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Laryngeal widening and adequate ventilation by expiratory pressure load training improve aerobic capacity in COPD: a randomised controlled trial

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ABSTRACT

Rationale Despite strategies acting on peripheral airway obstruction in chronic obstructive pulmonary disease (COPD), exercise intolerance remains inadequately improved. We hypothesised that laryngeal narrowing is a potential treatment target of expiratory pressure load training (EPT) to improve exercise intolerance in COPD.

Methods The effect of 3-month EPT was assessed in 47 patients with COPD divided into Global Initiative for Chronic Obstructive Lung Disease (GOLD) mild-to-moderate (I–II) and severe-to-very severe (III–IV), randomly allocating 1:1 to EPT or control groups. The primary outcome was endurance time in the constant work rate exercise test in GOLD III–IV patients.

Results Compared with controls, EPT increased: (1) endurance time, with estimated treatment effect: +703 (95% CI: 379 to 1031) s, p=0.0008 (GOLD I–II); +390 (95% CI: 205 to 574) s, p=0.0006 (GOLD III–IV); (2) peak oxygen uptake (p=0.0086 in GOLD I–II; p=0.0004 in GOLD III–IV); (3) glottic dilatation ratio at maximum collapse on laryngoscopy in the submaximal exercise (p=0.0062 in GOLD I–II; p=0.0001 in GOLD III–IV); and (4) the inflection point of expiratory tidal volume relative to minute ventilation during the incremental exercise (p=0.0015 in GOLD I–II; p=0.0075 in GOLD III–IV). Across GOLD grades, the responses of glottic dilatation ratio at maximum collapse and the expiratory tidal volume at the inflection point were selected as more influential variables correlating with the improvement in peak oxygen uptake and endurance time, respectively.

Conclusion These results show that EPT improved aerobic capacity and endurance time with larger laryngeal widening and adequate ventilation despite advanced COPD.

Trial registration number UMIN000041250.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Exercise intolerance remains a major concern with the progression of chronic obstructive pulmonary disease (COPD), despite various strategies acting on peripheral airway obstruction. We hypothesised that laryngeal narrowing is a potential treatment target of expiratory pressure load training (EPT) to improve exercise tolerance in COPD, and we assessed the effect of 3-month EPT in patients with COPD to determine the mechanisms of the beneficial effects of EPT.

WHAT THIS STUDY ADDS

⇒ We found that EPT for 3 months results in pronounced improvement of aerobic capacity as well as endurance time, which correlates well with greater glottic widening and adequate expiratory ventilation during exercise, respectively, despite advanced COPD grade.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results suggest that the non-optimal relationship between laryngeal narrowing and expiratory-mechanical constraints should be recognised as a novel therapeutic target for improvement of exercise intolerance, and it can be expected to have considerable effects on anaerobic capacity as well as endurance capacity, leading to potential health benefits even in patients with advanced COPD .

INTRODUCTION

The fact that small airway disease is a part of the pathology of chronic obstructive pulmonary disease (COPD) was first described in the 19th century,[1] and the concept was incorporated into the definition of COPD in the American Thoracic Society statement in 1987.[2] More recently, expiratory mechanical constraints due to airflow obstruction in COPD, which is the main cause of exertional dyspnoea, and are caused primarily by small airway narrowing resulting in dynamic airway collapse and dynamic hyperinflation, have become more well-recognised.[3–7] Although, to date, strategies centred on bronchodilators acting on peripheral airways and pulmonary rehabilitation including pursed-lip breathing have been tried to reduce airflow obstruction and improve the patients' health status or endurance capacity, there is limited evidence on improvement in incremental exercise tolerance, that is, aerobic capacity, especially in patients with advanced COPD.[8–12]

Dynamic airway collapse of not only small airways, but also the glottis that is, the extramediastinal central airway, might play a role in expiratory

mechanical constraints, often with dynamic hyperinflation, leading to the exertional dyspnoea and exercise intolerance in COPD. Baz *et al*[13] reported that with progression of COPD, expiratory glottic narrowing occurs from rest to exertion, leading to exertional prolonged expiration and exercise intolerance. Separately, we reported that patients with COPD with exertional prolonged expiration and poor exercise tolerance tend to depend more on expiratory muscle strength for adequate expiration, and we hypothesised that expiratory pressure load training (EPT) might promote glottic widening, which would enable deep strong breathing that is fundamentally different from pursed-lip breathing, potentially improving exercise tolerance in these patients.[14] Next, we conducted a pilot study of 11 patients with severe and very severe COPD who received 3-month EPT to test our hypothesis, and we demonstrated significant improvements in endurance time on the constant work rate exercise test (WRET) and in peak oxygen uptake (V'_{O2}) on the incremental exercise test.[15] Further verification of the hypothesis might expand our understanding of how the underlying disorder in COPD causes pathophysiological abnormalities via airflow obstruction and enable us to identify the therapeutic targets that should be treated to improve exertional airflow obstruction.

This multicentre, prospective, randomised, controlled study was conducted to validate the effect and safety of 3-month EPT: (1) in patients with severe-to-very severe COPD using confirmatory analyses; (2) those with mild-to-moderate COPD as exploratory research; and (3) to show how EPT confers these benefits related to effective ventilation.

MATERIALS AND METHODS

This trial enrolled patients at two sites in Japan between August 2020 and March 2022. The study as shown in the online supplemental protocol was approved by the respective ethics committees at each site (National Hospital Organisation Osaka Toneyama Medical Centre, TNH-R-2020018; and Kitano Hospital, Tazuke Kofukai Medical Research Institute, P201200601), conducted in accordance with the Declaration of Helsinki, and registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN000041250). All participating subjects provided written informed consent. Based on the results of our pilot study,[15] a total sample size of n=40 patients was planned (for details regarding sample size determination, see the online supplemental methods).

Study subjects

Patients with mild-to-very severe COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades I–IV) according to airflow limitation severity, as categorised by the GOLD classification,[3] were eligible for the study if they were aged between 40 and 80 years, were in stable condition and able to tolerate cardiopulmonary exercise testing (CPET) to ensure adequate evaluation, and provided signed agreement for study participation. 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 treatment regimen during the study; (6) receiving pulmonary rehabilitation; (7) receiving oxygen therapy during exercise; (8) a history of pneumothorax or having the risk of developing pneumothorax; and (9) judged by their physician to be ineligible to participate in this study.

Randomisation and blinding

Adaptive random allocation was performed by a person not involved in data collection or recruitment. A computer-generated randomisation list was created by a senior manager independent of this research department. After baseline assessment including pulmonary functions, in each group with mild-to-moderate COPD (GOLD I–II) and severe-to-very severe COPD (GOLD III–IV), patients were randomly allocated at a ratio of 1:1 to receive EPT with standard of care or standard of care alone (control) with equal populations of GOLD grades in each group (figure 1). Owing to the nature of the intervention, it was not possible to mask the participants. Data collection and assessment were performed by a person outside our hospital blinded to the details of the intervention.

Intervention

Patients in the EPT group performed EPT of 30 repetitions a set, two sets a day for 3 months at home. The expiratory muscle strength trainer (EMST) 150 or EMST 75 (Aspire Products LLC, Atlanta, Georgia, USA) device was used for EPT. A cylindrical

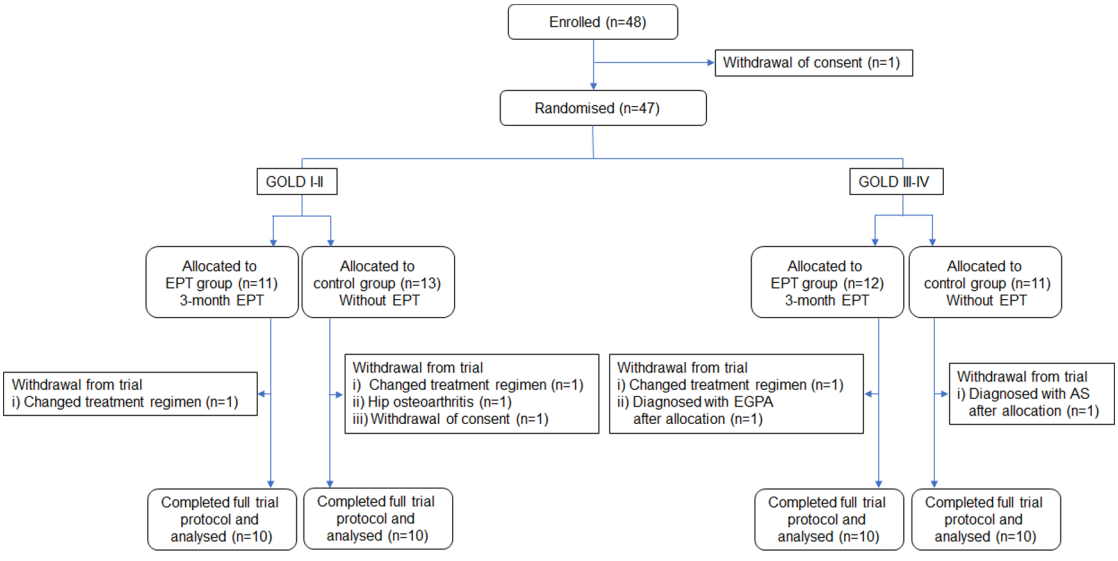

Figure 1 Consolidated Standards of Reporting Trials diagram for enrolment and study completion. AS, aortic valve stenosis; EGPA, eosinophilic granulomatosis with polyangiitis; EPT, expiratory pressure load training; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

mouthpiece rather than a flat mouthpiece was used in this EPT. The load applied was divided into six levels. The training load was started at 20% of the maximum expiratory pressure (MEP) evaluated at baseline. Thereafter, if possible, the level was increased once every 2 weeks up to 50% of the maximum pressure. Patients received monthly instructions and feedback on how to perform their home training from experienced staff. Further details are presented in the online supplemental methods and online supplemental video. Patients in the control group received standard care alone without EPT.

