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Effects of external diaphragm pacing combined with breathing training on pulmonary function of chronic obstructive pulmonary disease patients

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Abstract

Background: Pulmonary rehabilitation training is effective for patients with chronic obstructive pulmonary disease (COPD). External diaphragm pacing is a method to induce the change of nerve potential of the diaphragm by electrical stimulation and then stimulate the regular contraction of the diaphragm to improve the function of the diaphragm.

Objective: To explore the effects of external diaphragm pacing combined with breathing training on pulmonary function of COPD patients.

Methods: One hundred COPD patients admitted to our hospital from January 2021 to January 2023 were chosen and divided into control group (CG) and observation group (OG). Patients in the CG received breathing training. Patients in the observation group received external diaphragmatic pacing intervention after 30 minutes of respiratory training, with the pulse frequency adjusted to 30 ~ 40 Hz according to the patient's comfort level, and the pacing frequency adjusted to 9-12 times/minute, 30 minutes/times, 2 times/day. The clinical efficacy, lung function, arterial blood gas, oxidative stress, adverse effects that occurred during the treatment process along with quality of life in both groups was compared.

Results: Due to the patient's own reasons to fall off 3 cases, the final completion of 97 cases, including 48 cases in the control group and 49 cases in the observation group. The indicators and scores of the two groups of patients before treatment were not statistically different, and were comparable between the two groups ($P>0.05$). After treatment, the total effective rate, FEV1, FVC , and FEV1/FVC levels of OG were higher than those of CG group indicating that the improvement of lung function by combined treatment was better ($P<0.05$). Compared with CG, OG had lower $PaCO_2$ levels and higher PaO_2 levels, suggesting that combined treatment improved patients' ventilatory function ($P<0.05$). In addition, lower MDA levels and higher SOD and GSH levels suggested that the combination therapy reduced COPD-induced oxidative stress. The probability of adverse events in OG (8.89%) increased somewhat compared to CG (4.17%), but there was no statistical difference ($P>0.05$).The CAT score of OG was higher than that of CG, suggesting that the combination therapy gave patients a better experience.

Conclusion: Compared with respiratory training, external diaphragmatic pacing combined with respiratory training has a better effect on improving lung function and quality of life in patients with chronic obstructive pulmonary disease. However, due to the small sample size of this study, the single source of the sample, and the limitations of the sample selection, the conclusions drawn from this study need to be further justified. This study also suggests the potential of external diaphragmatic pacing combined with respiratory training in the clinical treatment of obstructive lung disease.

Keywords: chronic obstructive pulmonary disease, external diaphragm pacing, breathing training, pulmonary function

Introduction

Chronic obstructive pulmonary disease (COPD) belongs to a lung disease mainly featured by continuous restricted air flow (1). Patients with chronic hypoxia and weak contraction of respiratory muscles due to continuous restricted air flow, which is manifested by symptoms such as reduced exercise tolerance along with dyspnea, especially in patients with moderate to severe COPD (2). The morbidity and mortality rate of COPD rank first in the world, and it is a global public health problem (3). According to a survey, the number of COPD patients in China has reached 100 million, which has caused a serious burden to China's economy and society, and also brought great pain to patients and their families (4).

Studies have shown that pulmonary rehabilitation training for COPD patients can effectively promote the rehabilitation of lung function (5). Conventional pulmonary rehabilitation training generally adopts respiratory training, that is, deep and slow breathing exercise to control the respiratory muscle, so that patients can change from shallow and rapid breathing to deep and slow breathing (6). However, due to the cumbersome movement and slow effect of respiratory muscle exercise, most patients have poor exercise compliance, resulting in them missing the best opportunity for lung function rehabilitation (7). Therefore finding other suitable treatment methods has become a focus of attention. Studies have shown that obvious damage to the diaphragm of COPD patients will lead to reduced lung function (8). The diaphragm consists of muscle fibres and is located between the thoracic and abdominal cavities, and is responsible for 3/4 of the respiratory movements of the organism, so diaphragmatic movements play a crucial role in the respiratory process. In the case of COPD patients, the airway obstruction and the accumulation of residual air volume lead to a decrease in the contraction endurance of the diaphragm, which results in diaphragmatic weakness. Therefore, how to restore diaphragm function in COPD patients as soon as possible is an urgent problem to be solved by clinical respiratory medical staff. Currently, strategies to restore diaphragmatic function include mechanical therapies such as electrical stimulation(9) and endoscopic lung reduction(10).

