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Case report

Intolerance to and limitations of inspiratory muscle training in patients with advanced chronic obstructive pulmonary disease: A report of two cases

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ABSTRACT

Inspiratory muscle training (IMT) has been attracting attention as one of the useful treatments in patients with chronic obstructive pulmonary disease (COPD). IMT is reportedly effective in most patients with COPD. However, little is known about the benefits of IMT, especially in patients with advanced COPD.

We reported two cases of COPD that received 12-week IMT to explore intolerance to and the limitations of IMT in advanced COPD. The effectiveness of IMT was evaluated using cardiopulmonary exercise testing (CPET), spirometry, and respiratory muscle strength testing before and after the training.

A 75-year-old man with normal body mass index (BMI) and forced expiratory volume in 1 s (FEV_1) of 1.63 L responded well to IMT, but a 78-year-old man with low BMI and FEV_1 of 0.83 L did not. In the responder, IMT resulted in increased minute ventilation (V'_E) and oxygen uptake at peak exercise in incremental load testing. Moreover, IMT increased endurance time in constant load testing and maximal inspiratory pressure. In both patients, breathing frequency (f_R) increased, but tidal volume and the inspiratory-expiratory ratio were not improved during exercise. Despite the high f_R obtained after IMT, V'_E at peak exercise did not increase and endurance time shortened in the non-responder.

In underweight patients with advanced COPD, IMT might lead to tachypnea and ventilatory inefficiency, which in turn might decrease exercise performance. Therefore, underweight patients with advanced COPD might be unable to tolerate IMT and should avoid receiving the training.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death [1] and a major disease associated with global morbidity and mortality [2]. Earlier studies reported that patients with COPD have a fundamental deficit of diaphragm fiber contractile force [3], which correlates with patient prognosis [4]. Hence, inspiratory muscle training (IMT) has been suggested as an effective non-pharmacological treatment, which can delay lung function deterioration by increasing inspiratory muscle strength and endurance [5].

However, IMT is reportedly not always effective in patients with COPD [6,7], and studies for assessing the precise clinical characteristics of patients responding to IMT have been published. As an approach to clarify the applicable criteria, the mechanism of how IMT improves exercise tolerance was hypothesized; IMT can increase type II fibers, shorten inspiratory time, lengthen expiratory time, and result in decreased dynamic hyperinflation [8–10]. Contrary to the hypothesis, however, Beaumont et al. reported that dynamic hyperinflation was not improved by IMT in patients with COPD [11]. From the observations abovementioned, IMT might change a breathing pattern other than dynamic hyperinflation and subsequently affect exercise tolerance in patients with COPD. Given that IMT activates inspiratory muscles and induces deeper breathing [12,13], we hypothesized that the improvement of exercise tolerance might be depended on the degree of ventilatory efficiency obtained from IMT.

We herein report two cases of COPD that received IMT for 12 weeks, suggesting the mechanism of how IMT works and showing that the utility appears to be limited.

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Abbreviations

BMI	body mass index
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
ERS	European Respiratory Society
f_R	breathing frequency
FiO_2	inspired oxygen concentration
FeO_2	expired oxygen concentration
FVC	forced vital capacity
IC	inspiratory capacity
ICS	inhaled corticosteroids
IMT	inspiratory muscle training
LABA	long-acting β_2 agonist
LAMA	long-acting muscarinic antagonist
MEP	maximum expiratory pressure
MIP	maximum inspiratory pressure
$P_{ET}CO_2$	end-tidal carbon dioxide tension
RMS	respiratory muscle strength
Ti/Ttot	inspiratory duty cycle
VC	vital capacity
V'_{CO2}	carbon dioxide output
V_D	dead space ventilation
V_D/V_T	physiologic dead space/tidal volume ratio
V'_E	minute ventilation
V'_{O2}	oxygen uptake
V_T	tidal volume
V_T ex	expiratory tidal volume
V_T in	inspiratory tidal volume

2. Materials and methods

2.1. Patients and study design

Two Japanese patients with COPD who received IMT and were evaluated using CPET were included in the present study. The patients' primary diagnoses of COPD were confirmed based on the Global Initiative for Chronic Obstructive Lung Disease definition and classification [14]. Both patients did not experience acute exacerbations of COPD, and their drug regimens were not changed at least for three months before IMT. Both patients received 12-week IMT, and its effectiveness was evaluated using cardiopulmonary exercise testing (CPET), spirometry, and respiratory muscle strength (RMS) testing before and after the training.

