

Assessments and Targeted Rehabilitation Therapies for Diaphragmatic Dysfunction in Patients with Chronic Obstructive Pulmonary Disease: A Narrative Review

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Purpose: This review summarizes the characteristics, assessment methods, and targeted rehabilitation therapies of diaphragm dysfunction in patients with chronic obstructive pulmonary disease (COPD).

Methods: Extensive literature was searched in PubMed, the Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure Database, Wanfang, and SinoMed.

Results: Under the influence of oxidative stress, inflammation, and other factors, the diaphragm function of patients with COPD changes in mobility, muscle strength, thickness, and thickening. In patients with COPD, diaphragm mobility can be assessed using ultrasound, X-ray fluoroscopy, and magnetic resonance imaging. Diaphragmatic strength can be measured by transdiaphragmatic pressure and maximal inspiratory pressure. Diaphragmatic thickness and thickening can be assessed using ultrasound. Rehabilitation therapies targeting the diaphragm include diaphragmatic breathing, diaphragm-related manual therapy, and phrenic nerve electrical stimulation. Diaphragmatic breathing is safe, simple, and not limited by places. Diaphragmatic manual therapies, which require patient cooperation and one-on-one operation by a professional therapist, are effective. Phrenic nerve electrical stimulation is suitable for patients with severe conditions. These therapies improve the diaphragmatic function, lung function, dyspnea, and exercise capacity of patients with COPD.

Conclusion: The diaphragmatic function is commonly assessed in terms of mobility, strength, thickness, and thickening. Diaphragmatic targeted rehabilitation therapies have proven to be efficient, which are recommended to be included in the pulmonary rehabilitation strategy for patients with COPD.

Keywords: chronic obstructive pulmonary disease, diaphragmatic dysfunction, assessment, diaphragmatic breathing, manual therapy, phrenic nerve electrical stimulation

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable respiratory disease characterized by persistent respiratory symptoms and airflow limitation.¹ A 2018 epidemiological survey showed that 13.7% of Chinese adults aged 40 years and older have COPD.² This disease causes more than three million deaths worldwide each year, and it is one of the three leading causes of death.³ Direct medical costs account for 33.33–118.09% of annual per capita income.⁴ The diaphragm is the most important muscle for human respiratory movements and is responsible for approximately 60–80% of the ventilation workload during respiration.⁵ Given the increased respiratory load, oxidative stress, inflammation, and other factors, reduced and altered muscle fibers, diaphragmatic dysfunction occurs in COPD

patients.^{6–9} The dysfunction of the diaphragm in patients with COPD is inextricably linked to reduced pulmonary function, increased dyspnea, and reduced exercise tolerance.^{10,11} Therefore, the role of the diaphragm in respiratory diseases, especially in chronic respiratory diseases, has received increased attention and is considered an important target of interventions for COPD disease progression and improving the pulmonary function, dyspnea, and exercise capacity of patients.^{12,13}

In recent years, diaphragmatic dysfunction in COPD patients has gained increasing attention.^{9,14} The main clinical manifestations of diaphragmatic dysfunction include reduced mobility, decreased muscle strength, and changes in diaphragmatic thickness (Tdi) and thickening. Diaphragmatic mobility in patients with COPD can be assessed through ultrasound, X-ray fluoroscopy, and magnetic resonance imaging (MRI), whereas diaphragmatic muscle strength can be measured with transdiaphragmatic pressure (Pdi) and maximal inspiratory pressure (MIP). The thickness and thickening of the diaphragm can also be assessed by ultrasound. Diaphragm rehabilitation therapies refer to rehabilitation treatments in which the diaphragm is the treatment target, and they include diaphragmatic breathing Training, manual therapy, and phrenic nerve electrical stimulation. The enhancement of diaphragm function can lead to improvements in pulmonary function, subjective perception, and exercise capacity in COPD patients. A literature search revealed that diaphragmatic rehabilitation treatment modalities have not been reviewed. Therefore, we also explored different rehabilitation therapies in terms of operation, effects, and suggestions for COPD patients with diaphragm dysfunction in this narrative review.

Diaphragm Dysfunction in Patients with COPD

Decreased Diaphragm Mobility

Reduced diaphragmatic mobility is a typical manifestation of diaphragmatic dysfunction in patients with COPD. Diaphragm mobility is lower in patients with COPD than in healthy normal subjects.^{7,11,15–17} Diaphragmatic mobility correlates with pulmonary function, subjective perception, and exercise capacity in these patients. Fu et al¹¹ showed that diaphragm mobility in patients with COPD decreased with increasing severity, which was determined using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification. Moreover, diaphragmatic mobility is related to forced expiratory volume in one second /forced vital capacity (FEV1/FVC), the percentage of predicted values of FEV1 (FEV1%pred), and the percentage of inspiratory volume predicted. The percentage of maximal inspiratory capacity predicted is positively correlated, where diaphragm mobility is negatively correlated with residual air volume/total lung volume as a percentage of the predicted value. Zhang et al¹⁷ observed that the motion of the diaphragm in patients with COPD is positively correlated with FEV1 and total lung volume. Similar findings were found in the study by Hellebradova et al.¹⁴ These results suggested that diaphragm mobility is positively correlated with pulmonary function. A negative correlation was found between diaphragm mobility and modified Medical Research Council Dyspnea Scale (mMRC) scores.¹⁷ Diaphragm mobility decreases with the increased degree of dyspnea in patients with COPD.^{15,17–19} Diaphragmatic mobility is positively correlated with the 6-minute Walking Distance (6MWD).^{19,20} In conclusion, diaphragm mobility is closely related to pulmonary function, subjective perception, and exercise capacity in patients with COPD and decreases with disease progression.

Decreased Diaphragm Muscle Strength

Decreased diaphragmatic muscle strength is also a major manifestation of diaphragmatic dysfunction in patients with COPD. Zheng et al²¹ reported that MIP, maximum Pdi, and maximum sniff Pdi were significantly lower in the severe COPD group than in the normal control group, and twitching Pdi was significantly lower in the mild and severe COPD groups than in the normal control group. Polkey et al²² proposed the reduced ability of the diaphragm to produce twitch Pdi in patients with severe COPD. The MIP of patients with COPD was lower than that of control groups and significantly reduced from the moderate to the severe stage of the disease.^{23–25} This result showed that patients with different degrees of COPD severity have impaired diaphragmatic strength. In the study of Zheng et al,²¹ the decrease in twitch Pdi in the COPD group was positively correlated with FEV1. Yu et al²⁶ observed that the maximum Pdi was significantly negatively correlated with the partial pressure of arterial carbon dioxide and significantly positively correlated with vital capacity, deep inspiratory volume, FVC, and maximum inspiratory volume. These results showed

that the severity of impairment in a patient's pulmonary function, especially ventilation, increases with the decline in diaphragmatic strength.

