Enhanced diaphragm excursion and exercise tolerance in COPD patients through inspiratory muscle training after standardised pulmonary rehabilitation: randomised controlled trial

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Shareable abstract (@ERSpublications)
This study aimed to evaluate the effect of IMT on maximum diaphragmatic excursion using ultrasonography in patients with COPD. IMT following the PR programme improved maximum diaphragmatic excursion (DE_{max}) and exercise tolerance. https://bit.ly/3yMfj9v

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Abstract

Objective Inspiratory muscle training (IMT) is used to improve inspiratory muscle strength in patients with COPD. However, the effect of IMT on diaphragmatic function has not yet been thoroughly evaluated. This study aimed to evaluate the effect of IMT on maximum diaphragmatic excursion (DE_{max}) using ultrasonography in patients with COPD.

Methods This was a single-centre, randomised, prospective, parallel-group, unblinded controlled trial involving 38 participants with stable COPD. Participants underwent a standardised 12-week pulmonary rehabilitation (PR) programme followed by a 12-week IMT programme, consisting of home-based IMT and low-frequency outpatient PR sessions supervised by physiotherapists (once every 2 weeks), *versus* low-frequency outpatient PR alone as a control. The DE_{max} and exercise tolerance were measured.

Results Out of the 38 patients initially enrolled in the PR programme, 33 successfully completed it and were subsequently randomised to the IMT programme. Finally, 15 (94%) and 14 (88%) patients from the IMT and control groups, respectively, completed the study. Following the IMT programme, DE_{max} increased in the IMT group (mean±SD 50.1±7.6 mm to 60.6±8.0 mm, $p<0.001$), but not in the control group (47.4±7.9 mm to 46.9±8.3 mm, $p=0.10$). Changes in DE_{max} and exercise tolerance (peak oxygen uptake) were greater in the IMT group than in the control group (both $p<0.01$).

Conclusions IMT following the PR programme improved DE_{max} and exercise tolerance. Therefore, DE_{max} may be an important outcome of IMT.

Introduction

COPD is a progressive disease characterised by minimally reversible airflow limitation. The chief limitation imposed by COPD is the inability of patients to manage their daily activities due to breathlessness. Although the pathophysiological mechanisms involved in the development of dyspnoea and poor exercise tolerance in patients with COPD are complex, dynamic lung hyperinflation (DLH) plays a central role [1]. Despite compensatory mechanisms, the major consequences of DLH are increased ventilatory workload and decreased pressure-generating capacity of the inspiratory muscles [2]. The diaphragm is the main muscle involved in respiration, and diaphragm dysfunction exists in all stages of COPD [3]. Therefore, we evaluated the diaphragm using ultrasound and reported that maximum diaphragmatic excursion (DE_{max}) was closely associated with exercise tolerance and DLH in patients with COPD [4].

Exercise training is a central component of pulmonary rehabilitation (PR) programmes and inspiratory muscle training (IMT) is used to improve inspiratory muscle function, including that of the diaphragm. While available evidence indicates inconsistent effectiveness of IMT without a clear training dose–response relationship in patients with COPD [5], both the American Thoracic Society and the European Respiratory Society [6] advocate for IMT as a supplemental intervention in PR programmes for treating patients with chronic lung diseases, particularly when inspiratory muscle weakness is evident. The proposed beneficial effects of IMT include improvements in inspiratory muscle strength and endurance, functional exercise capacity, dyspnoea, and quality of life [7–9]. IMT may be associated with an improvement in diaphragmatic mobility; however, the underlying mechanisms are poorly understood. In a previous study, IMT enhanced diaphragm muscle strength and reduced the required electrical activity of the diaphragm in relation to its peak activity, potentially alleviating dyspnoea during exercise in COPD patients [10]. However, it is unclear whether IMT improves DE_{max}. In addition, although IMT alone significantly improves inspiratory muscle strength, exercise capacity and quality of life, the additive effect of IMT was reported to be questionable in a programme conducting PR and IMT simultaneously [11, 12].

This study was conducted to examine the hypothesis that in patients with COPD strengthening inspiratory muscles would improve DE_{max}, which might reduce DLH and improve exercise tolerance when IMT training was performed in a sequential design, *i.e.* after a standardised PR programme. While the primary objective of this study was to evaluate whether IMT performed after a standardised PR programme was associated with an improvement in DE_{max} in patients with COPD, the secondary objective was to evaluate the effect of IMT on exercise tolerance, DLH and perception of dyspnoea.

Materials and methods

Study design, participants and standardised PR

This was a single-centre, randomised, prospective, parallel-group, unblinded controlled trial. Clinically stable COPD patients who visited the Department of Respiratory Medicine and Allergology at Kindai University Hospital between April 2019 and January 2023 and were referred to the PR unit were included. The main inclusion criteria were as follows: 1) age between 65 and 85 years at the time of consent; 2) stable disease without infection or acute exacerbation within 3 months prior to enrolment; and 3) dyspnoea on exertion (modified Medical Research Council (mMRC) grade scale 1–3). Eligible patients were registered and received standardised PR before randomisation (figure 1). Details of standardised PR and randomisation are shown in the supplemental methods. This study was approved by the Committee for Ethics of the Kindai University School of Medicine (No 31-086) and registered in the UMIN-CTR (number: 000043099). All the participants provided written informed consent. This research was conducted according to the principles of the World Medical Association Declaration of Helsinki.