2.2. CPET

Symptom-limited exercise tests were performed using an electrically-braked cycle ergometer (CV–1000SS, Lode, Groningen, The Netherlands) using a CPET system (Marquette CASE series T 2001, GE Healthcare, Tokyo, Japan; Aero monitor AE 310S, Minato Medical Science Co., Ltd, Osaka, Japan) [15,16]. Incremental load testing was performed by increasing 10W per 2 minutes. The starting workload of incremental load testing was 10 W. Moreover, constant load testing was performed at 70% of each patient's maximum load obtained on incremental load testing at the baseline examination. Before CPET, patients were asked to exert maximum effort. CPET was performed until exhaustion without encouragement, especially during exercise. Both patients were asked to keep a cycle ergometer speed of about 60 rpm. Pre-exercise resting measurements were taken after reaching a steady-state period during at least 3 min of breathing through a mask. Measurements taken during CPET were as follows: minute ventilation (V'_E), oxygen uptake (V'_{O2}), carbon dioxide output (V'_{CO2}), breathing frequency (f_R), inspiratory duty cycle (Ti/Ttot), tidal volume (V_T), inspired oxygen concentration (FiO_2), expired oxygen concentration (FeO_2), physiologic dead space/tidal volume ratio (V_D/V_T), and end-tidal carbon dioxide tension ($P_{ET}CO_2$). These data were measured breath-by-breath and collected as 30 s averages at rest, during exercise at 2 min intervals, and at the end of exercise. In addition, dyspnea intensity (10-point modified Borg category-ratio scale) was evaluated at rest, at the last 15 s of each exercise stage, and at the end of exercise.

2.3. Spirometry

Both patients underwent spirometry using the CHESTAC 8800 spirometer (Chest MI, Inc., Tokyo, Japan) within 2 weeks before CPET according to the recommendations of the American Thoracic Society and the European Respiratory Society (ERS) [17]. Predicted vital capacity (VC), forced vital capacity (FVC), and forced expiration volume in 1s (FEV_1) were calculated according to the formula for Japanese patients developed by the Japanese Respiratory Society [18].

2.4. RMS testing

RMS was evaluated during maximal voluntary effort against occluded airways (Vitaropov KH-101; Chest Scientific Instruments Ltd; Westerham, United Kingdom) [19]. Maximum inspiratory and expiratory mouth pressure were measured at rest according to the ERS statement [20]. Patients underwent the examination for four times, and the maximum value of respiratory pressure was adopted.

2.5. IMT

Both patients received daily two sessions of IMT for 30 times each, 2 times a day, for 12 weeks, supervised by physiotherapists. IMT was performed using a threshold inspiratory muscle trainer (POWERbreathe®MedicPLUS; POWERbreathe International, Stratford Upon Avon, UK). The maximal inspiratory mouth pressure (MIP) was measured at the baseline evaluation by the previously mentioned method during the training program. The initial IMT resistance pressure was adjusted to 20% of the MIP. If possible, the load was increased by 5% every two weeks to maximal 50% for 12 weeks.

3. Results

3.1. Baseline characteristics

The patients' baseline characteristics are shown in Table 1 and the following sentences. Notably, Case 2 was underweight and showed decreased VC, FVC, and FEV_1/FVC ratio, which showed that Case 2 had mixed ventilatory defect.

Case 1. Responder to IMT

A 75-year-old man with COPD and asthma for 14 years had exertional dyspnea despite treatment with inhaled corticosteroids (ICS), a long-acting β_2 agonist (LABA), and a long-acting muscarinic antagonist (LAMA). He had a smoking history of 60 pack-years. His body mass index was (BMI) was 23.9 kg/m^2.

Case 2. Non-responder to IMT

A 78-year-old man with COPD for 12 years had exertional dyspnea despite LABA and LAMA treatment. He had a smoking history of 141 pack-years. His BMI was 17.0 kg/m^2.

Table 1
Baseline characteristics.