Changes in Tdi and Thickening

Changes in Tdi and thickening in COPD patients are also signs of diaphragm dysfunction. Baria et al²⁷ showed no significant difference in Tdi between COPD patients and normal subjects except for the severe air residual subgroup. Zhang et al²⁸ reported a significant decrease in Tdi in COPD patients compared with the controls. However, the Tdi significantly increased in the mild COPD group compared with the control group. Smargiassi and Zhang et al^{28,29} suggested that Tdi changes are closely related to air trapping.

Similar findings were found in the changes in diaphragmatic thickening fraction (TF). Rittayamai et al³⁰ reported significantly higher diaphragm tidal thickening fraction during resting breathing in patients with COPD than in controls; the severe COPD was approximately twice as high as in controls. During the Muller maneuver, the maximal TF exhibited a significantly positive correlation with post-bronchodilator FEV1 and MIP and a negative correlation with total lung capacity, residual volume, and residual volume/total lung capacity. Zhang et al²⁸ also observed similar changes in TF. However, apart from airway obstruction, Eryuksel et al³¹ reported no association between TF and exacerbation frequency, the COPD Assessment Test and mMRC scores, or GOLD ABCD risk/symptom assessments. Tdi and thickening were strongly associated with air trapping in COPD patients, but correlations with other clinical symptoms could not be determined.

The changes in Tdi and thickening may be due to the fragile balance between adaptive and deleterious biological mechanisms in the diaphragm in stable COPD. Adaptive changes predominate in the early stages. As the disease progresses, deterioration, nutritional abnormalities, and aging dominate. This condition can cause the balance to tip toward a negative phenotype.^{8,9,32} Therefore, the changes in thickness and thickening are more pronounced in patients with severe COPD.

The Pathophysiology of the Diaphragm in COPD

Due to the hyperinflated state of a patient's lungs, which results from the chronic airflow limitation and thereby depresses the diaphragm and reduces its ability to generate tension.⁸ On the other hand, elastic load (eg, caused by changes in the chest wall and lung parenchyma), resistance (eg, caused by airway stenosis), and threshold (eg, caused by intrinsic positive end-expiratory pressure) increases in patients, resulting in an overload of the diaphragm contraction preload and increased work of breathing.^{7,9} The increase load induces the diaphragm to produce fatigue-resistant changes and increase in the proportion of type I fibers.⁷ In patients with mild to moderate COPD, Doucet et al⁶ observed that the diaphragms of patients with COPD had higher proportions of type I fibers and showed a relative decrease in type IIA fibers. Testelmans et al³³ attained similar findings in the diaphragms of patients with severe COPD. Zhang et al³⁴ reported a similar observation in a rat model. If change in muscle strength is considered only in terms of diaphragm muscle fibers, type I fibers produce less isometric contraction than type II fibers.³⁵ Thus, change in fatigue resistance occurs at the cost of a decrease in diaphragmatic strength.

Oxidative stress, inflammation, and other factors contribute to the development of diaphragmatic dysfunction in COPD patients. Barreiro et al³⁶ found that the mRNA and protein levels of TNF- α and IL-6 in the diaphragm of patients with severe COPD and normal weight were significantly higher than those of healthy people. Increased production of oxidants in the mitochondrial and membrane compartments of diaphragm fibers has been reported in severe COPD.^{37,38} Different scholars reported alterations in signaling pathways closely associated with diaphragm fiber atrophy, particularly the upregulation of nuclear factor- κ B pathway, ubiquitin-proteasome pathway, and muscle growth inhibitor and downregulation of myocyte assay protein 1.^{6,9,13,39} These changes are closely associated with diaphragm dysfunction in COPD patients. The diaphragm atrophies, the cross-sectional area is reduced. Several authors observed a reduction in the cross-sectional areas of diaphragm type I and II muscle fibers in patients with moderate and severe COPD.^{6,33} Zhang et al³⁴ discovered a reduction in diaphragm type I and II fiber diameters in a rat model of COPD.

Assessments for Diaphragmatic Function of COPD

Assessments of Diaphragmatic Mobility

Diaphragmatic mobility assessment in patients with COPD can be performed with noninvasive methods, such as ultrasound, X-ray fluoroscopy, and MRI. Ultrasound is easy to operate, inexpensive, safe, and harmless.⁴⁰ It is now a widely used clinical modality for diaphragm mobility assessment. Boussuges et al⁴¹ suggested that in ultrasound examination of diaphragmatic mobility, the lower limit is close to 0.9 cm for women and 1 cm for men during quiet breathing and close to 3.7 cm for women and 4.7 cm for men during deep breathing. Ultrasound examination can be performed at the bedside and is therefore preferred for bedridden patients. However, examination results are susceptible to factors, such as the subject's level of exertion and operator experience.⁴¹ X-ray fluoroscopy has the advantage of facilitating the observation of diaphragm movement in real time, but the images lack clarity, and the subjects are at risk of radiation exposure, which can be used as an initial assessment.^{42,43} MRI evaluation allows the acquisition of images of the entire coronal and sagittal planes of the diaphragm and facilitates the unilateral, local, or complete observation of abnormal diaphragm movements.^{43,44} This method is an effective tool for assessing diaphragm mobility because of its clear imaging and objective accuracy. However, MRI examinations are time consuming, expensive, and need to be selected with caution. Currently, a standardized method or standard parameters for assessing diaphragm mobility in patients with COPD are unavailable, and current methods and values are limited by age, gender, body mass index, and other factors. Most studies have judged changes in diaphragm mobility based on changes in values before and after treatment or comparison with data from control groups.

