Managing COPD with expiratory or inspiratory pressure load training based on a prolonged expiration pattern

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ABSTRACT

Background: Exertional prolonged expiration should be identified as a therapeutic target in COPD. The efficacy of expiratory or inspiratory pressure load training (EPT/IPT) based on the degree of prolonged expiration was investigated.

Methods: A total of 21 patients with COPD were divided into two groups according to the exertional change in the inspiratory duty cycle (T_I/Ttot). For 12 weeks, patients whose exertional T_I/Ttot decreased received EPT (EPT group, n=11, mean percentage forced expiratory volume in 1 s (%FEV$_1$), 32.8%) and those whose exertional T_I/Ttot increased received IPT (IPT group, n=10, mean %FEV$_1$, 45.1%).

Results: The therapeutic responses were as follows. In both groups, endurance time (EPT, +5.7 min, p<0.0001; IPT, +6.1 min, p=0.0004) on the constant work rate exercise test (WRET) and peak oxygen uptake increased (EPT, p=0.0028; IPT, p=0.0072). In the EPT group the following occurred: 1) soon after commencement of exercise with the constant WRET, the expiratory tidal volume ($V_T$ex) increased, reducing dyspnoea; 2) $V_T$ex and mean expiratory flow increased and then prolonged expiration (p=0.0001) improved at peak exercise with the incremental exercise test (ET); and 3) St. George's Respiratory Questionnaire total, activity and impact scores were improved. In the IPT group, on both the constant WRET and incremental ET, breathing frequency increased, which led to greater exercise performance with effort dyspnoea.

Conclusions: This study showed the benefits of EPT/IPT on exercise performance. If the choice of managing COPD with EPT/IPT is appropriate, inexpensive EPT/IPT may become widespread as home-based training.

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Expiratory or inspiratory pressure load training (EPT/IPT) based on the degree of prolonged expiration improves exercise performance in COPD patients. If managing COPD with EPT/IPT is chosen appropriately, it could become widespread as home-based training. https://bit.ly/2ZWutWq

Introduction

Globally, COPD was the third leading cause of death in 2018 and 65 million people have moderate to severe COPD [1]. Furthermore, due to the prediction that global health spending will escalate from US$10 trillion in 2015 to $20 trillion in 2040 [2], countermeasures against COPD are thus pressing medical, economic and social issues.

Without reducing intolerable exertional dyspnoea, which is a hallmark, especially of the advanced stage of COPD, improving aerobic capacity and prognosis cannot be achieved. In COPD, exertional dyspnoea is recognised as correlating with dynamic air trapping and mechanical constraints on exertional tidal volume (V_T) expansion, which contribute the wasted ventilation. Given that humans develop exertional dyspnoea and a string of studies reported that exertional dyspnoea in COPD was associated with progressive mechanical constraints on V_T irrespective of the presence of dynamic hyperinflation [3–5], achieving the ability to expand V_T to obtain enough ventilation is extremely interesting as a treatment goal for COPD. Traditionally, as the stage of COPD advances, it has been recognised that, with rapid and shallow breathing, that is, with a lower V_T, a higher breathing frequency (f_R) is required during exercise [6]. In fact, however, it is found that most such patients breathe slowly and shallowly with prolonged expiration during exercise. Both breathing patterns should be distinguished to select therapeutic approaches.

Inspiratory pressure load training (IPT), which has been extensively studied as inspiratory muscle training, has been recommended as a pulmonary rehabilitation (PR) programme. Several reviews suggested the effects of IPT as a stand-alone therapy, but, at least in advanced patients with COPD, no large studies have reported the adjunctive effects of IPT when added to PR [7–10]. In contrast, most reports related to expiratory pressure load training (EPT), known as expiratory muscle training, have investigated the expulsive effort, including sputum [11], perhaps because most EPT devices could provide a low-pressure load alone. Furthermore, WEINER et al. [12] reported that the effects of EPT added to IPT were not obtained in severe and very severe COPD. Therefore, the clue to investigate EPT has not been obtained in patients with COPD.

In our previous report, the hypothesis was formulated that EPT could be more effective in COPD patients when prolonged expiration patterns are confirmed by a decreased ratio of inspiratory time to total respiratory cycle time (T_I/Ttot) during exercise, whereas IPT could be more effective when nonprolonged expiration patterns are confirmed by increased exertional T_I/Ttot [13]. To improve exercise performance of COPD patients with better exertional T_I/Ttot, 1) in the prolonged expiration patterns, a larger expiratory V_T ($V_T$ex) and a higher mean expiratory flow ($V_T$ex/expiratory time (T_E)) by EPT might be needed, although based on the Bernoulli principle, pursed-lip breathing needs the low expiratory flow and prolonged expiratory time to reduce airway collapse [14], and 2) in nonprolonged expiration patterns, the larger inspiratory V_T ($V_T$in) and higher mean inspiratory flow ($V_T$in/inspiratory time (T_I)) obtained by IPT might be needed.

Ghrelin has two forms including des-acyl ghrelin and acyl ghrelin; the latter is considered the major active form that has various physiological effects [15]. Edible medium-chain triglycerides (MCTs) change des-acyl ghrelin to acyl ghrelin [16]. Especially in patients with more advanced COPD, if the programme using IPT or EPT results in excessive training, and leads to a cachectic condition, edible MCTs might improve or maintain the patient's condition.

This open-label pilot study was conducted to prove the above hypothesis. The efficacy and safety of EPT or IPT with MCT administration were investigated in COPD patients, who were categorised according to their prolonged expiration pattern assessed by T_I/Ttot during cardiopulmonary exercise testing (CPET).

Material and methods

Study design and patients

Patients with moderate and very severe COPD were recruited in the National Hospital Organization Osaka Toneyama Medical Center from February 2018 to August 2019. Patients whose exertional T_I/Ttot decreased (resting T_I/Ttot>peak T_I/Ttot) received 12-week EPT, while those whose exertional T_I/Ttot increased (resting T_I/Ttot⩽peak T_I/Ttot) received 12-week IPT. Nutritional treatment with MCTs was given along with both training programmes.