Parameter	Case 1	Case 2
Age, y	75	78
Sex, male/female	male	male
BMI, kg m^{-2}	23.9	17.0
Cigarette smoking, pack years	60	141
GOLD stage, I/II/III/IV	II	III
FEV_1, L	1.63	0.83
FEV_1, % predicted	60.8	34.3
FVC, L	3.84	1.78
FVC, % predicted	108.5	56.0
FEV_1/FVC, %	42.4	46.6
VC, L	4.08	1.94
%VC, %	110.3	58.3
IC, L	2.93	1.35
Medications	LAMA, LABA, ICS	LAMA, LABA

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; IC, inspiratory capacity; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; VC, vital capacity.

3.2. Minute ventilation and oxygen uptake in incremental load testing after IMT

In Case 1, V'_{O2} and the V'_E at peak exercise increased from 893 mL/min to 939 mL/min and from 40.2 L/min to 44.8 L/min, respectively. In Case 2, however, both V'_{O2} and V'_E at peak exercise were not improved (V'_{O2}, from 313 mL/min to 277 mL/min; V'_E, from 21.4 L/min to 21.6 L/min) (Fig. 1A and B, and Table 2). The results showed that IMT contributed to the improved ventilation and the better exercise tolerance in Case 1, but not in Case 2.

3.3. Breathing pattern in incremental load testing after IMT

To assess the cause of treatment failure in Case 2, the breathing pattern in both patients were compared. In both patients, the f_R at peak exercise increased (Case 1, from 34/min to 44/min; Case 2, from 34/min to 39/min) (Fig. 1C). Moreover, the expiratory V_T (V_T ex) at peak exercise decreased in both patients (Fig. 1D), although FEV_1 did not change significantly in both patients after IMT (Table 3). The results indicated that the breathing pattern in both patients became more rapid and shallower after IMT.

Regarding parameters of CPET related to tidal ventilation, Ti/Ttot was lower and V'_E/V'_{CO2} was higher in Case 2 than in Case 1 before IMT throughout the exercise. V'_E/V'_{CO2} increased during exercise in Case 2, but not in Case 1 (Fig. 1E and F). The results showed that the ventilatory efficiency in Case 2 was worse than that in Case 1 at pretreatment baseline. Moreover, the ventilatory efficiency declined during exercise only in Case 2.

Comparing the exertional patterns of Ti/Ttot and V'_E/V'_{CO2} before IMT with those after IMT, no significant changes were observed in both patients (Fig. 1E and F). Moreover, the difference between inspiratory V_T (V_T in) and V_T ex (V_T in–V_T ex) was not reduced significantly either in Case 1 or in Case 2 (Table 2). The results indicated that IMT seemed not to affect the ventilatory efficiency. In Case 1, furthermore, V_D/V_T increased slightly and $P_{ET}CO_2$ decreased after IMT during exercise (Fig. 1G and H). The results showed that, even in Case 1 that was considered a responder to IMT, the ventilatory efficiency declined after IMT.

3.4. Exercise endurance in constant load testing after IMT

In constant load testing, dyspnea intensity (Borg scale) and endurance time improved in Case 1. Notably, endurance time increased by 6.1 min, which was greater than the threshold for clinical significance: 100 s. In contrast, no change was observed in these measurements in Case 2 (Fig. 2). Other results of CPET are shown in Table 2. These results showed that IMT contributed to the improvement of exercise endurance only in Case 1.

3.5. MIP improved in both patients after IMT

MIP and maximum expiratory mouth pressure (MEP) improved after IMT in Case 1 (Table 2). MIP in Case 2 improved from 56.7 cmH_2O to 63.5 cmH_2O. However, MEP was worsened from 96.2 cmH_2O to 75.2 cmH_2O.

4. Discussion

The present study highlights two major findings: 1) IMT might not improve the ventilatory efficiency in patients with advanced COPD; and 2) IMT might not be effective in underweight patients with advanced COPD when it induces tachypnea, reduces ventilatory efficiency, and fails to increase V'_E.

IMT has been recommended in patient with inspiratory muscle weakness [21]. IMT reportedly increases ribcage and neck muscle activation, and these muscle recruitment serve as a reserve to overcome increasing demand [12]. As the inspiratory muscles might become already trained [22], IMT is not effective in patients with COPD and high MIP (inspiratory muscle function > 60 cmH_2O) [6]. Moreover, earlier studies showed that IMT induced respiratory muscle strength and deeper breathing, reduced f_R, and contributed to dyspnea relief and the improvement of exercise tolerance in patients with COPD and maintained BMI [13]. Hence, IMT had been hypothesized to improve dynamic hyperinflation by reinforcing inspiratory muscles [8–10].