Measures

The primary outcome was endurance time, evaluated by the constant WRET in GOLD III–IV patients with COPD. The secondary outcomes included: (1) endurance time, evaluated by the constant WRET in GOLD I–II patients with COPD; and (2) in both GOLD III–IV and GOLD I–II patients, (i) V'_{O2}, minute ventilation (V'_E), expiratory tidal volume ($V_T$ex), mean expiratory flow ($V_T$ex/T_E), inspiratory tidal volume ($V_T$in), $V_T$in−$V_T$ex, ratio of inspiratory time to total respiratory cycle time (T_I/T_{tot}) and dyspnoea (10-point modified Borg Scale) during the incremental exercise test or constant WRET, (2) the glottic dilatation ratio (GDR) using laryngoscopy during the incremental exercise test, (3) health status assessed by the St George's Respiratory Questionnaire (SGRQ), (4) MEP and (5) respiratory function. All participants were included in the safety analyses.

Evaluation

Exertional variables and glottic movement

During the trial, three types of CPETs[15 16] were performed for the evaluation of ventilatory variables at baseline and at the 3-month evaluation with a similar protocol. The incremental exercise test, which consisted of 1 min or 2 min increments of exercise intensity up to 10 W, and the constant WRET at 70% of the peak work load in the incremental exercise test at baseline were performed. The inflection points of $V_T$ex, end-tidal carbon dioxide pressure (P_{ETCO2}) and dyspnoea (Borg Scale) were investigated by confirming the contributions of $V_T$ex, P_{ETCO2} and the Borg Scale to V'_E during the incremental exercise test by plotting $V_T$ex, P_{ETCO2} and the Borg Scale as a function of V'_E.[5 17–19] The larynx was examined using a fibreoptic nasendoscope,[13] during a submaximal incremental exercise test. This test followed a similar protocol to the baseline evaluation, which was performed until 90% of the peak heart rate (HR) observed during the baseline incremental exercise test (defined as iso-90% HR) was reached. From the video recording, the image stills were captured every 1/3 s at iso-90% HR. Defining the period from the point of first maximum glottic opening to the next maximum opening as one breathing cycle, the glottic areas were measured during each of the stable two breathing cycles at iso-90% HR. The GDR was calculated relative to the first maximum glottic area as 1 (ie, respective glottic area/glottic area at first maximum opening, %). Next, a single breathing cycle was divided from 0 to 1 by intervals of 0.1 cycle, and the GDR in each breathing cycle was calculated by proportional calculation between the two GDRs measured at each 1/3 s, as shown in online supplemental figure S1. When the glottic area was the lowest, the GDR was evaluated as the GDR_{lowest} for that breathing cycle. The averages of the

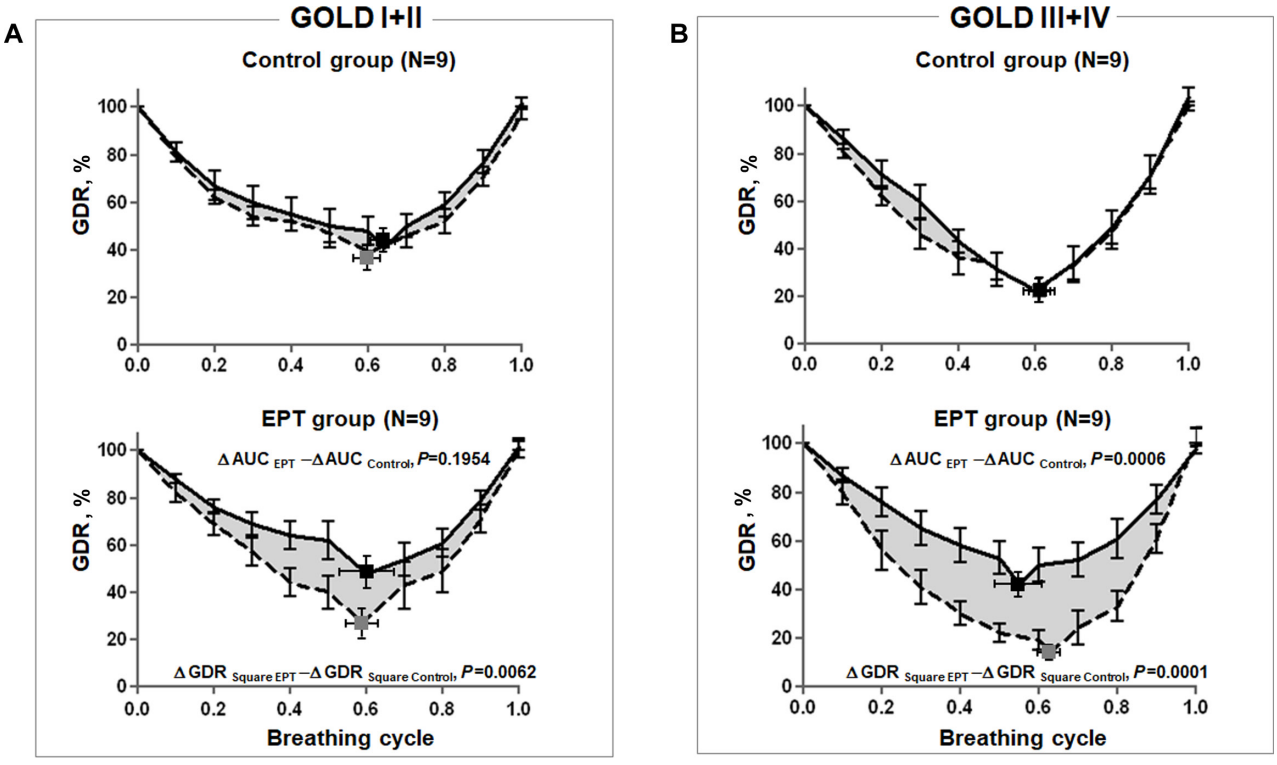

Figure 2 Exertional change in glottic dilatation during a breathing cycle in the incremental exercise test. (A) In patients with GOLD I–II COPD; (B) in patients with GOLD III–IV COPD. Dotted line: at baseline evaluation; solid line: at 3-month evaluation; shaded area: Δ area under the GDR curve (AUC); square: GDR_{lowest} at maximum glottic collapse during a breathing cycle; Δ AUC and Δ GDR_{lowest}: 3-month change from baseline of the AUC of GDR and GDR_{lowest}, respectively. Δ AUC_{EPT} – Δ $AUC_{Control}$ and Δ $GDR_{lowest\ EPT}$ – Δ $GDR_{lowest\ Control}$: difference in estimated treatment effect between the EPT and control groups. EPT, expiratory pressure load training; GDR, glottic dilatation ratio; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

two breathing cycles of the GDR, the GDR_{lowest} and the breathing cycle where the GDR_{lowest} was obtained, were evaluated. The area under the GDR curve (AUC) was evaluated (figure 2). More detailed information is provided in the online supplemental methods.

Health status

The validated Japanese version of the SGRQ was used as previously described.[20 21]

Static respiratory variables

Maximal inspiratory pressure and MEP were measured,[15] and pulmonary function tests were performed,[22] as previously described.

