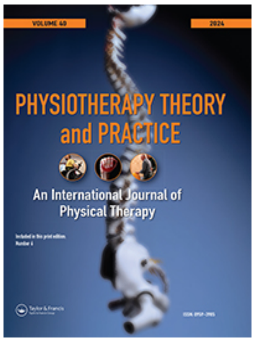

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The effects of inspiratory muscle warm-up prior to inspiratory muscle training during pulmonary rehabilitation in subjects with chronic obstructive pulmonary disease: a randomized trial

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ABSTRACT

Background: While a whole-body warm-up may not adequately prepare the inspiratory muscles for exercise, inspiratory warm-up is an effective approach in preparing the inspiratory muscles for exertion.

Objectives: To investigate the effects of inspiratory muscle warm-up performed prior to inspiratory muscle training (IMT) during pulmonary rehabilitation (PR) in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) and inspiratory muscle weakness.

Methods: Pulmonary function tests, maximal inspiratory and expiratory pressures (MIP and MEP), 6-minute walk test distance (6MWD), modified Medical Research Council Dyspnea Scale(mMRC), St. George's respiratory questionnaire and the 36-item short-form health survey were evaluated. Both groups performed IMT during PR for 8 weeks. The warm-up group (n = 15), in addition to the standard IMT group (n = 15), performed an inspiratory muscle warm-up protocol before each IMT session.

Results: At the end of the 8-week intervention, improvements in dyspnea (mMRC in score, p =0.033, effect size =0.76); exercise capacity (6MWD in meters, p =0.001, effect size =1.30); pulmonary function [forced expiratory volume in 1 second (FEV_1) in %predicted, p =0.006, effect size =1.10]; and inspiratory muscle strength (MIP in cmH_2O, p =0.001, effect siz e = 1.35) were significantly greater in the warm-up group. Moreover, there were significant improvements in health-related quality of life (HRQoL) sub-scores after the training in both groups (p <0.05).

Conclusions: This study demonstrated improvements in both groups, surpassing or closely approaching the established minimal clinically important difference values for the respective outcomes. Performing a warm-up for inspiratory muscles before IMT boosts benefits for pulmonary function, inspiratory muscle strength, exercise capacity, dyspnea, and HRQoL in subjects with moderate-to-severe COPD and inspiratory muscle weakness.

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Chronic obstructive pulmonary disease; inspiratory muscle training; pulmonary rehabilitation

Introduction

Chronic obstructive pulmonary disease (COPD) leads to increased morbidity and mortality with severe pulmonary complications (Global Initiative for Chronic Obstructive Lung Disease, 2023). However, COPD affects not only the lungs but also other organs and systems, causing a loss of strength in the respiratory and peripheral muscles. The reduction in strength and/or endurance in respiratory muscles leads to muscle dysfunction (Charususin et al., 2018), which causes a decrease in exercise capacity in subjects with COPD (Global Initiative for Chronic Obstructive Lung Disease, 2023).

Studies have demonstrated that pulmonary rehabilitation (PR) combined with medical treatment is the most effective way to reduce the systemic effect of COPD (Global Initiative for Chronic Obstructive Lung Disease, 2023). The effectiveness of PR in COPD has been proven and inspiratory muscle training (IMT) can be part of PR. However, IMT does not have a standardized protocol, as the frequency and intensity of IMT vary from study to study. Beaumont et al. (2015) applied IMT in addition to PR with a 3-week training protocol to COPD patients and had no changes in pulmonary function. However, Weiner et al. (2004) applied IMT at 60% of the maximal inspiratory pressure (MIP) value for 12 weeks. The study

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showed a significant difference in pulmonary function within the study group.

Muscle warm-up was defined as any pre-performance performed to prepare the muscles before physical activity (Lomax, Grant, and Corbett, 2011). General whole-body warm-up prior to exercise had a short-term positive effect on exercise (Andrade et al., 2015). As a result of decreased joint stiffness, increased nerve transmission, reduced stability of actin and myosin, and lower muscle stiffness, short-term performance improves (Andrade et al., 2015; Jeffreys, 2022). The respiratory muscles are the skeletal muscles and, therefore, can be trained based on the principles of exercise just like peripheral muscles (Boswell-Ruys et al., 2020). It has been known that during exercise training in peripheral muscles, a higher level of performance can be achieved by warming up those muscles before the loading phase (Andrade et al., 2015; Jeffreys, 2022). Although it has been proven that general whole-body warm-up has beneficial effects on respiratory muscles activity (Jung and Kim, 2015), general whole-body warm-up may not be adequate for preparing the inspiratory muscles for exercise (Barnes and Ludge, 2021; Lomax, Grant, and Corbett, 2011). However, the inspiratory muscles specific warming protocol, which is referred to in the literature as the "inspiratory muscle warm-up" (Lomax, Grant, and Corbett, 2011), is an effective approach to prepare the inspiratory muscles for exercise and reduces the perceived dyspnea during exercise (Barnes and Ludge, 2021). It has been shown to increase respiratory muscle strength, pulmonary function, and exercise performance without causing excessive fatigue in the inspiratory muscles during subsequent inspiratory muscle activity (Barnes and Ludge, 2021).