Electrical stimulation has been studied more extensively because it is non-invasive, economical, and well tolerated, and mainly includes methods such as diaphragmatic electrical stimulation(11) and neuromuscular electrical stimulation (12). External diaphragm pacing of the diaphragm is a method of inducing changes in diaphragmatic nerve potentials by electrical stimulation, which in turn stimulates regular contraction of the diaphragm in order to improve diaphragmatic function, and has been used in clinical practice for more than a decade (13). The method is mainly used in pulmonary rehabilitation of COPD patients. It has been pointed out in literature that external diaphragm pacing can induce reactive diaphragm contraction by stimulation of body surface electrodes, thus improving ventilation, oxygen metabolism and lung function (14). However, this method may lead to increased inspiratory load and easily induce respiratory muscle fatigue(15), so we attempted to combine extracorporeal diaphragmatic pacing with respiratory training to explore whether the combination of the two methods could make up for the deficiencies and provide a gainful effect when treated alone. In this study, we aimed to explore the impact of external diaphragm pacing in combination with breathing training on pulmonary function of COPD patients.

1. Methods

2.1 General data

Patients with chronic obstructive pulmonary disease admitted to our hospital from January 2021 to January 2023 were selected as study subjects. According to the requirements of α of 0.05, β of 0.2, and Power value of 0.8, and taking into account that the shedding rate of the test was around 10%, we determined the sample size of 100 cases. According to the randomised concealed grouping method, they were divided into control group (CG) and observation group (OG), with 50 cases in each group. Two of them were dislodged in CG and one in OG, thus there were 48 CG and 49 OG included in the study. There were 28 males and 20 females in the CG. The average age was 66.38±6.36 years, ranging from 48 to 78 years. The course of disease ranged from 3 to 14 years, with an average course of 7.29±1.78 years. There were 29 males and 20 females in the OG. The average age was 66.42±6.43 years, ranging from 50 to 78 years. The course of disease ranged from 3 to 15 years, with an average course of 7.32±1.83 years. No difference was seen in general data between 2 groups ($P>0.05$).

Inclusion criteria: (1) Met the relevant diagnostic criteria for COPD in the Guidelines for Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease. (2) Consistent with the indication of external diaphragm pacing. (3) No malignant tumor or cognitive dysfunction. Exclusion criteria: (1) Existence of neuromuscular disease caused by muscle weakness, thoracic malformation or other causes. (2) Patients with malignant tumor disease, malignant hydrothorax or abdominal cavity surgery recently. (3) History of trauma. (4) Accompanied by other respiratory diseases.

