Heliyon 9 (2023) e20079

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Changes in diaphragm thickness and 6-min walking distance improvement after inspiratory muscle training in patients with chronic obstructive pulmonary disease: Clinical trial

Tomomi Ichiba [a,*], Tetsuo Miyagawa [b], Toru Tsuda [c], Takeshi Kera [d], Osamu Yasuda [e]

[a] Department of Physical Therapy, Faculty of Health Sciences, Kyorin University, Tokyo, Japan
[b] Kochi Professional University of Rehabilitation, Kochi, Japan
[c] Department of Respiratory Medicine, Kirigaoka Tsuda Hospital, Fukuoka, Japan
[d] Department of Physical Therapy, Takasaki University of Health and Welfare, Gunma, Japan
[e] National Institute of Fitness and Sports in Kanoya, Department of Sports and Life Sciences, 1 Shiromizucho, Kanoya-city, Kagoshima, 891-2393, Japan

ARTICLE INFO

Keywords:
Chronic obstructive pulmonary disease
Inspiratory muscle training
Airway-occlusion pressure
The thickness of the diaphragm
Elderly

ABSTRACT

Aim: Inspiratory muscle training (IMT) improves respiratory muscle function and exercise tolerance in patients with chronic obstructive pulmonary disease (COPD), but the detailed mechanism is unclear. The purpose of this study is to elucidate the mechanism of functional improvement by IMT from $P_{0.1}$, an index of respiratory central output, and thickness of diaphragm (Tdi), a noninvasive and reliable ultrasound examination.

Methods: This clinical trial study enrolled 13 elderly patients with COPD. IMT was performed using the POWER breathe® Medic Plus breathing trainer in combination with each participant's outpatient rehabilitation regimen. Starting at 20% of the maximal inspiratory pressure (PImax) and increasing to 50%, the participants performed 30 IMT repetitions twice a day for 2 months. $P_{0.1}$ is the value of airway-occlusion pressure at 0.1 s after the start of inspiratory flow, and Tdi was measured at rest and maximal breathing.

Results: PImax and 6-min walking distance(6MWD) significantly increased after training. Tdi at resting inspiration and expiration, and maximal inspiration also significantly increased after training. In addition, the Borg Scale scores for dyspnea and leg fatigue and the respiratory rate of the 1-min recovery period after the 6MWD significantly decreased. There was no significant difference in $P_{0.1}$.

Conclusions: These results suggest that the effects of IMT may be attributed to the improved peripheral factors rather than to the central factors in elderly COPD patients.

1. Introduction

Pulmonary rehabilitation is centered on exercise therapy and is a combination of conditioning and daily living training activities. Respiratory muscle training is one of the fundamental disciplines in exercise therapy [1] and includes inspiratory (IMT) and expiratory

* Corresponding author. Department of Physical Therapy School of Health Sciences, Kyorin University, 5 Shimorenjyaku, Mitaka-shi, Tokyo, 181-8612, Japan.

E-mail address: tomo330@ks.kyorin-u.ac.jp (T. Ichiba).

https://doi.org/10.1016/j.heliyon.2023.e20079
Received 18 January 2023; Received in revised form 7 September 2023; Accepted 11 September 2023
Available online 15 September 2023
2405-8440/

muscle training; however, IMT is mainly performed [2]. IMT is expected to improve respiratory muscle strength and endurance, exercise tolerance, dyspnea, respiratory function, daily living activities, and health-related quality of life (HRQOL) [3]. Equipment such as Threshold-IMT, and POWER breathe is used for IMT. Currently, chronic obstructive pulmonary disease (COPD) is the most common target for respiratory muscle training [4]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (http://www.goldcopd.org, accessed January 16, 2020) recommended the incorporation of respiratory muscle training as a part of the comprehensive respiratory rehabilitation program for COPD. In the meta-analysis of 32 studies including 830 cases of COPD, Gosselink et al. [5] revealed significant improvements in the maximal inspiratory pressure (PImax), respiratory muscle endurance, exercise tolerance, Borg Scale scores, dyspnea, and HRQOL after IMT. In another meta-analysis of 37 studies including 1427 cases of COPD, which was conducted by Beaumont et al. [6], dyspnea, inspiratory muscle strength, and 6-min walking distance (6MWD) improved following IMT. However, it was reported that improvements in dyspnea were not related to respiratory muscle strength, and there was no combined effect with respiratory rehabilitation. Charususin et al. [7] reported that the combined effect of respiratory rehabilitation and IMT on elderly COPD improved inspiratory muscle strength but not 6MWD. As mentioned above, there is no consistent view on the effectiveness of IMT and the effects of concomitant use.