The inspiratory muscle warm-up (IMW) protocol provides to cope with perceived dyspnea during exercise by reducing the fatigue of inspiratory muscles (Cirino et al., 2023). A few studies that have investigated IMW in different populations have shown its beneficial effects (Barnes and Ludge, 2021; Cirino et al., 2023; Kantasorn, Jalayondeja, Chaunchaiyakul, and Pongurgsorn, 2010; Leicht et al., 2010; Lomax, Grant, and Corbett, 2011; Wilson et al., 2014). Warming up the inspiratory muscles has been shown to enhance respiratory muscle coordination by eliminating reflex inhibition and reducing co-contraction between inspiratory and expiratory muscles (Cirino et al., 2023). Thus, athletes prepare their inspiratory muscles for exercise, boosting respiratory muscle strength, pulmonary function, and exercise capacity. It also helps reduce dyspnea during physical activity (Barnes and Ludge, 2021). Exacerbations may also impair the function of the respiratory muscles, which is another reason to recommend IMT with IMW in patients with COPD and inspiratory muscle weakness (Mesquita et al., 2013). However, to our knowledge, no study directly combined IMW and IMT protocols in patients with COPD in the existing literature. This study aimed to investigate the effects of inspiratory muscle warm-up performed prior to IMT during PR in patients with COPD and inspiratory muscle weakness.

Methods

Study design and subjects

This prospective randomized study included subjects with COPD, recruited from the Department of Chest Diseases of Dokuz Eylul University Hospital, with a 1:1 allocation ratio. The inclusion criteria were a diagnosis of moderate-to-severe COPD according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (2023) guideline criteria, having inspiratory muscle weakness defined by a MIP below 60 cmH_2O (Ammous et al., 2023; Beaumont, Forget, Couturaud, and Reychler, 2018). In addition, the subjects had to be in a clinically stable condition with the same medication routine without taking any antibiotics for the last 4 weeks and/or no acute exacerbation in the last 3 months. The subjects who had a previous pneumonectomy or lobectomy operation, pneumonia in the last 3 months, any pulmonary infection during the study, a requirement for supplemental oxygen therapy, or any other pulmonary, neurological, orthopedic, or systemic inflammatory diseases, were excluded. The subjects, who had not quit smoking at least one year before inclusion, were also excluded.

Subjects with COPD were divided into 2 training groups. The randomization was performed by an independent and blind researcher not involved in the recruitment, evaluation, or training of the subjects, using a sequence generated from the www.randomizer.org website. The recruitment sequence was kept in sealed opaque envelopes. The assessor was trained as a cardiopulmonary physiotherapist who was blinded to the groups and familiar with the assessment methods. Subjects were also blinded to the groups. However, the therapist who administered the therapy was not blinded. To prevent bias, a different physiotherapist created a statistical analysis file by removing any personal information related to the patient. Thus, the researcher who performed the statistical analysis was blind to the groups and patients. The study was conducted by the Declaration of Helsinki and approved by the local ethical committee of the Dokuz Eylul University Non-Invasive Research Ethics Board (Date: June 01, 2017, approval number: 2017/14–17). All participants gave informed consent before the study. The study was registered with ClinicalTrials.gov registration number: NCT04655534

All assessments were performed for each patient before the study and after the 8-week training sessions. Once the demographic and clinical parameters were recorded, lung functions, respiratory muscle strength, exercise capacity, and dyspnea were assessed as primary outcomes, and health-related quality of life was assessed as a secondary outcome. We followed the CONSORT guidelines for reporting this trial.

Lung function

Lung function was measured as pre-bronchodilator according to the American Thoracic Society/European Respiratory Society criteria by a single technician using a digital spirometer (Sensor Medics Vmax 22 machine, SensorMedics Inc., Anaheim, CA, USA) following a standardized method (Miller et al., 2005). The forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio were recorded as a percentage of the predicted value (Miller et al., 2005).

Respiratory muscle strength

Respiratory muscle strength was evaluated, according to the American Thoracic Society/European Respiratory Society (2023) testing protocol guidelines by using an intraoral pressure measuring device (Sensor Medics Vmax 22 machine, SensorMedics Inc., Anaheim, CA, USA) which provided measures of the MIP and the maximal expiratory pressure (MEP) at the mouth. Both pressures were measured from the residual volume and total lung capacity; the tests were performed in the sitting position, wearing a nose clip and using a standard disposable bacterial/viral filtered tube mouthpiece during the maneuver. The maximum values of three maneuvers that vary by less than 10% were considered and the highest value was recorded and used for analysis (Beaumont et al., 2015). If the MIP value was less than 60 cmH_2O, it was considered inspiratory muscle weakness (Ammous et al., 2023; Beaumont, Forget, Couturaud, and Reychler, 2018).

Exercise capacity

Exercise capacity was assessed with a 6-minute walk test distance (6MWD), following the methodology specified by the American Thoracic Society/European Respiratory Society (2023) testing protocol guidelines. Subjects were instructed to walk as far as possible for 6 minutes in a covered, flat, corridor that is 30 meters long and meter-by-meter marked. The distance covered was calculated at the end of the test and used in the analysis.

Dyspnea

The severity of perceived dyspnea was measured using the modified Medical Research Council Dyspnea Scale (mMRC), which is scored ranging from 0 to 4. Current guidelines advocate using mMRC to measure the severity of perceived dyspnea related to physical activity. A high score on the scale indicates a high severity of perceived dyspnea (Global Initiative for Chronic Obstructive Lung Disease, 2023).