This prospective study was conducted according to the Declaration of Helsinki and the Good Clinical Practice guidelines, was approved by the ethics committees of our centre (approval number, TNH-2018007) and was registered with the University Hospital Medical Information Network in Japan: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000035288, number: UMIN000030937. All patients gave their written informed consent.

The inclusion criteria were as follows: 1) moderate to very severe COPD based on spirometry: post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.7, and FEV_1 percent predicted normal <80% with modified British Medical Research Council: grade 1 and higher; 2) in a stable condition and able to tolerate CPET to ensure adequate evaluation; 3) aged between 40 and 85 years; and 4) provision of a signed agreement to participate in this study. Participants were excluded for any of the following reasons: 1) malignant tumours; 2) active infection; 3) severe heart disease; 4) asthma; 5) change in the drug regimen during this study; 6) receiving PR; 7) receiving oxygen therapy at rest; 8) on therapy for diabetes mellitus or with a glycated haemoglobin level >7.0%; and 9) judged by the physician to be inappropriate to participate in this study.

Interventions
Respiratory pressure load training
All patients received the training (30 times a set, two sets a day) for 12 weeks at home. The training load was started at 20% of the maximum expiratory pressure (MEP) or maximum inspiratory pressure (MIP) at baseline. If possible, the level was increased once every 2 weeks up to 50% of the maximum pressure. The EMST150 (Aspire Products, Atlanta, GA USA) and the POWERbreathe Medic plus (POWERbreathe International, Stratford Upon Avon, UK) were used for EPT and for IPT, respectively. Details are in the supplementary material.

MCT administration
Edible oil containing octanoic acid (C8) and decanoic acid (C10) (The Nisshin OilliO Group, Tokyo, Japan) was given at a dose of 2.5 g daily, orally, for 12 weeks.

Evaluation
Pulmonary function tests were done, as previously described [13, 17]. Symptom-limited exercise tests were conducted on 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 AE310S, Minato Medical Science Co., Ltd, Osaka, Japan), as previously described [13, 18]. An incremental exercise test (ET), which consisted of 2-min increments to 10 W, was performed until patient exhaustion without encouragement, especially during exercise. The constant work rate exercise test (WRET) was performed at 70% of the peak workload in the incremental ET before treatment. All patients were asked to maintain a cycle ergometer speed of about 60 rpm while looking at the rpm meter. Minute ventilation (V'_E), oxygen uptake (V'_{O_2}), carbon dioxide output (V'_{CO_2}), f_R, $V_T$in, $V_T$in/T_I, $V_T$ex, $V_T$ex/T_E, T_I/Ttot, physiologic dead space/tidal volume ratio (V_D/V_T), and O_2 pulse (V'_{O_2}/heart rate (HR)) were measured breath by breath and collected as 30-s average values at rest, during exercise at 2-min intervals and at the end of exercise. The anaerobic threshold (AT) was identified using the V-slope method and the nadir of the parameter V'_E/V'_{O_2} was measured during exercise. The severity of dyspnoea, intensity of leg fatigue and percutaneous oxygen saturation (S_{pO_2}) were evaluated by the modified Borg scale [19] at rest and during the last 15 s of each exercise stage and at the end of exercise. $V_T$in−$V_T$ex was evaluated as the volume of air remaining in the lung after expiration. Iso-time was defined as the highest equivalent exercise time for each subject among three evaluations. Dual-energy radiography absorptiometry and respiratory muscle strength evaluation by the MIP and MEP, respectively were performed as described previously [13, 20]. The validated Japanese version of the St. George's Respiratory Questionnaire (SGRQ) was used as described previously [16, 21, 22].

Outcome measures
Efficacy
The primary outcomes was the exertional change in T_I/Ttot. The secondary outcomes included: 1) the SGRQ score; 2) CPET parameters (peak V'_{O_2}, endurance time and dyspnoea intensity (Borg scale)); and 3) MEP and MIP.

Safety
All participants were included in the safety analyses.

Sample size and statistical analysis
At the time of the study design, no studies had investigated the efficacy of EPT or IPT in COPD patients based on the exertional prolongation of expiration by T_I/Ttot. As this study protocol has never been previously performed, the sample size could not be calculated. This open-label pilot study evaluated at least 10 participants each for EPT and IPT.

The effects of the intervention were examined twice (*i.e.* at Week 6 and Week 12) and were analysed in only each group. When no evaluations in the outcome were performed at Week 6, the changes between at pretreatment and at Week 12 were analysed using the Wilcoxon signed rank test. The changes during the treatment time course (*i.e.* pretreatment, Week 6 and Week 12) were analysed using a linear mixed-effects model. The least squares means Tukey's honestly significant difference test was used for the comparison of each variable among the treatment points [23]. A p-value <0.05 was considered significant. Statistical analyses were performed using JMP software, version 11 (SAS Institute, Cary, NC, USA).

Results

Of the 22 enrolled patients, 21 completed this study protocol, because 1 patient dropped out after enrolment due to having his first episode of bronchial asthma during this study (figure 1). Eleven patients completed the EPT added to MCT administration (EPT group) protocol and 10 completed the IPT added to MCT administration (IPT group) protocol, whose data were used to ensure efficacy using a per-protocol analysis. All patients enrolled in the EPT group had severe to very severe airway obstruction with reduced exercise tolerance and seven patients had a history of PR. The EPT group had a higher frequency of hospitalisation than the IPT group. Table 1 shows the patients' baseline characteristics.

EPT and IPT progression

The ratio of the attained pressure after the 12-week programme to the target pressure was 78%±19% in the EPT group and 95%±16% in the IPT group.

Evaluation in the EPT group

Only MEP increased during the whole EPT treatment course (table 2).