1.2 Interventions

Patients in the two groups accepted conventional treatment and patients in the CG received breathing training at the same time. During breathing training, patients' blood oxygen saturation and respiratory rate were observed. If cyanosis, dyspnea, severe cough and dyspnea occurred, patients were stop immediately, and received oxygen inhalation and blood oxygen saturation monitoring and other treatment, and respiratory training was performed after symptoms subsided or relieved. Specific methods of breathing training: (1) Abdominal breathing. The patient took a comfortable position and relaxed the whole body, the left hand of patient was put on the chest and the right hand of patient was put on the upper abdomen, and then the patient shut up and took a deep breath slowly through the nose. When inhaling, the abdomen heaved, the right hand of patient was lifted up, and when exhaling, the abdomen collapsed, and the right hand of patient was pressed forward and down to promote the recovery of the diaphragm and exhaled as much as possible. The ratio of inhalation to exhalation was kept 1:2, and the breathing rate was 8 ~ 10 times/min. 10 min each time, 3 ~ 4 times/day. (2) Lip contraction breathing. The patient relaxed the abdomen, inhaled deeply through the nose, and then shrunk the lips to slowly exhale the gas as "blowing a candle," the ratio of inhalation and exhalation was 1:2, and the breathing rate was 8 ~ 10 times/min, 15 minutes each, 3 ~ 4 times/day. (3) Holding the breath after deep breathing. The patient took the relaxed position, inhaled slowly and deeply through the nose, and maintained for a few seconds to facilitate the full exchange of gas, so as to promote the re-expansion of the collapsed alveoli, and then slowly exhaled the gas through the mouth or with the contraction of the lips breathing method (blowing out candles). Each training time was 8 ~ 10 min, 3 ~ 4 times/day.

On the basis of the CG, patients in the OG were given external diaphragm pacing intervention: alcohol cotton tablet (75%) was used to clean local skin and wait for alcohol volatilizing. During the treatment process, the patient was observed to take a seated/semi-lying position, told to avoid leaning forward, keep the body relaxed, and tilt the head backward. The four electrodes of the pacemaker were evenly applied with conductive adhesive, and two negative electrodes were affixed to the lower 1/3 position of the left and right edges of the sternocleidomastoid muscle, and two positive electrodes were affixed to the second intercostal space of the midclavicular line to ensure that scars and carotid sinus were avoided. Patients with heart disease are advised to move the large left electrode pad slightly laterally. The pacemaker was fixed with adhesive tape, and the parameters of the pacemaker were adjusted according to the patient's own tolerance and feelings, so as to ensure the stimulation intensity from weak to strong. The pulse frequency was adjusted to 30 ~ 40 Hz according to the patient's own comfort. The pacing frequency was adjusted to 9-12 times/min, 30 minutes/time, and 2 times/day. Diaphragmatic pacing was performed 30 minutes after the end of breathing exercises, and the treatment time was ≥5 days per week for a total of 20 days. If patients experience adverse reactions such as dizziness, blurred vision, general discomfort, pain in the patch area, and muscle fatigue such as chest tightness and shortness of breath during treatment, the stimulation intensity should be adjusted downward or stopped. Patients were told to rest quietly after treatment.

Participants in this study were required to undergo centralised training by professionally trained respiratory physicians and were only enrolled after passing the examination. Patients with OG were required to go to the hospital once a week for centralised training and the rest of the time the training was completed at home.Patients with CG were required to go to the hospital on the day of external diaphragm pacing for centralised treatment, and the rest of the time the respiratory training could be completed at the aggravated level.

2.3 Observation indicators

(1) Clinical efficacy: The efficacy was evaluated following the evaluation criteria for the severity of dyspnea in COPD patients in the Guidelines for Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2013 Revision): Obvious effect: the severity of dyspnea decreased by 2 or more levels; Effective: The severity of dyspnea decreased by 1 level; Ineffective: the severity of dyspnea remained unchanged or even worsened. The total effective rate = Obvious effect rate + Effective rate.

(2) Lung function: a lung function detector was used to assess patient's forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) along with its ratio FEV_1/FVC.

(3) Arterial blood gas index: 5 mL of the patient's radial artery blood was drawn before and after treatment. The partial pressure of carbon dioxide in artery ($PaCO_2$) and partial pressure of oxygen (PaO_2) were measured within 1 h.

(4) Oxidative stress index: 3 mL fasting peripheral venous blood was gathered from patients, and the levels of superoxide dismutase (SOD), serum Malonaldehyde (MDA) and Glutathione (GSH) were detected by chemical colorimetry.

(5) Closely observe patients for adverse reactions during treatment, including dizziness, chest tightness and shortness of breath, and skin redness.