Health-related quality of life

Health-related quality of life (HRQoL) was assessed as disease-specific and overall HRQOL. Disease-specific HRQoL was assessed with the St. George's Respiratory Questionnaire (SGRQ) and the overall HRQoL with Medical Outcomes Study 36-item Short Form (SF-36). The SGRQ, a specific questionnaire for respiratory diseases, is a standardized, self-administered questionnaire. It consists of 3 domains with a total of 50 items: symptoms (8 items), activity (16 items), and impact (26 items). Scores range from 0 to 100 for all domains, and high scores indicate poor health (Jones, Quirk, and Baveystock, 1991).

The SF-36 questionnaire contains 8 domains: 1) physical functioning (10 items); 2) physical role functioning (4 items); 3) bodily pain (2 items); 4) social role functioning (2 items); 5) emotional role functioning (3 items); 6) mental health (5 items); 7) vitality (4 items); and 8) general health perceptions (5 items). Each section is scored from 0 to 100, with high scores indicating a good HRQoL (Ware, 2000).

Training procedure

The subjects were randomly divided into 2 groups as previously described. Both groups underwent physical training, but the standard IMT group performed only IMT, while the warm-up group performed an IMW protocol for warming up the inspiratory muscles before each IMT session. The whole training regime was carried out under the supervision of a physiotherapist, for 8 weeks, 3 times a week on alternate days, a total of 24 sessions. A standardized education including breathing retraining, proper use of medications, and self-management skills was given individually, to each patient. The training consisted of general body warming with stretching of the upper and lower limbs, respiratory exercises (i.e. pursed-lip and diaphragmatic breathing and thoracic expansion exercises), and treadmill exercise. The loading phase of the treadmill exercise was 20 min, progressing to 30 min according to patient tolerance. The perceived dyspnea was used as a parameter to adjust the intensity of the treadmill exercise training, keeping it between 4 to 6 on the modified Borg scale (Basso-Vanelli et al., 2016; Global Initiative for Chronic Obstructive Lung Disease, 2023) The treadmill exercise starts with 5 min warm-up and finished with 5 min cool-down. This training procedure is an adaptation of the training procedure of Basso-Vanelli et al. (2016). For resistance training, in each session, patients performed at least three strengthening exercises for both upper and lower extremities. Upper and lower extremity strengthening exercises with free weights included one to three sets of 8–12 repetitions, using loads progressing from 50–85% of a current one-repetition maximum (1-RM) (Storer, 2001).

Inspiratory muscle training basically involves forced inspiratory ventilation against resistance determined by MIP measurement. Usually, the training load for IMT is 50% or more of the MIP. Inspiratory warm-up is applied to the inspiratory muscles by increasing the number of repetitions of inspiratory ventilation with a lower resistance, just as we perform when training other muscles (Lomax, Grant, and Corbett, 2011; McConnell, 2013). Therefore, the training of the inspiratory muscles was carried out twice daily using a threshold inspiratory muscle trainer device (Threshold IMT Philips® Respironics, Inc). Inspiratory muscle training sessions were performed as 1 set, 30 breath repetitions at 60% of the MIP (McConnell, 2013). The protocol of IMW consists of 2 sets of 30 breaths at 40% of MIP, with 1 min rest between sets (Lomax, Grant, and Corbett, 2011). The patients were trained under the supervision of a physiotherapist on the days they came to the PR unit for exercise training (3 days a week for 8 weeks), the other sessions were followed by a home-based diary. The MIP was measured to adjust the training intensity every two weeks.

Statistical analysis

All data were analyzed using SPSS 24.0 for Windows. Complete case analysis was performed on only those subjects with a complete set of outcome data observed. Subjects with any missing data are excluded from analysis. Therefore, only data from subjects completing the study with no missing data were used for per-protocol analysis. The Shapiro-Wilk test was used to evaluate the distribution of data. The data were expressed as mean ± SD if it is distributed normally, and as median (interquartile range) if it is not. Categorical variables were expressed in percentages (%). For intergroup analyses, the independent Student t-test was used for variables with parametric distribution and the Mann-Whitney test was used for the nonparametric distributions. For intragroup analyses, the paired Student t-test was used for variables with parametric distribution and the Wilcoxon test was used for the nonparametric distributions. Also, the chi-square test for categorical variables was used to compare the groups. For all statistical analyses, $p < 0.05$ was considered statistically significant (Field, 2009).

A pilot study was conducted for the required sample size. The sample size was calculated based on the post-rehab MIP values obtained from the pilot study ($n = 4$ for each group, mean post-rehab MIP values = 74.3 ± 10.1/64.2 ± 9.8) with an 0.05 α value and 80% power, using the G*Power program for Windows. The number of samples required for each group was calculated as 14 subjects with COPD. Cohen's d was used for presenting the effect size, as follows: $d = 0.2$ considered a small, 0.5 a medium and 0.8 a large effect size (Cohen, 1988). Cohen's d is determined by calculating the mean difference between two groups, and then dividing the result by the pooled standard deviation (Cohen, 1988).