Assessments of Diaphragmatic Strength

Diaphragm strength can be assessed by Pdi and MIP. Pdi represents the pressure difference between the lower esophagus and stomach, and the pressure measured in the lower esophagus and stomach represents pressure in the thoracic cavity and abdominal cavity, respectively. The pressure is often measured by passing balloon catheters through the nose, following local anesthesia of the nasal mucosa and pharynx.⁴⁵ The patient consciously controls breathing movement, and pressure in the chest and abdominal cavity changes. An operator evaluates the strength of the diaphragm muscle with the measured pressure difference.⁴⁵ Pdi includes maximal, maximal sniff, and twitch Pdi. The maximal and maximal sniff Pdi can be measured with Muller maneuvers and maximal nasal inspiratory maneuvers, respectively. Twitch Pdi can be measured during the transcutaneous electrical (magnetic) stimulation of the phrenic nerve.⁴⁵ Maximal sniff and maximal Pdi greater than 80 cmH₂O for men and 70 cmH₂O for women can rule out clinically evident diaphragm weakness.⁴⁶ A twitch Pdi greater than 10 cmH₂O during unilateral phrenic nerve stimulation or greater than 20 cmH₂O during bilateral phrenic nerve stimulation can rule out notable diaphragmatic weakness.⁴⁶ Twitch Pdi is unaffected by subjective factors and can sensitively and objectively reflect the functional state of the diaphragm. Its repeatability is better than that of maximal and maximal sniff Pdi.²¹ Although the Pdi test can directly detect changes in diaphragmatic muscle strength, its operation is invasive. The process requires placing a balloon catheter into a patient's esophagus and stomach, and thus, its use in clinical practice is limited.⁴⁶

MIP is the oral pressure generated by the subject inhaling with maximal effort in the functional residual air position.^{43,45} MIP greater than 80 cmH₂O can exclude diaphragmatic weakness.⁴² The MIP measures the muscle force of the entire respiratory muscle group and not the diaphragm alone. Therefore, MIP can be used as a reference indicator to determine diaphragm dysfunction but not the primary indicator. MIP testing is convenient and noninvasive but is susceptible to factors, such as subjective exertion, age, and lung volume.⁴²

Assessments of Tdi and Thickening

Recognized Tdi and thickening measurements are performed by ultrasound: end-expiratory Tdi is the static measurement; the dynamic evaluation of the ratio of inspiratory to expiratory Tdi is reported as the thickening ratio (TR; inspiratory thickness/expiratory thickness) or thickening fraction (TF; (inspiratory thickness–expiratory thickness)/end-expiratory thickness).⁴⁷ In normal individuals at rest, Tdi at functional residual capacity varies widely, ranging from 1.2 mm to 11.8 mm, with group means ranging from 1.6 mm to 3.4 mm. The lower limit of normal adults is 0.80 mm to 1.60 mm.⁴⁸

A minimum of 20% increase in TF is normal.⁴⁹ Tdi and thickening thresholds for the identification of diaphragm dysfunction in COPD patients are unavailable.

Targeted Rehabilitation Therapies of COPD Diaphragm

Currently, pulmonary rehabilitation is a beneficial measure to improve the pulmonary function, subjective perception, and exercise capacity of patients with COPD. Diaphragmatic rehabilitation is a category of comprehensive pulmonary rehabilitation. Common diaphragmatic rehabilitation modalities include diaphragmatic breathing training, manual therapy, and phrenic nerve electrical stimulation. In this section, we review these diaphragm-focused rehabilitation modalities.

Screening Studies

We screened studies using a methodology similar to that of a systematic review.⁵⁰ To be closer to the current state of research, we included a wide variety of clinical studies.

Inclusion Criteria

1) Type of studies: clinical trials; 2) Participants: patients with stable COPD; 3) Intervention methods: experimental groups of randomized controlled trials, grouping trials, and self-controlled trials that received breathing training, manual therapy, or phrenic nerve electrical stimulation and control groups of randomized controlled trials that received drug treatment, sham treatment, and nursing; 4) Outcomes: A. Diaphragm function: diaphragmatic mobility, Pdi, MIP, Tdi, and TF; B. Lung Function: FEV1, FEV1%pred, FVC, FEV1/ FVC, maximal mid-expiratory flow (MMEF), and maximal voluntary ventilation (MVV); C. Degree of dyspnea: mMRC; D. Functional exercise capacity: 6MWD.

Exclusion Criteria

1) duplicated data; 2) not clinical trials; 3) inconsistent with our intervention measures or interventions are combined with other rehabilitation measures.

Data Collection

Six databases (PubMed, the Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure Database, Wanfang, and SinoMed) were used as data resources to retrieve clinical trials from 2011 to 2021. The search was conducted with the following keywords in Chinese or English: (Pulmonary Disease, Chronic Obstructive OR Chronic Obstructive Lung Disease OR Chronic Obstructive Pulmonary Disease OR COAD OR COPD OR Chronic Obstructive Airway Disease OR Airflow Obstruction, Chronic OR Chronic Airflow Obstruction) AND (diaphragmatic breathing OR diaphragmatic respiration OR abdominal breathing OR abdominal respiration OR diaphragmatic releasing technique OR diaphragmatic stretching technique OR external diaphragmatic pacing).

Study Selection

Two reviewers independently screened the studies in accordance with the inclusion and exclusion criteria. They used Endnote software to find and delete duplicate studies. They browsed the title and abstract to exclude irrelevant research, re-screened by reading the full text of the remaining studies, and then excluded studies that did not meet the inclusion criteria. When the two reviewers were inconsistent, a third party intervened to discuss and reach a consensus. [Figure 1](#) outlines the screening process for studies. The results of the study screening are shown in [Tables 1–3](#).

Diaphragmatic Breathing Training

Respiratory muscle training has been extensively studied because of its recognized effects.^{51–53} Xia et al⁵⁴ reported that respiratory muscle training improves diaphragmatic dysfunction in patients with COPD. Respiratory muscle training methods, such as resistance loading method, pressure threshold loading method, and carbon dioxide hyperventilation method, have been used to delay the weakening of diaphragmatic contractile function, improve pulmonary function, and enhance quality of life. In this part of the review, we choose to study the rehabilitative method of diaphragmatic breathing with the diaphragm as the focus.