(6) The Chronic obstructive pulmonary disease assessment test (CAT) scores of the two groups were compared. CAT included 6 subjective dimensions and 8 daily exercises, and the score ranged from 0 to 40 points. The higher the score, the greater the impact of the disease on the life of the patients, that is, the lower the quality of life.

2.4 Statistical analysis

SPSS 20.0 software was adopted for statistical analysis. Measurement data were expressed as x±s, and t-test was implemented for comparison between groups. Count data were expressed as (n, %), and χ^2 test was implemented for comparison. P<0.05 meant significance.

2. Results

3.1 Clinical efficacy in both groups

Table 1 displayed that compared to the CG(83.33%), the total effective rate in the OG(95.92%) presented higher (P<0.05). It indicates that respiratory training combined with external diaphragmatic pacing is more effective in the treatment of COPD.

Table 1 Clinical efficacy in both groups

Groups	Cases	Obvious effect	Effective	Ineffective	Total effective rate
Control group	48	25	15	8	40 (83.33%)
Observation group	49	30	17	2	47 (95.92%)
χ^2					5.005
P					0.025

3.2 Lung function in both groups

Figure 1 displayed no difference in FEV_1, FVC and FEV_1/FVC levels between 2 groups prior to intervention (P>0.05). After intervention, FEV_1, FVC and FEV_1/FVC levels were increased in both group, and those in the OG（FEV_1-95% Cl: 1.32~1.8; FVC -95% Cl: 1.82~2.56; FVC-95% Cl: 51.44~70.16）presented higher when comparing with the CG (FEV_1-95% Cl: 1.05~1.43; FVC -95% Cl: 1.3~1.88; FVC-95% Cl: 49.35~68.65）(P<0.05). This indicates that the ventilation dysfunction was alleviated after the intervention in both groups, and the efficacy of the combined treatment group was better.