Changes at peak exercise in the incremental ET for 12 weeks are shown in figure 2a−e and table 2. The V'_{O_2} (p=0.0028), $V_T$ex (p=0.0418), $V_T$ex/T_E (p=0.0025), $V_T$in−$V_T$ex (p=0.0339) and T_I/Ttot (peak−rest) (p=0.0001) improved significantly during the whole EPT treatment course. When comparing each parameter among the treatment points, significant improvements compared with pretreatment, which were confirmed at both 6 and 12 weeks, were observed in $V_T$ex/T_E and T_I/Ttot (peak−rest).
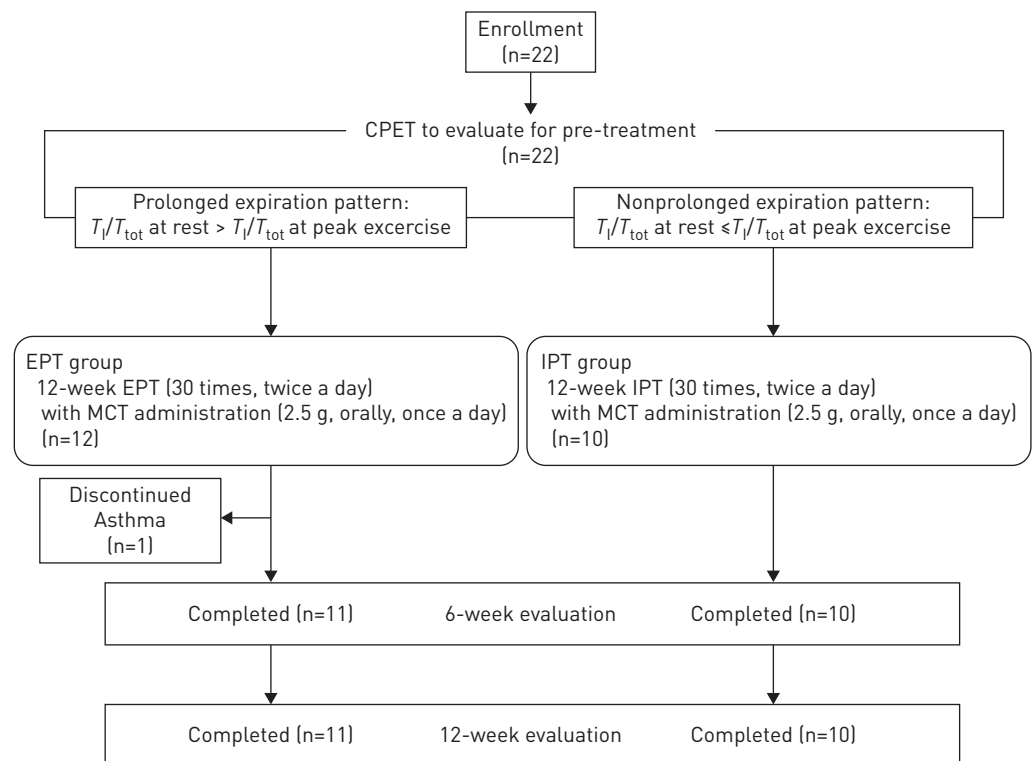

FIGURE 1 Trial profile. CPET: cardiopulmonary exercise testing; EPT: expiratory pressure load training; IPT: inspiratory pressure load training; MCT: medium-chain triglycerides; T_I/Ttot: the ratio of inspiratory time to total respiratory cycle time.

TABLE 1 Baseline characteristics of the patients (n=21)			
	EPT group (n=11)	**IPT group (n=10)**	**p-value**
Age years	67.3±5.3	73.4±4.6	0.1111
Sex male/female n	10/1	10/0	0.3286
BMI kg·m^{-2}	20.7±2.5	20.8±3.5	1.0000
Cigarette smoking pack-years	62.0±26.9	70.2±29.0	0.7245
GOLD, II/III/IV n	0/7/4	4/5/1	0.0346
Pulmonary function test			
FEV_1 L	0.87±0.19	1.18±0.40	0.1486
FEV_1 % predicted	32.8±7.0	45.1±14.2	0.0448
FEV_1/FVC %	33.9±6.0	38.9±6.5	0.1130
VC L	2.75±0.56	3.14±0.80	0.2048
VC % predicted	84.8±12.3	98.0±22.8	0.0980
Incremental work rate exercise testing			
Peak V'_{O_2} mL·min^{-1}·kg^{-1}	10.7±2.7	11.6±3.4	0.5968
AT mL·min^{-1}·kg^{-1}	8.8±1.9	10.8±2.0	0.0736
Medications n			
LAMA/LABA/ICS	10/11/8	10/10/4	0.6321
Triple inhalation therapy	8	4	0.1301
Long-term oxygen therapy#	3	2	0.6959
History of pulmonary rehabilitation	7	4	0.2787
History of hospitalisation	8	2	0.0157

Data are presented as mean±SD, unless otherwise stated. EPT: expiratory pressure load training; IPT: inspiratory pressure load training; BMI: body mass index; GOLD: global initiative for chronic obstructive lung disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; VC: vital capacity; AT: anaerobic threshold; V'_{O_2}: oxygen uptake; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroids. Triple inhalation: a combination of LAMA, LABA and ICS. Medications are presented separately. ATs were not detectable in four patients in the EPT group, and in three patients in the IPT group. History of hospitalisation owing to a deteriorated condition in relation to COPD was investigated. #: All patients used long-term oxygen therapy only on exertion.

Changes at the limit of tolerance and during exercise on the constant WRET for 12 weeks are shown in figure 3a–c and tables 3 and 4. The increased endurance time was highly significant (p<0.0001) and the significance was evident already from 6 weeks. Increased leg fatigue seemed to stop the prolonged exercise obtained from EPT. The exertional dyspnoea was reduced significantly at iso-time (figure 3b and table 4). The $V_T$ex increased from the early exercise phase (figure 3c) and the f_R was reduced at iso-time (table 4).