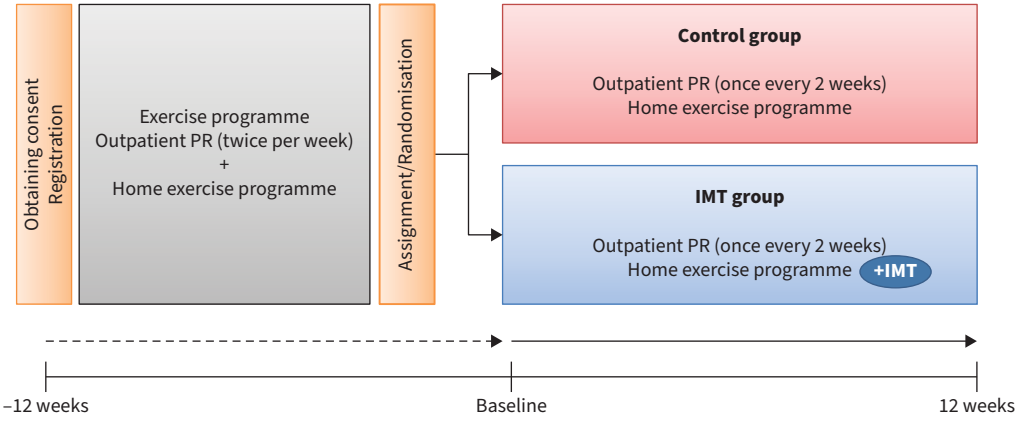

FIGURE 1 The study protocols. After registration, a standardised pulmonary rehabilitation (PR) programme was implemented for all patients. Standardised initial PR included twice-weekly sessions of monitored exercise training and self-training at home for 12 weeks, followed by randomisation to the IMT or control group. After randomisation, all patients were instructed to continue self-training at home and attend outpatient maintenance PR supervised by physiotherapists (once every 2 weeks). The inspiratory muscle training (IMT) group underwent IMT at home for 12 weeks.

12-week IMT programme

During the 12-week IMT programme, all patients were instructed to perform self-training at home (home exercise programme, shown in the supplemental methods) and attend outpatient maintenance PR supervised by physiotherapists (once every 2weeks) (figure 1). IMT was performed according to the method laid out by LANGER *et al.* [10] with the intervention group receiving IMT training (self-training, 30 breaths per set, 2 sets per day) using the POWERbreathe K3 device (POWERbreathe International, Stratford-upon-Avon, UK) for 12 weeks at home. All patients started IMT at 30% of maximum inspiratory pressure (P_{Imax}) at baseline. Details of training quality and adherence are shown in the supplemental methods.

Measurements

Details of measurements including DE_{max}, lung function test, P_{Imax} and calculation of predicted values of P_{Imax} and 6-min walk distance (6MWD) are presented in the supplemental methods. Maximum DE_{max} was measured using ultrasonography (Xario 200; Canon Medical Systems, Tokyo, Japan). Excursions of the right hemidiaphragm were measured using a 3.5-MHz convex probe (figure S1) [4].

A symptom-limited cardiopulmonary exercise test was performed on a bicycle ergometer according to the Ramp 10 Watts (W) protocol (load increase of 10 W per 1 min − 1 W per 6 s) incremental loading testing. Continuous inspiratory capacity (IC) measurements were taken every minute throughout the exercise regimen and again at its conclusion. We measured the change in IC (ΔIC=IC lowest − IC at rest) during exercise as a surrogate marker for DLH [13, 14]. During the incremental loading testing and constant-loading testing, we analysed the following indices: endurance time, peak oxygen uptake (peak $\dot{V}_{O_2}$), minute ventilation ($\dot{V}_E$), ventilatory equivalents for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$), $\dot{V}_E/\dot{V}_{CO_2}$ slope, peak tidal volume-to-inspiratory capacity ratio (peak V_T/IC), inspiratory time-to-total respiratory cycle time (t_i/t_{tot}), inspiratory tidal volume (V_{T_I}), and expiratory tidal volume (V_{T_E}).

To assess the respiratory muscle strength, we measured the P_{Imax} generated against an occluded airway at a residual volume (IOP-01; Kobata Instrument Manufacturing Ltd., Osaka, Japan) [15].

The 6MWD protocol according to American Thoracic Society guidelines was used as an index of exercise tolerance; the 10-point Borg scale was used to assess the intensity of dyspnoea, and leg fatigue was evaluated post-6MWD [16]. Additionally, the COPD assessment test (CAT) was conducted to assess the patient's condition.