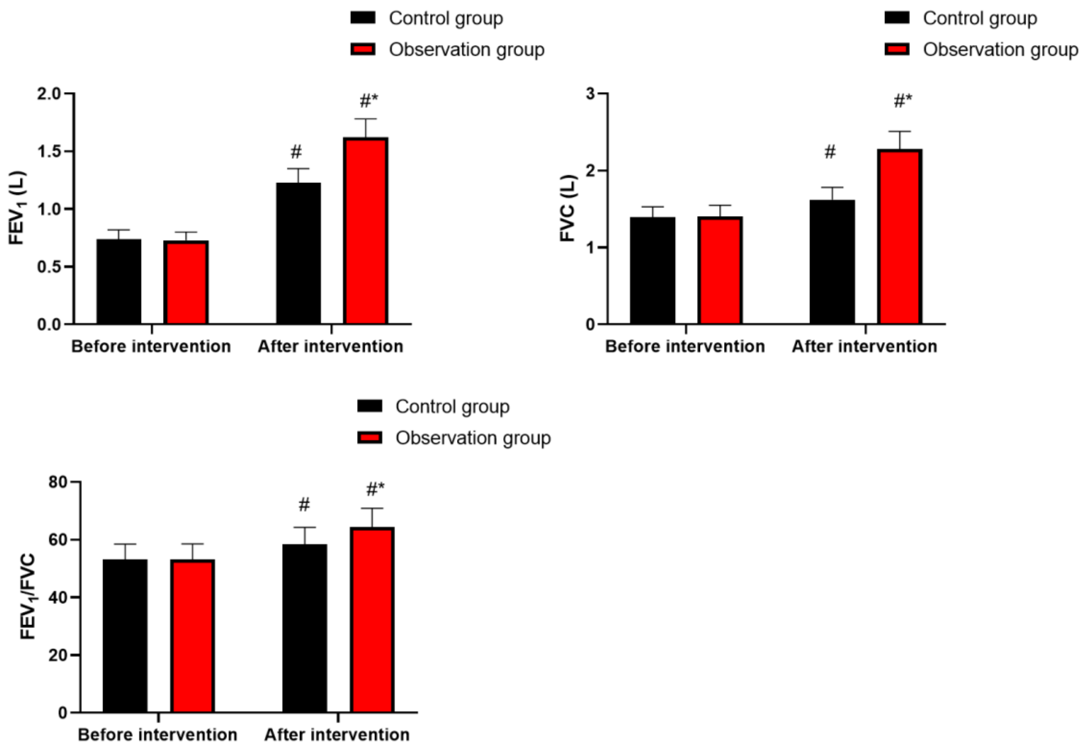

Figure 1 Lung function in both groups. #P<0.05, compared with before intervention. *P<0.05, compared with the CG.

3.3 Arterial blood gas index in both groups

Figure 2 displayed no difference in $PaCO_2$ and PaO_2 levels between 2 groups prior to intervention (P>0.05). After intervention, $PaCO_2$ level was declined in both groups, and that in the OG（95%Cl: 36.37~53.63）presented lower when comparing with the CG（95%Cl: 39.14~60.86）(P<0.05). At the same time, PaO_2 level was increased in both groups, and that in the OG（95%Cl: 52.62~80.54）presented higher when comparing with the CG（95%Cl: 49.86~77.04）(P<0.05). This suggests that combination therapy improves respiratory hypoxia and alveolar ventilation status in COPD patients and contributes to the convergence of the indexes towards normal values.

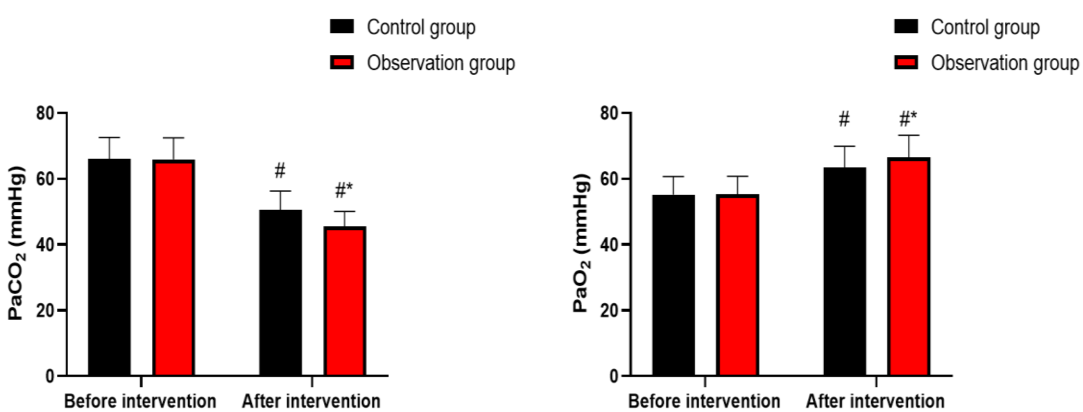

Figure 2 Arterial blood gas index in both groups. #P<0.05, compared with before intervention. *P<0.05, compared with the

CG.

3.4 Oxidative stress index in both groups

Figure 3 displayed no difference in MDA, SOD and GSH levels between 2 groups prior to intervention (P>0.05). After intervention, MDA level was declined in both groups, and that in the OG（95%Cl: 4.45~4.91）presented lower when comparing with the CG（95%Cl: 5.16~5.76）(P<0.05). At the same time, SOD and GSH levels were increased in both groups, and those in the OG（SOD-95%Cl: 41.56~122.75; GSH-95%Cl: 156.11~344.21）presented higher when comparing with the CG（SOD-95%Cl: 37~116.74; GSH-95%Cl: 136.78~342.54）(P<0.05). This indicates that the degree of oxidative stress in the set organism was reduced, which suggests that the combined treatment can alleviate airway injury and protect cells from oxidative stress damage.