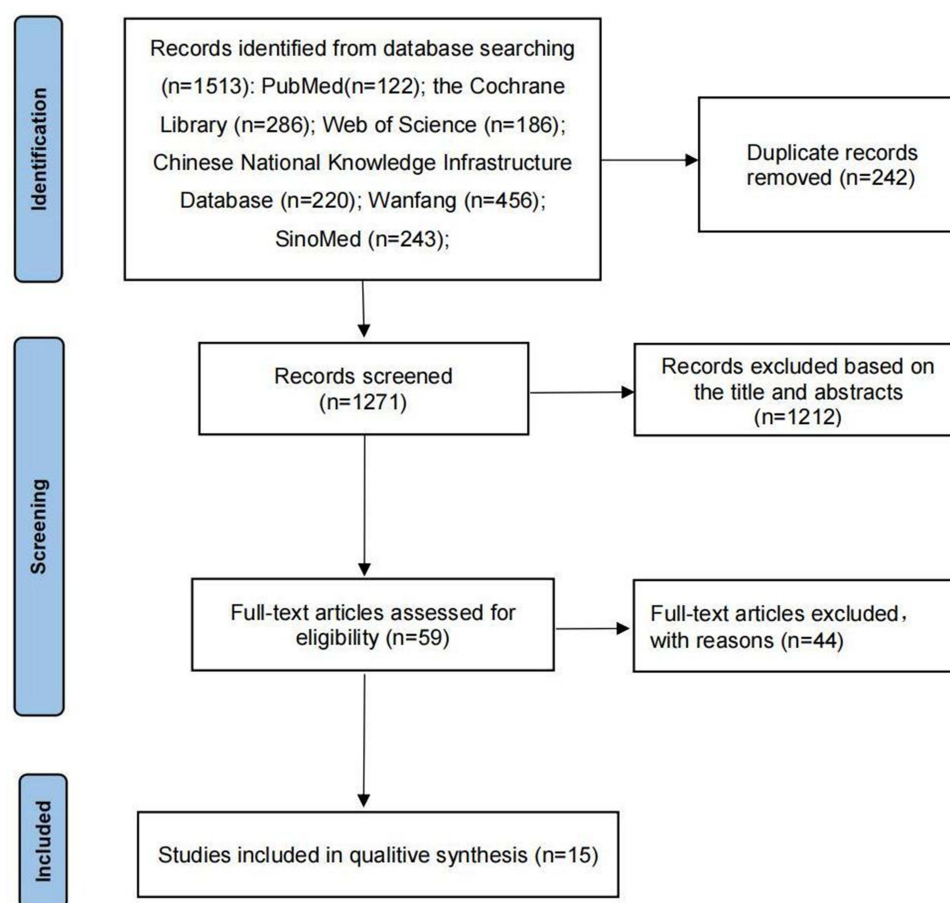


Figure 1 Systematic search flowchart.

During diaphragmatic breathing, a patient reduces the use of auxiliary respiratory muscles and completes respiratory movements with the activity of the diaphragm; thoracic activity is minimized, and abdominal movements during breathing is increased (Figure 2).⁵⁵ The aim is to improve dyspnea, correct the patient's abnormal breathing pattern, increase the magnitude of diaphragmatic up and down movements, reduce the activation of auxiliary muscles, increase tidal volume, reduce functional residual capacity, and improve lung ventilation.^{56–58}

Clinical Application of Diaphragmatic Breathing Training

Diaphragm breathing can improve diaphragmatic dysfunction, dyspnea, lung ventilation and exercise capacity of patients with COPD (Table 1). Yamaguti et al⁵⁹ reported that after diaphragmatic breathing intervention, the diaphragmatic mobility of the diaphragmatic breathing group was higher than the baseline; in comparison between the groups, the diaphragmatic breathing group was better than the control group. This result directly proves that diaphragmatic breathing can improve diaphragmatic dysfunction. Two studies reported improvements in dyspnea.^{59,60} Ma et al⁶⁰ reported that the mMRC score of patients with moderate COPD is better than baseline. Yamaguti et al⁵⁹ reported that the mMRC score of the diaphragmatic breathing group is lower than that of the control group. This finding shows that diaphragmatic breathing can alleviate the dyspnea of patients with COPD. Three studies used FVC, FEV1, and FEV1/FVC as indicators related to pulmonary ventilation function.^{60–62} Zhan et al⁶² found that the FVC of the diaphragmatic breathing group is better than that of the control group. Ma and Liu et al^{60,61} reported that the FVC, FEV1, and FEV1/FVC of the diaphragmatic breathing group are better than those at baseline. This finding shows that diaphragmatic breathing can improve the lung ventilation function of patients with COPD. Two studies mentioned the improvement of exercise performance.^{59,62} Ma et al⁶⁰ observed that the 6MWD in the diaphragmatic breathing group is longer than that before the

Table 1 Studies of Diaphragmatic Breathing

Study	Experimental Type	Group	Participants	Intervention	Frequency and Duration	Indicators
Yamaguti et al ⁵⁹ 2012	Randomized control trial	Experimental group/control group	15/15	Diaphragmatic breathing+ nursing care/ nursing care	3 times/week 4 weeks	Diaphragmatic mobility↑* mMRC↓* 6MWD↑*
Ma et al ⁶⁰ 2014	Grouping trial	Mild group/moderate group	25/35	Diaphragmatic breathing	2 times/day 1 year	Mild group: 6MWD↑* Moderate group: FEV1↑* FEV1/FVC↑* FVC↑* mMRC↓* 6MWD↑*
Liu et al ⁶¹ 2011	Randomized control trial	Experimental group/control group	21/21	Diaphragmatic breathing+ medication/medication	4 times/day 30 days	FEV1/FVC↑* FVC↑*
Zhan et al ⁶² 2020	Randomized control trial	Experimental group/control group	34/34	Diaphragmatic breathing+ nursing care/nursing care	2 or 3 times/day 1 year	FVC↑*

Notes: *Statistical difference between experimental and control groups ($P<0.05$); [‡]statistical difference between experimental groups before and after the experiment ($P<0.05$); ↑, increase; ↓, decrease.

Abbreviations: 6MWD, 6 minutes walking distance; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; mMRC, modified Medical Research Council Dyspnea Scale.

Table 2 Studies of Manual Therapy

Study	Experimental Type	Group	Participants	Intervention	Frequency and Duration	Indicators
Rocha et al ⁷² 2015	Randomized control trial	Experimental group/control group	9/10	Diaphragm release technique/fake treatment	6 times 2 weeks	Diaphragmatic mobility↑* Inspiratory volume↑* 6MWD↑*
Nair et al ⁷⁴ 2019	Randomized crossover trial	Experimental group/control group	10/10	Diaphragm stretching technique / diaphragm release technique	1 time	Diaphragmatic mobility↑* ^{##}

Notes: *Statistical difference between experimental and control groups ($P<0.05$); [‡]statistical difference between experimental groups before and after the experiment ($P<0.05$); [#] statistical difference between control groups before and after the experiment ($P<0.05$); ↑, increase.

Abbreviation: 6MWD, 6-minute walking distance.

intervention. In the experiment of Yamaguti et al,⁵⁹ the 6MWD in the diaphragmatic breathing group is longer than that in the control group.

Ma et al⁶⁰ only observed 6MWD improvement in patients with mild COPD after diaphragmatic breathing intervention. After intervention, patients with moderate COPD showed improvements in lung ventilation function, mMRC, and 6MWD. This result may be ascribed to the fact that the function of mild patients is less impaired and that diaphragmatic breathing is a relatively gentle training method and thus exerts insufficient training effects on patients with mild COPD.