Statistical analysis

Continuous data are presented as means (SD) or medians (IQR) depending on the normality of the distribution (Shapiro-Wilk test). Changes within each of the groups were compared using a paired t-test or Wilcoxon signed-rank test, depending on the normality of the distribution in within-group differences (Δ 3 months). Differences in response between groups were assessed as follows. When within-group differences were normally distributed in both groups: (1) if the hypothesis of homogeneity of variance was formed, an unpaired t-test was used, and (2) if it was not formed, Welch's t-test was used, with the mean difference of Δ 3 months between groups (EPT−control) being reported as the treatment effect for both. For other patterns of within-group differences, the Wilcoxon rank-sum test was used with Hodges-Lehmann estimates as a treatment effect. χ^2 tests or Fisher's exact tests were used for categorical variables. If the data were normally distributed, Pearson's correlation coefficient was used for quantifying correlation; otherwise, Spearman's correlation coefficient was used. Bidirectional stepwise variable selection was performed to determine the more influential variables that correlate with the change in exercise tolerance among the exertional variables related to expiratory airflow constraints with variance inflation factors less than 3. These variables were evaluated in the incremental exercise test and constant WRET in the present study. First, age and sex, which are widely known to influence exercise tolerance,[23 24] were included as mandatory adjustments in the stepwise variable selection process. Second, GDR_{lowest}, peak incremental exercise test results [$V_T$ex, $V_T$ex/T_E, $V_T$in−$V_T$ex and T_I/T_{tot} (peak – rest)] and $V_T$ex -V'_E inflection during the incremental exercise test were added for the analysis related to peak V'_{O2}; and GDR_{lowest}, constant WRET results at the limit of tolerance [$V_T$ex, $V_T$ex/T_E, $V_T$in−$V_T$ex and T_I/T_{tot} (peak – rest)] and $V_T$ex $-V'_E$ inflection during the incremental exercise test were added for the analysis related to endurance time. Furthermore, all possible models by stepwise estimation were also investigated to confirm the most appropriate selection model based on the lowest value of the corrected Akaike Information Criterion (AICc). In the stepwise regression models, the p values were set at 0.20 for variables to both enter and stay. No missing data were observed in the present study except for data on laryngoscopy. Of the 40 patients, four were excluded from the per-protocol set to analyse GDR data. A $p<0.05$ was considered to indicate significance (JMP software, version 11, SAS Institute, Cary, North Carolina, USA).

RESULTS

Forty-seven patients with COPD who were randomised to the EPT or control groups were subdivided into GOLD grades I–II and III–IV (figure 1). Of them, three discontinued participation before study completion, and four met one exclusion criterion during the study; data from the remaining 40 patients (n=20 each in GOLD I–II and III–IV) were analysed. Baseline characteristics were not significantly different between the study groups (table 1). There were no reported adverse events during this study.

Primary outcome (endurance time)

In GOLD III–IV patients, (1) compared with controls, EPT increased endurance time on constant WRET by an estimated treatment effect (ETE) of +390 (95% CI: 205 to 574) s, p=0.0006 (table 2); with an ETE of +90% (95% CI: 53% to 126%), from baseline, p=0.0002; and (2) the minimum difference in endurance time from baseline in the EPT group was +93 s.

Secondary outcomes

Anaerobic capacity

Compared with controls, EPT increased peak V'_{O2} on the incremental exercise test from baseline by an ETE of +2.1 (95% CI: 1.1 to 3.1) $mL{\cdot}min^{-1}{\cdot}kg^{-1}$, p=0.0004 (table 3), +17% (95% CI: 10% to 28%), p=0.0002 in GOLD III–IV patients, and +2.1 (95% CI: 0.6 to 3.6) $mL{\cdot}min^{-1}{\cdot}kg^{-1}$, p=0.0086 (table 4), +13% (95% CI: 4% to 22%), p=0.0085 in GOLD I–II patients. In GOLD III–IV patients, there were no cases in the EPT group in which peak V'_{O2} was reduced from baseline.

Peak incremental exercise test variables

The incremental exercise test results are presented in tables 3 and 4. In GOLD III–IV patients, compared with controls, EPT (1) increased V'_E (p=0.0017) due to the increased $V_T$ex (p=0.0120), while maintaining respiratory frequency; (2) reduced $V_T$in−$V_T$ex (p=0.0194), improving exertional prolonged expiration, that is, T_I/T_{tot} (peak – rest) (p=0.0462); and (3) reduced exertional dyspnoea, decreasing Borg Scale scores with an ETE of −1.0 (95% CI: –2 to 0), p=0.0341. The reasons for stopping exercise changed after 3-month EPT across the GOLD grades (n=20); the number of patients who stopped primarily because of dyspnoea changed from 13 at baseline to 7 after EPT (p=0.0160).

Inflection point during the incremental exercise test

In both GOLD III–IV and GOLD I–II patients, compared with controls, EPT increased: (1) $V_T$ex $_{inf.\ y\text{-}component}$, that is, the $V_T$ex value at the $V_T$ex $-V'_E$ inflection-point (p=0.0075 in GOLD III–IV; p=0.0015 in GOLD I–II) and $V_T$ex $_{inf.\ x\text{-}component}$, that is, the V'_E value at the $V_T$ex $-V'_E$ inflection point (p=0.0097 in GOLD III–IV; p=0.0151 in GOLD I–II) as shown in figure 3A; (2) $P_{ETCO2\ inf.\ x\text{-}component}$, that is, the V'_E value at the P_{ETCO2} − V'_E inflection point (p<0.0001 in GOLD III–IV: p=0.0019 in GOLD I–II), which was investigated as a post hoc exploratory analysis as shown in figure 3B, and dyspnoea $_{inf.\ x\text{-}component}$, that is, the V'_E value at the dyspnoea-inflection point (p=0.0156 in GOLD III–IV; p=0.0286 in GOLD I–II) as shown in figure 3C.

Constant WRET variables

The constant WRET results are presented in table 2 and online supplemental tables S1–S3. In GOLD I–II patients, compared with controls, EPT increased endurance time from baseline by an ETE of +703 (95% CI: 376 to 1031) s, (p=0.0008), +176% (95% CI: 65% to 287%), (p=0.0058). At isotime, EPT improved dyspnoea (p=0.0018 in GOLD III–IV; p=0.0037 in GOLD I–II) and $V_T$ex (p=0.0340 in GOLD III–IV; p=0.0091

Table 1 Baseline characteristics of the study subjects (n=40)

		GOLD I+II (n=20)			GOLD III+IV (n=20)		
	All patients (n=40)	EPT group (n=10)	Control group (n=10)	P value	EPT group (n=10)	Control group (n=10)	P value
Age, years	73 (68; 77)	74 (5)	77 (70; 78)	0.5177	70 (9)	70 (6)	1.0000
Sex, male/female	35/5	9/1	9/1	1.0000	10/0	7/3	0.0603
BMI, kg/m^{-2}	22.7 (2.7)	22.6 (2.3)	22.7 (2.9)	0.9238	22.8 (2.3)	22.4 (3.4)	0.7455
Cigarette smoking, pack years	53.4 (25.6)	43.9 (21.1)	63.1 (20.1)	0.0518	58.1 (23.7)	48.5 (34.3)	0.4758
Pulmonary function							
FEV_1, L	1.26 (0.92; 1.90)	1.85 (0.54)	1.89 (1.72; 2.08)	0.9698	1.03 (0.28)	0.89 (0.11)	0.1534
$\%FEV_1$, %predicted	52.9 (19.7)	69.4 (15.0)	70.2 (7.6)	0.8853	36.0 (10.1)	35.8 (4.4)	0.9418
FEV_1/FVC, %	42.4 (12.1)	49.3 (46.4; 63.9)	49.3 (7.4)	0.3642	34.1 (8.8)	32.2 (4.9)	0.5596
IC, L	2.21 (0.52)	2.29 (0.42)	2.47 (0.57)	0.4284	2.19 (0.56)	1.91 (0.39)	0.2093
FRC, L	3.65 (0.76)	3.55 (1.00)	3.63 (0.80)	0.8603	3.96 (0.72)	3.47 (0.47)	0.0867
RV, L	2.34 (2.02; 2.97)	2.08 (1.82; 2.73)	2.32 (0.56)	0.8501	2.99 (0.74)	2.23 (2.10; 2.58)	0.1212
RV/TLC, %	42.8 (8.4)	40.6 (9.4)	37.9 (5.4)	0.4436	48.0 (8.2)	45.0 (7.5)	0.4104
CPET							
peak V'_{O2}, $mL \cdot min^{-1} \cdot kg^{-1}$	12.6 (10.0; 17.0)	15.7 (3.9)	17.3 (3.7)	0.3470	10.6 (1.7)	10.6 (2.2)	0.9371
SGRQ							
Symptom domain	48.7 (23.9)	31.8 (20.1)	48.8 (17.1)	0.0566	60.2 (26.8)	53.8 (23.9)	0.5833
Activity domain	53.9 (37.0; 66.2)	34.0 (21.0)	41.2 (21.4)	0.4539	60.5 (15.3)	66.6 (58.1; 72.5)	0.5703
Impact domain	24.8 (17.5)	11.4 (12.5)	19.0 (12.3)	0.1852	34.9 (19.0)	33.8 (14.8)	0.8897
Total domain	36.3 (17.4)	21.6 (13.9)	30.7 (13.3)	0.1491	46.9 (18.2)	45.9 (10.9)	0.8862
Respiratory muscle strength							
MEP, cmH_2O	121.7 (46.9)	113.5 (61.2)	124.7 (34.9)	0.6068	129.7 (39.5)	118.5 (54.2)	0.6049
MIP, cmH_2O	75.2 (54.6; 97.6)	74.0 (42.6; 103.6)	78.5 (20.6)	0.5495	72.4 (26.4)	78.7 (32.9)	0.6446
Medications							
Triple therapy, n	13	1	3	0.2636	4	5	0.6531
LAMA/LABA/ICS, n	34/28/22	7/3/4	8/9/6	0.5072	9/9/4	10/7/8	0.4842
History of pulmonary rehabilitation, n	7	0	1	0.3049	3	3	1.0000

Data are presented as means (SD) or medians (IQR: 25th percentile–75th percentile), unless otherwise stated.
BMI, body mass index; CPET, cardiopulmonary exercise testing; FEV_1, forced expiratory volume in one second; FRC, functional residual capacity; 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; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity; V'_{O2}, oxygen uptake.

in GOLD I–II); $V_T in - V_T ex$ (p=0.0140) was decreased only in GOLD III–IV patients compared with controls.