Results

In total 46 patients with moderate-to-severe COPD were invited to participate in the study. 2 did not agree to participate, and 7 did not meet the inclusion criteria. The participants were randomly allocated to either the study group (warm-up group, $n = 19$) or the control group (standard IMT group, $n = 18$). In total, 7 participants lost to follow-up the study: 4 participants in the warm-up group and 3 participants in the standard IMT group. Three participants in the warm-up group and two participants in the standard IMT group were lost to follow-up due to acute exacerbations caused by flu infection during the first week of the study. Additionally, one participant in each group lacked cooperation in the second week, leading to their exclusion from the study. These individuals were lost to follow-up at the study's onset due to reasons unrelated to their participation. As both acute exacerbation and lack of cooperation are among the exclusion criteria, they were subsequently excluded, and a per-protocol analysis was performed. Therefore, the study was completed with the final sample of 30 participants, with 15 in each group. Figure 1 shows the flow chart of the study.

The demographic and clinical parameters of each group are presented in Table 1, with no difference between

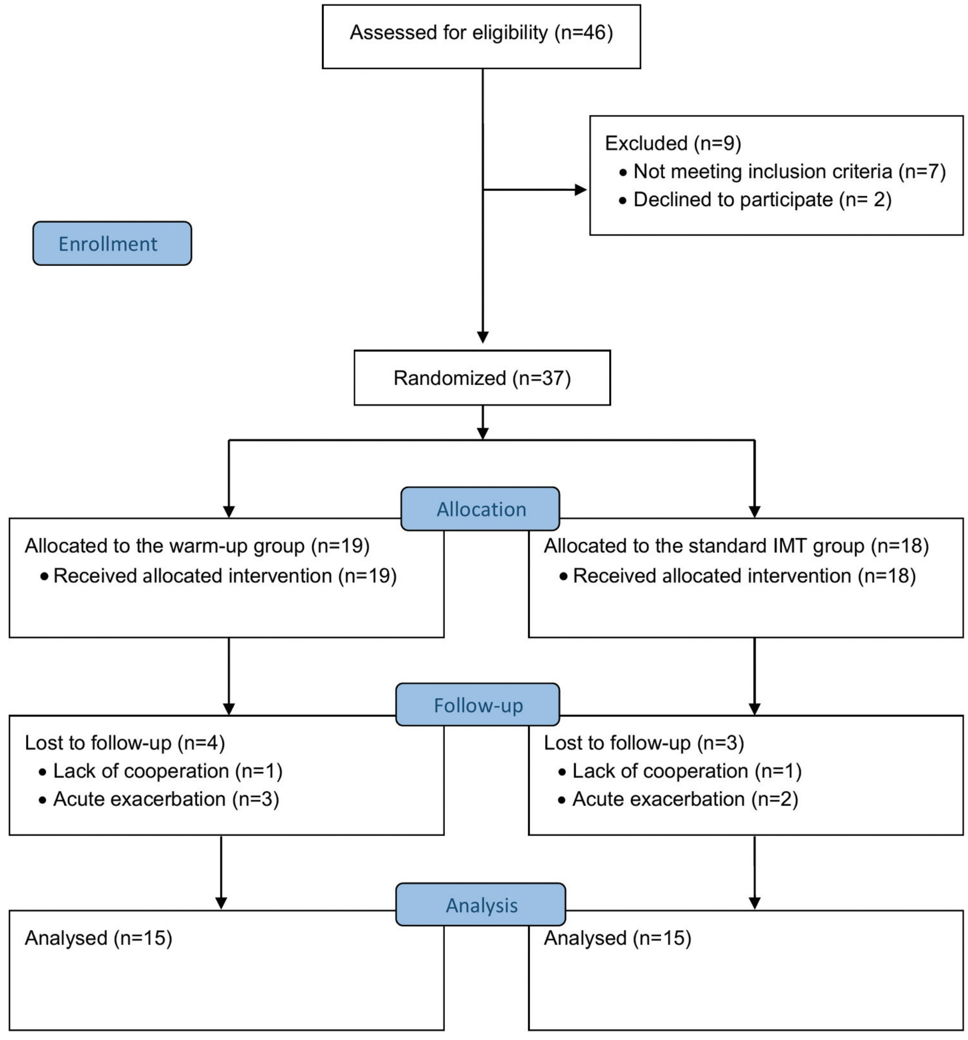

Figure 1. Flow chart of the study. Abbreviation: IMT inspiratory muscle training.

the groups before the training ($p > 0.05$) (Table 1). The changes in clinic parameters within and between the groups after the training are presented in Table 2. In the warm-up group, there were significant increases in FEV_1 % predicted ($p < 0.001$); FVC % predicted ($p = 0.01$); MIP cmH_2O ($p < 0.001$); and 6MWD meters ($p < 0.001$), in addition to a significant decrease in mMRC score ($p = 0.001$). Similarly, in the standard IMT group, there were significant increases in FEV_1 % predicted ($p < 0.001$); FVC % predicted ($p = 0.007$); MIP cmH_2O ($p < 0.001$); and 6MWD meters ($p < 0.001$), in addition to a significant decrease in mMRC score ($p = 0.001$) after the training. However, the improvements in FEV_1 % predicted ($p = 0.006$, effect size = 1.10); MIP cmH_2O ($p = 0.001$, effect size = 1.35); 6MWD meters ($p = 0.001$, effect size = 1.30); and mMRC score ($p = 0.033$, effect size = 0.76) were significantly greater in the warm-up group (Table 2).