Table 3 Studies of Phrenic Nerve Electrical Stimulation

Study	Experimental Type	Group	Participants	Intervention	Frequency and Duration	Indicators
Cao et al ⁸² 2020	Randomized control trial	Experimental group/control group	30/30	External diaphragm pacing + routine treatment / Routine treatment	1 time/day 20 days	Diaphragmatic mobility↑* MIP↑* FEV1%pred↑*
Wang JC et al ⁸³ 2019	Randomized control trial	Experimental group/control group	40/40	External diaphragm pacing + oxygen therapy+ medication/oxygen therapy + medication	2 times/day 14 days	Diaphragmatic mobility↑* ^{&#} FEV1↑ ^{&#} FEV1/FVC↑ ^{&#} FVC↑ ^{&#}
Feng et al ⁸⁴ 2019	Randomized control trial	Experimental group/control group	31/32	External diaphragm pacing + routine treatment / routine treatment	2 times/day 2 weeks	Diaphragmatic mobility↑* FEV1↑* FEV1/FVC↑*
Chang et al ⁸⁵ 2017	Randomized control trial	Experimental group/control group	33/32	External diaphragm pacing + routine treatment / routine treatment	1 time/day 14 days + 5 times/ week 3 months	MIP↑* 6MWD↑*
Wang GT et al ⁸⁶ 2019	Randomized control trial	Experimental group/control group	30/30	External diaphragm pacing + routine treatment / routine treatment	2 times/day 14 days	FEV1↑ ^{*^{&#}} FEV1/FVC↑ ^{*^{&#}} MVV↑ ^{*^{&#}}
Li et al ⁸⁷ 2019	Randomized control trial	Experimental group/control group	49/49	External diaphragm pacing + routine treatment / routine treatment	1 time/day 20 days	FEV1%pred↑ ^{*^{&#}} FEV1/FVC↑ ^{*^{&#}}
Zeng et al ⁸⁸ 2019	Self-control trial	Moderate group/severe group/very severe group; group B/group C/group D	32	External diaphragm pacing	2 times/day 20 days	6MWD↑ ^{&} FEV1: severe group↑ ^{&} very severe group↑ ^{&} group C↑ ^{&} group D↑ ^{&} mMRC: severe group↓ ^{&} very severe group↓ ^{&} group D↓ ^{&}
You et al ⁸⁹ 2018	Randomized control trial	Experimental group/control group	30/30	External diaphragm pacing + routine treatment / routine treatment	1 time/day 15 days	FEV1↑ ^{*^{&#}} FVC↑ ^{*^{&#}} 6MWD↑ ^{*^{&#}}
Cao et al ⁹⁰ 2018	Grouping trial	Experimental group/control group	30/30	External diaphragm pacing (2.5Hz+40 Hz)/external diaphragm pacing (40 Hz)	1 time/day 20 days	FEV1%pred↑ ^{*^{&#}} FEV1/FVC↑ ^{*^{&#}} FVC↑ ^{&#} MMEF↑ ^{&#} 6MWD↑ ^{*^{&#}}

Notes: *Statistical difference between experimental and control groups ($P<0.05$); [&]statistical difference between experimental groups before and after the experiment ($P<0.05$); [#]statistical difference between control groups before and after the experiment ($P<0.05$); ↑, increase; ↓, decrease.

Abbreviations: 6MWD, 6-minute walking distance; FEV1, forced expiratory volume in one second; FEV1%pred, the percentage of predicted values of FEV1; FVC, forced vital capacity; MIP, maximal inspiratory pressure; MMEF, maximal mid-expiratory flow; mMRC, modified Medical Research Council Dyspnea Scale; MVV, maximal voluntary ventilation.

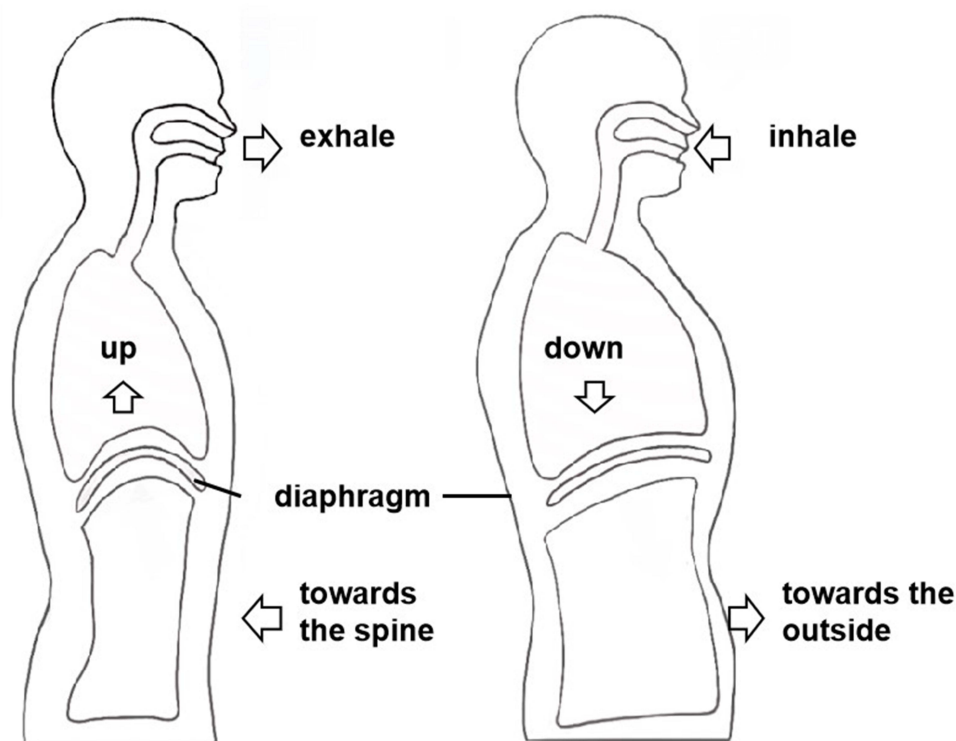


Figure 2 Diaphragmatic breathing.

Notes: When the patient inhales, the abdominal wall moves outward and the diaphragm descends; when the patient exhales, the abdominal wall relaxes and the diaphragm rises.