However, as consistent with an earlier study [11], the present study showed that the resultant ventilatory condition after IMT was not due to the improvement of dynamic hyperinflation. Given no significant change of the V_T in–V_T ex, dynamic hyperinflation did not improve significantly after IMT even in Case 1. It has been reported in patients with COPD that dynamic hyperinflation correlated with the expiratory time rather than with V'_E and $P_{ET}CO_2$, and that the exertional increase of $P_{ET}CO_2$ was negatively correlated with the V'_E/V'_{CO2} slope [23,24]. Thus, the decrease of $P_{ET}CO_2$ and the increase of V'_E in incremental load testing after IMT did not mean the improvement of dynamic hyperinflation in Case 1 (Fig. 1). From these observations, IMT might not improve dynamic hyperinflation even in patients with COPD who respond to IMT.

When IMT induces tachypnea and increased physiological dead space ventilation and fails to increase V'_E, IMT might not be effective in underweight patients with advanced COPD. The V'_E and peak V'_{O2} in incremental load testing and endurance time in constant load testing increased only in Case 1. Moreover, no significant changes of Ti/Ttot, V'_E/V'_{CO2}, and V_T ex in both cases showed that IMT did not improve ventilatory efficiency in patients with advanced COPD. Given that V'_E is calculated by the product of V_T ex and f_R and that IMT reduced V_T ex even in no significant range, the improvement of V'_E was purely attributed to the increase of f_R in Case 1. In contrast, V'_E did not change at peak exercise in Case 2, although f_R increased after IMT. These results suggest that V'_E is not always improved by increasing f_R especially in patients with advanced COPD.

A possible explanation of the resultant ventilatory condition after IMT can be attributed to wasted ventilation, which is a phenomenon that excessive exercise ventilation due to tachypnea increases physiological dead space ventilation and decreases ventilatory efficiency [25]. As in Case 2, underweight patients with COPD sometimes show mixed ventilatory defect [26]. The mechanism of this mixed ventilatory defect would be that they become too hyperinflated to serve enough inspiratory volume, although they maximally use their expiratory muscles. Given that FVC decreased despite the increased MIP and that the MEP decreased even though the need for an expiratory drive was increased after IMT in Case 2 (Tables 2 and 3), expiratory muscles might not