There were significant improvements in health-related quality of life sub-scores after the training in both groups. In the warm-up group, all SGRQ scores (symptoms $p < 0.001$; activity $p = 0.002$; impact $p = 0.003$; total $p < 0.001$) significantly decreased, additionally, some sub-parameters of SF-36 (i.e. physical functioning $p = 0.002$; role-physical $p = 0.001$; and general health $p < 0.001$) significantly increased after the training (Table 3). Although there were also some improvements in the standard IMT group (i.e. SGRQ symptoms $p < .001$; SF-36 physical functioning $p = 0.047$; and general health $p < 0.001$) these improvements were significantly greater (i.e. SGRQ symptoms $p = 0.027$; SF-36 role-physical $p = 0.044$; and SF-36 general health $p = 0.006$) in the warm-up group (Table 3).

Discussion

In this randomized prospective trial, both groups exhibited enhanced lung functions, inspiratory muscle strength, exercise capacity, and a reduction in dyspnea. The hypothesis asserting the effectiveness of warming up inspiratory muscles was substantiated, as evidenced by greater

Table 1. Demographic and clinical parameters of groups before the training.

	Warm-up group	Standard IMT group	p
Sex, Male/Female (%)	7 (46.7)/8 (53.3)	9 (60)/6 (40)	0.464
Age, years	62.7 ± 4.8	61.5 ± 5.7	0.540
Height, cm	168.3 ± 3.5	166.4 ± 7.6	0.393
Weight, kg	69.8 ± 2.7	68.3 ± 14.3	0.694
BMI, kg/m^2	24.7 ± 1.3	24.6 ± 4.3	0.939
Comorbidities, n (%)			
Hypertension	4 (26.7)	3 (2.0)	0.666
Diabetes mellitus	3 (2.0)	2 (13.3)	0.624
Other	1 (6.67)	2 (13.3)	0.543
GOLD Grades			
Grade II	11 (73.4)	12 (8.0)	0.666
Grade III	4 (26.6)	3 (2.0)	
Cigarette consumption, pack-years	29 (23–39)	33 (20–38)	0.617
mMRC score	3 (2–3)	3 (2–4)	0.080
6MWD, meters	427.9 ± 19.1	401.6 ± 6.1	0.117
FEV_1, % predicted	61.2 ± 9.4	59.6 ± 7.2	0.605
FVC, % predicted	82.2 ± 7.0	83.1 ± 7.5	0.726
FEV_1/FVC, %	56.5 ± 9.3	55.5 ± 8.7	0.765
MIP, cmH_2O	51.1 ± 6.4	54.1 ± 3.8	0.120
MEP, cmH_2O	7.9 ± 15.5	73.2 ± 1.3	0.627

p values were tested by the Independent Student t test, Mann-Whitney U or χ^2 as required. Data are expressed as mean ± SD, median (interquartile range) or n (%); IMT Inspiratory muscle training; cm centimeter; kg kilogram; kg/m^2 kilogram per square meter; n counts; GOLD Global initiative for chronic obstructive lung disease; BMI body mass index; mMRC modified medical research council dyspnea scale; 6MWD 6-min walk distance; FEV_1 forced expiratory volume in 1 second; FVC forced vital capacity; MIP maximal inspiratory pressure; MEP maximal expiratory pressure; % percentage; cmH_2O centimeter of water.

Table 2. Changes in clinical parameters of groups after the training.

	Warm-up group			Standard IMT group				
	Before Training	After Training	p^a	Before Training	After Training	p^a	*Cohen's d*	p^b
mMRC score	3 (2, 3)	1 (0, 1)*	0.001	3 (2, 4)	2 (1, 2)*	0.001		
Δ mMRC score		−2 (−2, −1)			−1 (−2, −1) †		0.76	0.033
6MWD, meters	427.9 ± 19.1	516.9 ± 44.8 §	<0.001	401.6 ± 60.1	455.3 ± 54.3 §	<0.001		
Δ 6MWD, meters		88.9 ± 31.2			53.7 ± 22.4 ‡		1.30	0.001
FEV_1, % predicted	61.2 ± 9.4	68.4 ± 8.7 §	<0.001	59.6 ± 7.2	62.4 ± 6.9 §	<0.001		
Δ FEV_1, % predicted		7.2 ± 5.4			2.7 ± 2.1 ‡		1.10	0.006
FVC, % predicted	82.2 ± 7.0	83.5 ± 6.9 §	0.012	83.1 ± 7.5	84.1 ± 7.3 §	0.007		
Δ FVC, % predicted		1.3 ± 1.7			0.9 ± 1.2		0.22	0.560
FEV_1/FVC, %	56.5 ± 9.3	57.6 ± 8.1	0.109	55.5 ± 8.7	56.3 ± 9.2	0.143		
Δ FEV_1/FVC, %		1.9 ± 2.8			0.8 ± 2.0		0.45	0.233
MIP, cmH_2O	51.0 ± 6.4	69.1 ± 7.9 §	<0.001	54.1 ± 3.8	63.5 ± 3.2 §	<0.001		
Δ MIP, cmH_2O		18.1 ± 7.0			9.4 ± 5.7 ‡		1.35	0.001
MEP, cmH_2O	70.9 ± 15.5	74.3 ± 14.8	0.102	73.2 ± 10.3	73.9 ± 9.9	0.101		
Δ MEP, cmH_2O		2.1 ± 3.4			0.7 ± 1.5		0.52	0.167

