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**RESEARCH ARTICLE**

# Inspiratory muscle training reduces diaphragm activation and dyspnea during exercise in COPD

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**Langer D, Ciavaglia C, Faisal A, Webb KA, Neder JA, Gosselink R, Dacha S, Topalovic M, Ivanova A, O'Donnell DE.** Inspiratory muscle training reduces diaphragm activation and dyspnea during exercise in COPD. *J Appl Physiol* 125: 381–392, 2018. First published March 15, 2018; doi:10.1152/japplphysiol.01078.2017.— Among patients with chronic obstructive pulmonary disease (COPD), those with the lowest maximal inspiratory pressures experience greater breathing discomfort (dyspnea) during exercise. In such individuals, inspiratory muscle training (IMT) may be associated with improvement of dyspnea, but the mechanisms for this are poorly understood. Therefore, we aimed to identify physiological mechanisms of improvement in dyspnea and exercise endurance following inspiratory muscle training (IMT) in patients with COPD and low maximal inspiratory pressure ($Pi_{max}$). The effects of 8 wk of controlled IMT on respiratory muscle function, dyspnea, respiratory mechanics, and diaphragm electromyography (EMGdi) during constant work rate cycle exercise were evaluated in patients with activity-related dyspnea (baseline dyspnea index <9). Subjects were randomized to either IMT or a sham training control group ($n = 10$ each). Twenty subjects ($FEV_1 = 47 \pm 19\%$ predicted; $Pi_{max} = -59 \pm 14$ $cmH_2O$; cycle ergometer peak work rate = $47 \pm 21\%$ predicted) completed the study; groups had comparable baseline lung function, respiratory muscle strength, activity-related dyspnea, and exercise capacity. IMT, compared with control, was associated with greater increases in inspiratory muscle strength and endurance, with attendant improvements in exertional dyspnea and exercise endurance time (all $P < 0.05$). After IMT, EMGdi expressed relative to its maximum ($EMGdi/EMGdi_{max}$) decreased ($P < 0.05$) with no significant change in ventilation, tidal inspiratory pressures, breathing pattern, or operating lung volumes during exercise. In conclusion, IMT improved inspiratory muscle strength and endurance in mechanically compromised patients with COPD and low $Pi_{max}$. The attendant reduction in $EMGdi/EMGdi_{max}$ helped explain the decrease in perceived respiratory discomfort despite sustained high ventilation and intrinsic mechanical loading over a longer exercise duration.

**NEW & NOTEWORTHY** In patients with COPD and low maximal inspiratory pressures, inspiratory muscle training (IMT) may be associated with improvement of dyspnea, but the mechanisms for this are poorly understood. This study showed that 8 wk of home-based, partially supervised IMT improved respiratory muscle strength and endurance, dyspnea, and exercise endurance. Dyspnea relief occurred in conjunction with a reduced activation of the diaphragm relative to maximum in the absence of significant changes in ventilation, breathing pattern, and operating lung volumes.

chronic obstructive pulmonary disease; diaphragm; dyspnea; electromyogram; exercise; inspiratory muscle strength; respiratory mechanics

## INTRODUCTION

Prevalence of chronic obstructive pulmonary disease (COPD) is increasing worldwide and is linked to increased mortality and poor health-related quality of life (53). Many patients with COPD have reported incapacitating dyspnea and activity restriction even after optimal bronchodilator therapy (52). Dyspnea and exercise limitation in such patients are multifactorial but are fundamentally linked to increased respiratory neural drive due to pulmonary gas exchange (e.g., high physiological dead space, critical hypoxemia) and metabolic abnormalities (e.g., lactic acidosis), severe dynamic mechanical constraints, and functional respiratory muscle weakness in variable combinations (14, 39, 40, 44). It has long been postulated that functional inspiratory muscle weakness is a contributor to dyspnea in advanced COPD (29). Thus, a meta-analysis and recent studies on the impact of IMT in this population concluded that increased inspiratory muscle strength was associated with reduced dyspnea (6, 19, 45). Moreover, IMT has been associated with favorable metabolic and structural adaptations of the ribcage inspiratory muscles in patients with advanced COPD (47). However, it has also been argued that specific IMT may be unnecessary, as the inspiratory muscles may already become "trained" by chronic intrinsic mechanical loading in the setting of high ventilatory demand (12).

Although the respiratory muscles of patients with COPD show impressive long-term adaptations to chronic shortening and increased intrinsic mechanical loading, functional muscle weakness likely occurs under conditions of acute physiological stress (e.g., exercise) in patients with severe COPD (9, 18, 23, 29, 32, 46). During exercise, dynamic hyperinflation causes an

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inspiratory threshold load that acutely increases the elastic work of breathing substantially while it simultaneously reduces the capacity of the inspiratory muscles to generate pressure (9, 32, 34). In addition, the velocity of shortening of diaphragm muscle fibers is increased, contributing to further functional inspiratory muscle weakness at higher exercise intensities (32). To maintain ventilation on pace with metabolic demands in this setting of functional inspiratory muscle weakness, inspiratory neural drive from motor centers in the brain to the respiratory muscles must increase toward maximum, and this may contribute to perceived respiratory discomfort.

In this context, the ratio of diaphragm activation (by electromyography) during inspiration to its maximum [diaphragm electromyography/(EMGdi/EMGdi$_{max}$)] has been used as an index of inspiratory neural drive to the diaphragm (27, 35). Physiological experiments have confirmed that dyspnea intensity during incremental exercise in COPD rises with increased EMGdi/EMGdi$_{max}$, reflecting progressive load-capacity imbalance of this muscle (14, 20, 27). It follows that interventions such as IMT that increase the capacity denominator by increasing diaphragmatic strength should reduce EMGdi/EMGdi$_{max}$ and associated dyspnea. Indeed, two previous studies of the effects of IMT in healthy humans (25, 49) provided evidence that reduction in indirect indices of motor command output to the inspiratory muscles (e.g., mouth pressure or mouth occlusion pressure at 0.1 s of inspiration) diminished in conjunction with increased inspiratory muscle strength. In line with this finding, other studies found that for a specific level of skeletal muscle activity, the magnitude of the EMG responses to transcranial stimulation were smaller following resistance training (6). Consequently, the current controlled study extended previous work and was designed to test the hypothesis that IMT increases diaphragmatic strength, thereby reducing EMGdi/EMGdi$_{max}$ and the associated dyspnea during exercise in patients with COPD. This hypothesis would be supported if, in contrast to sham training, dyspnea relief following IMT was associated with decreased EMGdi/EMGdi$_{max}$ during exercise after accounting for possible changes in ventilation and operating lung volumes.

## METHODS

Participants were clinically stable COPD patients with reduced inspiratory muscle strength [Pi$_{max}$ $<$70 cmH$_2$O measured at plethysmographic functional residual capacity (FRC)] and persistent activity-related dyspnea (baseline dyspnea index $<$ 9) despite optimal medical therapy. The Pi$_{max}$ of $<$70 cmH$_2$0 cutoff has been associated with clinical and physiological findings indicative of significant respiratory muscle weakness (50). Exclusion criteria were as follows: inability to perform physiological testing, active cardiovascular comorbidity (i.e., severe heart failure with reduced left ventricular ejection fraction, cardiomyopathy, recent acute myocardial infarction, cardiac arrhythmias, or stroke), or other conditions that could impact dyspnea or exercise capacity. This project was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (DMED-1579-13) and registered with ClinicalTrials.gov (NCT01900873). After providing informed consent, participants were randomized to an IMT or a control (sham training) group. Randomization and allocation concealment was conducted using a previously published method (11); opaque sealed envelopes were prepared and numbered sequentially by a researcher not involved in the study, and IMT and control interventions were distributed evenly in randomly ordered block sizes of 4 and 6. Therapists providing the intervention were aware of group allocation; however, both subjects and outcome assessors were blinded to group assignment. Interventions were presented to participants as strength (IMT) or endurance (control) training; this deception was performed to enhance treatment adherence and ensure a full placebo effect in the control group. There were three testing visits: a visit to assess eligibility and familiarize participants with procedures and visits conducted immediately before and after the 8-wk training program for measurement of primary and secondary end points.