Health status

In only GOLD III–IV patients, the EPT group experienced benefits compared with controls in SGRQ total with an ETE of −9.7 (95% CI: −16.6 to −2.8) from baseline (p=0.0088) and SGRQ impact (p=0.0165) (tables 3 and 4).

Dynamic glottic widening

GDR responses to 3-month EPT were investigated (figure 2A,B, n=36). Compared with controls, EPT increased the GDR_{lowest} by an ETE of+28% (95% CI: 17% to 38%), p=0.0001 in GOLD III–IV patients and+19% (95% CI: 6% to 32%), p=0.0062 in GOLD I–II patients, but did not change the breathing cycle where the GDR_{lowest} was detected; and increased the AUC of GDR during the breathing cycle in GOLD III–IV patients (ETE+16% · cycle (95% CI: 8% to 25% · cycle), p=0.0006), but not in GOLD I–II patients (ETE+6% · cycle (95% CI: −3% to 15% · cycle), p=0.1954).

Static respiratory variables

The results of static respiratory variables are shown in online supplemental tables S4 and S5. As a post hoc analysis, across all GOLD grades, among patients who received EPT, the 3-month change in MEP was negatively correlated with 3-month change in GDR_{lowest} (r=−0.49, p=0.0413, n=18).

Post hoc analysis for contribution to exercise tolerance

First, the correlations between baseline GDR and other variables were investigated (n=36). Baseline exertional laryngeal collapse, expressed by GDR_{lowest}, was correlated with exercise intolerance and poor health status across all GOLD grades (online supplemental table S6). Next, whether the 3-month changes in exercise tolerance affected 3-month changes in other variables was investigated. Across all GOLD grades, as shown in online supplemental table S7, the 3-month change in peak V'_{O2} was correlated with 3-month changes in: (1) GDR_{lowest} (r=0.70, p<0.0001, n=36, figure 4A); (2) in the incremental exercise test results at peak exercise, $V_T in - V_T ex$ (r=−0.39, p=0.0124, n=40, especially in GOLD III–IV: r=−0.66, p=0.0015, n=20), and $V_T ex/T_E$ (r=0.51, p=0.0009, n=40); and (3) during exercise in the incremental exercise test results, $V_T ex_{\text{inf. y-component}}$ (r=0.56, p=0.0002, n=40), and $P_{ETCO2\ \text{inf. x-component}}$ (r=0.65, p<0.0001, n=40). Moreover, in GOLD III–IV patients, the 3-month change in GDR_{lowest} was negatively correlated with the 3-month change in $V_T in - V_T ex$ (r=−0.55, p=0.0180, n=18). In the constant WRET, across all GOLD grades, the 3-month change in endurance time

Table 2 Changes in constant work rate exercise test parameters at the limit of tolerance in GOLD stages III and IV

	EPT group		Control group		Treatment effect	
	Baseline (n=10)	Δ 3 months (n=10)	Baseline (n=10)	Δ 3 months (n=10)	Difference in responses between groups(95% CI)	P value
Endurance time, s	435 (199)	+321** (247) (144 to 497)	565 (186)	−69 (103) (−143 to 5)	+390 (205 to 574)	**0.0006**
Dyspnoea, Borg Scale	7.1 (2.7)	−1.1 (2.6) (−3.0 to 0.8)	7.2 (2.8)	−0.6 (1.5) (−1.7 to 0.5)	−0.5 (−2.5 to 1.5)	0.6096
V'_{O2}, mL·min^{-1}·kg^{-1}	10.9 (1.5)	0.1 (1.9) (−1.2 to 1.4)	10.7 (2.4)	−0.4 (0.8) (−1.0 to 0.2)	+0.5 (−0.9 to 1.9)	0.4389
R	0.98 (0.05)	−0.02 (0.06) (−0.06 to 0.02)	1.00 (0.97; 1.02)	−0.01 (0.02) (−0.03 to 0.01)	−0.01 (−0.05 to 0.03)	0.5918
V'_E, L·min^{-1}	31.6 (5.8)	−1.4 (4.6) (−4.7 to 2.0)	27.8 (6.0)	−2.0* (2.7) (−3.9 to −0.1)	+0.6 (−2.9 to 4.2)	0.7175
$V_T$ex, mL	1122 (211)	+38 (168) (−82 to 159)	990 (255)	+15 (124) (−73 to 104)	+23 (−116 to 162)	0.7326
$V_T$in/T_I, mL·sec^{-1}	1737 (395)	−100 (261) (−286 to 87)	1369 (288)	−99 (162) (−215 to 17)	0 (−204 to 204)	0.9984
$V_T$ex/T_E, mL·sec^{-1}	776 (166)	−35 (131) (−129 to 59)	715 (182)	−41 (68) (−90 to 8)	+6 (−92 to 104)	0.9010
$V_T$in−$V_T$ex, mL	24 (25)	−11 (33) (−34 to 13)	9 (14)	+24* (31) (2 to 46)	−35 (−64 to −5)	**0.0260**
T_I/T_{tot} (peak − rest)	−0.03 (0.07)	+0.01 (0.04) (−0.02 to 0.03)	0.03 (0.04)	+0.01 (0.04) (−0.02 to 0.04)	0 (−0.04 to 0.03)	0.8683
f_R, breaths·min^{-1}	27 (25; 30)	−2 (7) (−7 to 2)	29 (4)	−3* (3) (−5 to −1)	0 (−4 to 5)	0.8396
V'_E/V'_{O2}	45.9 (4.9)	−1.1 (4.2) (−4.1 to 1.9)	46.3 (8.0)	−0.9 (5.5) (−4.9 to 3.1)	−0.2 (−4.8 to 4.4)	0.9284
V'_E/V'_{CO2}	46.9 (4.1)	−0.4 (4.6) (−3.7 to 2.9)	45.5 (5.3)	−0.3 (5.3) (−4.1 to 3.5)	−0.1 (−4.8 to 4.6)	0.9645
V_D/V_T	0.41 (0.04)	0 (0.04) (−0.03 to 0.03)	0.42 (0.03)	+0.01 (0.02) (−0.01 to 0.02)	−0.01 (−0.04 to 0.03)	0.6668
HR, beats·min^{-1}	120 (17)	−3 (20) (−18 to 11)	120 (19)	−2 (14) (−12 to 9)	−2 (−18 to 15)	0.8401
O_2 pulse, mL·beats^{-1}	5.9 (1.5)	+0.1 (0.6) (−0.4 to 0.5)	5.2 (1.3)	−0.2 (0.6) (−0.6 to 0.2)	+0.2 (−0.3 to 0.8)	0.4131
SpO_2, %	90 (6)	−2 (3) (−4 to 1)	87 (6)	+1 (3) (−1 to 2)	−2 (−5 to 1)	0.1593
Leg discomfort, Borg Scale	5.5 (3.4)	+0.1 (3.0) (−2.1 to 2.2)	6.5 (3.4)	−0.3 (1.9) (−1.6 to 1.1)	+0.3 (−2.1 to 2.7)	0.7918

Data are presented as means (SD) or medians (25th percentile; 75th percentile). Δ 3 months are presented as within-group differences, means (95% CI) or medians. Differences in Δ 3 months between groups (EPT−control) are reported as the mean (95% CI), or Hodges–Lehmann estimation (95% CI).
*p <0.05, **p <0.01, significant intragroup differences from baseline.
Bold values highlight significance.
EPT, expiratory pressure load training; f_R, respiratory frequency; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, heart rate; O_2 pulse, V'_{O2}/HR; R, respiratory quotient; SpO_2, percutaneous oxygen saturation; T_E, expiratory time; T_I, inspiratory time; T_I/T_{tot}, inspiratory duty cycle; V'_{CO2}, carbon dioxide output; V_D/V_T, physiologic dead space/tidal volume ratio; V'_E, minute ventilation; V'_{O2}, oxygen uptake; $V_T$ex, expiratory tidal volume; $V_T$in, inspiratory tidal volume.

was correlated with 3-month changes in: (1) GDR_{lowest} (r=0.67, p<0.0001, n=36) and AUC of GDR (r=0.49, p=0.0027, n=36); $V_T ex_{\text{inf. y-component}}$ (r=0.62, p<0.0001, n=40, figure 4B), $P_{ETCO2\ \text{inf. x-component}}$ (r=0.65, p<0.0001, n=40) and dyspnoea $_{\text{inf. x-component}}$ (r=0.64, p<0.0001, n=40) during the incremental exercise test; and (3) SGRQ total (r=−0.77, p<0.0001) in GOLD III–IV patients (n=20). The investigations of more influential variables that correlate with the 3-month change in exercise tolerance across all GOLD grades among all peak, throughout exercise or submaximal exercise variables related to expiratory airflow constraints were performed using stepwise variable selection. The bidirectional stepwise method for the aforementioned purpose yielded the same results with and without age and sex adjustment. With adjustment for age and sex, as more influential variables that correlate with the 3-month change in peak V'_{O2}, the analysis selected the following three variables in the most appropriate model (R^2=0.73, AICc=102.8): the 3-month changes in $V_T$in − $V_T$ex (p=0.1124), $V_T$ex/T_E (p<0.0001) and GDR_{lowest} (p<0.0001) in the incremental exercise test; and as more influential variables that correlated with the 3-month change in endurance time, the analysis selected the following two variables in the most appropriate model (R^2=0.47, AICc=518.7): the 3-month changes in GDR_{lowest} (p=0.0117), and $V_T ex_{\text{inf. y-component}}$ (p=0.0017) in the incremental exercise test. Figure 5 shows an example GOLD III case illustrating the dynamic glottic response following 3-month EPT.