Data are expressed as mean ± standard deviation or median (interquartile range). p^a within-groups analysis; p^b between-groups analysis, Cohen's *d* effect size, Δ after – before difference. Abbreviations: IMT Inspiratory muscle training; mMRC modified medical research council dyspnea scale; 6MWD 6-min walk distance; FEV_1 forced expiratory volume in 1 second; FVC forced vital capacity; % percentage; MIP maximal inspiratory pressure; MEP maximal expiratory pressure; cmH_2O centimeter of water; *Wilcoxon test, $p < 0.05$ (within-groups analysis); † Mann-Whitney test, $p < 0.05$ (between-groups analysis); § Paired Student t test, $p < 0.05$ (within-groups analysis); ‡ Independent Student t test, $p < 0.05$ (between-groups analysis).

improvements in lung functions, inspiratory muscle strength, exercise capacity, and dyspnea within the warm-up group compared to the standard IMT group. Additionally, HRQoL was comparable between the groups before the intervention but favored the warm-up group post-intervention, further supporting our hypothesis.

The minimal clinically important difference (MCID) has been used in clinical research and healthcare, defining the smallest change in treatment outcomes deemed meaningful or significant to patients. Various studies have been conducted to determine the MCID for outcomes such as 6MWD, mMRC, and MIP (Beaumont et al., 2021, 2023; Holland et al., 2010). Over the years, a widely accepted MCID of 54 meters for 6MWD has been used to assess the efficacy of COPD treatments (Holland et al., 2010). It has also been reported a 50-meter increase in mean 6MWD with exercise and IMT in COPD patients (undefined). Moreover, a meta-analysis on COPD revealed a mean effect of 44 meters for PR on 6MWD (McCarthy et al., 2015). In our study, the 6MWD in the warm-up group exceeded the reported MCID (mean difference was 88.9 meters), while in the standard IMT group, it approached the MCID closely (mean difference was 53.7 meters). Furthermore, both groups exhibited noteworthy improvements in the modified Medical Research Council (mMRC) score, with

Table 3. Comparison of health-related quality of life of groups before and after the training.

	Warm-up group			Standard IMT group				
	Before Training	After Training	p[a]	Before Training	After Training	p[a]	*Cohen's d*	p[b]
SGRQ Scores								
Symptoms	67.5 ± 11.3	26.1 ± 7.9	<0.001 §	68.6 ± 10.0	36.1 ± 7.0 §	<0.001 §		
Δ Symptoms		−41.4 ± 12.1			−32.5 ± 8.3		0.86	0.027 ‡
Activity	64.1 ± 25.6	36.8 ± 16.9	0.002 §	69.2 ± 25.0	62.3 ± 27.4	0.461		
Δ Activity		−27.2 ± 28.3			−6.9 ± 35.3		0.64	0.093
Impact	38.0 ± 23.1	15.0 ± 10.1	0.003 §	44.2 ± 22.3	41.3 ± 28.9	0.801		
Δ Impact		−23.1 ± 25.4			−2.9 ± 44.5		0.56	0.139
Total	50.8 ± 19.8	23.43 ± 8.8	<0.001 §	55.8 ± 18.4	46.8 ± 21.7	0.302		
Δ Total		−27.4 ± 21.9			−9.1 ± 32.7		0.66	0.082
SF-36 Scores								
Physical functioning	39.3 ± 15.3	52.2 ± 3.4	0.002 §	41.1 ± 12.2	48.7 ± 2.8 §	0.047 §		
Δ Physical functioning		12.9 ± 13.5			7.6 ± 13.5		0.39	0.292
Role-physical	41.9 ± 13.1	55.8 ± 2.4	0.001 §	45.0 ± 14.3	46.2 ± 14.1	0.821		
Δ Role-physical		13.9 ± 12.6			1.2 ± 19.7		0.77	0.044 ‡
Bodily pain	48.2 ± 13.1	48.7 ± 12.5	0.914	47.8 ± 12.4	50.5 ± 9.7	0.506		
Δ Bodily pain		0.5 ± 16.9			2.7 ± 15.2		0.14	0.711
General health	34.9 ± 10.5	58.3 ± 2.8	<0.001 §	40.2 ± 5.9	54.1 ± 4.1 §	<0.001 §		
Δ General health		23.3 ± 9.9			13.9 ± 7.5		1.07	0.006 ‡
Vitality	44.3 ± 15.6	53.7 ± 9.9	0.101	42.5 ± 10.8	45.6 ± 10.9	0.504		
Δ Vitality		9.4 ± 20.8			3.1 ± 17.3		0.33	0.370
Social functioning	41.3 ± 14.3	45.2 ± 12.3	0.359	42.7 ± 14.6	43.2 ± 14.1	0.936		
Δ Social functioning		3.9 ± 15.8			0.5 ± 24.2		0.17	0.657
Role-emotional	44.9 ± 8.8	51.8 ± 12.9	0.058	47.4 ± 12.2	50.9 ± 10.9	0.449		
Δ Role-emotional		6.9 ± 12.9			3.5 ± 17.5		0.22	0.549
Mental health	53.0 ± 11.2	54.9 ± 11.6	0.528	52.1 ± 13.3	55.3 ± 10.7	0.512		
Δ Mental health		1.9 ± 11.6			3.3 ± 19.1		0.09	0.812