### *Inspiratory Muscle Training*

Training was performed and monitored in accordance with a previously published and largely home-based protocol using the electronic POWERbreathe KH2 device (HaB International, Southam, UK) (7, 30). This handheld device has several specific characteristics that make it more suitable for IMT programs in COPD compared with traditional mechanical pressure threshold loading devices; in addition to its potentially beneficial loading characteristics, the device is able to store information from the training sessions performed without supervision in the home setting. The program consisted of two to three daily sessions of 30 breaths (4–5 min/session) performed 7 days/wk for 8 wk. Weekly measurements of Pi$_{max}$ were performed in both groups. The IMT group performed two daily sessions at a training load that started at ~40% of their initial Pi$_{max}$ and increased weekly to the highest tolerable intensity, always making sure to reach ≥40–50% of the current Pi$_{max}$. This training load was selected to provide the highest tolerable resistance and still allow full vital capacity inspirations; this would hopefully improve training specificity by applying a training stimulus over the full range of motion of the inspiratory muscles, including the lengths at which these muscles operate during exercise. Ratings of perceived respiratory effort (4–6 on the modified 10-point Borg Scale) were also used to support decisions on increasing training load; we also hoped that IMT sessions conducted within this level of effort would improve training compliance. The control group performed three daily sessions at an unaltered load of ≤10% of their initial Pi$_{max}$.

### *Assessments*

Activity-related dyspnea was assessed with the MRC dyspnea scale and the baseline/transition dyspnea index. Spirometry, body plethysmography, and lung diffusing capacity were performed ($V_{max}$, 229 days with Vs62j Autobox; SensorMedics, Yorba Linda, CA).

*Tests of respiratory muscle function.* Maximal mouth pressure was measured at total lung capacity (TLC) for expiration (Pe$_{max}$) and at both FRC and residual volume (RV) for Pi$_{max}$ (1, 2).

Inspiratory muscle endurance was measured during a constant-load breathing test, using the POWERBreathe KH2 device with the same breathing instructions as during the training sessions (30, 31). At baseline, an inspiratory load was selected that allowed participants to breathe against the resistance for 3–7 min (typically 50–60% Pi$_{max}$) before reaching a symptom-limited end point, i.e., when breathing discomfort became too severe to continue or when the participant could no longer successfully inspire against the load. Previous work showed that this protocol of limiting duration of baseline tests helped avoid ceiling effects during postintervention testing (30, 31). The identical load was used for posttraining assessments. Diaphragm electromyography and respiratory pressures were recorded continuously during the tests and processed as described below.

*Exercise testing.* Symptom-limited exercise tests were conducted on an electrically braked cycle ergometer (Ergometrics 800S; SensorMedics) with a cardiopulmonary testing system (Vmax229d; SensorMedics), as previously described in detail (20, 40). Incremental tests used a 10 W/min stepwise protocol. Subsequent constant work rate (CWR) tests were performed at 75% of the peak incremental work rate. Breath-by-breath measurements were evaluated as 30-s averages, and "peak" was defined as the last 30 s of loaded pedaling. Inspiratory

capacity (IC) was measured at rest, every second minute during exercise, and at the end of exercise (21). Participants rated the intensity of their perceived "breathing discomfort" (dyspnea) and leg discomfort at rest, every minute during exercise, and at the end of exercise using the modified 10-point Borg scale (4).

*EMG measurement and analysis.* A combined EMGdi-electrode catheter with esophageal/gastric balloons was inserted nasally after topical anesthesia and positioned in accordance with established methodology, as previously reported (26, 35). EMGdi, esophageal pressure (Pes), gastric pressure (Pga), and transdiaphragmatic pressure (Pdi = Pga-Pes) were recorded during CWR exercise and constant-load breathing tests and analyzed as previously described (14, 26, 27, 35). The raw EMGdi signal was sampled at 2,000 Hz (PowerLab, model ML880; ADInstruments, Castle Hill, NSW, Australia), band-pass filtered between 20 and 1,000 Hz (Bioamplifier model RA-8; Guangzhou Yinghui Medical Equipment, Guangzhou, China), and converted to a root mean square; the largest value from the five electrode pairs in each inspiration was used for the analysis. As others have done, $EMGdi_{max}$ was determined as the highest value during any IC or sniff maneuver during each test (14, 26, 27). EMGdi/$EMGdi_{max}$ was used as an index of inspiratory neural drive to the crural diaphragm based on previously described assumptions (14, 35). The esophageal and gastric balloon catheters were connected to differential pressure transducers (model DP15-34; Validyne Engineering, Northridge, CA) for continuous measurement of respiratory pressures, and the PowerLab system received continuous flow signal input from the $V_{max}$ 229d system for offline analysis. Maximal sniff esophageal ($Pes_{sniff}$) and transdiaphragmatic ($Pdi_{sniff}$) pressures were measured from FRC pre-exercise and immediately at the end of exercise (1). Inspiratory Pes/$Pes_{sniff}$ and Pdi/$Pdi_{sniff}$ were used as indices of global inspiratory muscle effort and diaphragmatic effort, respectively. The ventilatory muscle recruitment (VMR) index was determined as the slope of the line between points of zero flow at the end of expiration and end of inspiration for the Pga-Pes plots ($\Delta$Pga/$\Delta$Pes); more negative slopes represent increased contribution by the diaphragm, and less negative slopes represent increased contribution by inspiratory muscles of the ribcage and of the accessory inspiratory muscles (36).

### *Statistical Analysis*

It was initially estimated that a sample size of 16 patients per group would be required to detect a between-group difference in dyspnea intensity of one Borg scale unit at "isotime" during CWR cycling tests (primary outcome), assuming a SD of 1 unit in the change in dyspnea intensity between pre- and postintervention measurements, a statistical power of 80%, and a risk for a type I error ($\alpha$) <5%. Statistical procedures were carried out using either SPSS 24.0 for Windows (SPSS, Chicago, IL) or SAS 9.4 for Windows (SAS Institute, Cary, NC).

Visual inspection of data as well as normality testing (Shapiro-Wilk and Kolmogorov-Smirnov) were performed to confirm the normal distribution of data before proceeding with parametric testing. A mixed-model analysis was performed to assess treatment differences in continuous assessments of dyspnea intensity and EMGdi/$EMGdi_{max}$ during cycle ergometer exercise; interactions with group (IMT vs. control), period (pre- vs. postintervention), and ventilation (VE) were taken into account. Both linear and quadratic models were considered; for the quadratic model, a quadratic term for VE or minutes together with the corresponding interactions was included. Model selection was based on the maximum likelihood rule of thumb. Post hoc tests were performed to compare measures at isotime.

For all other outcomes derived from respiratory muscle tests, pulmonary function tests, constant work rate cycle ergometer testing, and questionnaires with only two measurements (pre- and postintervention), the difference between measurements was calculated, and unpaired *t*-tests were applied to test for between-group differences. Differences between groups were also verified after adjusting for baseline differences using an analysis of covariance. One-sample *t*-tests were applied to test for within-group differences between pre- and postintervention measurements. A secondary analysis was conducted using Pearson correlations to identify whether treatment-induced improvements in $Pi_{max}$ were associated with improvements in exertional dyspnea intensity and cycle ergometer exercise endurance or other relevant variables.

## RESULTS

A consort flow diagram is provided in Fig. 1 to show the progress of participants through different phases of the study. Twenty participants with moderate to very severe COPD were enrolled within the 1-yr recruitment period (June 2013–July 2014), at which time an interim analysis was conducted to determine whether a study extension was required. The majority ($n = 15$) were on "triple therapy" with a long-acting $\beta_2$-agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS), whereas the others used $\beta_2$-agonist and muscarinic antagonist bronchodilators in accordance with practice recommendations (42, 53). Comorbidities included stable (no./group): hypertension (3 IMT, 3 control), hypercholesterolemia (4 IMT, 1 control), gastresophageal reflux disease (4 IMT, 2 Ccntrol), osteoporosis (1 IMT, 2 control), type 2 diabetes mellitus (1 IMT, 1 control), hypothyroidism (1 IMT, 2 control), ischemic heart disease (1 IMT, 1 control), mild depression (1 IMT, 3 control), and mild anxiety (2 control).