DISCUSSION

Our study showed a key finding that EPT is well tolerated and results in pronounced improvement of aerobic capacity, while leading to greater glottic widening with the release of expiratory-mechanical constraints despite advanced COPD grade, thus reducing end-exercise dyspnoea, as well as in prolonged endurance time and improved health status.

Improved aerobic capacity provides physiological benefits. Peak V'_{O2} is a gold standard index of aerobic capacity and is predictive of mortality in both healthy subjects and those with COPD.[25 26] There are, however, only a few reports about the minimal clinically important difference (MCID) in peak V'_{O2} in patients with COPD. However, Ward *et al*[12] reported in a systematic review that exercise training produced small changes in peak V'_{O2} with a standardised mean difference of +0.52 mL·min^{-1}·kg^{-1}, and that patients with advanced COPD achieved smaller improvements in peak V'_{O2} compared with earlier stage patients. The reason for the small response to exercise training might be directly related to the degree of expiratory airflow constraints, although exercise intolerance in COPD occurs by a variety of mechanisms.[7] In this study, the incremental exercise test results showed that across all GOLD grades, the 3-month change in peak V'_{O2} had a significant positive correlation with 3-month change in $V_T$ex and $V_T$ex/T_E at peak exercise and $V_T ex_{\text{inf. y-component}}$ during exercise, and a significant negative correlation with residual air in the lungs after expiration per breath, that is, $V_T$in − $V_T$ex at peak exercise, more significantly in GOLD III–IV patients than in patients of all GOLD grades. Although, in the present study, exertional measurements of inspiratory capacity as a measure of dynamic hyperinflation were not performed, the $V_T$in − $V_T$ex, which is evaluated unconsciously during exercise, might be

Table 3 Changes in incremental exercise parameters at peak exercise and health status in GOLD stages III and IV

	EPT group		Control group		Treatment effect	
	Baseline (n=10)	Δ 3 months (n=10)	Baseline (n=10)	Δ 3 months (n=10)	Difference of responses between groups (95% CI)	P value
CPET						
Maximum workload, watts	44 (16)	+10* (0;13)	40 (30; 43)	0 (0; 0)	+10 (0 to 20)	**0.0071**
Dyspnoea, Borg Scale	6.8 (1.9)	−1.0* (−2.0; 0)	6.3 (1.4)	0 (1.1) (−0.8 to 0.8)	−1.0 (−2.0 to 0)	**0.0341**
V'_{O2}, mL·min^{-1}·kg^{-1}	10.6 (1.7)	+1.2** (0.9) (0.6 to 1.9)	10.6 (2.2)	−0.9 (1.2) (−1.7 to 0)	+2.1 (1.1 to 3.1)	**0.0004**
V'_E, L·min^{-1}	31.5 (6.0)	+0.7* (0.1; 2.8)	27.7 (5.2)	−3.4* (3.7) (−6.1 to −0.8)	+4.5 (1.1 to 8.2)	**0.0017**
$V_T$ex, mL	1155 (267)	+46 (113) (−35 to 128)	1093 (284)	−119* (148) (−225 to −13)	+165 (41 to 289)	**0.0120**
$V_T$in/T_I, mL·sec^{-1}	1661 (310)	+134 (54; 183)	1298 (269)	−105 (162) (−222 to 11)	+211 (64 to 357)	**0.0113**
$V_T$ex/T_E, mL·sec^{-1}	796 (195)	+27 (87) (−35 to 89)	657 (582; 865)	−65** (−144; −14)	+91 (20 to 218)	**0.0073**
$V_T$in−$V_T$ex, mL	27 (15)	−24* (28) (−44 to −4)	8 (30)	+4 (20) (−10 to 18)	−28 (−51 to −5)	**0.0194**
T_I/T_{tot} (peak − rest)	−0.03 (0.07)	+0.02* (0.02; 0.03)	0.03 (0.04)	0 (0.02) (−0.02 to 0.01)	+0.02 (0 to 0.05)	**0.0462**
f_R, breaths·min^{-1}	28 (4)	0 (4) (−2 to 3)	26 (5)	−1 (4) (−4 to 2)	+1 (−3 to 4)	0.7218
V'_E/V'_{O2}	46.8 (4.3)	−2.5 (−4.5; −0.8)	46.7 (6.4)	−1.7 (5.3) (−5.5 to 2.1)	−1.0 (−5.0 to 5.0)	0.6217
V'_E/V'_{CO2}	46.5 (4.3)	−2.0 (−3.0; −0.3)	43.7 (3.5)	+0.1 (3.7) (−2.6 to 2.8)	−1.5 (−5.0 to 2.0)	0.7316
V_D/V_T	0.41 (0.03)	0 (0.02) (−0.01 to 0.02)	0.42 (0.03)	−0.01 (0.02) (−0.02 to 0.01)	+0.01 (−0.01 to 0.03)	0.4504
ΔFO_2, %	2.61 (0.24)	+0.11 (0.22) (−0.04 to 0.27)	2.67 (0.29)	+0.10 (0.27) (−0.09 to 0.29)	+0.01 (−0.22 to 0.24)	0.8994
HR, beats·min^{-1}	118 (16)	0 (19) (−13 to 14)	116 (16)	−3 (8) (−8 to 3)	+3 (−11 to 17)	0.6836
O_2 pulse, mL·beats^{-1}	5.9 (1.5)	+0.7* (−0.1; 1.0)	5.2 (1.2)	−0.3 (0.9) (−1.0 to 0.3)	+0.7 (0 to 1.4)	**0.0308**
SpO_2, %	91 (4)	0 (3) (−2 to 2)	89 (5)	0 (2) (−2 to 1)	0 (−2 to 3)	0.7947
Leg discomfort, Borg Scale	4.9 (2.3)	+0.2 (1.3) (−0.7 to 1.1)	4.9 (2.6)	+0.7 (1.4) (−0.4 to 1.7)	−0.5 (−1.7 to 0.8)	0.4711
SGRQ						
Symptom domain	60.2 (26.8)	−5.5 (11.6) (−13.8 to 2.8)	53.8 (23.9)	−3.6 (20.6) (−18.4 to 11.1)	−1.8 (−17.5 to 13.9)	0.8097
Activity domain	60.5 (15.3)	−8.4 (12.8) (−17.5 to 0.8)	66.6 (58.1; 72.5)	+1.6 (9.1) (−4.9 to 8.1)	−10.0 (−20.5 to 0.4)	0.0582
Impact domain	34.9 (19.0)	−8.2** (7.6) (−13.6 to −2.8)	33.8 (14.8)	+2.9 (10.9) (−4.9 to 10.7)	−11.1 (−19.9 to −2.3)	**0.0165**
Total domain	46.9 (18.1)	−7.8** (7.3) (−13.0 to −2.6)	45.9 (10.9)	+1.9 (7.5) (−3.5 to 7.3)	−9.7 (−16.6 to −2.8)	**0.0088**

Data are presented as means (SD) or medians (25th percentile; 75th percentile). Δ 3 months are presented as within-group differences, means (95% CI) or medians. Differences in Δ 3 months between groups (EPT− control) are reported as the mean (95% CI), or Hodges-Lehmann estimation (95% CI).
*p<0.05, **p<0.01, significant intragroup differences from baseline.
Bold values highlight significance.
CPET, cardiopulmonary exercise testing; EPT, expiratory pressure load training; f_R, respiratory frequency; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, heart rate; O_2 pulse, V'_{O2}/HR; SGRQ, St George's Respiratory Questionnaire; SpO_2, percutaneous oxygen saturation; T_E, expiratory time; T_I, inspiratory time; T_I/T_{tot}, inspiratory duty cycle; V'_{CO2}, carbon dioxide output; V_D/V_T, physiologic dead space/tidal volume ratio; V'_E, minute ventilation; V'_{O2}, oxygen uptake; $V_T$ex, expiratory tidal volume; $V_T$in, inspiratory tidal volume; ΔFO_2, the difference between inspired O_2 concentration (FiO_2) and expired O_2 concentration (FeO_2).