Data are expressed as mean ± standard deviation. p[a] within-groups analysis; p[b] between-groups analysis, Cohen's *d* effect size, Δ after – before difference. Abbreviations: IMT Inspiratory muscle training; SGRQ St. George's respiratory questionnaire; SF-36 Short form health survey; § Paired Student t test, $p < 0.05$ (within-groups analysis); ‡ Independent Student t test, $p < 0.05$ (between-groups analysis).

a decrease of −1 unit in the standard IMT group and −2 units in the warm-up group. This change aligns with the previously reported MCID of −1 unit for mMRC (Beaumont et al., 2021), signifying a substantial reduction in dyspnea. In a recent study, the MCID for MIP was calculated as 7.9–13.5 cmH_2O in patients with severe and very severe COPD (Beaumont et al., 2023). In our study, the warm-up group demonstrated a MIP change surpassing the reported MCID, also, the standard IMT group showed improvement within this value range. It is worth noting that in their study Beaumont et al. (2023) focused on patients with severe and very severe COPD, indicating a clinically worse condition compared to our population.

In patients with COPD, exacerbations are a dynamic process of obstruction and destruction. The majority of exacerbations are brought on by bacterial or viral infections, with the rhinovirus working as the primary cause and the influenza virus as one of the most prevalent viruses (Liao et al., 2022). Liao et al. (2022) reported that COPD patients had a significantly higher risk of pneumonia and respiratory failure following influenza infection, compared with those without influenza. In our study, five participants were lost to follow-up due to acute exacerbations caused by flu infection during the first week of the study. We considered that the exacerbations that occurred in the first week of the study were not intervention-related. In COPD patients, since exacerbations are a dynamic process that may show poor prognosis, we excluded these patients and referred them to the relevant physician for exacerbation management. The exclusion of COPD patients experiencing exacerbations is a prudent clinical decision rooted in the need to prioritize patient safety and optimize intervention outcomes. During exacerbations, COPD patients often exhibit a heightened state of respiratory distress characterized by increased dyspnea, cough, and sputum production. Engaging in strenuous exercise during such periods may further exacerbate respiratory symptoms, compromise oxygenation, and contribute to a decline in overall health status.

Inspiratory muscle training has been extensively investigated in subjects with COPD (Ammous et al., 2023; Beaumont, Forget, Couturaud, and Reychler, 2018). It is based on the principle of using a resistive loading device, which increases inspiratory muscle strength and endurance (Ammous et al., 2023). As a result of an IMT program MIP, an indicator of inspiratory muscle strength, increases. The increased MIP reduces dyspnea by decreasing hyperinflation and improving the capacity of ventilation (Cirino et al., 2023). Inspiratory muscle training has been recommended as an additional intervention to a PR program, and the combination of PR and IMT has been proven to significantly improve inspiratory muscle strength and pulmonary function, especially in COPD subjects with inspiratory muscle weakness (Ammous et al., 2023;

Beaumont, Forget, Couturaud, and Reychler, 2018). Regarding the definition of respiratory muscle weakness, a cutoff 60 cm H_2O was chosen as referenced for COPD, although there is no consensus on the best cutoff value in the literature (Ammous et al., 2023). Studies examining the effects of IMT have shown that different training protocols have different effects on respiratory functions (Ammous et al., 2023; Beaumont, Forget, Couturaud, and Reychler, 2018). Beaumont et al. (2015) applied IMT in addition to PR with a 3-week training protocol to subjects with COPD, who did not have inspiratory muscle weakness, and found no significant change in pulmonary function. However, Weiner et al. (2004) conducted a study on 38 subjects with COPD and applied IMT at 60% of the MIP value for 12 weeks. They have found a significant difference in FEV_1 in the study group. In a recent meta-analysis, Figueiredo, Azambuja, Cureau, and Sbruzzi (2020) demonstrated that even isolated IMT showed an improvement in FEV_1. In our study, even though lung functions improved similarly in both groups, these gains were greater in the warm-up group.

Respiratory muscle weakness has been proven to contribute to hypercapnia, dyspnea, nocturnal oxygen desaturation and reduced exercise capacity in subjects with COPD (Ammous et al., 2023). It has been shown that diaphragm workload increases during exercise in COPD, and that subjects with COPD use a greater MIP than healthy individuals (Langer et al., 2018; O'Donnell, Bertley, Chau, and Webb, 1997). This breathing pattern is closely related to the feeling of dyspnea and respiratory muscle fatigue during exercise (O'Donnell, Bertley, Chau, and Webb, 1997). Studies have proven that IMT leads to improvements in inspiratory muscle strength and endurance, exercise capacity, dyspnea, and HRQoL (Ammous et al., 2023; Beaumont, Forget, Couturaud, and Reychler, 2018). O'Donnell, Bertley, Chau, and Webb (1997) proved that increased dyspnea perception is associated with a low MIP value. As a result of the increase in the MIP with IMT, the severity of dyspnea decreases and thus exercise capacity, restricted by dyspnea, increases. In a meta-analysis, Gosselink et al. (2011) reported that IMT increased inspiratory muscle strength by 13 cmH_2O in the study group compared to the control group. In a randomized study, Basso-Vanelli et al. (2016) performed IMT with 60% of MIP after 4th weeks in COPD subjects with and without respiratory muscle weakness in a 16-week PR program. They showed that IMT increased inspiratory muscle strength and exercise capacity, with further gains in subjects with respiratory muscle weakness. It has been proven that increased severity of dyspnea during exercise is associated with the baseline MIP in subjects with COPD, and the highest dyspnea perception occurs in patients with the lowest MIP value (Ammous et al., 2023). Moreover, it has been shown that respiratory muscle weakness is an independent contributor to dyspnea (Cirino et al., 2023). For this reason, dyspnea and exercise capacity are frequently evaluated in studies using IMT in COPD. Studies have shown that 6–12 weeks of IMT is effective in reducing dyspnea and improving exercise capacity (Ammous et al., 2023). In a meta-analysis, it was proven that IMT clinically significantly improved dyspnea compared to the control group (Beaumont, Forget, Couturaud, and Reychler, 2018). In our study, we found that respiratory muscle strength and exercise capacity increased, and dyspnea decreased in both groups. However, these gains were greater in the warm-up group.

