm contractility and heightened pressure across the diaphragm.^{50,51} The development of dyspnea is predominantly influenced by dynamic lung hyperinflation, resulting in shortness of breath after activity, which is closely associated with the pathophysiology of COPD. Both dynamic pulmonary hyperinflation and dyspnea play role in determining the improvement of 6MWD in patients.

Moreover, the positive cycle observed in our PR program, which included moderate-intensity aerobic training, could potentially be attributed to enhanced respiratory patterns, even though certain patients utilized LTOT and PAP while exercising. The findings from studies on mechanically ventilated patients suggest that⁵² enhanced diaphragm function and morphology may facilitate the improvement of ventilation patterns. This could potentially result in decreased dyspnoea after a period of 12 weeks participating in PR, as well as an improvement in exercise capacity. Exercise therapy is a pivotal element of PR, exerting significant effects on the reduction of blood lactate levels, decrease in minute ventilation, and enhancement of exercise tolerance.⁵³ The moderate-intensity aerobic exercise, which is performed at 50–70% of the peak oxygen uptake, elicits a greater physiological response compared to low-load exercise. Individuals with enhanced diaphragm excursion may demonstrate improved tolerance towards high-load exercise, thereby leading to more efficient PR.

The strength of our study lies in the finding that baseline lung function and diaphragm characteristics are key determinants of rehabilitation responders among patients with COPD-OSA overlap syndrome. Specifically, DE during deep breathing $>3.61\text{cm}$ and $\text{DTF} > 17.26\%$ predicted a significant improvement in exercise ability after PR. However, the present study is subject to certain limitations. The study was conducted at a single research center and had a relatively limited sample size, potentially leading to the preservation of participants' baseline condition. Nevertheless, 50% of the patients had $\text{FEV}_1 < 50\%$, 43% were on LTOT, and 36% used PAP. Additionally, there is a lack of standardization in procedures pertaining to the selection of hemi-diaphragm, patient positioning, and breathing patterns, which poses challenges for the routine implementation of DE assessment. Standardizing these parameters would enhance the clinical and research utility of DE. Furthermore, we did not assess the impact of malnutrition factors or resistance training prescription, both of which are potentially significant determinants influencing diaphragmatic mobility. In future studies,

attention should be given to strengthening nutrition, combining aerobic and resistance training, and establishing standardized evaluation criteria for PR.

Conclusion

We conclude that diaphragm excursion is a reliable and easily measurable parameter that can demonstrate its effectiveness in predicting the enhancement of exercise tolerance following PR in individuals with COPD-OSA overlap syndrome. Assessing diaphragm excursion may be valuable in guiding medical decisions pertaining to therapeutic approaches.

Data Sharing Statement

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethical Statement

It has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki (Revised in 2013). The study received approval from the Ethics Committee of The Fourth Rehabilitation Hospital of Shanghai (SP202002), and written informed consent was obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations.

Author Contributions

All authors have made significant contributions to the reported work, encompassing conception, study design, execution, data acquisition, analysis and interpretation. They have also participated in drafting, revising, or critically reviewing the article. Furthermore, they have provided final approval for the publication of this version and agreed upon its submission to the journal. Additionally, they acknowledge their accountability for all aspects of the work.

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Disclosure

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