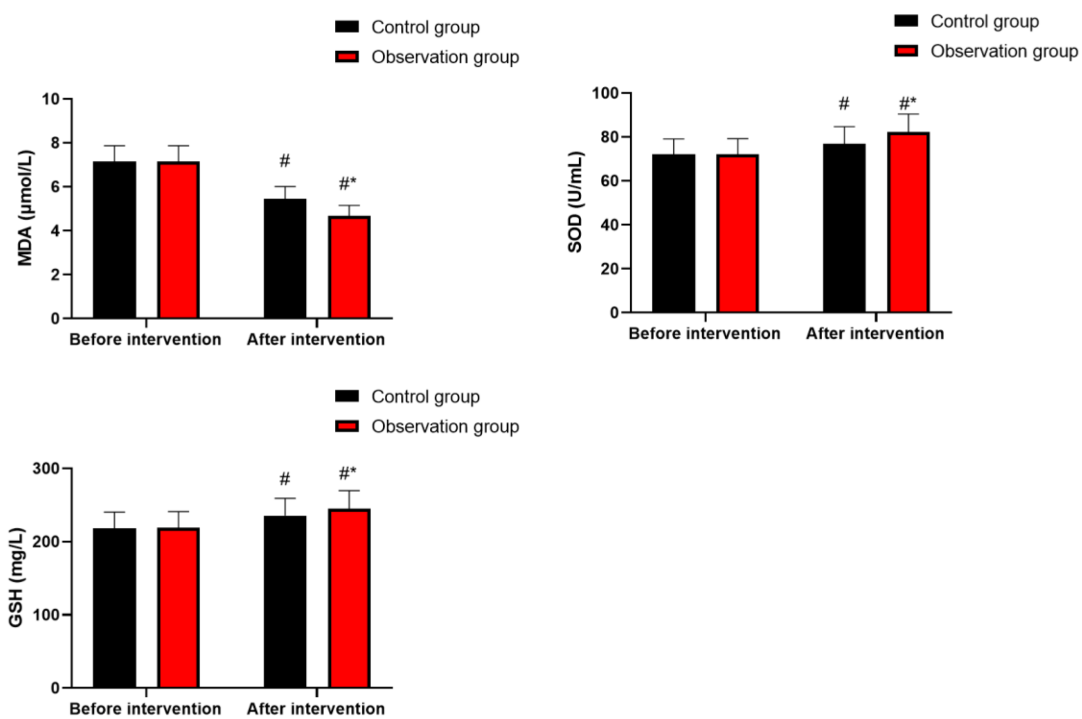

Figure 3 Oxidative stress index in both groups. #P<0.05, compared with before intervention. *P<0.05, compared with the CG.

3.5 Adverse reactions in both groups

Table 2 displayed that the adverse reactions occurring in both groups included dizziness, chest tightness and shortness of breath and skin redness, in which the probability of skin redness was higher in patients with OG than with CG, and the incidence of adverse reactions (8.89%) tended to be higher compared with that of CG (4.17%), but there was no statistical difference(P>0.05). This indicates that the combination therapy is safe and feasible.

Table 2 Statistics on adverse reactions

Groups	Cases	dizziness	chest tightness and shortness of breath	skin redness	Total rate
Control group	48	0	2	0	2 (4.17%)
Observation group	49	1	1	2	4 (8.89%)
χ^2					0.817
P					0.414

3.6 Quality of life in both groups

Figure 4 displayed no difference in CAT score between 2 groups before intervention (P>0.05). After intervention, CAT score was declined in both groups, and that in the OG（95%Cl: 8.38~12.7）presented lower when comparing with the CG（95%Cl: 10.15~14.97）(P<0.05)