Suggestions for the Application of Diaphragmatic Breathing Training

Diaphragmatic breathing was previously reported to be harmful to people with severe respiratory diseases, exacerbating breathing difficulties and disrupting respiratory function.^{63,64} Gosselink et al⁶⁵ reported that the mechanical efficiency of breathing is significantly reduced in patients with severe COPD after diaphragmatic breathing intervention; no obvious changes in tidal volume and respiratory rate occur during breathing, and the feeling of dyspnea increases. Vitacca et al⁶⁶ showed that tidal volume, dyspnea, and inspiratory muscle force increase and respiratory rate decreases. The difference in the results of the above ventilatory function may be related to the manner that the technology was used or to the severity of a patient's illness. In recent studies, most patients involved in diaphragm breathing training are grades II and III, and exacerbated dyspnea has not been reported. This method should be used with caution for patients with grade IV COPD.

Diaphragmatic rehabilitation using diaphragmatic breathing can effectively improve diaphragmatic dysfunction, dyspnea, lung ventilation, and exercise capacity with stable COPD. It is suitable for patients with mild to moderate stable COPD. The advantages of diaphragmatic breathing are as follows. First, it is simple and easy to implement, requiring little in the way of implementation sites, and can be performed in hospital and home environments. Second, it is relatively safe, can be performed independently by conscious patients after professional guidance, and can be used as a home rehabilitation training measure. Third, it is inexpensive, requires only the participation of therapists and patients, and does not require expensive equipment. Fourth, it is flexible and can be combined with other rehabilitation methods according to clinical needs. However, single diaphragmatic breathing training is repeatedly monotonous and boring, which does not stimulate patients' interest and affects their motivation and compliance. If more effective training benefits are desired, diaphragmatic breathing should be combined with other types of methods, such as threshold inspiratory muscle trainer and aerobic exercise.^{67–71}

Manual Therapy

Manual therapy is a common method used by rehabilitation therapists. It is widely used in the treatment of musculoskeletal dysfunction and internal diseases. Commonly used diaphragm manual treatments for patients with COPD include diaphragm release technique and diaphragm stretching technique.^{72,73} Both techniques achieve the distraction or release of the anterior part of the diaphragm during respiration by expanding the diameter of the anterolateral lower edge of the thorax. The aim is to increase thoracic mobility, enhance oxygen transport and lymphatic return, and improve respiratory efficiency while promoting autonomic regulation, vasodilation, and smooth muscle relaxation, thus improving diaphragmatic mobility.⁷⁴

Diaphragm release requirements are shown in Figure 3. The subject is asked to lie supine with all four limbs relaxed. The therapist stands on the cephalad side of the patient and uses the hypothenar and three fingers on the ulnar side to reach the inferior aspect of the seventh cartilage to the tenth rib cartilage. The therapist's forearms are aligned with the subject's shoulders. During the inhalation phase, as the rib cage is raised, the therapist gently pulls the point of contact of the hands toward the head and slightly outward. On exhalation, the therapist's hands are deepened toward the inner edge of the rib cage, maintaining resistance. In subsequent breathing cycles, the therapist gradually deepens the contact of the hands toward the inner edge of the rib cage.⁷²

Diaphragm stretching requirements are displayed in Figure 4. The subject receives intervention in a seated position. The therapist stands behind the patient with his or her hands around the thorax and introduces his fingers at the lower edge of the rib cage. The subject's trunk is slightly flexed to relax the rectus abdominis muscle. As the subject exhales, the therapist pulls on the lower edge of the lower rib cage with his or her hands. As the patient inhales, traction is maintained to keep the diaphragm in tension. The tension lasts for 5–7 min.⁷⁵

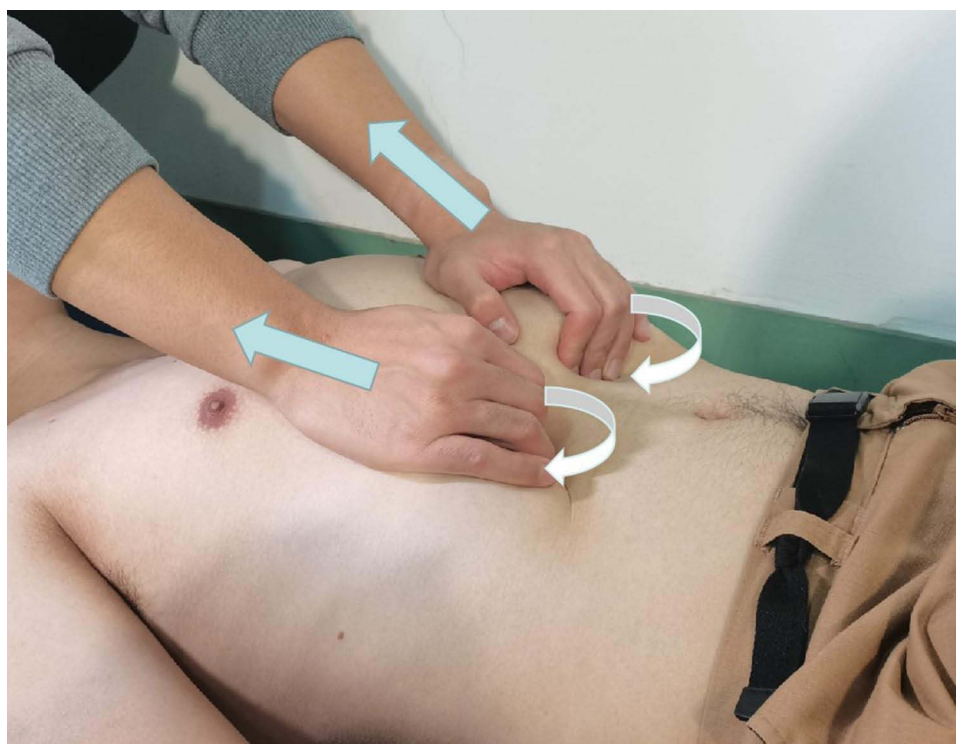


Figure 3 Diaphragm release technique.

Notes: The subject was lying supine. The therapist stands on the cephalic side of the patient and reaches the inferior aspect of the seventh cartilage to the tenth rib cartilage with the ulnar side of the hypothenar and three fingers. The therapist's forearm is aligned with the subject's shoulder. During the inhalation phase, the therapist gently lifts up the chest, pulling the point of contact of the hands toward the head and slightly outward. On exhalation, the therapist's hands are deepened toward the inner edge of the thorax, maintaining resistance. During subsequent breathing cycles, the therapist gradually deepens the contact of the hands toward the inner edge of the chest cavity. ➡ The direction of the therapist's hand force when the subject inhales; ↻ the direction of the therapist's hand force when the subject exhales.