The primary outcome was the change in DE_{max} from baseline to the end of the IMT programme, and the secondary outcomes were changes in ΔIC during the constant-loading testing and other outcomes during the incremental loading testing. ΔIC was measured to estimate DLH, peak $\dot{V}_{O_2}$, and 6MWD for exercise tolerance; and $\dot{V}_E$ and $\dot{V}_E/\dot{V}_{CO_2}$ for ventilation volume. These parameters, along with other physiological indices, were measured at registration, baseline (after standardised PR), and post-intervention. Values at the end of the IMT programme minus values at baseline are expressed as Δ except for IC. ΔΔIC indicates ΔIC at the end of the IMT programme minus ΔIC at baseline. Data are presented as mean±SD or median (interquartile range).

Statistical analysis

Details of sample size estimation are shown in the supplemental methods. Outcomes before and after the intervention were analysed using a two-way repeated measures analysis of variance. The relationships between ΔDE_{max} and changes in the exercise measurements (Δpeak $\dot{V}_{O_2}$, $\Delta\dot{V}_E$, $\Delta\dot{V}_E/\dot{V}_{O_2}$, $\Delta\dot{V}_E/\dot{V}_{CO_2}$ slope, Δpeak V_T/IC, $\Delta t_i/t_{tot}$ and ΔΔIC=Δ(ΔIC)) were evaluated by calculating Pearson correlation coefficients. Statistical data were analysed using the JMP software, version 17 (JMP, SAS Institute Inc., Cary, NC, USA). For all analyses, statistical significance was set at $p<0.05$.

Results

38 patients were registered for this study (table S1), but five patients were excluded as they were registered during the coronavirus disease 2019 pandemic and could not continue rehabilitation. Therefore, 33 patients received a standardised PR programme before randomisation (from −12 weeks to baseline), which improved exercise tolerance (peak $\dot{V}_{O_2}$ 11.9±3.0 mL·min^{-1}·kg^{-1} to 13.0±3.1 mL·min^{-1}·kg^{-1}, $p<0.001$; 6MWD 412±88 m to 445±92.5 m, $p<0.001$); however, it did not improve DE_{max} (48.6±7.9 mm to 48.8±8.0 mm, $p=0.91$). CAT was also improved after the standardised PR programme (13±4 to 9±4, $p<0.001$).

Effects of 12-week IMT

Following the completion of the standardised PR programme, 33 patients were allocated to the IMT (n=17) and control (n=16) groups (figure 2). Throughout the 12-week IMT programme, four participants withdrew:

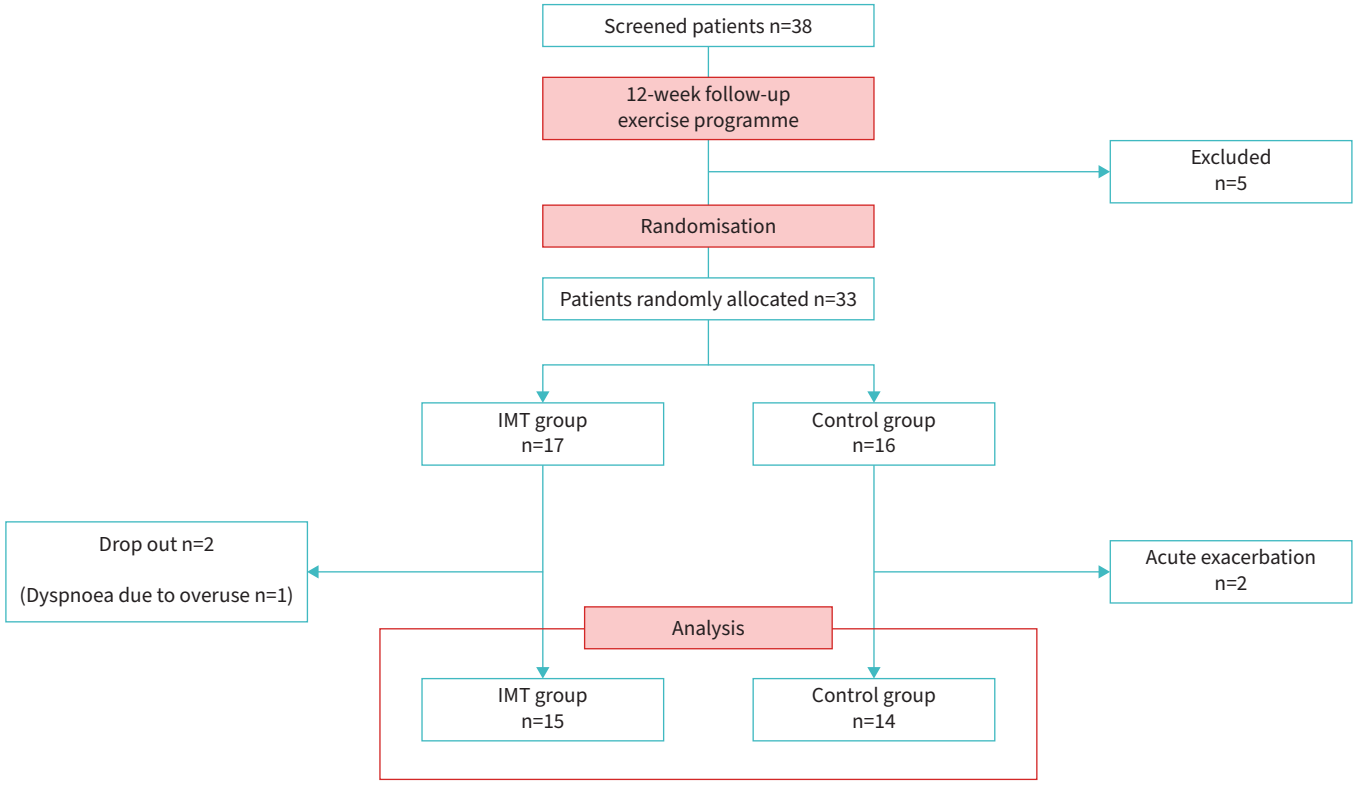

FIGURE 2 Flow chart of patient selection. IMT: inspiratory muscle training.