One of the important issues in respiratory rehabilitation is the reduction of dyspnea. One of the most popular mechanisms for sensing dyspnea at present is motor command theory [8], which is thought to involve respiratory central output. As an index of this respiratory central output, there is airway-occlusion pressure at 0.1 s after the start of inspiratory flow ($P_{0.1}$) [9]. We used $P_{0.1}$ to investigate whether the relaxation posture affects $P_{0.1}$and whether manual chest wall compression affects $P_{0.1}$ in elderly COPD [10,11]. No significant difference was found in $P_{0.1}$ in the two studies, suggesting that relaxation posture and manual chest wall compression did not affect respiratory central output. However, it has not been examined whether IMT affects $P_{0.1}$.

It has also been reported that IMT causes muscle hypertrophy of the diaphragm [12]. On the other hand, it has been reported that in IMT, the muscle activity of the respiratory assist muscles is enhanced, making it difficult to select the diaphragm [13]. Ultrasound of the diaphragm is a noninvasive, reliable and relatively inexpensive diagnostic tool. Sonographic assessment of diaphragm function would be a useful clinical tool in patients with COPD. However, studies detailing the motion of the diaphragm in patients with COPD are limited [14].

There are no consistent reports of the combined effects of pulmonary rehabilitation and IMT. In addition, there is no study using respiratory central output to determine whether the effects of IMT are due to central or peripheral factors. Furthermore, there are few detailed reports on whether IMT affects thickness of the diaphragm (Tdi). The purpose of this study was to clarify the effect of IMT in combination with pulmonary rehabilitation, using $P_{0.1}$ and Tdi with ultrasound.

2. Methods

2.1. Participants

This clinical trial study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). After obtaining approval from the Kyorin University institutional ethics committee (approval no. 29-10 in 2017), study purpose and the method of personal information management were explained to all participants, who thereafter provided written informed consent.

In addition, we fully explained the IMT training period, method, equipment, etc. before participating, and explained the adaptation and effects of IMT based on previous research. The participants were also instructed to continue their usual respiratory rehabilitation during the participation period.

This study included 20 ambulatory elderly patients with COPD who visited Kirigaoka Tsuda Hospital, Fukuoka, Japan, for outpatient rehabilitation. Inclusion criteria were patients had been diagnosed with COPD by a respiratory physician for at least one year after being diagnosed with COPD according to COPD diagnostic guidelines. Patients who were able to walk without the use of a cane and had no history of falls were included. Since 6MWT is one of the measurement items, the selection criteria were based on the ability to perform a stable gait and a stable respiratory condition. Exclusion criteria were patients with severe orthopedic disease, cardiovascular disease, central nervous system disorders, and cognitive impairment. In addition, patients requiring oxygen inhalation both at rest and during exercise were also excluded. This is due to the difficulty of measuring $P_{0.1}$ under oxygen inhalation and to eliminate the influence of other diseases.

Using EZR and using PImax as a parameter from previous studies, the mean difference was 25, the SD was 20, the α error was 0.05, the power was 0.8, and the sample size was 8 under two-tailed test conditions.

2.2. Procedures

Outpatient rehabilitation consisted of walking and a bicycle ergometer as exercise therapy, and thoracic excursion training and expectoration as conditioning, twice a week for 60 min per session. We used a threshold-type IMT device, POWER breathe® Medic Plus (POWER breathe International Ltd., Southam, United Kingdom), for IMT in combination with the outpatient rehabilitation regimens. The respiratory function, respiratory muscle strength, $P_{0.1}$, 6MWD, Tdi, and CAT scores were measured before and after 2 months of IMT.

The peripheral artery oxygen saturation (SpO_2), heart rate (HR), respiratory rate (RR), as well as dyspnea and lower limb fatigue (using the Borg Scale) were measured before and after the 6-min walk test (6MWT). These measurements were also recorded during a 2-min recovery period.

2.3. IMT

PImax was measured twice before starting IMT training. POWER breathe® Medic Plus was set to a load of 20% of the highest PImax obtained, training was started and then the load was increased to 50%. IMT was performed in two sets of 30 times per day for 2 months and recorded daily using a checklist. For data collection, the Physical Therapist in charge checked the checklist every time during outpatient rehabilitation and whether it was implemented in the correct way and adjusted the load. In addition, the researchers measured each item before and after training, and collected the checklists after completing the measurements two months later. The final completion rate was 89%.

2.4. Measuring equipment

2.4.1. Respiratory function

We used an electronic spirometer (AS-507, Minato Medical Science, Osaka, Japan) to evaluate respiratory function. Evaluation items were forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_{1.0}$), $FEV_{1.0}$/FVC ratio ($FEV_{1.0}$%), vital capacity (VC), tidal volume (V_T), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), inspiratory capacity (IC), peak expiratory flow rate (PEFR), maximum mid-expiratory flow (MMF), and maximum expiratory flow rate at 25% VC/height (V25/Ht). Each item was measured twice in the sitting position, and the highest value was adopted. For respiratory muscle strength, the PImax and maximum expiratory pressure (PEmax) were used to measure the intraoral pressure. The PImax at residual capacity in the sitting position and the PEmax at whole lung capacity were measured according to the method described by Black and Hyatt [15]. The participants were maintained pressure for at least 1.5 s and the maneuver was repeated three times; the respiratory muscle strength was determined as the highest of the three recorded values.