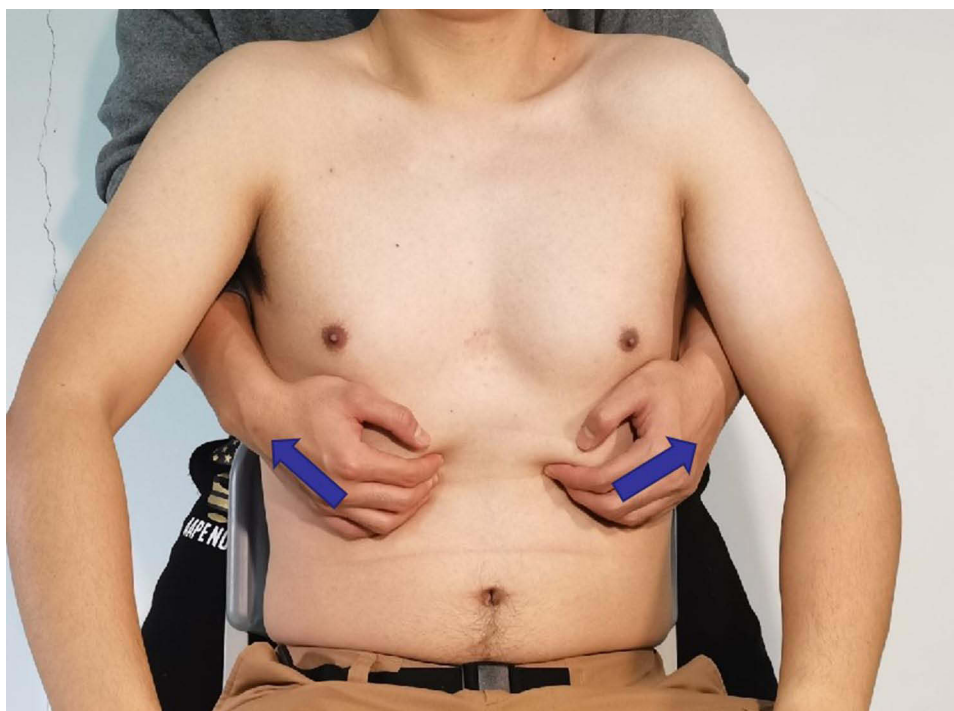


Figure 4 Diaphragm stretching technique.

Notes: The subject sits with the trunk slightly flexed. The therapist stands behind the patient with his or her hands around the chest and places his or her fingers at the lower edge of the rib cage. As the subject exhales, the therapist pulls on the lower edge of the rib cage with his or her hands. As the patient inhales, the traction is maintained to keep the diaphragm under tension. ➡ Direction of force of the therapist's hand as the subject breathes.

Clinical Application of Manual Therapy

The diaphragmatic release technique improves diaphragmatic mobility, pulmonary function, and exercise capacity in patients with stable COPD (Table 2). Rocha et al⁷² found that after clinically stable COPD patients received six discontinuous diaphragmatic muscle release treatments within 2 weeks, the diaphragm mobility and 6MWD increased relative to that of the control group, and the inspiratory volume of the experimental group increased to 330 mL. Susmitha et al⁷⁶ reported that diaphragmatic release technique and conventional diaphragmatic strengthening training (resistance applied at the rib cage during inspiration) significantly improve diaphragmatic mobility and exercise capacity in the patients, but the former technique shows superior results to the latter. Diaphragmatic stretching techniques improve diaphragmatic mobility in patients with COPD. Nair et al⁷⁴ found an immediate improvement in diaphragm mobility in patients with mild to moderate COPD after intervention with diaphragm stretching techniques, with no significant difference with diaphragm release techniques.

Suggestions for the Application of Manual Therapy

Diaphragmatic release technique and diaphragmatic stretching technique show no significant difference in improving diaphragmatic mobility in a short time. Apart from diaphragmatic mobility, diaphragmatic release techniques can also improve inspiratory capacity and exercise capacity in patients with COPD. Diaphragmatic release techniques are beneficial not only for patients with COPD but also for those with other diseases involving diaphragmatic dysfunction. Li et al⁷⁷ found that combining the diaphragm release technique with inspiratory muscle training can significantly improve pulmonary ventilation and inspiratory muscle function in stroke patients. The diaphragm release technique is an effective rehabilitation treatment that improves diaphragm dysfunction, and its use for treating diseases with respiratory muscle involvement, especially diaphragm involvement, is worth promoting.

In addition to the effect on diaphragmatic mobility, diaphragmatic stretching provides immediate improvement in pulmonary function and joint mobility in healthy adults. Gonzalez et al^{73,75} found that diaphragm stretching improves pulmonary function in healthy adults in a short period. The maximal respiratory pressure, FVC, and FEV1 significantly

improve after 5 and 20 min of stretching treatment. Diaphragm stretching improves cervical mobility, posterior chain muscle group flexibility, and thoracic mobility at the xiphoid level in healthy adults compared with those in the controls. The investigators concluded that diaphragm stretching not only improves the function of the diaphragm itself but also causes the contraction of the muscle chain. These effects lead to changes in the range of motion of the other distal structures, thereby improving posterior chain muscle group flexibility and spinal flexibility. Patients with COPD develop a “barrel chest” deformity with a stiff chest wall and reduced flexibility.⁷⁸ However, no study focused on the changes in the posterior chain muscle groups after diaphragmatic stretching techniques in patients with COPD. The study of Gonzalez et al is a great foundation for an in-depth discussion of the influence of diaphragm stretching technique on the musculoskeletal function of patients with COPD.

Diaphragmatic manual therapy is indicated for patients with limited mobility but clear cognition. It requires a trained respiratory therapist to instruct a patient one-on-one, and the patient must cooperate with the therapist's instructions. Other techniques that can be used for patients with COPD include soft tissue therapy and spinal manipulation. A systematic review on manual therapy in patients with COPD reported that manual therapy exerts no effect on the pulmonary function of patients with COPD, which contradicts the results of several diaphragmatic manual therapy trials mentioned above.⁷⁹ Four of the six studies in the systematic review reported joint-like techniques or soft tissue therapies and showed negative pulmonary function results, except the diaphragmatic release technique studied by Rocha et al.⁷² One study showed positive results for respiratory muscle distraction techniques. Inconsistent evaluation may be due to the high heterogeneity of inclusion criteria, types of manipulation, and outcome indicators. Large samples of randomized controlled trials are needed to assess the clinical significance of different manipulative treatments in patients with COPD. Manual therapy can be considered an adjunctive treatment modality to a comprehensive pulmonary rehabilitation program.