All SGRQ scores except for the SGRQ symptoms domain improved (table 5). Pulmonary functions and body weight were unchanged (table 5).

Evaluation in the IPT group
During the whole IPT treatment course: 1) only MIP increased; 2) at peak exercise in the incremental ET during 12 weeks, V'_{O_2} (p=0.0072) and V'_E (p=0.0147) improved and exertional dyspnoea worsened with increased f_R and unchanged $V_T$ex (figure 2f–j and table 2); and 3) on the constant WRET, the increased endurance time was highly significant (p=0.0004). At the limit of tolerance, however, the f_R and V_D/V_T were increased with worsened exertional dyspnoea and leg fatigue (figure 3e,f and table 3). All SGRQ scores, pulmonary functions and body weight did not improve (table 5).

Safety
Loose stools were observed in 2 of the 22 enrolled patients. No treatment-related serious events such as a pneumothorax were reported.

Discussion

The main findings of this study were as follows. First, 12-week EPT with MCT administration: 1) improved quality of life (QOL) based on the SGRQ scores, the peak V'_{O_2}, and the endurance time; 2) increased $V_T$ex and $V_T$ex/T_E and decreased $V_T$in−$V_T$ex at peak exercise on the incremental ET, which improved prolonged expiration (primary outcome); and 3) increased $V_T$ex from the commencement of the exercise on the constant WRET and then the exertional dyspnoea was reduced at iso-time. Second, 12-week IPT with MCT administration: 1) did not improve the SGRQ scores, but it improved peak V'_{O_2}

TABLE 2 Changes at peak exercise in the incremental exercise parameters and resting respiratory muscle strength after respiratory pressure load training

	EPT group (n=11)			p-value	IPT group (n=10)			p-value
	Pretreatment	After 6 weeks	After 12 weeks		Pretreatment	After 6 weeks	After 12 weeks	
Maximum workload W	35.5±15.7	40.9±13.8*	44.5±13.7***	0.0005	43.0±15.7	47.0±17.7	49.0±19.1**	0.0096
V'_{O_2} mL·min^{-1}	613.9±199.2	639.5±223.0	670.2±233.2**	0.0025	646.0±220.9	657.6±243.7	694.5±255.7**,#	0.0091
V'_{O_2} mL·min^{-1}·kg^{-1}	10.7±2.7	11.2±3.1	11.6±3.1**	0.0028	11.6±3.4	11.7±3.7	12.4±3.9*,#	0.0072
V'_E L·min^{-1}	27.9±7.0	29.1±7.3	30.1±8.3***	0.0006	30.1±8.5	30.8±9.8	32.3±11.0*	0.0147
$V_T$ex mL	998±232	1061±207	1073±222*	0.0418	1104±259	1055±287	1104±310	0.3443
f_R breaths·min^{-1}	28±5	28±5	29±5	0.3215	28±5	29±7	31±8*	0.0164
V'_E/V'_{O_2}	46.5±4.8	46.7±6.3	46.1±5.6	0.7966	48.3±8.4	48.8±10.5	47.7±8.3	0.4216
V'_E/V'_{CO_2}	47.0±5.7	46.8±6.8	46.2±6.6	0.7626	48.6±9.7	48.4±11.0	47.9±9.6	0.7709
V_D/V_T	0.42±0.04	0.41±0.04	0.41±0.04	0.2974	0.41±0.05	0.41±0.05	0.41±0.05	0.8071
HR beats·min^{-1}	119±13	120±12	125±12*	0.0142	113±15	117±19	117±17	0.4643
O$_2$ pulse mL·beats^{-1}	5.1±1.3	5.3±1.5	5.3±1.5	0.3072	5.8±1.7	5.5±1.7	5.6±1.7	0.2675
S_{pO_2} %	89±5	89±4	88±4	0.1970	91±4	89±4	91±4	0.1433
Dyspnoea Borg scale	6.3±2.6	6.0±2.6	6.7±2.0	0.1768	6.3±1.8	7.5±1.9*	7.8±1.5**	0.0040
Leg discomfort Borg scale	4.2±3.7	4.9±3.5	6.2±2.2	0.0867	5.5±1.5	6.8±1.9**	7.2±1.5***	0.0002
$V_T$in/T_I mL·s^{-1}	1524±407	1523±322	1600±413	0.1450	1318±248	1346±274	1374±328	0.3770
$V_T$ex/T_E mL·s^{-1}	651±169	706±202*	728±217**	0.0025	820±276	847±334	884±365*	0.0347
$V_T$in − $V_T$ex mL	25±44	5±19	1±26*	0.0339	2±26	0±44	−15±40	0.2506
T_I/Ttot peak − rest	−0.04±0.06	−0.00±0.02***	−0.01±0.03**	0.0001	0.04±0.02	0.02±0.04	0.02±0.03	0.5356
MEP cmH$_2$O	125.4±24.7	149.2±33.0*	153.4±32.4**	0.0047	114.9±45.4	110.5±40.7	117.9±47.1	0.5943
MIP cmH$_2$O	77.9±19.3	81.2±20.2	85.9±21.8	0.1530	67.9±17.2	74.2±17.4	78.0±19.0*	0.0217

Data are presented as mean±SD. EPT: expiratory pressure load training; IPT: inspiratory pressure load training; V'_{O_2}: oxygen uptake; V'_E: minute ventilation; $V_T$ex: expiratory tidal volume; f_R: breathing frequency; V'_{CO_2}: carbon dioxide output; V_D/V_T: physiologic dead space/tidal volume ratio; HR: heart rate; O$_2$ pulse: V'_{O_2}/HR; S_{pO_2}: percutaneous oxygen saturation; T_I: inspiratory time; $V_T$in: inspiratory tidal volume; T_E: expiratory time; T_I/Ttot: inspiratory duty cycle; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure. *: p<0.05; **: p<0.01; ***: p<0.001, by the least squares means Tukey honestly significant difference, compared with the pretreatment; #: p<0.05, by the least squares means Tukey's honestly significant difference, compared with the values after 6 weeks of IPT.

and endurance time; and 2) increased the f_R with increased exertional dyspnoea and without a change of exertional T_I/Ttot (primary outcome) on the incremental ET and the constant WRET.