2.4.2. $P_{0.1}$ measurement

$P_{0.1}$ has been used as an indicator of respiratory center output related to dyspnea [9]. In our study, an airway occlusion system (model 9326, Hans Rudolph, Shawnee, KS, USA; dead space 48.9 mL) was used to measure $P_{0.1}$. Airway pressure was measured using a differential pressure meter (DP-10, Validyne, Northridge, CA, USA), while ventilation parameters were measured using a metabolic gas analyzer (AE-300S, Minato Medical Science). A hot wire flow transducer was connected to the outlet of the airway occlusion system, and a mask (MAS0215, Minato Medical Science) was connected to the mouth port. A differential pressure transducer was connected to the airway occlusion system via a tube (4-mm diameter) to measure the airway pressure. Entrance to the airway obstruction system was manually occluded using a balloon at the end of each expiration and held until the start of inspiration. The $P_{0.1}$ measurement was obtained by closing the inhalation port with a balloon shutter at the end of expiration and by measuring the intraoral pressure after 100 ms, when the intraoral pressure became negative at the start of resting inhalation [16]. $P_{0.1}$ was randomly measured five times, and the average calculated from four stable measurements was recorded, as previously reported.

Analog signals from raw flow pressure were downloaded to a personal computer via an analog-to-digital converter (PowerLab 16/30, ADInstruments, Sydney, Australia) at a sampling frequency of 1000 Hz. These signals were analyzed using commercially available software (Chart 5.3, ADInstruments) to calculate $P_{0.1}$. COPD was characterized by decreased inspiratory muscle strength, and $P_{0.1}$ was corrected to PImax ($P_{0.1}$/PImax).

2.4.3. Tdi measurement

The Tdi was measured via a linear probe in B mode using an ultrasonic diagnostic imaging apparatus (ARIETTA Prologue, Hitachi, Ltd., Tokyo, Japan). The measurement position was between the eighth and ninth ribs on the right axillary line, referring to the method of Chon et al. [17], and the Tdi in the zone of apposition (ZOA) was measured. The Tdi at the ZOA (the part of the rib diaphragm angle in contact with the chest wall at the origin) was measured by placing a probe coated with an ultrasonic gel on the body surface. For the measurement, continuous measurement in B mode was performed, and the thickness at each lung volume level at rest was measured. The parameters measured were resting inspiration, resting expiration, maximal inspiration, and maximal expiration. Resting respiration was measured first, and then maximal respiration was measured. We measured twice before and after training and adopted the average value.

2.4.4. 6MWT

The 6MWT is a field walking test for assessing exercise capacity and is an essential evaluation item for respiratory rehabilitation. The guidelines for the 6MWT were published by the American Thoracic Society in 2002 [18]. According to these guidelines, the walkway was used by folding back a flat straight course of 30 m, and the participants were instructed to “walk a long distance as fast as possible in 6 min,” and a call was made every min. The primary evaluation item of the 6MWT was the 6MWD, which was measured once before and after training.

2.4.5. COPD assessment test (CAT)

The CAT is a tool used to comprehensively assess HRQOL. It consists of the following eight items: (1) cough, (2) sputum, (3) breathlessness, (4) shortness of breath during exertion, (5) daily life, (6) self-confidence in going out (mental), (7) sleep, (8) vitality [19]. The subjective symptoms were evaluated once before and after training using the CAT questionnaire.

2.4.6. Other measurements

Dyspnea and lower limb fatigue were assessed using the Borg Scale; the RR, SpO_2, and HR were measured before and after the 6MWT and after the 1- and 2-min recovery periods.

2.4.7. The description of measurement techniques

Respiratory function and $P_{0.1}$ measurements were performed by a single trained examiner. In addition, Tdi measurement was performed by one examiner who is familiar with the handling of ultrasound. Measurements before and after training were performed by the same examiner.

2.5. Statistical analysis

SPSS version 21.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analyses. A paired *t*-test was used to compare the values of each item before and after training. All values were expressed as means ± standard error, and statistical significance was set at $P < .05$. Effect size was assessed using the R family index, indicating the strength of association between variables. Effect sizes were assessed as Small; r = 0.1, Medium; r = 0.3, Large; r = 0.5. And the 95% confidence interval (95%CI) was expressed as an absolute value.