The specific causes of the inspiratory muscle weakness in our participants were not determined. Clinical evaluation did not uncover differences between groups in arterial blood gas or acid base disturbance; no participants were prescribed opiate or sedative medication or any sort of noninvasive ventilation; no participant had frequent (>2/yr) severe exacerbations of COPD, and none were receiving long-term oral steroids; no participants had significant nutritional problems, but most had reduced cardiorespiratory fitness and some degree of global skeletal muscle deconditioning related to reduced physical activity. Groups had comparable baseline pulmonary function, respiratory muscle strength, activity-related dyspnea, and exercise capacity (Table 1). Peak exercise capacity was very poor, with all participants showing significant respiratory/mechanical constraints at the end of exercise (IRV $\leq$ 0.5 L). All but four participants indicated that breathing discomfort contributed more to their reason for stopping exercise than leg discomfort.

All participants completed their assigned training program and pre- and postintervention evaluations. Data on progression of training intensity and compliance with the training programs are provided in Fig. 2. Overall compliance with the prescribed training sessions was 95 $\pm$ 6 and 90 $\pm$ 12% in the IMT and control group, respectively.

### *Training Responses Measured at Rest*

Changes in important outcomes are shown in Table 2. Significant postintervention differences in favor of the IMT group were found in measurements of inspiratory muscle strength (Fig. 3) and endurance (Table 2). The reduction in FRC and increase in IC/TLC after IMT compared with control (Table 2) is consistent with the coexisting significant prolongation of expiratory time ($T_E$) and reduction in breathing frequency (Fb) seen at rest. Activity-related dyspnea question-

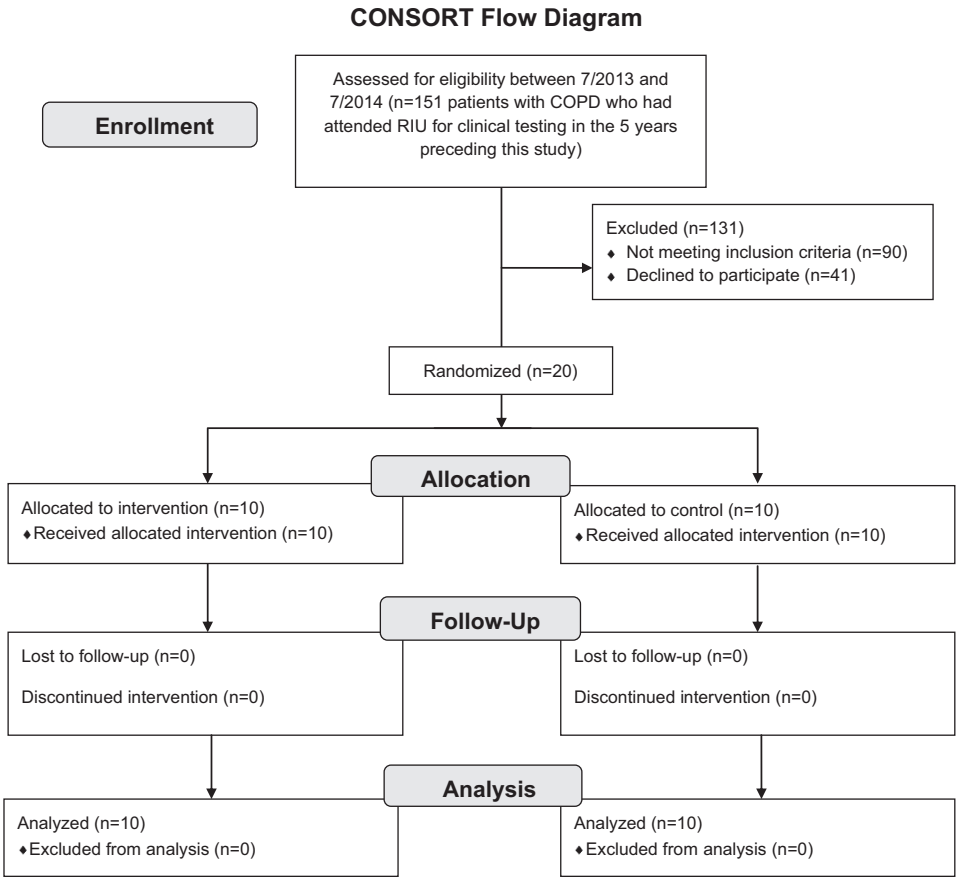


Fig. 1. Consort flow diagram showing the progress of participants through different phases of the study.

naires (MRC scale, transition dyspnea index) improved significantly after IMT vs. control.

*Training Responses During Exercise*

CWR exercise time increased significantly after IMT compared with control (Table 2 and Fig. 4). Significant improvements in dyspnea intensity during CWR cycling were observed after the IMT but not control intervention. Pre/postintervention differences between groups (IMT vs. control) of quadratic linear model estimates of dyspnea intensity at isotimes during exercise are presented in Table 3. Decreases in Borg ratings at isotime ($P = 0.036$) and in the slope of Borg ratings over exercise time ($P = 0.022$) were observed only in the IMT group (Fig. 4).

See Table 4 for measurements at isotime exercise; there were no significant training-induced changes in ventilation ($V_E$), breathing pattern ($V_T$, $F_b$), operating lung volumes (IC, IRV), gas exchange [oxygen consumption ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), end-tidal $CO_2$ ($P_{ET_{CO_2}}$), and oxygen saturation ($Sp_{O_2}$)], or tidal respiratory pressures (Pes, Pdi, and Pga) after either intervention. Figure 5 illustrates the lack of training-induced change in operating lung volumes, Pes, and Pdi during exercise.

$EMGdi/EMGdi_{max}$ decreased significantly after IMT vs. control (Table 4 and Fig. 4); this was achieved primarily by increasing $EMGdi_{max}$ ($P = 0.018$), although there was a tendency for tidal inspiratory EMGdi to decrease at isotime and peak exercise within the IMT group ($P = 0.1$) (Fig. 6). Average values of the EMGdi obtained during different maximal inspiratory maneuvers are summarized in Table 5. In all participants, the largest $EMGdi_{max}$ was recorded during an IC maneuver; all but two were during an exercise IC, and the majority was the end-of-exercise IC when $V_E$ was at its peak.

*Physiological Correlations*

Across groups, training-induced changes in CWR endurance correlated significantly with changes in $Pi_{max}$ at FRC ($r = 0.697$, $P = 0.001$), inspiratory muscle endurance ($r = 0.655$, 0.002), $Pes_{sniff}$ ($r = 0.490$, $P = 0.028$), and dyspnea ratings at isotime exercise ($r = -0.721$, $P < 0.0005$). The decrease in dyspnea ratings at isotime during exercise correlated with improvements in $Pes_{sniff}$ ($r = -0.662$, $P = 0.001$), $Pi_{max}$ at FRC ($r = -0.660$, $P = 0.002$), and inspiratory muscle endurance ($r = -0.541$, $P = 0.014$).

## DISCUSSION

The main findings of this study were that 8 wk of home-based IMT (compared with control) was associated with an increased capacity to sustain high ventilation for a longer duration accompanied by consistent improvements in diaphragmatic strength, reductions in $EMGdi/EMGdi_{max}$ ratio, and exertional dyspnea intensity ratings. The results support the hypothesis that increased ratio of diaphragmatic activation to maximum contributes to perceived dyspnea during exercise in COPD and that this can be reduced by IMT.