one due to self-interruption and another due to experiencing worsening dyspnoea from excessive use of the IMT device in the IMT group, while the control group experienced two acute exacerbations. Finally, 15 (94%) and 14 (88%) patients in the IMT and control groups completed the 12-week IMT programme, respectively (figure 2). There were no differences in the baseline parameters (table 1), or changes in the parameters during the initial standardised PR programme (table S2), between the IMT and control groups. The numbers of patients with good adherence to home-based maintenance PR in the IMT and control groups were 14 and 13, respectively. Data on the adherence and training quality of the IMT programme are shown in table S4.

In the IMT group, DE_{max}, peak V_{O_2} and P_{Imax} increased from baseline to 12 weeks, but did not increase in the control group (table S3). As a result, ΔDE_{max} (figure 3), peak V_{O_2} (figure 4), and ΔP_{Imax} were significantly higher in the IMT group than in the control group (table 2). IMT also significantly improved most of the other parameters (CAT score, dyspnoea score, $\dot{V}_E/\dot{V}_{CO_2}$, peak V_T/IC, V_{T_I}, V_{T_E}, and $V_{T_I} - V_{T_E}$), but not in the control group (table S3), and the changes were significantly greater in the IMT group (table 2). Meanwhile, against our hypothesis, ΔIC did not change after the intervention (baseline to 12 weeks) in both groups (data not shown) and ΔIC were comparable between the two groups (table 2). IMT did not improve the 6MWD, and the Δ6MWD was comparable between the two groups. IMT increased the endurance time on the constant work rate exercise test by +139±124 s from baseline ($p<0.01$) (table 2). In the two-way repeated measures analysis of variance, a significant interaction between time and treatment group was observed for ΔDE_{max} (figure 3) and Δpeak $\dot{V}_{O_2}$ (figure 4). Significant improvement in DE_{max} was only observed in the IMT group after the intervention (figure 3).

Within the IMT group, ΔDE_{max} exhibited moderate to strong correlations with ΔP_{Imax}, Δpeak $\dot{V}_{O_2}$, $\Delta\dot{V}_E$, $\Delta\dot{V}_E/\dot{V}_{CO_2}$, $\Delta\dot{V}_E/\dot{V}_{CO_2}$ Slope, Δ_{peak} V_T/IC, $\Delta t_I/t_{tot}$, ΔV_{T_I}, $\Delta V_{T_I} - V_{T_E}$, Δpeak dyspnoea perception (Borg scale), and ΔCAT score, while ΔDE_{max} demonstrated modest correlations with Δ6MWD and ΔIC (table 3). Furthermore, in the IMT group, ΔDE_{max} was strongly correlated with Δendurance time (table 3).

Discussion

The main finding of this study was that DE_{max} and exercise tolerance, expressed as peak $\dot{V}_{O_2}$, increased after 12 weeks of home-based IMT compared with the control arm. To the best of our knowledge, this is the first study to demonstrate that IMT increases DE_{max} in patients with COPD.

TABLE 1 Characteristics of study participants at baseline: inspiratory muscle training (IMT) *versus* control