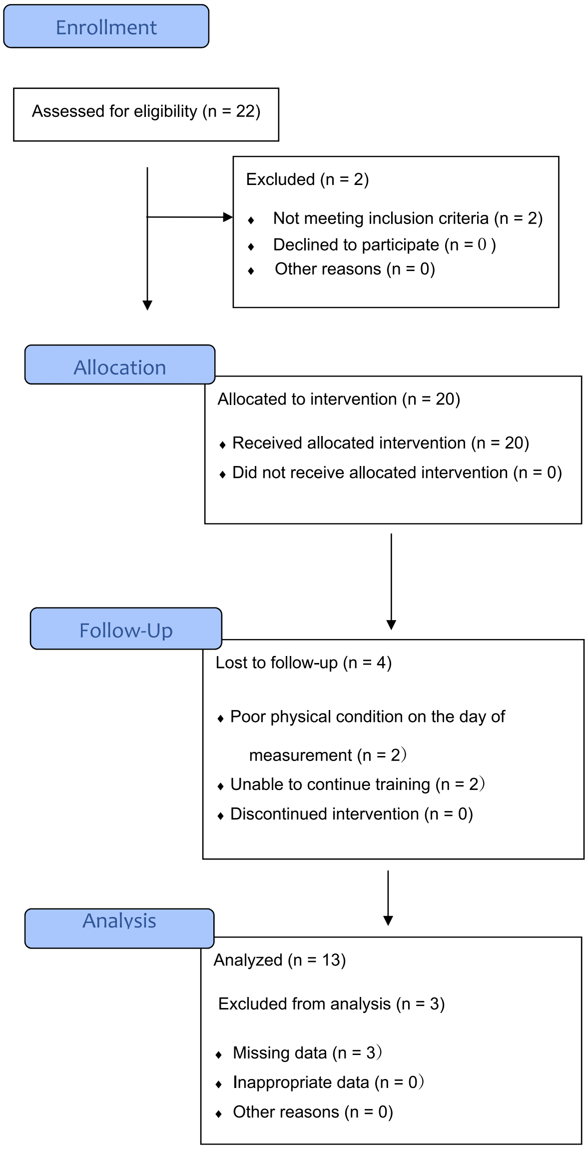

Fig. 1. Study flowchart.

3. Results

Of the 20 subjects, 13 were able to perform the training (11 male, 2 female; mean age, 72.9 ± 7.35 years; height, 160.9 ± 8.67 cm; body weight, 56.8 ± 10.6 kg; body mass index, 21.4 ± 2.6 kg/m^2). A flow chart of the study is presented in Fig. 1. A total of 7 out of 20 subjects with poor physical condition on the day of measurement (n = 2), unable to continue training (n = 2) and excluded from analysis (n = 3) were excluded. The changes in respiratory function before and after 2 months of IMT are presented in Table 1. FVC, % FVC, $FEV_{1.0}$, %$FEV_{1.0}$, expiratory reserve volume (ERV), maximum expiratory flow rate at 25% vital capacity/height (V25/Ht) are significantly increased after training ($r = 85$, $P = .001$, $r=.88$, $P = .001$, $r=.62$, $P = .019$, $r=.65$, $P = .012$, $r=.65$, $P = .012$, $r=.57$, $P = .033$, respectively). The changes in respiratory muscle strength and respiratory central output, 6MWD, and CAT scores, are presented in Table 2, respectively. The PImax, 6MWD significantly increased ($r=.81$, $P = .001$, $r=.66$, $P = .01$) and only $P_{0.1}$/PImax significantly decreased ($r=.71$, $P = .01$). The changes in the Tdi are presented in Table 3. The resting inspiration, resting expiration, and maximal inspiration significantly increased ($r=.68$, $P = .008$, $r=.65$, $P = .011$, $r=.82$, $P = .001$, respectively). The changes in the Borg Scale scores for dyspnea and lower limb fatigue, RR, SpO_2, and HR before and after the 6MWD and after the 1- and 2-min recovery periods are presented in Table 4. The Borg Scale scores for dyspnea and lower limb fatigue and the RR significantly decreased during the 1-min recovery period ($r=.60$, $P = .050$, $r=.70$, $P = .016$, and $r=.63$, $P = .036$, respectively).

4. Discussion

In this study, we found that IMT combined with respiratory rehabilitation for 2 months significantly increased PImax and 6MWD in elderly COPD, affecting respiratory function, Tdi, exercise tolerance, and dyspnea. At present, performing IMT for 15 min twice a day at a load pressure of ≥30% of the PImax is a standard practice for patients with COPD [20]. Considering previous reports [20], in this study we increased the load pressure from 20% to 50% and asked the participants to perform 30 repetitions twice a day. Interestingly, improvements were also observed in the PImax and 6MWD, similar to the results of the meta-analysis conducted by Beaumont et al. [6] In an ATS/ERS systematic review [21], there was a moderate to strong correlation (coefficient 0.38–0.85) between the 6MWD and physical activity and a strong correlation between low 6MWD (300–450 m) and high mortality. It has been reported that in patients with moderate to severe COPD, 6MWD needs to change by about 35 m to show a significant effect [22]. The results of our study was classified 6MWD as low, but increased significantly from 354 m to 384 m after training. It is considered that the training effect was recognized even in the patients with low 6MWD.