Our participants reported significant activity-related dyspnea and exercise intolerance despite optimal bronchodilator ther-

Table 1. *Baseline characteristics at study enrolment*

| | All Subjects ($n$ = 20) | Control ($n$ = 10) | IMT ($n$ = 10) |
|---|---|---|---|
| Men/Women, $n$ | 7/13 | 3/7 | 4/6 |
| Age, yr | 70 ± 7 | 67 ± 8 | 73 ± 4 |
| Height, cm | 162 ± 8 | 164 ± 10 | 161 ± 7 |
| Body mass index, kg/m$^2$ | 24.6 ± 5.6 | 25.1 ± 6.7 | 24.1 ± 4.6 |
| BDI total score (0–12) | 5.3 ± 1.7 | 4.7 ± 1.5 | 5.9 ± 1.6 |
| MRC dyspnea scale (1–5) | 3.0 ± 1.0 | 3.0 ± 1.1 | 2.9 ± 1.0 |
| | *Symptom-limited peak incremental cycle ergometer exercise test* | | |
| Work rate, W (%predicted) | 49 ± 21 (47 ± 21) | 48 ± 20 (41 ± 15) | 49 ± 23 (52 ± 25) |
| $\dot{V}O_2$, l/min (%predicted) | 0.95 ± 0.30 (60 ± 18) | 0.97 ± 0.36 (56 ± 16) | 0.94 ± 0.24 (63 ± 20) |
| HR, beats/min (%predicted) | 126 ± 18 (77 ± 11) | 129 ± 20 (78 ± 12) | 123 ± 16 (76 ± 10) |
| Ventilation, l/min (%MVV) | 32.6 ± 9.9 (83 ± 18) | 32.9 ± 12.5 (88 ± 17) | 32.2 ± 7.2 (78 ± 18) |
| IRV, L | 0.32 ± 0.15 | 0.30 ± 0.18 | 0.35 ± 0.13 |
| Dyspnea, Borg units | 6.5 ± 2.4 | 6.2 ± 2.5 | 6.8 ± 2.3 |
| Leg discomfort, Borg units | 6.3 ± 2.8 | 6.5 ± 2.7 | 6.1 ± 3.1 |
| | *Pre-bronchodilator pulmonary function (% predicted)* | | |
| $FEV_1$, liters | 0.94 ± 0.29 (47 ± 19) | 0.88 ± 0.25 (40 ± 14) | 0.99 ± 0.32 (53 ± 22) |
| $FEV_1$/FVC, % | 35 ± 12 | 32 ± 11 | 37 ± 13 |
| IC, liters | 1.67 ± 0.55 (69 ± 19) | 1.70 ± 0.64 (69 ± 16) | 1.64 ± 0.48 (70 ± 22) |
| FRC, liters | 4.15 ± 1.26 (140 ± 38) | 4.49 ± 1.07 (152 ± 39) | 3.81 ± 1.40 (128 ± 34) |
| RV, liters | 3.00 ± 1.13 (139 ± 55) | 3.30 ± 1.04 (157 ± 56) | 2.71 ± 1.18 (122 ± 50) |
| TLC, liters | 5.82 ± 1.38 (108 ± 17) | 6.19 ± 1.25 (115 ± 16) | 5.45 ± 1.46 (102 ± 16) |
| sRaw, $cmH_2O{\cdot}s$ | 18.7 ± 14.7 (460 ± 370) | 22.3 ± 16.7 (556 ± 429) | 15.2 ± 12.7 (365 ± 291) |
| $D_LCO$, ml/min/mmHg | 7.9 ± 2.9 (44 ± 12) | 7.8 ± 3.2 (40 ± 14) | 7.9 ± 2.7 (43 ± 19) |
| $C_L$st, l/$cmH_2O$ | 0.38 ± 0.20 | 0.38 ± 0.19 | 0.39 ± 0.24 |
| Sniff Pes, $cmH_2O$ | −47 ± 10 | −48 ± 10 | −46 ± 11 |
| $Pi_{max}$ at FRC, $cmH_2O$ | −59 ± 14 | −58 ± 16 | −60 ± 12 |
| $Pi_{max}$ at RV, $cmH_2O$ | 76 ± 16 | −71 ± 16 | −80 ± 15 |
| $Pe_{max}$ at TLC, $cmH_2O$ | 105 ± 31 | 98 ± 31 | 112 ± 32 |

Values are means ± SD. BDI , baseline dyspnea index, with total scores ranging from 0 (most severe activity-related dyspnea) to 12 (no activity-related dyspnea); $C_L$st, static lung compliance; $D_LCO$, diffusing capacity of the lung for carbon monoxide; $FEV_1$, forced expiratory volume in 1 s; FRC, plethysmographic functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; IMT, inspiratory muscle training; MRC dyspnea scale, Medical Research Council dyspnea scale, with scores ranging from 1 (best) to 5 (worst); MVV, maximal voluntary ventilation; Pes, esophageal pressure; $Pe_{max}$, maximal expiratory mouth pressure; $Pi_{max}$, maximal inspiratory mouth pressure; RV, residual volume; sRaw, specific airway resistance; TLC, total lung capacity. Predicted peak work rate and $\dot{V}O_2$ were those of Blackie et al. (3). Predicted peak HR = 210 − (0.66 × age).

apy. Incremental cardiopulmonary exercise test (CPET) confirmed very low peak power output (~50 W) and identified severe dyspnea (Borg 6) as the dominant exercise-limiting symptom in the majority. Ventilatory limitation was the proximate contributor to exercise intolerance; at peak exercise, IRV had declined to an average of 0.3 L at a peak $V_E$ of only 33 L/min.

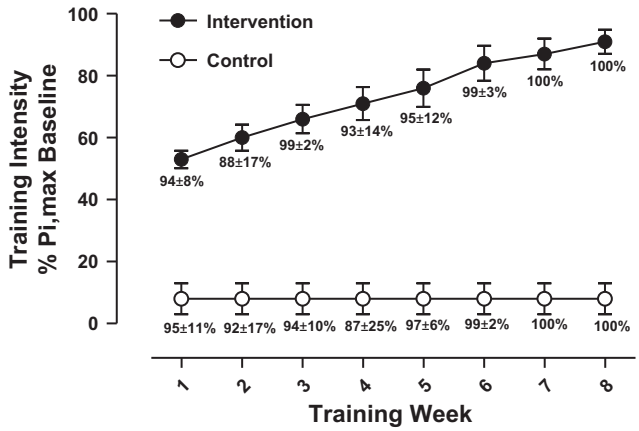


Fig. 2. Average inspiratory resistance that had to be overcome by participants during weekly inspiratory muscle training (IMT) sessions expressed as %baseline maximal static inspiratory mouth pressure ($Pi_{max}$) measured from residual volume. Percentages displayed below weekly averages indicate average compliance of participants with prescribed sessions each week. Values are means ± SD.

### *Effect of IMT on Resting Inspiratory Muscle Function*

In keeping with our selection criteria, values for $Pi_{max}$, $Pes_{sniff}$, and $Pdi_{sniff}$ (all measured from FRC) were uniformly low compared with age- and sex-matched healthy individuals (38, 50). The two groups were well matched for baseline activity-related dyspnea, pulmonary function, resting $Pi_{max}$, and exercise capacity. Participants reliably adhered to incremental IMT or sham protocols with no adverse events. Consistent with previous studies using the same device, supervised IMT was associated with significant and large increases in $Pi_{max}$ (effect sizes of 1.18 and 1.04 for measurements performed from FRC and RV, respectively) (7, 30). The lack of such improvements in the control group suggests genuine increases in strength in the IMT group that were not explained by a placebo effect or by improved technique of test performance.

Interestingly, inspiratory muscle endurance time during standardized resistive loading increased by almost threefold in the IMT group in comparison with a small increase in the control group that is compatible with a learning effect, as previously reported (24). Moreover, after training, patients performed more work and power per breath. This is in accordance with previous findings and indicates that patients were able to generate larger inspiratory volumes and faster in-