It has been considered that training patients with COPD to breathe slowly and deeply for rapid and shallow breathing during exercise, which leads to dynamic hyperinflation, is useful to reduce exertional dyspnoea [6]. However, slow and shallow breathing, instead of rapid and shallow breathing, unexpectedly leads to exertional dyspnoea to stop exercise. NEDER et al. [24] reported that, in a study of mild to end-stage COPD including healthy controls, the peak f_R with the incremental ET decreased to stop exercise as the disease stage advanced. Also, in the present study, reduced f_R accompanied by reduced $V_T$ex was confirmed in both groups pretreatment. Moreover, in the EPT group, patients with a more advanced stage than those in the IPT group breathed slowly and shallowly with the exertional prolongation of expiration (table 2). Training such patients using, for example, pursed-lip breathing, would be less useful, because slower breathing might be impossible and ineffective to obtain enough ventilation. Therefore, countermeasures against slow and shallow breathing with prolonged expiration of COPD have largely been effectively overlooked.

On the EPT, the increase in endurance time, measured with the constant WRET, was large. The 5.7-min increase with reduced exertional dyspnoea was long enough, given that: 1) the clinical meaningful difference is 100 s [18]; and 2) patients with severe and very severe COPD and severely reduced exercise tolerance, who had already taken most available treatments including PR enrolment (table 1), all obtained a prolonged endurance time (figure 3a). The adequate aerobic capacity with the improvement in QOL is rewarding. In the EPT group, all treatment differences in the SGRQ total, impact and total scores were more than seven units, which was higher than the four units accepted as clinically relevant [22]. MOTA et al. [25] reported that, in severe COPD, 5-week EPT improved the SGRQ scores but not ventilatory variables, including peak V'_{O_2}. Their findings are consistent with our results in which the unchanged peak V'_{O_2} was obtained after 6 weeks in the EPT group, suggesting that the duration of EPT needs to be more than 6 weeks. Of note, in the present study, it was demonstrated that the increase of $V_T$ex/T_E and the
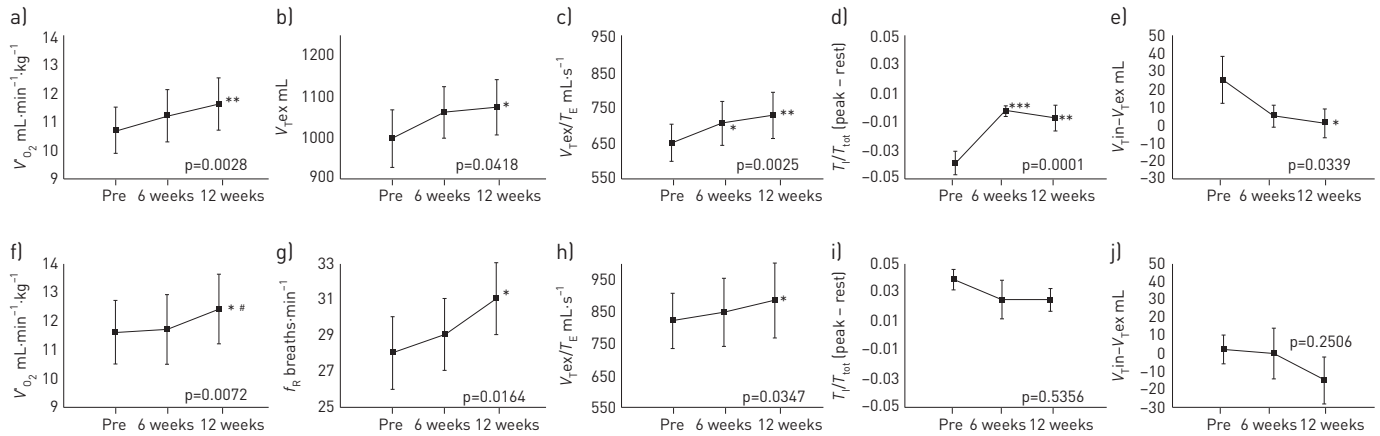
FIGURE 2 Changes at peak exercise on the incremental exercise testing after expiratory pressure load training (EPT, panels a–e) or inspiratory pressure load training (IPT, panels f–j). T_E: expiratory time; T_I/Ttot: the ratio of inspiratory time to total respiratory cycle time; V'_{O_2}: oxygen uptake; $V_T$ex: expiratory tidal volume; $V_T$ex/T_E: mean expiratory flow; $V_T$in: inspiratory tidal volume; f_R: breathing frequency. By a linear mixed-effect model: p-value. By the least squares means Tukey's honestly significant test: *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, compared with the pretreatment, #: $p < 0.05$, compared with after 6 weeks of treatment.