The CAT is an eight-item questionnaire that can be used to comprehensively evaluate patients' HRQOL, and has a clear and strong correlation with St George's Respiratory Questionnaire, which is widely used for the evaluation of quality of life in clinical trials [19]. There were no significant differences in the CAT scores before and after training in our study. These results suggested that although the performance of IMT for 2 months improved the respiratory muscle strength and 6MWD, it did not lead to improvement in HRQOL.

Regarding the Tdi, resting inspiration, resting expiration, and maximal inspiration also increased significantly after training. This is thought to be due to the increase in FVC and FEV1.0. Paulin et al. [23] investigated the relationship between diaphragmatic thickness and dyspnea in 54 cases of COPD using B-mode ultrasonography. The patients with COPD had decreased diaphragm thickness, which correlated with the 6MWD and a negatively with dyspnea. Kang et al. [24] reported that diaphragmatic thickness correlated with airway obstruction and with ventilatory capacity, pulmonary hyperinflation for the patients with COPD. Therefore, we thought that IMT improved pulmonary function and affected Tdi and exercise tolerance.

In this study, we used $P_{0.1}$ to investigate whether IMT is involved in the central nervous system. The normal range of $P_{0.1}$ is 1–2

Table 1
Comparison of respiratory function before and after inspiratory muscle training.

Parameter	Before IMT	After IMT	*P* value (ES)	*95%CI*
FVC (L)	2.15 (.21)	2.44 (.21)	.001* (.85)	.29(.41–.18)
%FVC (%)	68.0 (5.35)	77.5 (4.80)	.001* (.88)	9.47(12.7–6.21)
$FEV_{1.0}$ (L)	1.36 (.17)	1.45 (.16)	.019† (.62)	.09(.16–.02)
%$FEV_{1.0}$ (%)	53.6 (5.20)	57.3 (5.03)	.012† (.65)	3.73(6.49–0.97)
$FEV_{1.0}$% (%)	59.0 (3.29)	59.0 (3.22)	.979(.08)	.05(4.17–4.07)
VC (L)	2.77 (.27)	2.78 (.23)	.862(.05)	.01(.16–.14)
%VC (%)	84.1 (6.11)	85.2 (4.72)	.648(.14)	1.02(5.78–3.73)
V_T (L)	.85 (.12)	.93 (.10)	.319(.29)	.08(.25–.09)
IRV (L)	1.27 (.19)	1.07 (.16)	.071(.50)	.20(.02–.41)
ERV (L)	.54 (.05)	.86 (.13)	.012† (.65)	.32(.56–.09)
IC (L)	2.11 (.24)	2.03 (.19)	.592(.16)	.08(.24–.40)
PEFR (L/s)	4.01 (.59)	4.48 (.59)	.129(.42)	.47(1.10–.16)
MMF (L/s)	.81 (.23)	.85 (.19)	.535(.18)	.03(.15–.08)
V25/Ht (L/s/m)	.21 (.04)	.23 (.04)	.033† (.57)	.02(.04–.001)

Data are presented as means ± standard error.
Statistically significant values are marked as follows: *$P < .001$; †$P < .05$.
IMT: inspiratory muscle training; ES: effect size; 95%CI:confidence intervals; FVC: forced vital capacity; $FEV_{1.0}$: forced expiratory volume in 1 s; $FEV_{1.0}$%: $FEV_{1.0}$/FVC ratio; VC: vital capacity; V_T, tidal volume; IRV, inspiratory reserve volume; ERV: expiratory reserve volume; IC: inspiratory capacity; PEFR: peak expiratory flow rate; MMF: maximum mid-expiratory flow; V25/Ht: maximum expiratory flow rate at 25% VC/height.

Table 2
Comparison of the respiratory muscle strength and Respiratory central output, 6MWD, and CAT scores, before and after inspiratory muscle training.

Parameter	Before IMT	After IMT	*P* value (ES)	*95%CI*
PImax (cmH_2O)	61.1 (7.02)	77.3 (5.95)	.001* (.81)	16,2(23.7–8.71)
PEmax (cmH_2O)	68.3 (6.13)	87.2 (9.87)	.063(.51)	18.9(39.0–1.18)
$P_{0.1}$ (cmH_2O)	−1.86 (.23)	−1.84 (.24)	.904(.04)	.02(.39–.35)
$P_{0.1}$/PImax(%)	−3.92 (.01)	−2.80 (.01)	.010* (.71)	.01(.02–.01)
6MWD (m)	354.7 (32.9)	384.0(33.1)	.010* (.66)	29.3(50.3–8.33)
CAT	12.5 (1.33)	12.4 (2.14)	.962(.02)	.08(3.71–3.88)

Data are presented as means ± standard error.
Statistically significant values are marked as follows: *$P < .001$.
IMT: inspiratory muscle training; ES: effect size; 95%CI:confidence intervals; PImax: maximal inspiratory pressure; PEmax: maximal expiratory pressure; $P_{0.1}$: airway-occlusion pressure 0.1 s after the start of inspiratory flow; $P_{0.1}$/PImax: airway-occlusion pressure 0.1 s after the start of inspiratory flow/maximal inspiratory pressure; 6MWD: 6-min walking distance; CAT: COPD assessment test.