Table 2. *Responses to IMT: main outcome measurements*

| | Control | | IMT | | Mean Difference of Change: IMT/Control (95% CI) |
|---|---|---|---|---|---|
| | Preintervention | Change (Post/pre) | Preintervention | Change (Post/pre) | |
| $FEV_1$, liters | 0.90 ± 0.31 | 0.02 ± 0.11 | 1.05 ± 0.34 | 0.01 ± 0.10 | −0.01 (−0.11 to 0.09) |
| FRC, liters | 4.33 ± 1.16 | 0.06 ± 0.25 | 4.03 ± 1.43 | −0.17 ± 0.25† | −0.23 (−0.47 to 0.00) |
| IC, liters | 1.78 ± 0.67 | −0.02 ± 0.15 | 1.67 ± 0.49 | 0.11 ± 0.16 | 0.13 (−0.02 to 0.28) |
| IC/TLC, % | 29.6 ± 10.2 | −0.7 ± 2.3 | 30.3 ± 8.3 | 2.1 ± 2.4*† | 2.8 (0.5–5.0) |
| *Inspiratory muscle strength* | | | | | |
| $Pes_{sniff}$, $cmH_2O$ | −48 ± 10 | −1 ± 7 | −46 ± 11 | −14 ± 11*† | −13 (−20 to −6) |
| $Pdi_{sniff}$, $cmH_2O$ | 87 ± 24 | −4 ± 12 | 92 ± 21 | 14 ± 11*† | 18 (7–29) |
| $Pi_{max}$ at FRC, $cmH_2O$ | −61 ± 15 | −7 ± 12 | −61 ± 12 | −17 ± 11* | −11 (−19 to −2) |
| $Pi_{max}$ at RV, $cmH_2O$ | −76 ± 22 | −6 ± 13 | −74 ± 13 | −21 ± 16*† | −15 (−26 to −3) |
| *Inspiratory muscle endurance test* | | | | | |
| Inspiratory load, $cmH_2O$ | | −46 ± 8 | | −47 ± 20 | |
| Breathing time, s | 234 ± 133 | 111 ± 152* | 251 ± 62 | 467 ± 259*† | 357 (157–557) |
| Inspiratory power/breath, W | 2.3 ± 2.5 | 1.0 ± 2.3 | 2.9 ± 2.2 | 2.5 ± 1.8* | 1.5 (−0.5 to 3.5) |
| Total inspiratory work, J | 96 ± 105 | 67 ± 215 | 113 ± 70 | 321 ± 205*† | 254 (51–457) |
| *Constant work rate cycle ergometer exercise test* | | | | | |
| Work rate, W | | 35 ± 16 | | 35 ± 17 | |
| Exercise time, s | 355 ± 162 | 54 ± 89 | 436 ± 257 | 277 ± 303*† | 223 (39–407) |
| *Activity-related dyspnea* | | | | | |
| MRC dyspnea scale (1–5) | 3.0 ± 1.1 | 0.4 ± 0.7 | 2.9 ± 1.0 | −0.6 ± 0.7*† | −1 (−1.7 to −0.3) |
| TDI total score (−9 to 9) | | 1.2 ± 3.2 | | 4.3 ± 2.2*† | 3.1 (0.5–5.7) |

Values are means ± SD. Δ, within-group treatment difference; CI, confidence interval; MRC, Medical Research Council, with dyspnea scale scores ranging from 1 (best) to 5 (worst); FRC, plethysmographic functional residual capacity; Pdi, transdiaphragmatic pressure; Pes, esophageal pressure; $Pi_{max}$, maximal inspiratory mouth pressure; RV, residual volume; TDI, transition dyspnea index, with scores ranging from −9 (maximal worsening of symptoms) to +9 (maximal improvement of symptoms); TLC, total lung capacity. *$P < 0.05$, within-group difference, pre- vs. postintervention by paired *t*-test; †$P < 0.05$ by unpaired *t*-test comparing treatment differences for IMT vs. control.

spiratory flow rates against the same external load after training (30, 31).

The IMT protocol was nonspecific, as it encouraged recruitment of all inspiratory muscles in response to the extrinsic mechanical loading, and not just the diaphragm. However, consistent and large improvements in $Pdi_{sniff}$ in the IMT group confirm that the static strength of the diaphragm was, in fact, increased (effect size: 1.56) (51).

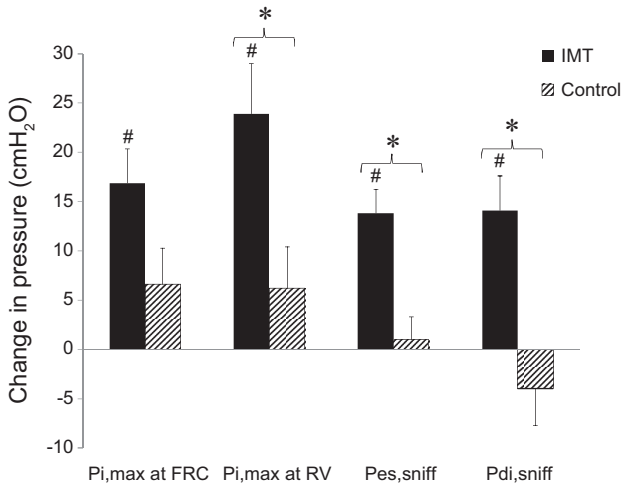


Fig. 3. Training-induced changes in measurements of inspiratory muscle strength are shown after inspiratory muscle training (IMT) and control. FRC, functional residual capacity; $Pdi_{sniff}$, maximal inspiratory sniff transdiaphragmatic pressure measured from FRC; $Pes_{sniff}$, maximal inspiratory sniff esophageal pressure measured from FRC; $Pi_{max}$, maximal inspiratory mouth pressure; RV, residual volume. Values are means ± SE. *$P < 0.05$, between-group difference; #$P < 0.05$, within-group difference.

### *Effect of IMT on Dyspnea and Exercise Performance*

In contrast to the control group, activity-related dyspnea measured by the TDI improved by +4 units after IMT, which exceeds the minimal clinically important difference of 1 unit (37). These improvements are similar to those reported after other IMT and pulmonary rehabilitation programs (33, 41). Both within the IMT group and between groups, dyspnea intensity ratings improved significantly at a standardized time together with dyspnea/time slopes (Fig. 3 and Table 3). Remarkably, following IMT, participants could breathe at a $V_E$ of 32 L/min and a $\dot{V}O_2$ equivalent to peak $\dot{V}O_2$ during incremental CPET for >4 min longer with no increase in peak dyspnea ratings. These improvements in dyspnea occurred in the setting of reduced EMGdi/$EMGdi_{max}$ despite little or no change in ventilation, breathing pattern, operating lung volumes, and tidal Pes and Pdi during exercise tests pre- and post-IMT. In other words, dyspnea was relieved at a standardized exercise time despite little or no change in intrinsic mechanical loading or in pulmonary gas exchange and metabolic abnormalities that stimulate $V_E$, thus allowing a unique opportunity to examine the role of inspiratory muscle weakness in isolation. The following question remains: What are the potential mechanistic linkages between increased diaphragmatic strength (post-IMT) and reduced EMGdi/$EMGdi_{max}$ and dyspnea ratings during exercise?

### *Dyspnea and Inspiratory Muscle Weakness in COPD*

It has long been recognized that increased dyspnea intensity during incremental cycle exercise varies with baseline $Pi_{max}$ in COPD populations (29). Thus, the highest dyspnea intensity ratings for a given work rate occurred in those with the lowest