a surrogate indicator of dynamic hyperinflation. The above findings might mean that improvement of exercise tolerance was more related to the reduction in dynamic hyperinflation with every breath by EPT in GOLD III–IV patients. Furthermore, given the report that the $V_T$ex − V'_E inflection point can be detected in most COPD cases, and exertional dyspnoea related to the exertional acidosis is associated with the $V_T$ex − V'_E inflection point regardless of the presence of dynamic hyperinflation,[5 17–19 27 28] the release by EPT of the expiratory-mechanical constraints from the middle exercise phase where the inflection point occurs to peak exercise in both GOLD I–II and III–IV patients (tables 3 and 4, figure 3, and online supplemental table S7) may be helpful for increasing peak V'_{O2}, because V'_{O2} is calculated using the product of ventilatory flow and oxygen extraction, that is, the difference between inspired O_2 concentration (FiO_2) and expired O_2 concentration (FeO_2) (ΔFO_2) of the entire body,[29 30] and in the present study, significant changes of EPT in ΔFO_2 were not obtained in either GOLD I–II or III–IV patients (tables 3 and 4). Therefore, the effective ventilation obtained from EPT significantly increased peak V'_{O2} in GOLD III–IV patients, with an ETE (2.1 mL·min^{-1}·kg^{-1}) similar to that in GOLD I–II patients (tables 3 and 4), representing contradictory results to those of Ward *et al*.[12] Admittedly, even in patients with GOLD III–IV in whom ventilatory ability can only be minimally increased, EPT increased V'_E via an increase in $V_T$ex, reducing $V_T$in − $V_T$ex and exertional dyspnoea, with an ETE of −1.0 on Borg Scale scores at peak exercise during the incremental exercise test (table 3 and figure 3). This improvement in exertional dyspnoea is noteworthy, because end-exercise dyspnoea is reportedly of similar intensity even after intervention,[31] and a modified Borg Scale change of 1 is considered an MCID, but is only used as a reference.[31] These findings suggest that EPT increases ventilatory variables from the middle exercise phase where the inflection point occurs to peak exercise and reduces residual air in the lungs and exertional dyspnoea evaluated in the incremental exercise test in GOLD III–IV patients, leading to a drastic increase in aerobic capacity, as with GOLD I–II patients. Given that an endurance time change of 100 s or 33% change is considered the MCID,[31] the ETEs of EPT on endurance time in both GOLD III–IV and I–II patients are promising (table 2 and online supplemental table S1), although constant WRET in the present study was

Table 4 Changes in incremental exercise parameters at peak exercise and health status in GOLD stages I and II

	EPT group		Control group		Treatment effect	
	Baseline (n=10)	Δ 3 months (n=10)	Baseline (n=10)	Δ 3 months (n=10)	Difference of responses between groups(95% CI)	P value
CPET						
Maximum workload, watts	69 (21)	+10 (−3; 10)	73 (16)	−10* (−10; 0)	+10 (0 to 20)	**0.0098**
Dyspnoea, Borg Scale	4.7 (1.3)	+0.9 (1.7) (−0.3 to 2.1)	5.7 (2.1)	+1.1 (2.0) (−0.3 to 2.5)	−0.2 (−1.9 to 1.5)	0.8090
V'_{O2}, mL·min^{-1}·kg^{-1}	15.7 (3.9)	+1.2* (1.6) (0.1 to 2.4)	17.3 (3.7)	−0.9 (1.6) (−2.0 to 0.3)	+2.1 (0.6 to 3.6)	**0.0086**
V'_E, L·min^{-1}	48.0 (14.8)	+3.1 (6.6) (−1.7 to 7.8)	52.6 (9.3)	−2.1 (5.4) (−6.0 to 1.7)	+5.2 (−0.5 to 10.9)	0.0705
$V_T$ex, mL	1470 (400)	+137* (189) (2 to 272)	1491 (319)	−43 (130) (−137 to 50)	+180 (28 to 333)	**0.0231**
$V_T$in/T_I, mL·sec^{-1}	1976 (450)	+27 (312) (−197 to 251)	2184 (409)	−92 (189) (−227 to 43)	+119 (−124 to 361)	0.3178
$V_T$ex/T_E, mL·sec^{-1}	1359 (496)	+135 (220) (−22 to 293)	1479 (275)	−75 (191) (−211 to 62)	+210 (17 to 403)	**0.0350**
$V_T$in−$V_T$ex, mL	−8 (27)	−4 (42) (−33 to 26)	−5 (27)	+2 (51)(−35 to 38)	−5 (−49 to 38)	0.8053
T_I/Ttot (peak – rest)	0.01 (0.04)	+0.06** (0.04) (0.03 to 0.09)	0.03 (0.03)	−0.02 (0.03) (−0.04 to 0.01)	+0.08 (0.04 to 0.12)	**0.0005**
f_R, breaths·min^{-1}	33 (7)	0 (3) (−3 to 2)	36 (5)	−1 (5) (−5 to 3)	0 (−4 to 5)	0.8083
V'_E/ V'_{O2}	51.0 (13.2)	+3.0 (−9.3; 5.5)	49.5 (47.0; 51.0)	−0.2 (4.0) (−3.1 to 2.7)	+2.0 (−7.0 to 6.0)	0.5687
V'_E/ V'_{CO2}	45.0 (11.7)	+0.9 (4.9) (−2.6 to 4.4)	44.3 (4.4)	+0.8 (3.2) (−1.5 to 3.1)	+0.1 (−3.8 to 4.0)	0.9574
V_D/V_T	0.36 (0.07)	0 (0.04) (−0.03 to 0.02)	0.36 (0.04)	0 (0.03) (−0.02 to 0.02)	0 (−0.03 to 0.03)	0.7831
ΔFO_2, %	2.60 (0.67)	−0.05 (0.35) (−0.31 to 0.20)	2.49 (0.22)	+0.03 (0.20) (−0.11 to 0.17)	−0.09 (−0.35 to 0.18)	0.5101
HR, beats·min^{-1}	135 (23)	−4 (17) (−16 to 8)	129 (14)	−7 (14) (−17 to 3)	+3 (−11 to 18)	0.6355
O_2 pulse, mL·beats^{-1}	7.2 (1.6)	+0.9 (1.2) (0 to 1.7)	8.4 (2.1)	+0.1 (0.8) (−0.5 to 0.7)	+0.8 (−0.2 to 1.7)	0.1140
SpO_2, %	96 (90; 97)	+1 (0; 2)	95 (2)	0 (1) (−1 to 1)	+1 (−1 to 2)	0.4166
Leg discomfort, Borg Scale	5.2 (2.5)	+0.7 (2.8) (−1.3 to 2.7)	6.3 (2.9)	+0.9 (2.1) (−0.6 to 2.4)	−0.2 (−2.6 to 2.2)	0.8603
SGRQ						
Symptom domain	31.8 (20.1)	−3.8 (16.1) (−15.4 to 7.7)	48.8 (17.1)	+2.2 (17.1) (−10.0 to 14.5)	−6.1 (−21.7 to 9.6)	0.4250
Activity domain	34.0 (21.0)	+3.5 (10.1) (−3.7 to 10.7)	41.2 (21.4)	+2.0 (10.6) (−5.6 to 9.6)	+1.5 (−8.2 to 11.2)	0.7508
Impact domain	7.9 (2.0; 16.0)	−1.1 (4.9) (−4.5 to 2.4)	19.0 (12.2)	+0.1 (11.9) (−8.4 to 8.6)	−1.1 (−10.0 to 7.7)	0.7832
Total domain	21.6 (13.9)	−0.2 (5.9) (−4.4 to 4.0)	30.7 (13.3)	+0.9 (8.1) (−5.0 to 6.7)	−1.1 (−7.8 to 5.6)	0.7317

Data are presented as means (SD) or median (25th percentile; 75th percentile). Δ 3 months are presented as within-group differences, means (95% CI) or medians. Differences in Δ 3 months between groups (EPT−control) are reported as the mean (95% CI), or Hodges–Lehmann estimation (95% CI).
*p <0.05, **p <0.01, significant intragroup differences from baseline.
Bold values highlight significance.
CPET, cardiopulmonary exercise testing; EPT, expiratory pressure load training; f_R, respiratory frequency; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, heart rate; O_2 pulse, V'_{O2}/HR; SGRQ, St George's Respiratory Questionnaire; SpO_2, percutaneous oxygen saturation; T_E, expiratory time; T_I, inspiratory time; T_I/Ttot, inspiratory duty cycle; V'_{CO2}, carbon dioxide output; V_D/V_T, physiologic dead space/tidal volume ratio; V'_E, minute ventilation; V'_{O2}, oxygen uptake; $V_T$ex, expiratory tidal volume; $V_T$in, inspiratory tidal volume; ΔFO_2, the difference between inspired O_2 concentration (FiO_2) and expired O_2 concentration (FeO_2).