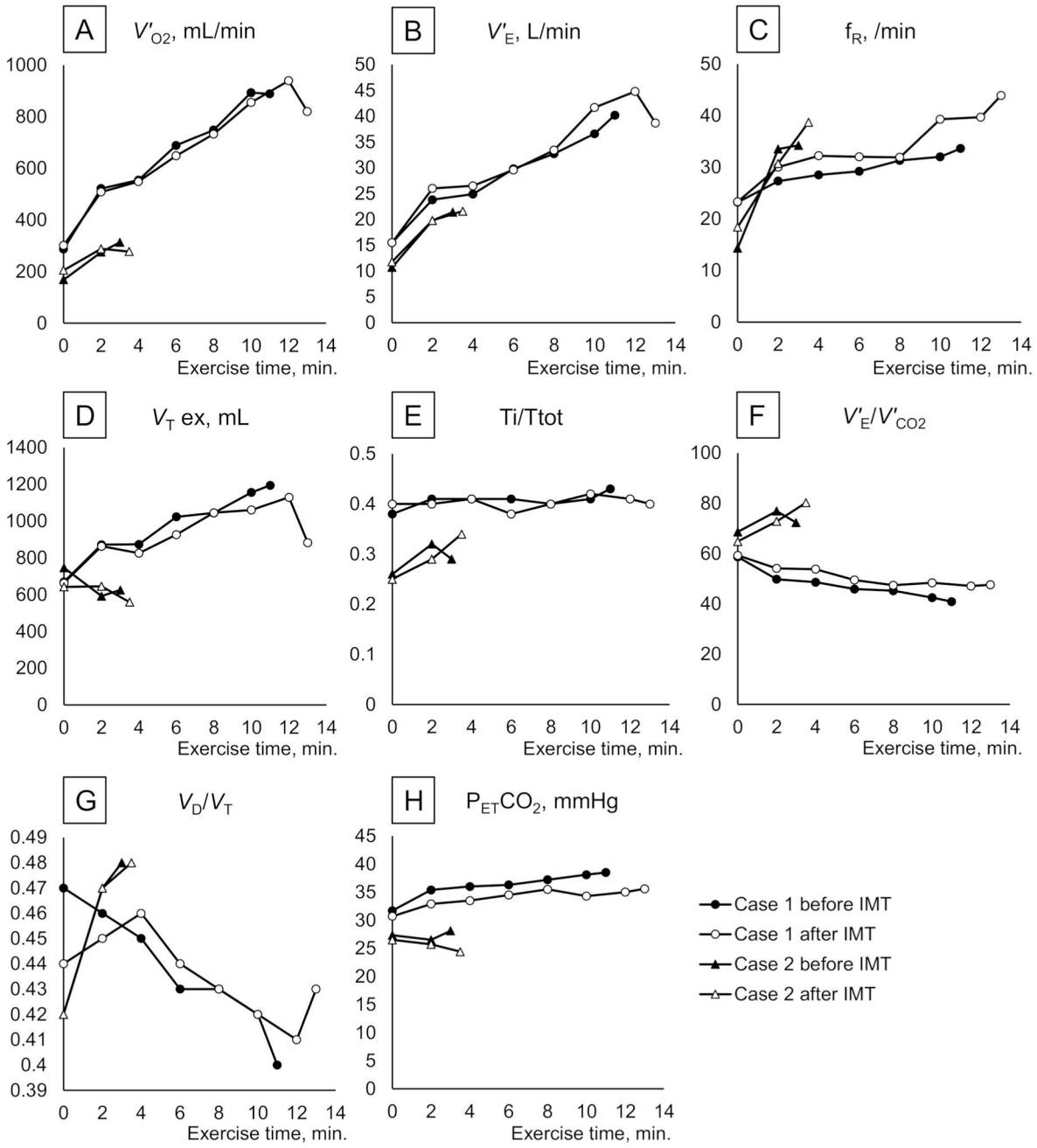

Fig. 1. Results of cardiopulmonary testing with incremental load. f_R, breathing frequency; IMT, inspiratory muscle training; $P_{ET}CO_2$, end-tidal carbon dioxide tension; Ti/Ttot, inspiratory duty cycle; V_D/V_T, physiologic dead space/tidal volume ratio; V'_{CO2}, carbon dioxide output; V'_E, minute ventilation; V'_{O2}, oxygen uptake; V_T ex, expiratory tidal volume.

overcome the obtained hyperinflation after IMT, and wasted ventilation might become severe. Therefore, IMT should not be recommended to underweight patients with advanced COPD who have severe findings such as extremely low FEV_1 and high MEP, prolonged expiration pattern during exercise, and decreased FVC. The present study is meaningful despite its scarcity of cases because CPET confirmed an exertional pathophysiological condition relevant to the evaluation and the clinical indications for IMT.

The present study had some limitations. First, this study included only two patients, and further large-scale studies are needed to validate the results of this study. Second, this study did not conduct inspiratory capacity maneuvers during exercise, and dynamic hyperinflation was not evaluated directly before and after IMT. Hence, studies for assessing the correlation between IMT and dynamic hyperinflation are needed.

In conclusion, we evaluated two patients with advanced COPD receiving IMT. When IMT induces wasted ventilation and decreases ventilatory efficiency, IMT may fail to increase V'_E and to improve exercise tolerance. Therefore, underweight patients with advanced COPD who have exertional wasted ventilation at pretreatment may not respond to IMT. IMT might be appropriate only for patients who have maintained BMI and can tolerate tachypnea and achieve adequate ventilation during exercise. Further investigations are necessary to clarify the limitations of IMT and the threshold conditions that are relevant to IMT effectiveness.

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None.

Table 2
Comparison of cardiopulmonary function between Case 1 and Case 2.