Phrenic Nerve Electrical Stimulation

Diaphragm electrical stimulation methods include internal diaphragm pacing and external diaphragm pacing. Internal diaphragmatic pacing has potential risks, such as damage to the phrenic nerve and chemical stimulation. Xie et al⁸⁰ designed and developed an external diaphragm pacing technique based on internal diaphragmatic pacing (Figure 5). This technique is easy to operate and noninvasive.

Clinical Application of Phrenic Nerve Electrical Stimulation

We included nine studies of external diaphragm pacing in patients with COPD (Table 3). Four studies demonstrated that external diaphragm pacing improves diaphragmatic dysfunction in patients with COPD.^{82–85} Wang et al⁸³ reported that diaphragm mobility is higher than baseline after intervention. Three studies found that after the intervention, the external diaphragm pacing group has greater diaphragmatic mobility than the control group.^{82–84} Two studies reported that MIP is

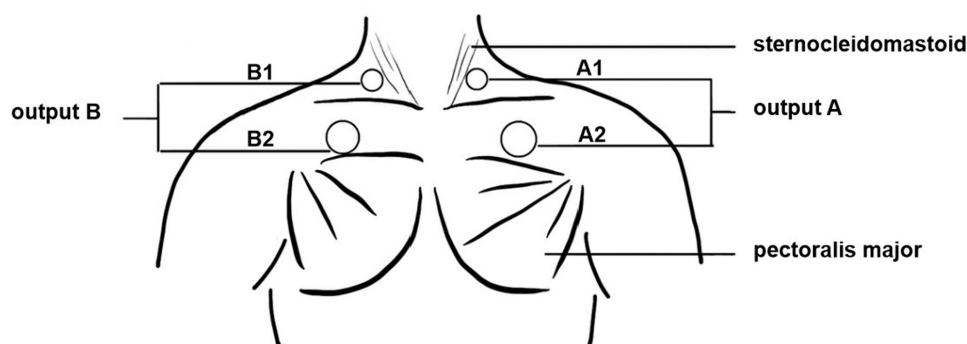


Figure 5 External diaphragm pacing.

Notes: Paste the polar plates on A1, A2, B1, B2 to form a loop. Turning on the machine stimulates the phrenic nerve, producing a nerve impulse that causes the diaphragm to contract. A1, A output channel cathode (small polar plate); A2, A output channel anode (large polar plate); B1, B output channel cathode (small polar plate); B2, B output channel anode (large polar plate); the small polar plate is attached to the lower 1/3 of the outer edge of the left and right sternocleidomastoid muscle, respectively; the large polar plate is placed on the surface of the left and right pectoralis major muscles, respectively. Data from Xie.⁸¹

higher than the control group after external diaphragm pacing intervention.^{82,85} Only Cao et al⁸² reported the results of diaphragm thickness after external diaphragm pacing intervention, and no significant difference was found between the intervention and control groups. This result suggests that the improvement of diaphragm function by external diaphragm pacing is limited. In addition, the intervention was possibly not long enough, and the included participants were not very ill.

The pulmonary ventilation function of patients with COPD clearly improves after external diaphragm pacing. Eight studies reported changes in pulmonary ventilation function.^{82–84,86–90} Four of these studies reported FEV1,^{83,86,88,89} two studies reported FEV1%pred,^{87,90} three studies reported FVC,^{83,89,90} four studies reported FEV1/FVC,^{83,86,87,90} Cao et al⁹⁰ reported MMEF, and Wang et al⁸⁶ reported MVV, with significant differences compared with baseline. Compared with the controls, three studies reported FEV1,^{84,86,89} three studies reported FEV1%pred,^{82,87,90} two studies reported FVC,^{83,89} four studies reported FEV1/FVC,^{84,86,87,90} and Wang GT et al⁸⁶ reported MVV, with better results in the intervention group than the control group.

Four studies reported the effect of external diaphragm pacing on exercise capacity in patients with COPD.^{85,88–90} Three studies reported prolongation of 6MWD after the intervention compared with pre-treatment.^{88–90} Three studies reported superior 6MWD in the intervention group compared with the control group.^{85,89,90} This result shows that external diaphragm pacing can improve the exercise capacity of patients with COPD.

Zeng et al⁸⁸ reported a reduction in mMRC scores compared with pre-treatment, but only among patients at a severe stage of the disease.

Suggestions for the Application of Phrenic Nerve Electrical Stimulation

External diaphragm pacing improves diaphragmatic dysfunction, pulmonary ventilation, exercise capacity, and dyspnea in patients with COPD. In terms of benefit, external diaphragmatic pacing is effective in the treatment of severely and very severely treated patients.⁸⁸ In terms of treatment frequency, using compound frequencies is more effective than using physiological frequencies.⁹⁰ The disadvantage is that as a passive treatment, it is not effective in treating mild patients.⁸⁸ It requires the accurate localization of the stimulation point. External diaphragm pacing is a worthwhile technique to incorporate into a pulmonary rehabilitation program when the development of active treatment methods is limited.

Conclusion

Diaphragmatic dysfunction in patients with COPD is characterized by decreased mobility and muscle strength, and increased thickening. The reduction in diaphragm thickness was only observed in severe patients, and changes in diaphragm thickness in mild-to-moderate patients require additional studies. Appropriate assessment and treatment must be selected for diaphragmatic dysfunction in patients with COPD. Ultrasound is a commonly used method of diaphragmatic assessment, which can be used to assess diaphragmatic mobility, thickness, and thickening. Diaphragmatic muscle strength can be assessed using Pdi and MIP. Targeted rehabilitation measures for diaphragmatic dysfunction in patients with COPD include diaphragmatic breathing, manual therapy, and phrenic nerve stimulation. Targeted rehabilitation measures for diaphragmatic dysfunction in patients with COPD can improve diaphragm function, pulmonary ventilation function, dyspnea, and exercise capacity.

Owing to the anatomical characteristics of the diaphragm, most studies only assessed the effects of diaphragm rehabilitation therapy on diaphragm dysfunction in an indirect way. A direct, non-invasive and standardized assessment for diaphragm dysfunction is required. Multi-center and large-sample randomized controlled clinical trials should be conducted to investigate the intervention effects and mechanisms of different diaphragm rehabilitation treatment modalities. It will provide effective guidance for the development and selection of diaphragmatic assessments and rehabilitation therapies for COPD.

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Disclosure

The authors report no conflicts of interest in this work.

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