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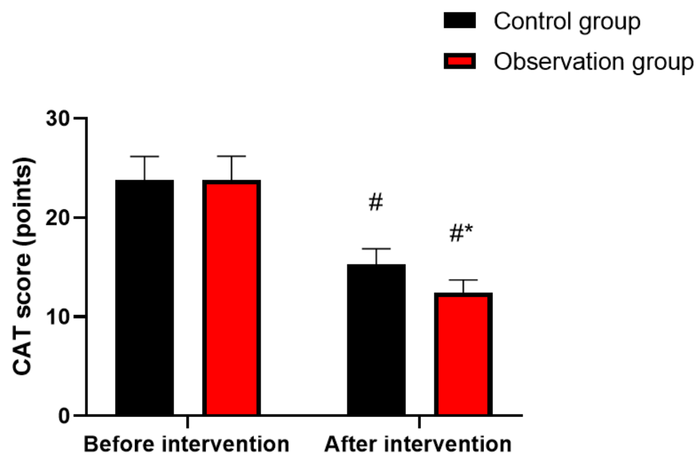

Figure 4 Quality of life in both groups. #P<0.05, compared with before intervention. *P<0.05, compared with the CG.

3. Discussion

COPD is a serious chronic respiratory disease with long-term chronic hypoxia as the main clinical manifestation (16). The disease not only affects the lungs, but also causes multiple system damage due to long-term chronic hypoxia (17). In particular, patients with moderate and severe COPD are often hospitalized due to repeated lung infections and lung function decline, poor quality of life and long hospitalization cycle, which bring heavy economic and psychological burden to patients (18). Therefore, how to effectively improve the pulmonary function of COPD patients and shorten their hospital stay has always been the goal of clinicians.

Breathing training is to prolong the expiratory time, correspondingly increase the pressure in the small airway cavity, avoid premature closure and collapse of the small airway, so as to keep the airway open, promote part of the alveoli to discharge residual air, ensure the respiratory pathway, and help improve ventilation and lung function (19). However, it has the disadvantages of slow curative effect and difficult for patients to persist.

External diaphragm pacing stimulates patients' phrenic nerve through body surface electrodes to promote regular phrenic contraction (9). The principle of external diaphragm pacing is functional electrical stimulation of phrenic nerve, movement and conduction of phrenic nerve, which causes phrenic contraction (20). Phrenic contraction is closely related to lung ventilation function, especially in the maintenance of normal lung ventilation and air exchange function, which can enhance the contractility of the diaphragm, expand the thoracic volume, further increase the tidal volume, effectively improve the arterial blood gas index, along with promote the pulmonary ventilation function (21).

In our study, it was displayed that compared to the CG, the total effective rate, FEV_1, FVC and FEV_1/FVC levels in the OG presented higher when comparing with the CG, indicating that external diaphragm pacing combined with breathing training had effective clinical efficacy on COPD and could promote the lung function of COPD patients. Consistently, the combination of aerobic training and external diaphragm pacing can obtain significant improvements in physical activity, respiratory function, body composition, arterial oxygen pressure, as well as diaphragm function in COPD patients (9).

Blood gas analysis is currently a commonly used indicator of pulmonary ventilation function in clinical practice (22). The treatment of COPD patients is to improve respiratory function and ventilation function (23). Most COPD patients have a certain degree of carbon dioxide retention and chronic hypoxia, and a large amount of viscous secretions are attached to the airways of patients, which can enhance airway inflammation and hypoxia (24). In our study, the results suggested that after intervention, $PaCO_2$ level was declined in both groups, and that in the OG presented lower compared to the CG. At the same time, PaO_2 level was increased in both groups, and that in the OG presented higher compared to the CG. All these results implied that external diaphragm pacing in combination with breathing training could improve the arterial blood gas of COPD patients, which was consistent with previous studies (20, 25). This may be because that external diaphragm pacing combined with breathing training could stimulate the strength of the respiratory muscle group and enhance its endurance, thereby increasing the patient's maximum expiratory pressure and inspiratory pressure, thereby increasing the depth of breathing and improving dyspnea (26, 27).