The whole-body warm-up before exercise has positive effects on performance in the short term. However, despite its beneficial effect, it is insufficient to warm up the inspiratory muscles (Andrade et al., 2015; Barnes and Ludge, 2021). The whole-body warm-up protocols are not enough to prepare the inspiratory muscles, because of their moderate-intensity and characterized by low ventilation demands (Andrade et al., 2015; Barnes and Ludge, 2021; Lomax, Grant, and Corbett, 2011). However, the IMW protocol both prepares the inspiratory muscles for exercise and reduces the severity of perceived dyspnea during exercise (Barnes and Ludge, 2021). Warming up the inspiratory muscles improves oxygen delivery and muscle microvascular utilization profiles by providing early contractions (Poole and Jones, 2011; Richard and Billaut, 2019). It has been thought that warming up the inspiratory muscles before exercise provides neural facilitation and contributes to inspiratory muscle activity (Cirino et al., 2023; Wilson et al., 2014). Previous studies have suggested that warming up the inspiratory muscles improves the coordination of respiratory muscles by eliminating reflex inhibition in the inspiratory muscles and reducing the degree of co-contraction between the inspiratory and expiratory muscles (Cirino et al., 2023). Moreover, it has been proven that warming up the inspiratory muscles in athletes before exercises requiring effort prepares the inspiratory muscles for exercise and increases respiratory muscle strength, pulmonary function, exercise capacity, and contributes to the reduction of dyspnea during exercise (Barnes and Ludge, 2021). For all these reasons, we thought that specific warming up the inspiratory muscles prepares the respiratory muscles for the next loading phase. Wilson et al. (2014) proved that sports-specific warm-up combined with IMW provided a significant performance improvement in athletes. Lomax, Grant, and

Corbett (2011) applied the IMW and IMT protocols to the athletes both as separate and combined. They showed that combined training has the most gains. Our study showed similar gains to the study conducted by Lomax, Grant, and Corbett (2011). The possible mechanism why inspiratory muscle strength is further increased by warming up the inspiratory muscles, before higher resistive loading, can be explained by the above evidence. Despite the explanations provided for the improvement due to the IMW protocol, we cannot rule out the possibility that this protocol may have functioned as an additional inspirational muscle training protocol.

It has been demonstrated that as exercise capacity decreases in subjects with COPD, HRQoL is affected and significantly worse as the disease severity increases. Also, these impairments are often out of proportion to the decline in pulmonary function (Global Initiative for Chronic Obstructive Lung Disease, 2023). Health-related quality of life has been frequently investigated in studies using IMT as an intervention. In comprehensive meta-analysis studies on this issue, it has been proven that IMT improves the HRQoL by reducing dyspnea and increasing exercise capacity in subjects with COPD (Ammous et al., 2023; Beaumont, Forget, Couturaud, and Reychler, 2018). In our study, while there was an increase in HRQoL in both groups, this gain was significantly higher in the warm-up group. It was noteworthy that there were improvements, especially in symptom scores and physical activity sub-scores in our study. In our study, we thought that HRQoL increased because of increased respiratory muscle strength and exercise capacity and decreased dyspnea.

We have some potential limitations in our study. The demographic and clinical characteristics of the groups included in the study were similar and homogenous, making it easier to compare and interpret the data. However, the participants in our study consisted of subjects with GOLD stage II-III COPD and inspiratory muscle weakness makes it difficult to generalize the results obtained to the entire COPD population. Another important limitation of this study is that only one trial of the 6MWD was performed at both pre- and post- intervention assessments. While this approach allowed for a comprehensive evaluation within the given timeframe, the reliance on a single trial may impact the generalizability of the results. Subjects with COPD have impaired diaphragm mobility compared to healthy subjects (Chun, Han, and Modi, 2015). Although it has been proven that IMT has positive effects on diaphragm mobility (Chun, Han, and Modi, 2015), another potential limitation is that we did not use any assessment method to evaluate it in our study.

Conclusions

Performing a warm-up for inspiratory muscles before IMT boosts benefits for pulmonary function, inspiratory muscle strength, exercise capacity, dyspnea, and HRQoL in subjects with moderate-to-severe COPD and inspiratory muscle weakness. Considering the notable benefits associated with warming up inspiratory muscles before IMT, it is concluded that incorporating an inspiratory muscle warm-up protocol could be beneficial and may be considered as an adjunct to PR programs.

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