improved prolonged expiration from baseline were confirmed from 6 weeks, but the increase of $V_T$ex was not significant (table 2 and figure 2). These responses might mean that after EPT, even if the T_E was markedly reduced, enough expiratory volume was obtained without airway collapse. Furthermore, at 12 weeks, a larger $V_T$ex or higher $V_T$ex/T_E obtained from EPT improved exercise performance and exertional dyspnoea in advanced COPD. EPT might thus prevent dynamic wasted ventilation, as the
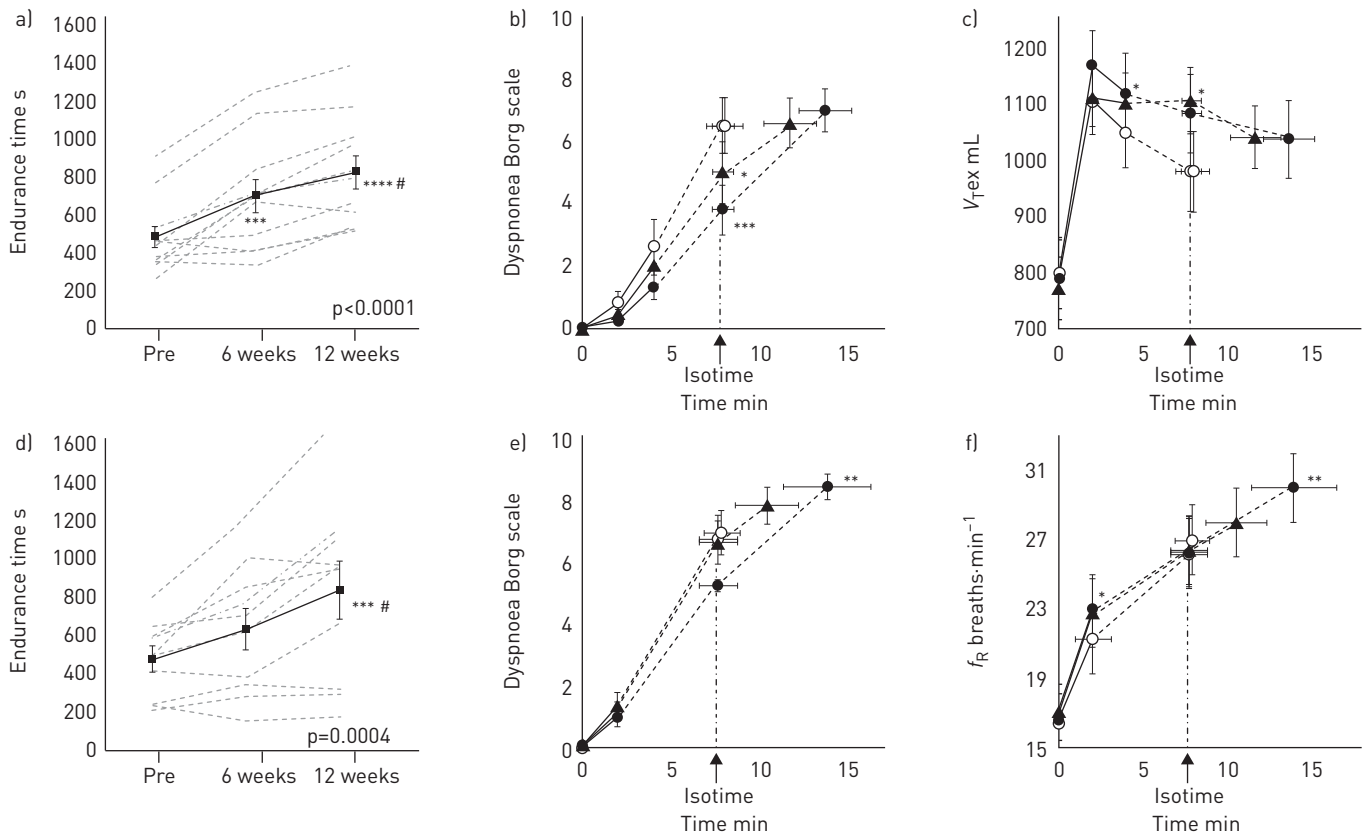

FIGURE 3 Changes at the limit of tolerance and during exercise on the constant work rate exercise testing after expiratory pressure load training (EPT, panels a–c) or inspiratory pressure load training (IPT, panels d–f). f_R: breathing frequency; iso-time: highest equivalent exercise time for each subject among three evaluations; $V_T$ex: expiratory tidal volume. Open circle: pretreatment; closed triangle: after 6 weeks of treatment; closed circle: after 12 weeks of treatment. By a linear mixed-effects model: p-value. By the least squares means Tukey's honestly significant test: *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, ****: $p < 0.0001$, compared with the pretreatment; #: $p < 0.05$, compared with after 6 weeks of treatment.

TABLE 3 Changes at the limit of tolerance in the constant work rate exercise parameters after respiratory pressure load training

	EPT group (n=11)			p-value	IPT group (n=10)			p-value
	Pretreatment	After 6 weeks	After 12 weeks		Pretreatment	After 6 weeks	After 12 weeks	
Endurance time s	481±195	699±293***	824±289****,#	<0.0001	472±197	631±344	835±481***,#	0.0004
V'_{O_2} mL·min^{-1}	628.3±191.7	603.1±171.4	614.2±198.9	0.6749	613.7±185.7	657.3±182.3	611.3±209.7	0.5825
V'_{O_2} mL·min^{-1}·kg^{-1}	10.9±2.9	10.6±2.4	10.8±2.8	0.7323	11.6±2.7	11.5±2.8	11.5±3.3	0.9970
V'_E L·min^{-1}	27.6±6.6	27.2±5.7	27.6±8.7	0.9328	28.1±7.4	28.6±8.5	29.2±8.7	0.5825
$V_T$ex mL	980±237	1041±187	1038±229	0.3737	1065±226	1029±242	997±280	0.6238
f_R breaths·min^{-1}	29±6	27±5	27±7	0.2127	27±5	28±6	30±7**	0.0090
V'_E/V'_{O_2}	44.9±4.6	46.2±5.3	45.3±5.1	0.7105	46.9±8.2	45.2±4.8	49.7±3.6*	0.0565
V'_E/V'_{CO_2}	47.0±4.5	46.7±4.5	46.7±4.7	0.9768	49.3±8.9	46.8±3.9	51.5±10.7	0.0649
V_D/V_T	0.41±0.03	0.42±0.04	0.42±0.04	0.8400	0.41±0.05	0.41±0.04	0.43±0.05*	0.0389
HR beats·min^{-1}	119±14	117±13	124±12	0.0780	111±15	112±16	113±16	0.6717
O_2 pulse mL·beats^{-1}	5.2±1.3	5.3±1.2	4.9±1.4	0.2559	5.5±4.0	5.6±1.3	5.3±1.6	0.7725
S_{pO_2} %	88±5	88±5	87±6	0.2381	91±4	90±5	91±4	0.2941
Dyspnoea Borg scale	6.5±3.0	6.6±2.5	7.0±2.3	0.5511	7.0±2.1	7.9±1.9	8.5±1.2**	0.0058
Leg discomfort Borg scale	4.5±3.4	5.8±3.2	6.8±2.6**	0.0108	6.4±2.2	6.9±2.3	8.1±1.7**,#	0.0061
$V_T$in/T_I mL·s^{-1}	1416±311	1495±315	1515±415	0.3622	1224±185	1264±253	1337±246	0.1439
$V_T$ex/T_E mL·s^{-1}	682±185	677±154	683±199	0.9548	752±222	778±279	802±311	0.3705
$V_T$in $-$ $V_T$ex mL	15±52	−4±43	−1±51	0.3183	5±37	−4±40	−8±29	0.4149
T_I/Ttot peak $-$ rest	−0.04±0.04	−0.01±0.04	0.01±0.03	0.0770	0.03±0.03	0.02±0.05	0.03±0.03	0.2959