Table 3
Comparison of diaphragm thickness before and after inspiratory muscle training.

Parameter	Before IMT	After IMT	*P* value (ES)	*95%CI*
Resting inspiration (mm)	2.18 (.10)	2.48 (.13)	.008* (.68)	.30(.50–.10)
Resting expiration (mm)	1.39 (.09)	1.58 (.09)	.011† (.65)	.19(.33–.05)
Maximal inspiration (mm)	3.68 (.16)	4.88 (.21)	.001‡ (.82)	1.19(1.71–.67)
Maximal expiration (mm)	1.12 (.09)	1.25 (.06)	.089(.47)	.14(.30–.02)

Data are presented as means ± standard error.
Statistically significant results are marked as follows: *$P < .01$; †$P < .05$; ‡$P < .001$.
IMT: inspiratory muscle training; ES: effect size; 95%CI:confidence intervals.

Table 4
Comparison of Borg Scale scores, RR, SpO_2, and HR during 6MWD before and after inspiratory muscle training.

Parameter		Before IMT	After IMT	*P* value (ES)	*95%CI*
Borg scale: dyspnea	Rest	.92 (.29)	.77 (.19)	.651(.13)	.15(.57–.88)
	After 6MWD	3.23 (.52)	2.81 (.56)	.236(.34)	.42(.32–1.16)
	Recovery 1 min	2.40 (.43)	1.60 (.37)	.050* (.60)	.80(.01–1.61)
	Recovery 2 min	1.10 (.22)	1.30 (.33)	.509(.22)	.20(.86–.46)
Borg scale: lower limb fatigue	Rest	.65 (.43)	.23 (.17)	.389(.25)	.42(.61–1.45)
	After 6MWD	2.00 (.46)	2.00 (.46)	.888(.04)	.04(.55–.62)
	Recovery 1 min	2.00 (.49)	1.05 (.41)	.016* (.70)	.95(.23–1.67)
	Recovery 2 min	1.15 (.26)	.80 (.36)	.132(.48)	.35(.13–.83)
RR (times/min)	Rest	24.0 (1.46)	21.8 (1.82)	.126(.49)	2.20(.76–5.16)
	After 6MWD	29.0 (1.59)	26.2 (1.32)	.128(.49)	2.8(.98–6.58)
	Recovery 1 min	25.8 (1.41)	22.1 (1.65)	.036* (.63)	3.7(.29–7.11)
	Recovery 2 min	23.2 (1.56)	21.1 (1.83)	.173(.44)	2.10(1.11–5.31)
SpO_2 (%)	Rest	94.9 (.59)	95.0 (.63)	.901(.04)	.08(1.39–1.24)
	After 6MWD	91.7 (.92)	92.0 (.72)	.613(.15)	.31(1.60–0.98)
	Recovery 1 min	94.3 (.75)	94.6 (.62)	.496(.23)	.30(1.26–.66)
	Recovery 2 min	95.7 (.52)	95.8 (.44)	.758(.11)	.10(.81–.61)
HR (times/min)	Rest	76.4 (2.56)	75.3 (3.02)	.588(.16)	1.08(3.14–5.29)
	After 6MWD	99.4 ± (3.45)	98.3 (3.43)	.618(.15)	1.08(3.51–5.66)
	Recovery 1 min	82.0 (2.95)	83.9 (4.62)	.632(.16)	1.90(10.6–6.76)
	Recovery 2 min	78.0 (3.57)	78.9 (3.87)	.810(.08)	.90(9.12–7.32)

Data are presented as means ± standard error.
Statistically significant values are marked as follows: *$P < .001$IMT: inspiratory muscle training; ES: effect size; 95%CI:confidence intervals; 6MWD: 6-min walking distance; RR: respiratory rate.
SpO_2: oxygen saturation of peripheral artery; HR: heart rate.

cmH_2O [16], and it increases with increased respiratory central activity. In patients with COPD, the value is much higher than that in healthy individuals, and increases with COPD severity [25]. The $P_{0.1}$/PImax index is obtained by normalizing the $P_{0.1}$ based on differences in inspiratory muscle strength among individuals. $P_{0.1}$ and $P_{0.1}$/PImax are used as prediction indicators for weaning and are regarded as a more accurate predictor compared to PImax [26]. In our study, there was no significant difference in $P_{0.1}$ before and after training, but a significant decrease in $P_{0.1}$/PImax was observed, reflecting the increase in the PImax. Moreover, the fact that the PImax, 6MWD, and Tdi significantly increased while $P_{0.1}$ did not change after IMT suggested that the IMT effects are probably attributed to improvements in peripheral factors rather than to improvements of central factors.