	All subjects (n=29)	IMT group (n=15)	Control group (n=14)	p-value
Male/female, n/n (%/%)	28/1 (97/3)	14/1 (93/7)	14/0 (100/0)	0.80
Age, years	75±4	76±3	76±4	0.74
Body mass index, kg·m^{-2}	22.7±2.3	22.7±2.51	23.7±1.98	0.28
GOLD (1/2/3/4), n	2/13/12/2	1/7/6/1	1/6/6/1	0.50
DE_{max}, mm	48.8±8.0	49.5±7.9	47.4±7.9	0.65
P_{Imax}, cmH_2O	65.1±21.4	65.7±16.8	64.3±26.1	0.86
%P_{Imax}, %	62.9±18.7	66.0±18.7	59.5±24.4	0.59
6MWD, m	437±91	456±81	434±108	0.53
6MWD, % pred	80.7±18.3	82.5±15.3	79.0 ±21.2	0.17
mBorg scale dyspnoea	4 (2 to 5)	4 (2 to 4)	5 (2 to 7)	0.23
mBorg scale leg fatigue	2 (1 to 4)	2 (1 to 4)	4 (1 to 5)	0.39
CAT	10 (5 to 11)	8 (5 to 10)	10 (5 to 12)	0.28
Spirometry				
IC, L	2.30±0.48	2.30±0.46	2.28±0.48	0.62
FEV_1, L	1.49±0.50	1.49±0.49	1.56±0.50	0.73
FEV_1, % pred	59.1±18.3	59.1±16.3	59.0±20.3	0.84
FVC, L	3.10±0.67	3.01±0.46	3.24±0.80	0.40
FVC, % pred	96.4±17.5	93.0±18.0	100±16.3	0.28
Incremental loading testing				
Peak Load, W	75.2±25.1	78.9±22.4	71.2±27.2	0.27
Peak $\dot{V}_{O_2}$, mL·min^{-1}·kg^{-1}	13.1±3.1	13.0±2.5	13.1±3.8	0.97
$\dot{V}_E$, L·min^{-1}	43.3±12.0	44.8±12.1	41.7±11.7	0.49
$\dot{V}_E/\dot{V}_{CO_2}$, mL/mL	48.0±8.8	49.4±7.9	46.6±9.8	0.41
$\dot{V}_E/\dot{V}_{CO_2}$ slope	48.6±11.3	50.1±8.8	47.0±13.7	0.47
Peak V_T/IC	56.1±12.3	57.6±9.9	54.4±14.6	0.74
V_{T_I}, mL	1273±333	1330±339	1212±327	0.34
V_{T_E}, mL	1243±322	1295±321	1187±325	0.37
t_i/t_{tot}, %	53±13	54±10	54±15	0.95
Constant-loading testing				
Endurance time, s	568±143	592±156	554±129	0.37
Peak $\dot{V}_{O_2}$, mL·min^{-1}·kg^{-1}	12.6±3.7	13.2±2.3	11.8±4.8	0.30
$\dot{V}_E$, L·min^{-1}	41.4±11.4	44.1±12.3	38.4±10.0	0.18
$\dot{V}_E/\dot{V}_{CO_2}$, mL/mL^{-1}	51±10.0	51.6±8.6	50.6±11.6	0.71
Peak V_T/IC	0.54±0.22	0.56±0.25	0.51±0.18	0.33
V_{T_I}, mL	1192±312	1264±284	1114±332	0.20
V_{T_E}, mL	1165±301	1234±263	1092±331	0.21
t_i/t_{tot}, %	45±13	49±0.14	41±13	0.14
IC at rest, L	2.15±0.49	2.30±0.49	1.96±0.46	0.07
ΔIC from rest, L	−0.46±0.20	−0.43±0.18	−0.49±0.21	0.50

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. 6MWD: 6-min walk distance; CAT: COPD assessment test; DE_{max}: maximum diaphragmatic excursion; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IC: inspiratory capacity; P_{Imax}: maximum inspiratory pressure; t_i/t_{tot}: inspiratory duty cycle; $\dot{V}_E$: minute ventilation; $\dot{V}_E/\dot{V}_{CO_2}$: minute ventilation/carbon dioxide production; $\dot{V}_{O_2}$: oxygen uptake; V_T/IC: tidal volume/inspiratory capacity; V_{T_I}: inspiratory tidal volume; V_{T_E}: expiratory tidal volume.

As the diaphragm is the most important inspiratory muscle, sufficient diaphragmatic mobilisation is the key to securing the training effect of IMT. However, the DE_{max} has not been examined as an IMT outcome in previous studies. Herein, we demonstrated that the DE_{max} increased with IMT training and may be an important outcome of IMT training. Wu *et al.* [17] measured diaphragmatic mobilisation, expressed as transdiaphragmatic pressure (P_{di}) and the corrected root mean square (RMS) of the diaphragmatic electromyogram (EMG_{di}) (RMS_{di}%), during IMT in patients with COPD. They reported that P_{di} and RMS_{di}% were higher during IMT, demonstrating an effective training effect on the diaphragm muscle. Langer *et al.* [10] also measured EMG_{di} and demonstrated that the ratio of EMG_{di} to its maximum (EMG_{di}/EMG_{dimax}) decreased post-IMT. They concluded that a reduction in EMG_{di}/EMG_{dimax} helped explain the decrease in the perceived respiratory discomfort. EMG_{di} and P_{di} may be more accurate for diaphragm muscle activation and function; however, these methods are relatively invasive and not easily implemented in clinical practice. However, the ultrasound measurement of DE_{max} would be a more practical and reliable measure for incorporation into PR assessment.