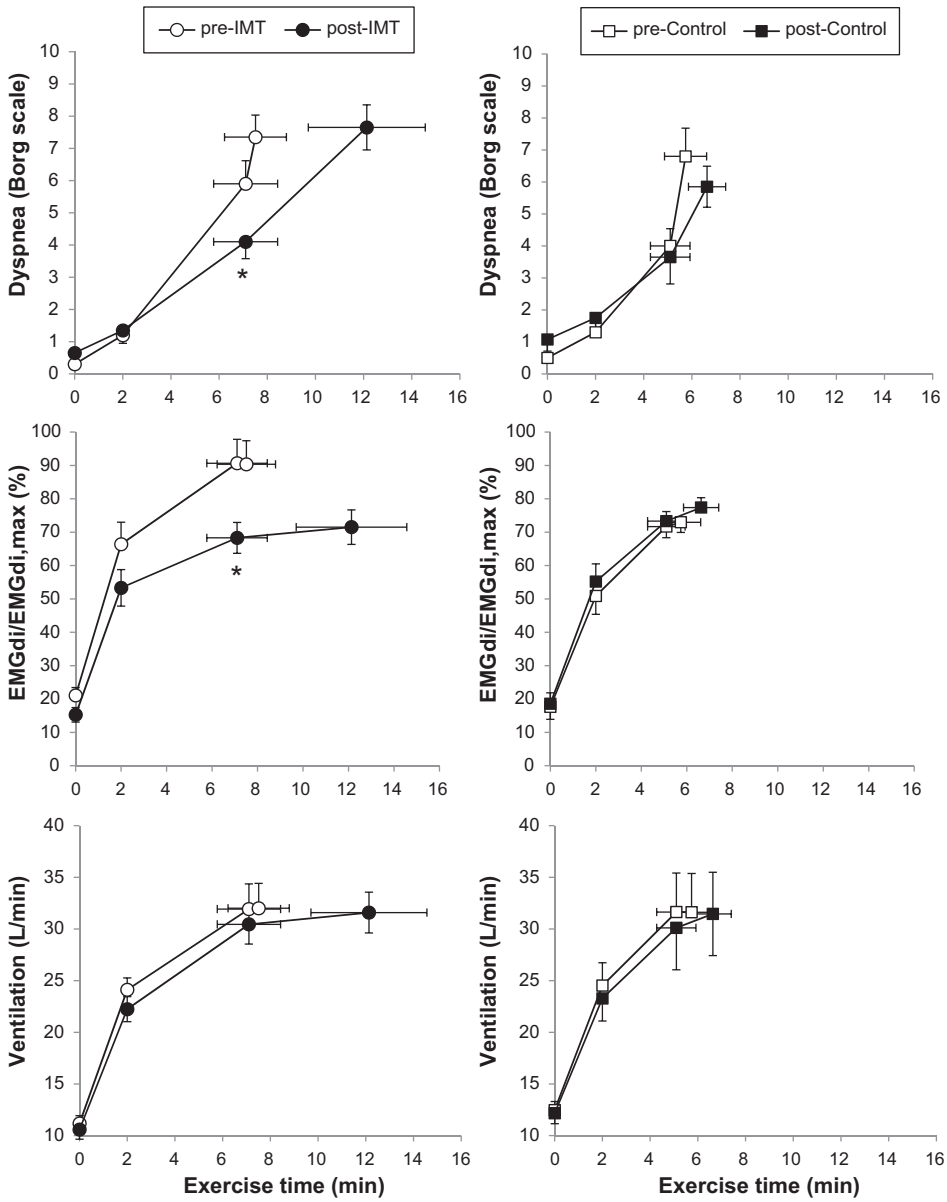


Fig. 4. Dyspnea intensity, electromyogram of the diaphragm measured during tidal inspiration/largest value during a maximum inspiratory maneuver (EMGdi/EMGdi$_{max}$), and ventilation during constant work rate exercise before and after inspiratory muscle training (IMT) and the control intervention. Values are means ± SE. *$P < 0.05$, post- vs. preintervention at isotime.

resting Pi$_{max}$ (19, 29). It is postulated that the sensation of increased perceived muscle effort that arises when any skeletal muscle is weakened (either experimentally or as a result of disease) fundamentally reflects the increased central motor command output from the cortex required to generate a given force or tension by the weakened muscle. The relative contribution of afferent inputs from mechanoreceptors in weakened muscles to perceived effort has not been determined conclusively, and such studies pose technical challenges. Further studies in this area are required. Davenport et al. (8) have used respiratory-related evoked potentials (RREP) to record cortical neural activity arising from synchronous afferent stimulation of specific cerebral cortical neurons. Using this approach, Huang et al. (25) examined the effects of increasing inspiratory muscle strength (by IMT) in healthy participants and found no changes in peak amplitude or latency of early components of RREP despite reduced mouth occlusion pressure, a surrogate for respiratory central motor drive.

In the context of the respiratory system, inspiratory motor command signals, and accompanying increased central corollary discharge to the somatosensory cortex may form the basis for perceived respiratory discomfort during experimental inspiratory muscle weakness (partial neuromuscular blockade, extrinsic mechanical loading, hyperinflation) (5, 17, 28). However, small psychophysical studies in healthy volunteers on the effects of IMT on indirect measures of inspiratory motor command output and respiratory sensation have shown inconsistent results (25, 48, 49). Clearly, the results of these studies cannot easily be extrapolated to COPD patients with severe dyspnea and chronically weak inspiratory muscles.

### *Dyspnea Relief and Reduced EMGdi/EMGdi$_{max}$ Following IMT*

The current study is the first to show that high-intensity IMT was associated with a consistent reduction in EMGdi/EMGdi$_{max}$

Table 3. *Parameter estimates and fit statistic of the best model (quadratic model −2ll:959) to describe dyspnea symptoms at different minutes during CWR exercise*

| Effect: IMT/Control (Post/Pre) | Estimate | SE | DF | *t*-Value | Pr > *t* |
|---|---|---|---|---|---|
| *Minute6* | −0.9 | 0.4 | 237 | −2.19 | 0.030 |
| *Minute5* | −0.8 | 0.4 | 237 | −2.01 | 0.045 |
| *Minute4* | −0.7 | 0.4 | 237 | −1.71 | 0.088 |
| *Minute3* | −0.5 | 0.4 | 237 | −1.24 | 0.215 |
| *Minute2* | −0.3 | 0.4 | 237 | −0.60 | 0.546 |
| *Minute1* | −0.0 | 0.6 | 237 | −0.00 | 0.999 |
| *Minute0* | 0.3 | 0.7 | 237 | 0.41 | 0.679 |

Values are response variable, dyspnea (Borg 0–10). CWR, constant work rate; DF, degrees of freedom. *t*-Values and probabilities are provided for estimates of pre/postintervention differences in dyspnea intensity between groups (IMT vs. control).

despite no change in $V_E$ during exercise in COPD (Fig. 3). The decrease in the EMGdi/EMGdi$_{max}$ ratio was explained mainly by a significant increase in EMGdi$_{max}$ obtained during IC maneuvers of similar magnitude pre- and post-IMT. The training-induced increase in EMGdi$_{max}$ may reflect an increased ability to recruit more motor units during maximal voluntary activation of the diaphragm due to a combination of increased strength and potential neuronal adaptations that facilitated motor unit recruitment over the 8-wk training period (22, 38). The trend toward decrease in tidal inspiratory EMGdi is compatible with a decrease in the motor unit recruitment required to generate a given force as a result of muscle hypertrophy (22, 38, 47). The absence of significant changes in the ventilatory muscle recruitment index (Table 4) (36) does not support a mechanism of reduced EMGdi amplitude being related to proportionally increased contribution of ribcage and accessory inspiratory muscles resulting in diaphragm sparing. Moreover, tidal inspiratory Pdi measurements were unchanged after training, and despite the fact that IMT did not specifically target the diaphragm, consistent increases in diaphragm strength were measured, confirming that this muscle was exposed to the external load.

Regardless of the precise neurobiological mechanism(s), our results suggest that improvement of exertional dyspnea following IMT is associated with reduction in the proportion of the maximal motor command output signals to the dia-

Table 4. *Measurements during symptom-limited constant work rate cycle ergometer exercise*