Data are presented as means±SD. EPT: expiratory pressure load training; IPT: inspiratory pressure load training; V'_{O_2}: oxygen uptake; V'_E: minute ventilation; $V_T$ex: expiratory tidal volume; f_R: breathing frequency; V'_{CO_2}: carbon dioxide output; V_D/V_T: physiologic dead space/tidal volume ratio; HR: heart rate; O_2 pulse: V'_{O_2}/HR; S_{pO_2}: percutaneous oxygen saturation; $V_T$in: inspiratory tidal volume; T_I: inspiratory time; T_E: expiratory time; T_I/Ttot: inspiratory duty cycle. *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$, ****: $p<0.0001$, by the least squares means Tukey honestly significant difference, compared with the pretreatment; #: $p<0.05$, by the least squares means Tukey's honestly significant difference, compared with the values after 6 weeks of EPT or IPT.

reduced air remaining in the lung after expiration, that is $V_T$in$-V_T$ex, on the incremental ET was confirmed. It is unclear, however, where the site of action for EPT is and how EPT affects it. Laryngeal narrowing occurs in humans during the expiratory phase, and as the stage of COPD advances, the larynx narrows more during exercise, and this response is related to longer prolonged expiration, lower $V_T$ex, and lower peak V'_{O_2} [26, 27]. As one of the possible mechanisms of EPT, EPT might promote laryngeal widening by affecting the laryngeal abductors [27], which could prevent the vocal cords with central airways from collapsing during exercise. In the future, observation of glottic function by laryngoscopy during exercise might prove the above possible mechanism.

In IPT, the increased ventilation resulting from rapid f_R leads to increased aerobic capacity and endurance time. On the constant WRET, figure 3f shows that the f_R levels were similar at iso-time among all evaluation points, and the slope of f_R to the endurance time was not changed after IPT. In addition, tables 3 and 4 show that, after IPT, all ventilatory variables were not changed at iso-time, but the increased f_R-related variables (V_D/V_T, V'_E/V'_{O_2} and dyspnoea) were increased at the limit of tolerance. These findings suggest that IPT enabled exercise by forcing greater additional effort than pretreatment levels using the rapid f_R. In fact, after IPT, only one patient with the highest %FEV$_1$ among the IPT group could exercise longer, reducing the f_R with the higher $V_T$ex. If wasted ventilation does not occur, the rapid f_R may be attractive for getting enough ventilation, because healthy subjects can reach a rapid f_R and patients with advanced COPD cannot reach it to stop exercise [24]. After IPT, three patients could not achieve enough prolongation of endurance time (figure 3d) due to the increased f_R-related wasted ventilation. These findings suggested that IPT is not indicated for patients with wasted ventilation. WEINER et al. [12] reported that adding IPT to EPT did not show additional effects, although the effect of EPT alone was confirmed. The forcing effort owing to the increased f_R by IPT might hide the effect of EPT in advanced COPD.

Weight and O_2 pulse, changes in both of which were attributed to the effect of MCT administration [16], were unchanged in both groups. There was, therefore, little effect of MCT administration.

This study had some limitations. First, further studies are necessary to investigate whether patients without exertional prolongation of expiration are appropriate for EPT. Second, the EMST150 is generally used by

TABLE 4 Changes at iso-time in the constant work rate exercise parameters after respiratory pressure load training