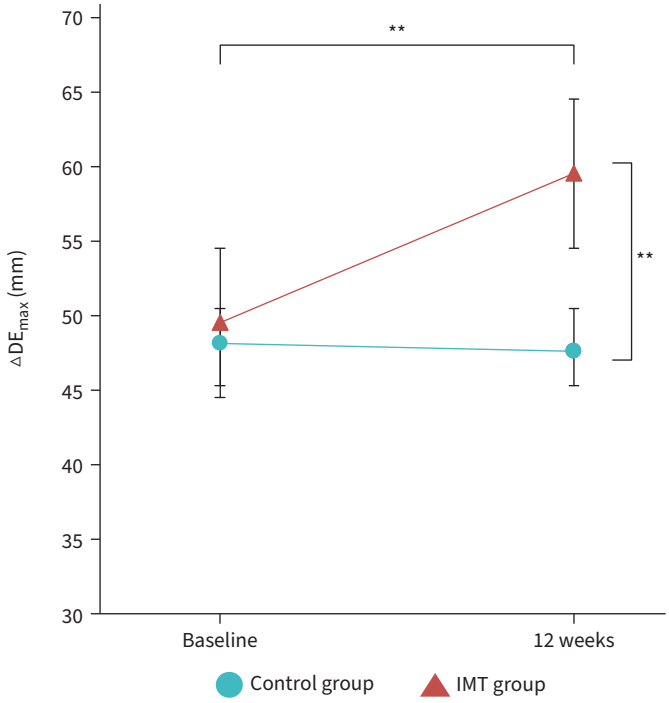

FIGURE 3 Change of maximum diaphragmatic excursion (DE_{max}) as measured by an ultrasonography at baseline and week 12. Error bars indicate the standard deviation. **: p<0.01.

We measured DE_{max}, but not diaphragm muscle thickness, because of the inconsistent results for diaphragm thickness. BARIA *et al.* [18] reported no significant difference in diaphragm thickness between COPD patients and controls, whereas OKURA *et al.* [19] found a significant association between diaphragm thickness in COPD patients and controls. Measurement of diaphragmatic thickening fraction is a

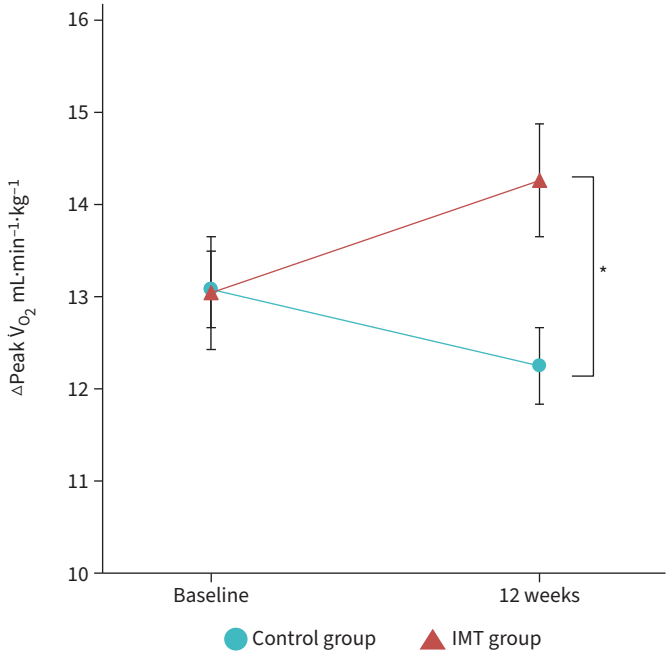

FIGURE 4 Change of peak oxygen uptake ($\dot{V}_{O_2}$) as measured by a cycle ergometer at baseline and week 12. Error bars indicate the standard deviation. *: p<0.05.

TABLE 2 Effect of inspiratory muscle training (IMT): changes from the baseline

	Changes from baseline		
	IMT group (n=15)	Control group (n=14)	p-value
ΔDE_{max}, mm	10.0±5.1	−0.5±1.1	<0.001
ΔPI_{max}, cmH_2O	22.7±9.2	3.4±11.1	<0.001
Δ6MWD, m	12±12	−7±38	0.09
Δ6MWD, % pred	5.6 ±0.4	−7.7 ±1.1	0.45
ΔmBorg scale dyspnoea	−1 (−2 to 0)	0 (−2 to 1)	<0.01
ΔmBorg scale leg fatigue	−1 (−2 to 0)	0 (1 to 0.25)	0.46
ΔCAT	−2 (−2 to 0)	0 (0 to 1)	<0.05
Incremental loading testing			
Δpeak $\dot{V}_{O_2}$, mL·min^{-1}·kg^{-1}	1.22±1.0	−0.8±1.4	<0.001
$\Delta\dot{V}_E$, L·min^{-1}	3.8±4.1	−0.02±5.6	<0.05
$\Delta\dot{V}_E/\dot{V}_{CO_2}$, mL/mL	−2.8±2.8	0.9±3.6	<0.01
$\Delta\dot{V}_E/\dot{V}_{CO_2}$ slope	−7.2±9.4	−0.6±9.2	<0.05
Δpeak V_T/IC, %	6.9±5.9	−1.5±5.9	<0.01
ΔV_{T_I}, mL	229±206	3±300	<0.01
ΔV_{T_E}, mL	231±297	73±138	<0.01
$\Delta t_i/t_{tot}$, %	6±6	0±6	0.053
Constant-loading testing			
Δendurance time, s	131±124	28±81	<0.01
Δpeak $\dot{V}_{O_2}$, mL·min^{-1}·kg^{-1}	0.70±2.9	0.11±4.3	0.53
$\Delta\dot{V}_E$, L·min^{-1}	5.6±13.8	−0.45±10.4	0.31
$\Delta\dot{V}_E/\dot{V}_{CO_2}$, mL/mL	−1.58±7.4	−0.4±9.7	0.21
Δpeak V_T/IC, %	16±24	−1.0±1.6	<0.01
ΔV_{T_I}, mL	349±250	3.0±330	<0.01
ΔV_{T_E}, mL	321±254	25±330	<0.01
$\Delta t_i/t_{tot}$, %	3±13	5±12	0.67
ΔIC at rest, L	0.23±0.07	−0.04±0.06	<0.01
Δ′IC, L	0.02±0.11	0.00±0.15	0.53