| | Control | | IMT | | Mean Difference of Change: IMT/control (95% CI) |
|---|---|---|---|---|---|
| | Preintervention | Change (Post/Pre) | Preintervention | Change (Post/Pre) | |
| Work rate, W | 35 ± 17 | | 35 ± 16 | | |
| Isotime | | | | | |
| Exercise time at isotime, s | 306 ± 156 | | 426 ± 252 | | |
| Dyspnea, Borg units | 4.0 ± 1.7 | −0.4 ± 2.1 | 5.7 ± 2.2 | −1.8 ± 2.3* | −1.5 (−3.5 to 0.6) |
| Leg discomfort, Borg units | 4.5 ± 2.3 | −0.7 ± 2.0 | 6.0 ± 3.3 | −1.1 ± 2.4 | −0.4 (−2.5 to 1.7) |
| $\dot{V}O_2$, l/min | 0.93 ± 0.35 | −0.06 ± 0.08 | 0.97 ± 0.24 | −0.03 ± 0.10 | 0.04 (−0.05 to 0.12) |
| HR, beats/min | 119 ± 16 | −5 ± 11 | 129 ± 16 | −10 ± 13* | −6 (−17 to 6) |
| $Sp_{O_2}$, % | 92.0 ± 7.4 | 1.8 ± 7.6 | 91.1 ± 4.5 | 1.7 ± 3.9 | −0.1 (−5.8 to 5.6) |
| Ventilation, l/min | 31.6 ± 11.9 | −1.5 ± 2.3 | 31.9 ± 7.7 | −1.5 ± 2.0 | 0.1 (−2.5 to 2.6) |
| $V_T$, liters | 1.01 ± 0.29 | 0.04 ± 0.08 | 0.97 ± 0.36 | 0.00 ± 0.10 | −0.04 (−0.12 to 0.04) |
| Fb, breaths/min | 31.5 ± 7.6 | −2.1 ± 2.7 | 35.3 ± 9.4 | −1.4 ± 2.3 | 0.7 (−1.7 to 3.0) |
| $T_I/T_{TOT}$ | 0.34 ± 0.05 | 0.00 ± 0.03 | 0.38 ± 0.07 | −0.01 ± 0.03 | −0.01 (−0.03 to 0.02) |
| IC, liters | 1.34 ± 0.34 | 0.09 ± 0.18 | 1.31 ± 0.27 | 0.09 ± 0.19 | −0.00 (−0.17 to 0.17) |
| IRV, liters | 0.33 ± 0.09 | 0.05 ± 0.14 | 0.34 ± 0.23 | 0.09 ± 0.22 | −0.07 (−0.24 to 0.10) |
| EMGdi, μV | 105 ± 42 | −9 ± 30 | 139 ± 87 | −21 ± 36 | −1 (−4 to 2) |
| EMGdi/EMGdi$_{max}$, % | 72 ± 11 | 2 ± 13 | 91 ± 23 | −22 ± 18*† | −24 (−39 to −9) |
| $Pes_{tidal}$, $cmH_2O$ | 26 ± 14 | −3 ± 9 | 27 ± 13 | 0 ± 4 | 2 (−10 to 13) |
| Inspiratory Pes, $cmH_2O$ | −14 ± 6 | −1 ± 4 | −15 ± 4 | 0 ± 2 | 1 (−2 to 4) |
| Inspiratory Pes/$Pes_{sniff}$, % | 27 ± 13 | 2 ± 8 | 35 ± 16 | −7 ± 7*† | −9 (−16 to −2) |
| Inspiratory Pdi, $cmH_2O$ | 25 ± 9 | 0 ± 5 | 34 ± 6 | 0 ± 4 | −0 (−5 to 4) |
| Inspiratory Pdi/$Pdi_{sniff}$, % | 31 ± 15 | 2 ± 8 | 38 ± 10 | −6 ± 9 | −8 (−16 to 0) |
| PTPdi, $cmH_2O \cdot s^{-1} \cdot min^{-1}$ | 262 ± 107 | −35 ± 86 | 336 ± 98 | −72 ± 96 | −37 (−123 to 50) |
| VMR | 0.8 ± 0.5 | −0.1 ± 0.6 | 0.1 ± 1.0 | 0.3 ± 0.7 | 0.4 (−0.2 to 1) |
| Peak exercise | | | | | |
| Dyspnea, Borg units | 6.8 ± 2.8 | −1.0 ± 2.4 | 7.4 ± 2.2 | 0.3 ± 2.2 | 1.3 (−0.9 to 3.4) |
| Leg discomfort, Borg units | 5.6 ± 3.2 | 0.3 ± 2.5 | 7.5 ± 2.7 | 0.7 ± 2.0 | 0.4 (−1.7 to 2.5) |
| $\dot{V}O_2$, l/min | 0.93 ± 0.35 | −0.03 ± 0.07 | 0.98 ± 0.24 | 0.01 ± 0.05 | 0.04 (−0.01 to 0.09) |
| HR, beats/min | 118 ± 15 | 0 ± 11 | 129 ± 16 | −6 ± 11 | −6 (−16 to 4) |
| Ventilation, l/min | 31.6 ± 11.9 | −0.2 ± 1.4 | 32.0 ± 7.6 | −0.4 ± 3.1 | −0.3 (−2.5 to 2.0) |
| Ventilation, %MVV | 84 ± 15 | −3 ± 5 | 70 ± 29 | 4 ± 27 | 7 (−11 to 26) |
| EMGdi/EMGdi$_{max}$, % | 73 ± 10 | 4 ± 9 | 90 ± 22 | −19 ± 19*† | −23 (−38 to −9) |
| Inspiratory Pes/$Pes_{sniff}$, % | 27 ± 13 | 2 ± 7 | 34 ± 16 | −6 ± 6*† | −8 (−14 to −2) |
| Inspiratory Pdi/$Pdi_{sniff}$, % | 64 ± 20 | 2 ± 8 | 84 ± 19 | −6 ± 8*† | −8 (−15 to −1) |

Values are means ± SD. EMGdi, electromyogram of the diaphragm measured during tidal inspiration; EMGdi$_{max}$, largest value during a maximum inspiratory maneuver; Fb, breathing frequency; HR, heart rate; IC, inspiratory capacity; IRV, inspiratory reserve volume; MVV, maximal voluntary ventilation; Pdi, transdiaphragmatic pressure; Pes, esophageal pressure; $Pes_{tidal}$, tidal swing of Pes; inspiratory Pes, the most negative Pes during a tidal inspiration; inspiratory Pdi, the most positive Pdi during a tidal inspiration; PTPdi, pressure time product of the diaphragm; $Sp_{O_2}$, oxygen saturation by pulse oximetry; $T_I/T_{TOT}$, inspiratory duty cycle; VMR, ventilatory muscle recruitment index (ΔPga/ΔPes between points of zero flow); $\dot{V}O_2$, oxygen consumption; $V_T$, tidal volume. Isotime refers to time of shortest endurance cycling test performed either pre- or postintervention that was common to both. *$P < 0.05$, within-group difference pre- vs. postintervention by paired *t*-test; †$P < 0.05$ by unpaired *t*-test comparing treatment differences for IMT vs. control.