performed at 70% of the peak work rate in the incremental exercise test, with 75%–80% of peak work rate being typically selected.[31] Interestingly, across all GOLD grades, the 3-month change in endurance time in the constant WRET was significantly correlated with 3-month changes in $V_{T\ ex\ inf.\ y\text{-}component}$ (figure 4B), $P_{ETCO2\ inf.\ x\text{-}component}$ and dyspnoea $_{inf.\ x\text{-}component}$. These findings mean that, after EPT, an increase in $V_T$ex at the middle phase in the incremental exercise test was associated with the delayed dyspnoea-inflection point, coinciding with the plateau level of CO_2 clearance, that was followed by a steeply accelerated dyspnoea level (figure 3), the response of which correlated with the prolonged endurance time. That is, after EPT, the inflection point could be shifted to the late exercise phase, allowing exercise with less dyspnoea relating to exertional acidosis if exercise load levels were lower. Therefore, the 3-month increase in endurance time correlated with an improvement in health status in GOLD III–IV patients. This is consistent with the already reported finding that the release of the $V_T$ex constraint during exercise is closely related to improvement in exercise tolerance and dyspnoea.[32 33] Moreover, EPT was well tolerated without adverse events in the present study. The above findings thus verify the exertional benefit and safety of EPT indicated in our previous pilot study,[15] which could not, however, show how EPT reduces expiratory airflow obstruction.

In COPD, the development of expiratory-mechanical constraints entails airway narrowing including the larynx, by which intrinsic positive end-expiratory pressure (PEEPi) is generated as one of the mechanisms.[13 34] Although an optimal relationship between effective ventilation and exertional PEEPi for exercise performance could not be investigated in the present study, at least, the excessive dynamic laryngeal narrowing might be in large part responsible for expiratory airflow obstruction, as suggested by the fact that dynamic laryngeal widening by EPT correlated with improvement in exercise tolerance and health status especially in patients with advanced COPD. In the present study, at baseline evaluation, as GDR_{lowest} decreased across all GOLD grades, aerobic capacity decreased, along with worsening of health status, which concurs with the report by Baz *et al*.[13] Moreover, the stepwise method selected the greater increase of GDR_{lowest} and expiratory flow as the more influential variables correlated with the major improvement of

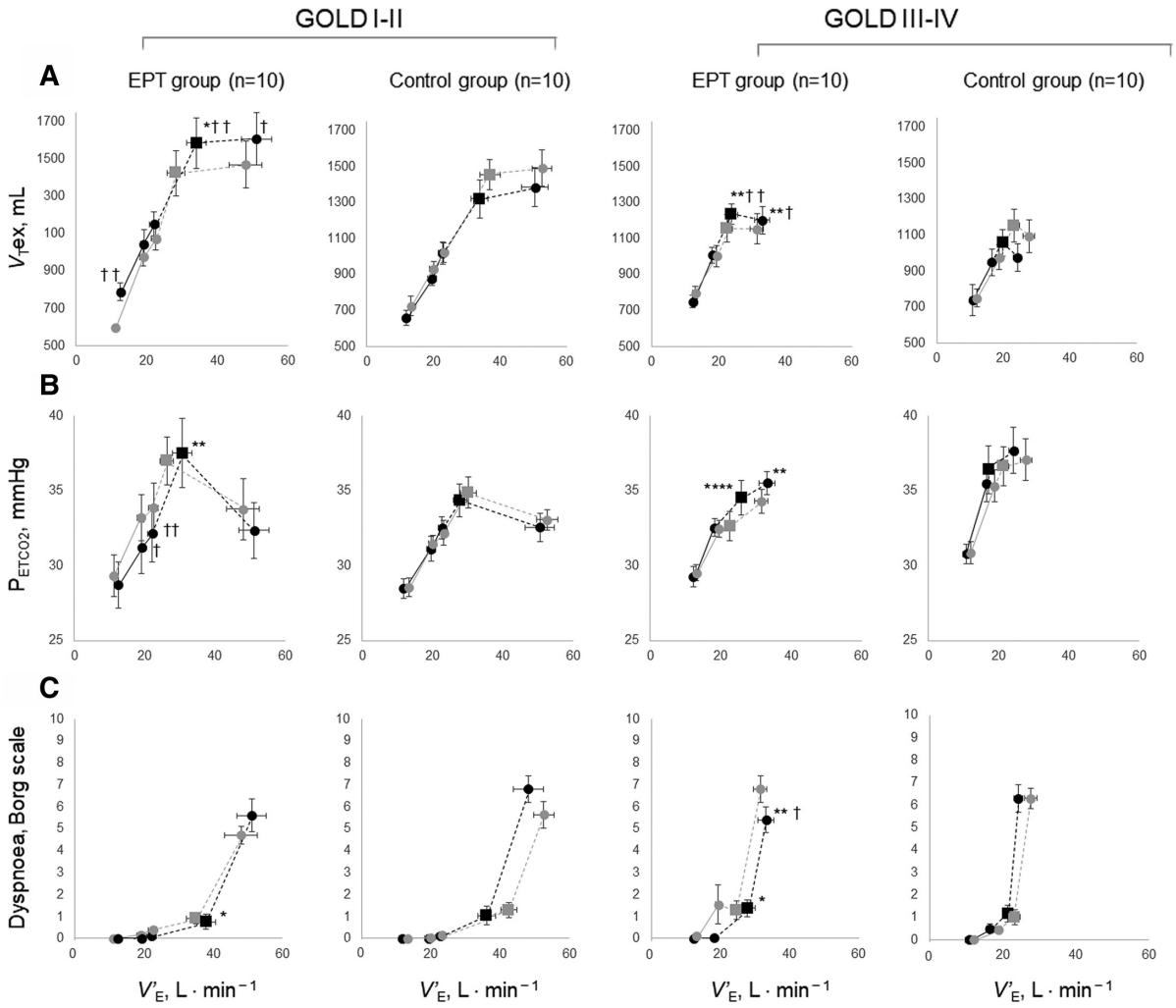

Figure 3 Change of 3-month EPT in (A) expiratory tidal volume ($V_T$ex), (B) end-tidal carbon dioxide pressure (P_{ETCO2}) and (C) dyspnoea intensity from rest to peak exercise shown in response to minute ventilation (V'_E) in the incremental exercise test in Global Initiative for Chronic Obstructive Lung Disease (GOLD) I–II and III–IV. Grey symbol: at baseline evaluation; black symbol: at 3-month evaluation; square: inflection point. After 3-month EPT, in GOLD I–II and III–IV patients, (1) each x-component of the $V_T$ex, $P_{ETCO2,}$ and dyspnoea inflection point is significantly shifted to the positive direction of the x-axis and (2) each y-component of the $V_T$ex inflection point is shifted to the positive direction of the y-axis. In GOLD III–IV patients, dyspnoea intensity level is significantly reduced at peak exercise after 3-month EPT. Data are presented as mean±SE at rest, at 10 W, at 20 W (if GOLD I–II), at the inflection point and at peak exercise. *p<0.05, **p<0.01, ****p<0.0001 (x-component); †p<0.05, ††p<0.01 (y-component): significant difference between groups at a given time-point. EPT, expiratory pressure load training; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

anaerobic capacity with EPT. This might be driven by the fact that GDR calculation by the area rather than the width of the glottis more directly evaluated the responses to EPT, because the resistance to flow through tubes is inversely related to the reduction in the radius raised to the fourth power, as indicated by the Hagen-Poiseuille law. Furthermore, the response of EPT on laryngeal widening was larger in GOLD III–IV than in GOLD I–II patients. Therefore, not only the release of expiratory-mechanical constraints but also a greater response in dynamic laryngeal widening by EPT might be more helpful for advanced COPD. Conversely, after EPT, the endurance time increased to a greater degree in GOLD I–II than in GOLD III–IV patients. This might be primarily attributed to the improved ventilation during exercise as indicated by the $V_T$ex − V'_E inflection point rather than dynamic laryngeal widening, as the stepwise method selected. Unexpectedly, in patients who received EPT across all GOLD grades, the 3-month change in MEP was negatively, not positively, correlated with the 3-month change in GDR_{lowest}. This reminds us that the respiratory or abdominal muscle fatigue might be eliminated secondarily following adequate ventilation with EPT, given that expiratory muscle activity is relatively increased in COPD, but fails to reduce airflow obstruction.[18 35 36] However, based on the hypothesis in our previous study[14] that more expiratory muscle strength might be needed for adequate expiratory ventilation to improve exercise intolerance, this unexpected post hoc result suggests that measurement of PEEPi may be helpful in clarifying the mechanism of EPT in the future. Since our previous study,[14] we have assumed that EPT might train the laryngeal muscle groups to open the central airway like a stent to withstand obstruction for effective ventilation, even though higher levels of PEEPi or maintenance of a certain level of PEEPi are required for exercise. Though we were unable to investigate whether EPT results in an optimal relationship among respiratory system pressure, laryngeal narrowing and expiratory ventilation in the present study, our findings deepen our understanding of how