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. 6MWD: 6-min walk distance; CAT: COPD assessment test; DE_{max}: maximum diaphragmatic excursion; IC: inspiratory capacity; P_{Imax}: maximum inspiratory pressure; t_i/t_{tot}: inspiratory duty cycle, $\dot{V}_E$: minute ventilation; $\dot{V}_E/\dot{V}_{CO_2}$: minute ventilation/carbon dioxide production; $\dot{V}_{O_2}$: oxygen uptake; V_T/IC: tidal volume/inspiratory capacity; V_{T_I}: inspiratory tidal volume; V_{T_E}: expiratory tidal volume. Δ: value at the end of IMT programme minus value at baseline except for IC, Δ′IC=Δ(ΔIC at the end of IMT programme minus ΔIC at baseline).

reproducible assessment [20]. However, the correlation between diaphragmatic thickening and effort is not strong, and only one-third (or less) of the variation in inspiratory effort can be explained by ultrasound measurements of diaphragm thickening [21]. Furthermore, the evaluation of diaphragm thickness and thickening fraction is difficult to perform in patients with severe COPD because the length of the zone of apposition is shorter in those with COPD than in controls [22]. In contrast, studies including measurements of diaphragm excursion during inspiration and expiration have reported more consistent results. Therefore, we decided to measure diaphragm excursion rather than thickness. Nonetheless, diaphragm thickness, thickness fraction, and other important indices should also be evaluated in future studies.

Scheibe *et al.* [23] showed a strong correlation between diaphragm mobility and forced expiratory volume in 1 s. Compared with healthy controls, COPD patients had reduced diaphragm mobility, which plays an important role in decreased exercise tolerance, DLH and increased dyspnoea in patients with COPD [4, 24]. Furthermore, DE_{max} was strongly associated with DLH [4]. Lung hyperinflation and the associated decrease in IC are closely related to the degree of breathlessness (dyspnoea) experienced by patients with COPD during physical activity. Moreover, therapeutic restoration of lung hyperinflation through improved IC has been shown to be associated with improved dyspnoea intensity and exercise endurance [25]. IMT was not beneficial for DLH as measured by ΔIC, against our hypothesis. However, IMT improved static IC, which may result in enhanced exercise endurance. Therefore, measurement of DE_{max} was prioritised in this study, on the hypothesis that improvement of diaphragm mobility could improve ventilatory capacity and DLH. Nonetheless, diaphragm thickness, another important index, should also be evaluated in a future study.

In this study, in addition to DE_{max}, IMT improved dyspnoea and exercise tolerance, as assessed by peak $\dot{V}_{O_2}$ and ventilation volume. The mechanism by which IMT improves dyspnoea is unknown; however,

TABLE 3 Correlations between ΔDE_{max} and ventilatory parameters/dyspnoea in the inspiratory muscle training (IMT) group (n=15)

	Pearson correlation coefficient (r)	p-value
ΔP_{Imax}, cmH_2O	0.69	p<0.001
Δ6MWD, m	0.34	0.07
Δ6MWD, % pred	0.35	0.20
ΔmBorg scale dyspnoea	−0.57	p<0.001
ΔmBorg scale leg fatigue	−0.01	0.98
ΔCAT	−0.52	p<0.01
Incremental loading testing		
Δpeak $\dot{V}_{O_2}$, mL·min^{-1}·kg^{-1}	0.76	p<0.001
Δ$\dot{V}_E$, L·min^{-1}	0.56	p<0.01
Δ$\dot{V}_E/\dot{V}_{CO_2}$, mL/mL	−0.63	p<0.01
Δ$\dot{V}_E/\dot{V}_{CO_2}$ slope	−0.63	p<0.01
Δ_{peak} V_T/IC, %	0.73	p<0.001
ΔV_{T_I}, mL	0.52	p<0.05
ΔV_{T_E}, mL	0.40	p<0.05
Δt_i/t_{tot}, %	0.54	p<0.01
Constant-loading testing		
Δendurance time, s	0.83	p<0.001
Δpeak $\dot{V}_{O_2}$, mL·min^{-1}·kg^{-1}	0.78	p<0.001
Δ$\dot{V}_E$, L·min^{-1}	0.39	0.15
Δ$\dot{V}_E/\dot{V}_{CO_2}$, mL/mL	−0.63	0.45
Δpeak V_T/IC, %	0.53	p<0.05
ΔV_{T_I}, mL	0.51	p<0.05
ΔV_{T_E}, mL	0.49	p<0.05
Δt_i/t_{tot}, %	0.11	0.68
ΔIC, L	0.54	p<0.05
Δ′IC, L	0.37	p<0.05

6MWD: 6-min walk distance; CAT: COPD assessment test; DE_{max}: maximum diaphragmatic excursion; IC: inspiratory capacity; P_{Imax}: maximum inspiratory pressure; t_i/t_{tot}: inspiratory duty cycle; $\dot{V}_E$: minute ventilation; $\dot{V}_E/\dot{V}_{CO_2}$: minute ventilation/carbon dioxide production; $\dot{V}_{O_2}$: oxygen uptake; V_T/IC: tidal volume/inspiratory capacity; V_{T_I}: inspiratory tidal volume; V_{T_E}: expiratory tidal volume. Δ: value at the end of IMT programme minus value at baseline except for IC, Δ′IC=Δ(ΔIC at the end of IMT programme minus ΔIC at baseline).