Parameter	Case 1		Case 2	
	Before IMT	After IMT	Before IMT	After IMT
CPET, at peak exercise incremental load testing				
V'_{O2}, mL/min/kg	14.0	14.1	7.5	6.3
V'_{O2}, mL/min	893	939	313	277
V'_{E}, L/min	40.2	44.8	21.4	21.6
f_R, breath/min	34	44	34	39
V_T ex, mL	1194	1129	625	559
V_T in–V_T ex, mL	21	18	12	16
Ti/Ttot	0.41	0.41	0.32	0.34
V'_E/V'_{CO2}	40.9	47.6	76.9	80.2
V_D/V_T	0.40	0.43	0.48	0.48
$P_{ET}CO_2$, mmHg	38.5	35.6	28.1	24.4
constant load testing				
exercise time, s	584	948	233	175
Respiratory muscle strength				
MIP, cmH_2O	52.0	77.0	56.7	63.5
MEP, cmH_2O	69.2	92.0	96.2	75.2

CPET, cardiopulmonary exercise testing; f_R, breathing frequency; IMT, inspiratory muscle training; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; $P_{ET}CO_2$, end-tidal carbon dioxide tension; Ti/Ttot, inspiratory duty cycle; V'_{CO2}, carbon dioxide output; V_D, dead space ventilation; V_D/V_T, physiologic dead space/tidal volume ratio; V'_E, minute ventilation; V'_{O2}, oxygen uptake; V_T, tidal volume; V_T ex, expiratory tidal volume; V_T in, inspiratory tidal volume.

Table 3
Spirometric parameters at rest before and after inspiratory muscle training.

Parameter	Case 1		Case 2	
	Before IMT	After IMT	Before IMT	After IMT
FEV_1, L	1.63	1.65	0.83	0.79
FEV_1, % predicted	60.8	61.6	34.3	32.6
FVC, L	3.84	3.81	1.78	1.42
FVC, % predicted	108.5	107.6	56.0	44.7
FEV_1/FVC, %	42.4	43.3	46.6	55.6
VC, L	4.08	4.05	1.94	1.47
%VC, %	110.3	109.5	58.3	44.1
IC, L	2.93	3.03	1.35	1.13

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; IMT, inspiratory muscle training; VC, vital capacity.

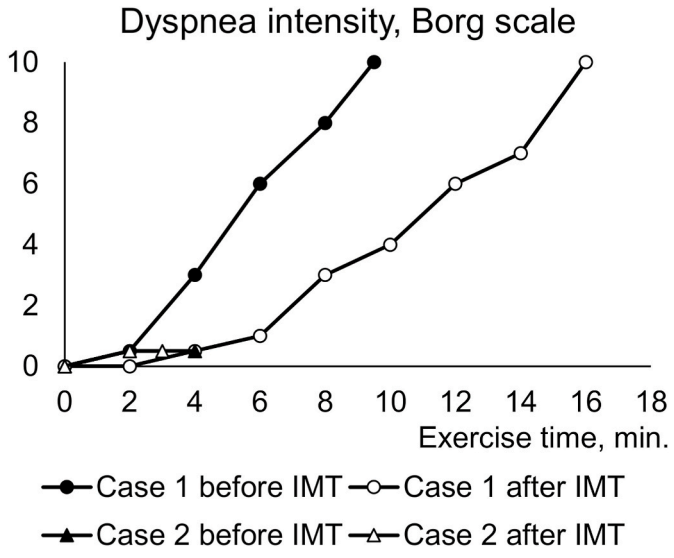

Fig. 2. Results of cardiopulmonary testing with constant load IMT, inspiratory muscle training.

Availability of data and materials

All data supporting our findings is contained within the manuscript.

Authors' contributions

Y.Y. contributed to conceptualize and design the study, collect and analyze data of all patients, and wrote the manuscript. K.M. cared all patients, contributed to conceptualize and design the study, analyzed data, and revised the manuscript. T.M., K.F., Y.O., H.K., K.T., and K.Y. contributed to collect data of all patients and revise the manuscript. M. M. and H.K. contributed to the interpretation of data and the design of the study. All authors reviewed and approved the submission of the final manuscript.

Ethics approval and consent to participate

Ethical approval to report this case was not required.

Consent for publication

Written informed consent was obtained from the patients for publication of this report and any accompanying images.

Declaration of competing interest

The authors declare that there are no conflicts of interest associated with this manuscript.

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