	EPT group (n=11)			p-value	IPT group (n=10)			p-value
	Pretreatment	After 6 weeks	After 12 weeks		Pretreatment	After 6 weeks	After 12 weeks	
Iso-time s	474±198				460±210			
V'_{O_2} mL·min^{-1}	627.1±192.3	613.4±187.8	613.4±203.1	0.8356	611.7±190.3	661.9±185.4	619.7±185.4	0.7722
V'_{O_2} mL·min^{-1}·kg^{-1}	10.9±2.9	10.8±2.7	10.8±2.9	0.9101	11.0±2.8	11.6±2.8	11.1±3.2	0.9070
V'_E L·min^{-1}	27.5±6.6	27.1±6.7	27.4±9.3	0.9306	27.9±7.6	28.3±8.4	28.6±8.8	0.7461
$V_T$ex mL	981±237	1107±195*	1085±231	0.0320	1068±229	1088±271	1109±292	0.7512
f_R breaths·min^{-1}	29±6	25±5*	26±7	0.0203	26±5	26±6	26±7	0.9782
V'_E/V'_{O_2}	44.7±4.4	45.1±5.4	45.0±4.8	0.9603	46.8±8.2	44.5±4.6	47.9±10.2	0.4200
V'_E/V'_{CO_2}	46.9±4.2	46.6±4.5	46.5±4.3	0.9481	49.4±9.5	46.2±3.9	49.5±10.4	0.8722
V_D/V_T	0.41±0.03	0.42±0.04	0.41±0.03	0.6059	0.41±0.04	0.40±0.04	0.41±0.05	0.4720
HR beats·min^{-1}	119±13	113±13	117±14	0.1541	111±16	109±15	109±13	0.5981
O_2 pulse mL·beats^{-1}	5.2±1.3	5.4±1.3	5.2±1.3	0.5359	5.5±1.5	5.8±1.4	5.6±1.8	0.7866
S_{pO_2} %	88±5	89±5	89±5	0.3361	91±4	91±4	92±3	0.3720
Dyspnoea Borg scale	6.5±3.0	5.0±3.2*	3.8±2.5***	0.0003	6.8±2.4	6.7±2.1	5.3±0.6	0.0576
Leg discomfort Borg scale	3.8±2.8	4.6±3.3	3.8±2.8	0.5140	6.2±2.5	6.1±2.1	5.1±0.8	0.1027
$V_T$in/T_I mL·s^{-1}	1413±310	1417±319	1429±456	0.9775	1227±182	1197±193	1214±238	0.3091
$V_T$ex/T_E mL·s^{-1}	680±185	671±171*	681±234	0.9387	746±228	795±304	778±306	0.3705
$V_T$in − $V_T$ex mL	13±49	−13±48	−3±29	0.1274	5±37	−12±42	−8±33	0.1896
T_I/Ttot peak − rest	−0.03±0.05	−0.00±0.04	−0.01±0.02	0.1554	0.02±0.02	0.06±0.10	0.05±0.03	0.3236

Data are presented as mean±SD. EPT: expiratory pressure load training; IPT: inspiratory pressure load training; V'_{O_2}: oxygen uptake; V'_E: minute ventilation; $V_T$ex: expiratory tidal volume; f_R: breathing frequency; V'_{CO_2}: carbon dioxide output; V_D/V_T: physiologic dead space/tidal volume ratio; HR: heart rate; O_2 pulse: V'_{O_2}/HR; S_{pO_2}: percutaneous oxygen saturation; $V_T$in: inspiratory tidal volume; T_I: inspiratory time; T_E: expiratory time; T_I/Ttot: inspiratory duty cycle. *: p<0.05; ***: p<0.001, by the least squares means Tukey honestly significant difference, compared with the pretreatment.

singers and athletes. Managing to get a suitable device for EPT, which can accurately select the specified pressure for each COPD patient, is necessary. Third, the profoundly improved exercise performance provided new problems: leg discomfort appeared as an exercise limitation, which required exercise training

TABLE 5 Changes in the resting parameters after respiratory pressure load training

	EPT group (n=11)		p-value	IPT group (n=10)		p-value
	Pretreatment	After 12 weeks		Pretreatment	After 12 weeks	
Body weight kg	57.2±9.8	57.3±10.1	0.9425	55.2±10.1	55.4±10.2	0.1354
Total lean mass kg	41.9±6.5	41.9±6.5	0.4648	41.2±4.8	37.5±13.6	0.0742
Total fat mass kg	12.0±4.6	12.3±5.1	0.3203	12.1±6.1	11.7±6.1	0.5703
MEP cmH$_2$O	125.4±24.7	153.4±32.4**	0.0047	114.9±45.4	117.9±47.1	0.5943
MIP cmH$_2$O	77.9±19.3	85.9±21.8	0.1530	67.9±17.2	78.0±19.0*	0.0217
PFT						
FEV$_1$ L	0.87±0.19	0.89±0.19	0.3516	1.18±0.40	1.15±0.41	0.1563
FEV$_1$/FVC %	33.9±6.0	33.4±4.1	0.9648	38.9±6.5	40.0±9.0	0.4316
%FEV$_1$ %	32.8±7.0	33.8±6.9	0.2500	45.1±14.2	44.0±14.9	0.1602
VC L	2.75±0.56	2.83±0.60	0.1758	3.14±0.80	2.98±0.91	0.0605
%VC %	84.8±12.3	87.8±13.2	0.1230	98.0±22.8	92.9±26.5	0.0645
IC L	1.72±0.21	1.83±0.38	0.1221	2.06±0.52	1.99±0.59	0.5566
SGRQ symptoms domain	47.4±21.7	43.5±21.0	0.7344	53.8±22.8	56.7±20.2	0.7344
SGRQ activity domain	66.9±19.1	59.6±19.3	0.0156	56.1±28.5	56.3±26.5	1.0000
SGRQ impacts domain	34.6±18.2	24.5±18.7	0.0049	25.7±15.9	28.0±21.2	0.7695
SGRQ total score	46.7±17.2	38.7±18.3	0.0137	38.8±19.8	41.2±21.8	1.0000

Data are presented as mean±SD. EPT: expiratory pressure load training; IPT: inspiratory pressure load training; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; PFT: pulmonary function test; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; VC: vital capacity; IC: inspiratory capacity; SGRQ: St. George's Respiratory Questionnaire. *: p<0.05; **: p<0.01, by the least squares means Tukey's honestly significant difference, compared with the pretreatment.

for the legs. Fourth, the increase of MIP after IPT was low, which might be related to insufficient IPT. Although the increase in endurance time, measured with constant WRET, was large enough with IPT, a suitable regimen for IPT is necessary. Given the useful results obtained, future studies, including randomised controlled trials, should be conducted to develop EPT/IPT.

In conclusion, this study showed the benefits of 12-week EPT and IPT based on the exertional prolonged expiration on aerobic capacity and endurance time in COPD patients. After EPT, a larger $V_T$ex and higher $V_T$ex/T_E reduced the air remaining in the lung after expiration and improved exertional prolongation of expiration, reducing exertional dyspnoea. After IPT, the increased ventilation from the increased f_R resulted in unchanged breathing timing and worsening of dyspnoea during exercise. Given that both EPT and IPT are inexpensive and can easily be handled by elderly patients, if managing COPD with EPT/IPT is selected appropriately, it could become widespread as home-based training.

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