Gosselink *et al*. [7] highlighted that the effects of IMT include a delay in respiratory muscle fatigue, redistribution of blood flow to the respiratory and locomotor muscles, and reduction in the perception of discomfort of the respiratory muscles. However, the additive effects of IMT on PR are questionable in parallel-designed programmes. Recent randomised controlled trials evaluating IMT did not identify a significant advantage of IMT in reducing dyspnoea in a programme conducting PR and IMT simultaneously compared with PR alone, despite a significantly higher improvement in P_{Imax} in the IMT group [11, 12]. A meta-analysis of randomised controlled trial studies [5] focused on IMT indicated that while IMT did not have an additive effect on PR, it did independently enhance dyspnoea outcomes as measured using the Borg scale at submaximal exercise capacity, transition dyspnoea index and mMRC scale. The discrepancy between the findings of previous studies and those of the current study is probably due to scheduling differences and overlapping effects on exercise tolerance between standard PR [26, 27] and IMT alone [17]. We conducted IMT after the initial standardised PR programme, and IMT was performed alone during the low-frequency and low-intensity maintenance PR programme (once every 2 weeks). This design schedule may be better for maximising the effects of IMT than parallel design programmes that conduct IMT and standardised PR simultaneously.

The effect of IMT on exercise tolerance is controversial and may vary depending on the assessment index used. Meta-analysis [5] showed that IMT alone without PR improved exercise tolerance, measured using 6MWD; however, it did not have an additive effect on PR in parallel design studies. In the current sequential design study, IMT did not improve 6MWD; however, it improved the exercise tolerance, measured as peak $\dot{V}_{O_2}$. In this study, the ventilation volume during exercise ($\dot{V}_E/\dot{V}_{CO_2}$ and peak V_T/IC) increased in the IMT group, possibly due to an increase in V_{T_I}. IMT improved diaphragm function and inspiratory muscles and increased at least Δ′IC at rest and V_{T_I} after exercise, with comparable increase in V_{T_E}. As a result, exercise tolerance may have improved, although DLH did not improve. Therefore,

increased ventilation volume during exercise may have contributed to the improvement in exercise tolerance. This increased ventilation volume may be due to the improvement in DE_{max} leading to increased respiratory strength, as shown in studies on mechanically ventilated patients [28]. Such improvements likely contributed to reduced dyspnoea during exercise following the 12-week IMT programme and enhanced exercise tolerance.

Contrary to our hypothesis, IMT in patients with COPD had no benefit for DLH, as measured by ΔIC. We hypothesised that IMT might improve dyspnoea and exercise tolerance by addressing DLH, given its pivotal role in the pathophysiology of COPD [1], elevating ventilatory workload while diminishing the pressure-generating capacity of the inspiratory muscles. Furthermore, DE_{max} was strongly associated with DLH [4] with adequate prediction of the improvement in exercise tolerance after PR in patients with COPD [29]. As a potential mechanism underlying the improved dyspnoea and exercise tolerance after IMT without changing the DLH, improvement in breathing patterns, as discussed above, may play a role. Indeed, the strength of association with ΔDE_{max} was numerically greater for Δpeak V_T/IC (r=0.73) than for ΔIC (r=0.37) in this study. Although further studies are required, the improved breathing patterns may prolong the time required to reach the DLH threshold.

One patient in this study experienced worsening dyspnoea due to overuse of the IMT device. Frequent instruction from a physiotherapist is necessary to maintain the IMT at home. However, the IMT can be performed without severe adverse events if the titration protocol is reliable.

A limitation of this study is that the sample size was relatively small and the study was conducted at a single institution, where patients' baseline conditions were relatively well preserved. However, this study is worth reporting as it demonstrates the importance of home-based IMT after a standardised PR programme for patients with COPD. Nonetheless, diaphragm thickness, another important index, should also be evaluated in a future study.

In conclusion, IMT after standardised PR improved DE_{max} associated with improvements in inspiratory muscle strength, exertional dyspnoea, CAT score and exercise tolerance. An improvement in DE_{max} may be an important outcome of IMT. In the future, a large-scale multicentre randomised controlled trial is warranted.

Provenance: Submitted article, peer reviewed.

Data availability: The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy and/or ethical restrictions.

This study is registered at https://www.umin.ac.jp/ctr/ with identifier number 000043099.

Ethics statement: This study was approved by the Ethics Committee of Kindai University School of Medicine (R04-192).

Conflict of interest: The authors have nothing to disclose.

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