Dyspnea improvement is also important in respiratory rehabilitation. The dyspnea sensing mechanism includes not only chemoreceptors, but also motor command [8] and neuromechanical dissociation [27], involving various factors, such as motor outputs and sensory projections in the central nervous system [28]. Polkey et al. [29] reported that classic IMT may control muscle and central circuits and is particularly useful for patients with neurological disorders. However, it remains unclear whether dyspnea improvement and IMT effects are central or peripheral.

In this study, during the 1-min recovery period following the 6MWD, the Borg Scale scores for dyspnea and lower limb fatigue and the RR significantly decreased. Furthermore, a negative correlation was found between the 6MWD and the Borg Scale dyspnea score (after the 6MWD), suggesting that dyspnea is one of the factors that limit performance in the 6MWD. Therefore, dyspnea improvement is necessary for continuous movement.

In this study, $P_{0.1}$ and Tdi were used to investigate the effects of IMT in combination with pulmonary rehabilitation. Concomitant use of IMT resulted in a prolongation of 6MWD, possibly related to an increase in Tdi. It was thought that the increase in Tdi increased PImax, improved respiratory function, affected dyspnea and respiratory rate, and possibly reducing relative respiratory effort, which led to the extension of 6MWD. One of the strengths of this study, which examined the scientific basis for IMT's effects from a ventilatory mechanics perspective, was the finding that the improvement in respiratory function induced by IMT is likely due to peripheral factors. Elucidating whether improvements in dyspnea and respiratory function are attributed to central or peripheral components would contribute to the design of more effective respiratory rehabilitation intervention methods, help determine more accurately the effects of respiratory rehabilitation.

This study had several limitations. The first was the small sample size. Since the subjects were outpatients, it was difficult for some patients to continue the training. And this limits the generalizability and statistical power of the findings. Second, it was not possible to establish a control group due to ethical issues. Respiratory muscle training was often performed as one of pulmonary rehabilitation, although the training method was different, and setting a control group without respiratory muscle training may be disadvantageous to patients. But a control group would allow for better comparison and evaluation of the effects of IMT. The third was the evaluation method. There were also reports that spirometry is strongly influenced by inter- and intra-variation, [30] and we believe that the method used to evaluate pulmonary function has limitations. This includes limitations such as the lack of compliance validation, technical outcome measurements, and potential biases. Therefore, it is difficult to study the effects of IMT in detail. In future research, we will further increase the number of participants and use a control group to examine the differences among different IMT devices and longer follow-up periods.

5. Conclusion

. The effect of 2 months of IMT in elderly COPD was studied using $P_{0.1}$ and Tdi. We observed a significant increase in PImax and 6MWD, and an improvement in Tdi and dyspnea. However, there was no significant difference in $P_{0.1}$, suggesting that the effect of IMT was attributed to the improvement of peripheral factors rather to the improvement of central factors in elderly COPD patients. This study had several limitations. The first was the small sample size. Second, it was not possible to establish a control group due to ethical issues. The third was the evaluation method.In the future, we plan to increase the number of participants, establish a control group, and use different IMT devices in order to more accurately compare the effects of IMT in COPD patients.

Funding

This project received no funding.

Author contribution statement

Tomomi Ichiba, Dr: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Tetsuo Miyagawa: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

Toru Tsuda: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Takeshi Kera: Analyzed and interpreted the data; Wrote the paper.

Osamu Yasuda: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors are grateful to the outpatients at Kirigaoka Tsuda Hospital who participated in this study.