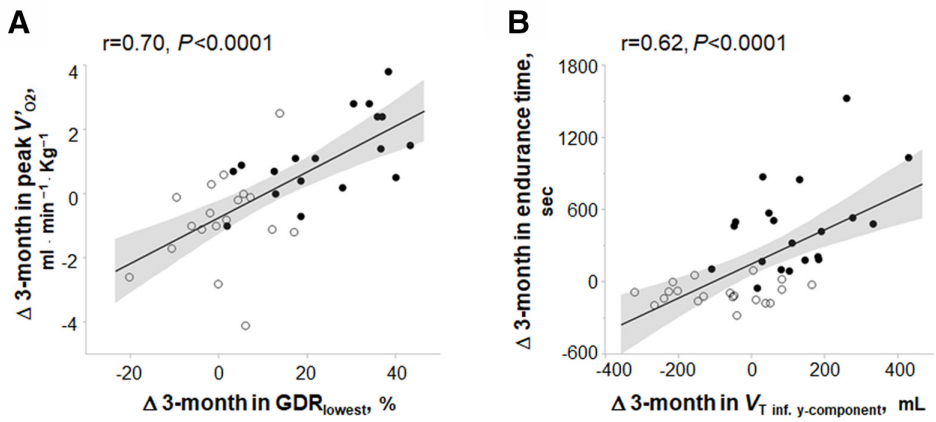

Figure 4 Correlation of (A) 3-month changes in peak oxygen uptake (V'_{O2}) (n=36) and (B) 3-month changes in endurance time (n=40) across all Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades. Δ 3-month: 3 month change from baseline; endurance time: time to the limit of tolerance on the constant work rate exercise test; GDR_{lowest}: glottic dilatation ratio at maximum glottic collapse evaluated in the incremental exercise test; peak V'_{O2}: obtained in the incremental exercise test; closed circle: the EPT group; open circle: the control group. The shaded area indicates the CI. GDR, glottic dilatation ratio.

excessive obstruction in the extramediastinal central airway, especially in advanced COPD, leads to stressful breathing by expiratory airflow constraints. Our findings suggest that excessive laryngeal narrowing should be considered a therapeutic target for improving expiratory airflow obstruction, and demonstrate that, even in advanced COPD, a greater response in dynamic laryngeal widening with the release of expiratory mechanical constraints by EPT might have effects on exercise tolerance and health status.

This study has some limitations. First, the number of participants was small. Second, during this trial, people's movements were curtailed due to the COVID-19 pandemic, and some might have become more immobile, which might have affected the results to a greater degree in the control group than the EPT group. Third, it is possible that patients can still exercise without dyspnoea even if they are hypoxaemic after EPT, because ventilatory limitation rather than hypoxaemia is often the cause of exercise limitation in COPD.[27 28] In one

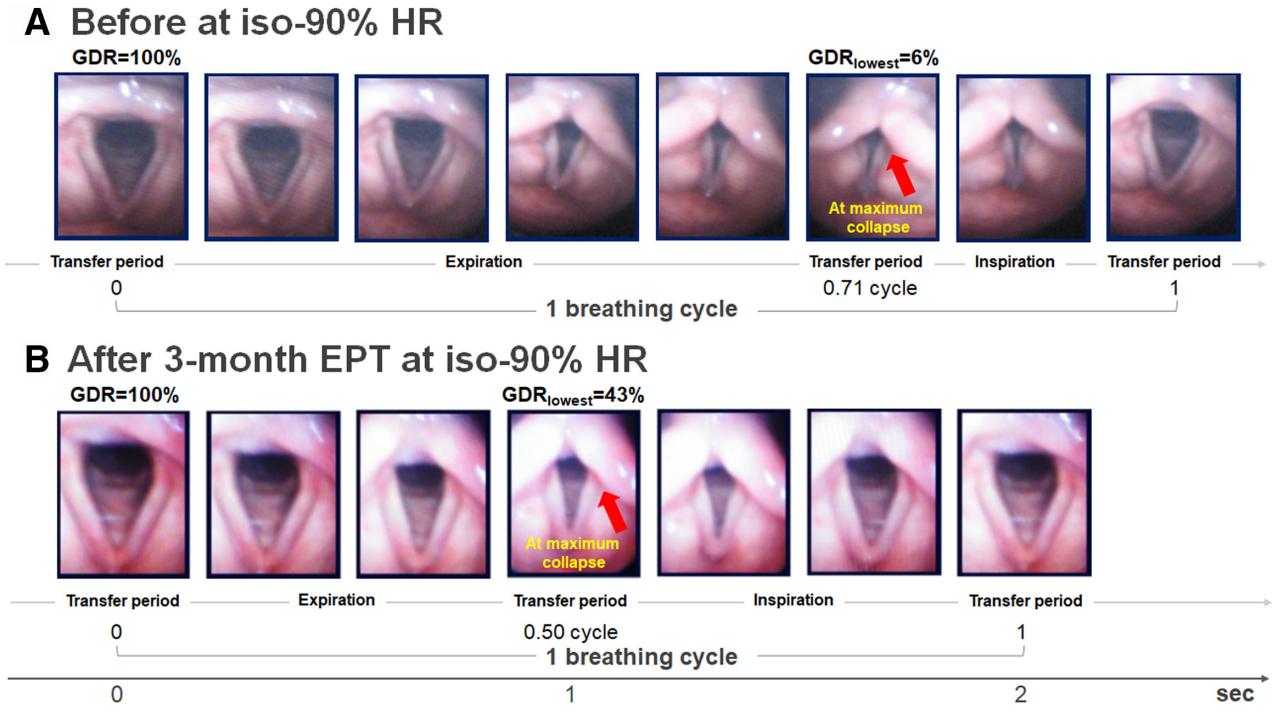

Figure 5 Example Global Initiative for Chronic Obstructive Lung Disease (GOLD) III case illustrating dynamic glottic narrowing: (A) before and (B) after 3 months of EPT in the incremental exercise test. Each still image was captured every 1/3 s from a continuous video recording at a HR of 85 beats·min^{-1}, which was equal to 90% of the peak HR in the incremental exercise test at baseline evaluation (defined as iso-90% HR). With the maximum glottic area as 1 at the start of the breathing cycle (0), the GDR at each 1/3 s is calculated as the ratio of the respective glottic area to the glottic area at the first maximum opening. A single breathing cycle is divided from 0 to 1 at intervals of 0.1 cycles. After 3-month EPT, GDR at maximum glottal collapse (GDR_{lowest}) changes from 6% at 0.71 breathing cycles to 43% at 0.5 breathing cycles.EPT, expiratory pressure load training; GDR, glottic dilatation ratio; HR, heart rate.

patient with GOLD III who received EPT, 3-month differences in peak V'_{O2} and dyspnoea at peak exercise were, respectively, $+1.1\,mL{\cdot}min^{-1}{\cdot}kg^{-1}$ and 0 on the Borg Scale, even though SpO_2 at peak exercise decreased from 84% to 79%. Therefore, some patients with advanced COPD might need supplemental oxygen therapy despite an adequate EPT effect. Fourth, exertional expiratory laryngeal narrowing occurs even in healthy people.[13] In the present study, although the severity of laryngeal narrowing increased with advancement of COPD grade, the response of GDR to EPT was greater. It is assumed that exertional laryngeal narrowing occurs with increased PEEPi[13] or as a compensatory response to tracheal obstruction.[37 38] For further clarification of the mechanism, investigation of how EPT affects such narrowing might provide further clues for ensuring adequate ventilation during exercise. Further investigations using measurements of respiratory system pressure or dynamic radiological imaging techniques[37–40] might be helpful.

In conclusion, a large effect of EPT on anaerobic capacity, as well as endurance capacity, was found, and it was observed to improve the health status of patients with advanced COPD. On post hoc analysis, the optimal relationship for improvement in exercise intolerance between the release of expiratory mechanical constraints and laryngeal widening after EPT was assumed, which may be considered hypothesis generating and is a potential novel therapeutic target for COPD. While confirmation in a larger population is required, these results might suggest the importance of regulating the larynx as part of the upper airway to reduce expiratory airflow obstruction in lower respiratory tract diseases, such as COPD. We believe these findings are a step towards further large trials to verify the suggestion that EPT could be part of physical rehabilitation of patients with COPD in different clinical scenarios.

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Contributors KM is the author responsible for the content of the manuscript. KM, KT, MF and MM developed the concept and design of the study. KM, KT, MF, MM, TK, HH, TN, TM and HK acquired the data. KM, KT, MF, MM, TK, HS, KH, MY, HH, TN, TM and HK analysed and were involved in the interpretation of data. KM wrote the manuscript. All authors participated in the development of the manuscript, gave final approval of the manuscript for submission and agree to be accountable for the integrity of the work. KM is the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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