Oxidative stress is a stress reaction caused by the excessive production of reactive oxygen species (ROS) in the body caused by external stimuli (28). Oxidative stress can be caused by the imbalance of oxidation/antioxidant system, the increase of oxidant ratio and the decrease of antioxidant level (29). Oxidative stress can cause lipid peroxidation and decrease antiprotease activity, thus increasing mucus secretion (30). At the same time, oxidative stress can damage airway epithelium and lung tissue and aggravate COPD patients' condition (31). The results of our study revealed that after intervention, MDA level was declined in both groups, and that in the OG presented lower compared to the CG. At the same time, SOD and GSH levels were increased in both groups, and those in the OG presented higher compared to the CG. Some studies have found through Nazi analysis that breathing exercises increase the activity of SOD and GSH, improve oxidative stress due to COPD, hypertension and other diseases, and improve ventilation difficulties (32). However, there are no reports to discuss whether external diaphragmatic pacing improves oxidative stress. The results of our study suggest that external diaphragmatic pacing combined with respiratory training is better at improving oxidative stress in patients with COPD compared to respiratory training alone. This may be because that external diaphragm pacing combined with breathing training could effectively increase the breathing depth of COPD patients, reduce the ineffective cavity, improve the distribution of gas, improve the hypoxia state, and alleviate the oxidative stress reaction. However, more definitive conclusions and mechanistic investigations need to be supported by further data and experiments.

In addition, our study indicated that after intervention, CAT score was declined in both groups, and that in the OG presented lower compared to the CG, indicating that external diaphragm pacing combined with breathing training could promote the quality of life of COPD patients, which was in accordance with previous studies (33, 34). This may be the improvements of lung function and diaphragm function could promote sputum discharge, improve exercise endurance, avoid acute exacerbation of the disease, as well as promote the quality of life of COPD patients.

At present, the research on pulmonary rehabilitation for COPD patients at home and abroad has been deepening, and external diaphragmatic pacing should receive more and more attention as a part of pulmonary rehabilitation training in the clinic. In addition, external diaphragmatic pacing has a certain degree of adjuvant therapy in lung cancer chemotherapy patients(21), stroke patients (35) and other people with respiratory failure and respiratory abnormalities, and external diaphragmatic pacing can improve the respiratory muscle strength of the patients, alleviate respiratory failure, and promote the ventilation function.

4.1 Limitations

There are still some shortcomings in our trial. Firstly, this study could not be blinded due to the special appearance of the device used for pacing, which may result in a certain degree of bias. Secondly, due to the small sample size and the fact that it is a single-centre study, it is recommended that the sample size and the source of the sample be increased at a later stage in order to further argue for the authenticity of the conclusions. Finally, the inconsistency of efficacy due to the inconsistency of training and treatment practices among different patients and different therapists may affect and interfere with our conclusions.

5. Conclusion

In conclusion, through this study, we can conclude that external diaphragmatic pacing combined with respiratory training has a better effect on the improvement of lung function and quality of life in patients with chronic obstructive pulmonary disease compared with respiratory training. This study was devoted to investigate the effect of combined therapy on blood gas analysis, oxidative stress and adverse effects, which was not mentioned in the previous literature. However, due to the limitations of the sample selection method and sample size in this study, the conclusions may have some bias. Therefore, we need to collect more sample sources and numbers for validation, standardise the therapeutic behaviors of participants and therapists as much as possible, and suggest that the therapist for each patient needs to be fixed to be the same person in order to narrow down the bias of the conclusions due to external bias. In addition, it is hoped that smarter and more effective pacing products can be iterated, which will be conducive to their dissemination in the clinic.

Ethical statement: This study was approved by the medical committee of the No.215 Hoapital of Shaanxi Nuclear Industry.

Acknowledgments: None.

Conflicts of Interest: None.

Author's contributions: Jie Li concepted the study and performed data analysis, Xu Fan and Yafei Liu wrote the initial manuscript and collected data, Yu Guo revised the manuscript and drew figures, Qiang Dong managed data, supervised the study, and was responsible for the conduction of the whole project.

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Availability of data and materials: The data that support the findings of this research are available from the corresponding author upon reasonable request.

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