References

[1] M.A. Spruit, S.J. Singh, C. Garvey, et al., An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation, Am. J. Respir. Crit. Care Med. 188 (2013) e13–e64.
[2] F. Lötters, B. van Tol, G. Kwakkel, R. Gosselink, Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis, Eur. Respir. J. 20 (2002) 570–576.
[3] A.L. Ries, G.S. Bauldoff, B.W. Carlin, et al., Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines, Chest 131 (2007) 4s–42s.
[4] K. O`Brien, E.L. Geddes, W.D. Reid, D. Brooks, J. Crowe, Inspiratory muscle training compared with other rehabilitation interventions in chronic obstructive pulmonary disease: a systematic review update, J Cardiopulm Rehabil Prev 28 (2008) 128–141.
[5] R. Gosselink, J. De Vos, S.P. van den Heuvel, J. Segers, M. Decramer, G. Kwakkel, Impact of inspiratory muscle training in patients with COPD: what is the evidence? Eur. Respir. J. 37 (2011) 416–425.
[6] M. Beaumont, P. Forget, F. Couturaud, G. Reychler, Effects of inspiratory muscle training in COPD patients: a systematic review and meta-analysis, Clin. Res. J 12 (2018) 2178–2188.
[7] N. Charususin, R. Gosselink, M. Decramer, et al., Randomised controlled trial of adjunctive inspiratory muscle training for patients with COPD, Thorax 73 (2018) 942–950.
[8] K.J. Killian, S.C. Gandevia, E. Summers, E.J. Campbell, Effect of increased lung volume on perception of breathlessness, effort, and tension, J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 57 (1984) 686–691.
[9] J. Milic-Emili, W.A. Whitelaw, J.P. Derenne, New tests to assess lung function: occlusion pressure–a simple measure of the respiratory center's output, N. Engl. J. Med. 293 (1975) 1029–1030.
[10] T. Ichiba, T. Yamada, T. Miyagawa, et al., Efficacy of relaxation posture in patients with chronic obstructive pulmonary disease, Respir. Care 20 (2010) 146–151.
[11] T. Ichiba, T. Miyagawa, T. Kera, T. Tsuda, Effect of manual chest wall compression in participants with chronic obstructive pulmonary disease, J. Phys. Ther. Sci. 30 (2018) 1349–1354.
[12] A. Bisschop, G. Gayan-Ramirez, H. Rollier, et al., Intermittent inspiratory muscle training induces fiber hypertrophy in rat diaphragm, Am. J. Respir. Crit. Care Med. 155 (1997) 1583–1589.
[13] A.D. de Andrade, T.N. Silva, H. Vasconcelos, et al., Inspiratory muscular activation during threshold therapy in elderly healthy and patients with COPD, J. Electromyogr. Kinesiol. 15 (2005) 631–639.
[14] M.R. Baria, L. Shahgholi, E.J. Sorenson, et al., B-mode ultrasound assessment of diaphragm structure and function in patients with COPD, Chest 146 (2014) 680–685.
[15] L.F. Black, R.E. Hyatt, Maximal respiratory pressures: normal values and relationship to age and sex, Am. Rev. Respir. Dis. 99 (1969) 696–702.
[16] W.A. Whitelaw, J.P. Derenne, Airway occlusion pressure, J. Appl. Physiol. 74 (1985) (1993) 1475–1483.
[17] D. Cohn, J.O. Benditt, S. Eveloff, F.D. McCool, Diaphragm thickening during inspiration, J. Appl. Physiol. 83 (1985) (1997) 291–296.
[18] ATS statement: guidelines for the six-minute walk test, Am. J. Respir. Crit. Care Med. 166 (2002) 111–117.
[19] P.W. Jones, G. Harding, P. Berry, I. Wiklund, W.H. Chen, N. Kline Leidy, Development and first validation of the COPD assessment test, Eur. Respir. J. 34 (2009) 648–654.
[20] J.L. Larson, M.J. Kim, J.T. Sharp, D.A. Larson, Inspiratory muscle training with a pressure threshold breathing device in patients with chronic obstructive pulmonary disease, Am. Rev. Respir. Dis. 138 (1988) 689–696.
[21] S.J. Singh, M.A. Puhan, V. Andrianopoulos, et al., An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease, Eur. Respir. J. 44 (2014) 1447–1478.
[22] M.A. Puhan, M.J. Mador, U. Held, R. Goldstein, G.H. Guyatt, H.J. Schünemann, Interpretation of treatment changes in 6-minute walk distance in patients with COPD, Eur. Respir. J. 32 (2008) 637–643.
[23] E. Paulin, W.P. Yamaguti, M.C. Chammas, et al., Influence of diaphragmatic mobility on exercise tolerance and dyspnea in patients with COPD, Respir. Med. 101 (2007) 2113–2118.
[24] H.W. Kang, T.O. Kim, B.R. Lee, et al., Influence of diaphragmatic mobility on hypercapnia in patients with chronic obstructive pulmonary disease, J. Kor. Med. Sci. 26 (2011) 1209–1213.
[25] M. Montes de Oca, B.R. Celli, Mouth occlusion pressure, CO2 response and hypercapnia in severe chronic obstructive pulmonary disease, Eur. Respir. J. 12 (1998) 666–671.
[26] S.N. Nemer, C.S. Barbas, J.B. Caldeira, et al., Evaluation of maximal inspiratory pressure, tracheal airway occlusion pressure, and its ratio in the weaning outcome, J. Crit. Care 24 (2009) 441–446.
[27] D.E. O'Donnell, Breathlessness in patients with chronic airflow limitation. Mechanisms and management, Chest 106 (1994) 904–912.
[28] T. Kera, A. Aihara, T. Ichiba, Respiratory rehabilitation approach from the viewpoint of dyspnea sensing mode, Physiother.-Clinic Res. Educ. 18 (2011) 9–14.
[29] M.I. Polkey, N. Ambrosino, Inspiratory muscle training in COPD: can data finally beat emotion? Thorax 73 (2018) 900–901.
[30] L.B. Herpel, R.E. Kanner, S.M. Lee, et al., Variability of spirometry in chronic obstructive pulmonary disease. Results from two clinical trials, Am. J. Respir. Crit. Care Med. 173 (2006) 1106–1113.