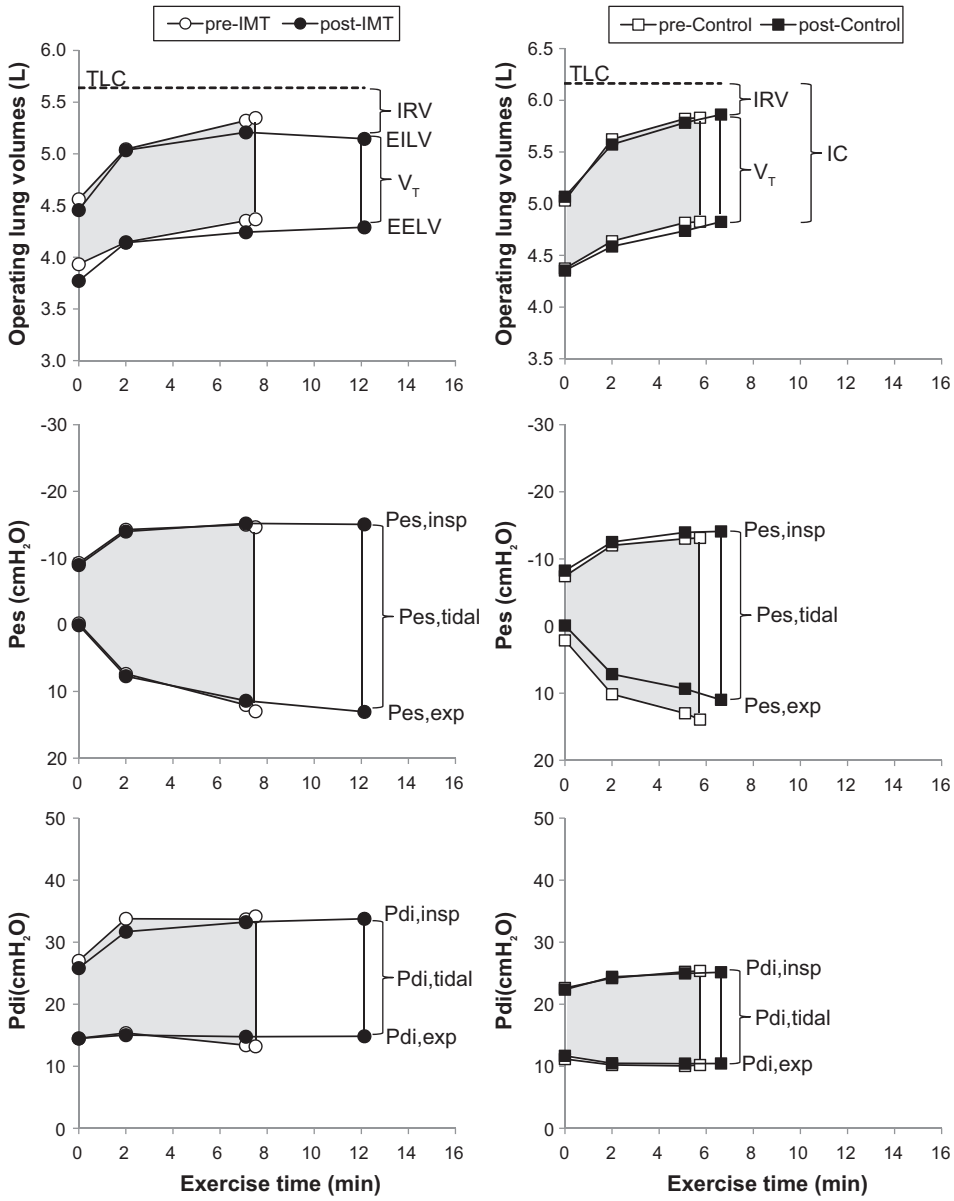


Fig. 5. Tidal operating lung volumes, esophageal pressures (Pes), and transdiaphragmatic pressures (Pdi) during constant work rate exercise before and after inspiratory muscle training (IMT) and the control intervention. Shaded areas represent the tidal volume ($V_T$) and tidal swings of Pes and Pdi before each intervention. There were no significant within-group differences pre- vs. postintervention at rest or at a standardized time during exercise. Values are means ± SE. EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; exp, expiratory; IC, inspiratory capacity; insp, inspiratory; IRV, inspiratory reserve volume; TLC, total lung capacity.

phragm required to sustain $V_E$. Ultimately, reduced EMGdi/$EMGdi_{max}$ is likely related to improved load-capacity imbalance of the diaphragm after training due mainly to improvement in strength and capacity and not reduced loading. Dyspnea at the end of exercise increased despite a plateau in EMGdi/$EMGdi_{max}$ in conjunction with progressive increases in the pressure-time product of the inspiratory muscles in the post-IMT arm. This likely reflects additional sources of dyspnea during sustained mechanical loading that were not measured in the current study [e.g., increases in expiratory and accessory muscle activation, afferent inputs from muscle mechanoreceptors, or metabolic acidosis and increased ergoreceptor activation (16)].

*Limitations*

The relatively small sample size reflects the difficulty in recruiting patient volunteers with troublesome dyspnea to undertake demanding and extensive physiological testing. Nevertheless, the sample size was sufficient to demonstrate a significant between-group difference in our primary outcome. Our study did not allow us to evaluate the specificity of IMT; recruitment and activation patterns of different respiratory muscle during exercise in response to training were not ascertained. Concomitant EMG measurements of the ribcage, scalene, and sternocleidomastoid and abdominal muscles and electromagnetic stimulation techniques to assess respiratory muscle weakness were not available. There is debate as to whether $EMGdi_{max}$ should be derived from maximal maneuvers undertaken at rest or during exercise. In keeping with previous studies (14, 26, 27), the highest EMGdi values in the current study were obtained consistently during exercise IC maneuvers. IC during exercise accounts for the prevailing dynamic mechanics and represents the effective reserves for maximal diaphragmatic activation under these specific conditions. Measurements of blood lactate and central hemodynamics, as well as local muscle $O_2$ delivery and utilization, were

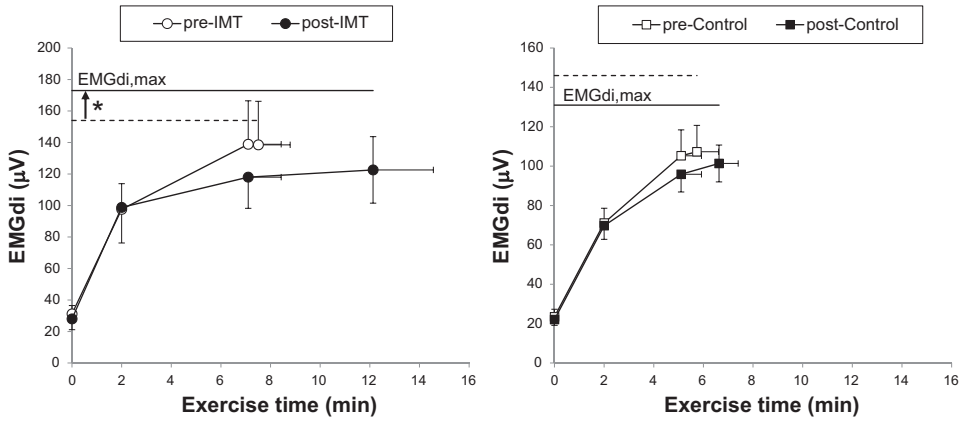


Fig. 6. Tidal inspiratory electromyogram of the diaphragm measured during tidal inspiration (EMGdi) and maximal EMGdi [largest value during a maximum inspiratory maneuver ($EMGdi_{max}$); dashed lines are preintervention, solid lines are postintervention] are shown during constant work rate exercise testing before and after inspiratory muscle training (IMT) and the control intervention. *$P < 0.05$, significant increase in $EMGdi_{max}$ after IMT. Values are means ± SE.

not available. These measurements would be helpful in quantifying the degree to which a possible delay in the rate of respiratory muscle fatigue after the intervention might impact on blood flow distribution and the competition of respiratory and locomotor muscles for limited energy supplies during exercise.

### *Future Perspectives*

Additional studies are required to determine whether neural activation of extradiaphragmatic muscles is also influenced by IMT and to determine their relative contribution to improved exertional dyspnea. The competition of respiratory and locomotor muscles for limited energy supplies is an exercise-limiting factor that might be acted upon by improving respiratory muscle function (10). Therefore, assessment of the effects of IMT on $O_2$ consumption of the respiratory muscles during exercise and simultaneous $O_2$ delivery to the peripheral muscles would be of specific interest. Blood flow redistribution between respiratory and locomotor muscles induced by fatiguing respiratory muscle work is an additional exercise-limiting factor that might be influenced by improving respiratory muscle function (10). Therefore, future evaluation of the potential role of IMT in delaying diaphragmatic fatigue and its downstream consequences in COPD would be important. Studies are needed to see whether IMT techniques can be refined to specifically strengthen various respiratory muscle groups based on detailed individual functional assessments. These studies would help to answer the question of whether individualized IMT can optimize clinical outcomes. More studies are required to establish selection criteria for initiation of IMT among patients with COPD. For example, since diaphragmatic weakness can be present even in smokers with only mild COPD, clinical trials of the effects of early IMT in this population would be of particular interest (13, 15, 43). New studies should investigate the clinical efficacy of novel technologies that allow long-term monitoring and adherence to IMT and study whether this may help to maintain improvements in respiratory muscle function (54).

### *Conclusions*

The current study is the first to show that supervised IMT reduced the proportion of inspiratory neural drive to the diaphragm that is utilized in breathing during a demanding physical task in patients with moderate-to-severe COPD and a low baseline $Pi_{max}$. This in turn had favorable consequences for respiratory sensation and exercise tolerance, even in the setting of high ventilatory requirements, severe respiratory mechanical loading, and tidal volume constraints. Therefore, the results provide a physiological rationale for IMT in selected patients with COPD who remain disabled by dyspnea despite optimal bronchodilator therapy.

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Table 5. *Measurements of EMGdi (μV) during different maximal inspiratory maneuvers*

| | Control | | IMT | |
|---|---|---|---|---|
| Maneuver | Preintervention | Postintervention | Preintervention | Postintervention |
| Resting $Pi_{max}$ at RV | 79 ± 25 | 69 ± 29 | 97 ± 65 | 105 ± 58 |
| Resting $Pi_{max}$ at FRC | 86 ± 36 | 79 ± 25 | 96 ± 46 | 108 ± 59 |
| Pre-exercise sniff | 103 ± 33 | 90 ± 26 | 111 ± 52 | 121 ± 57 |
| End-of-exercise sniff | 129 ± 46 | 102 ± 32 | 102 ± 57 | 135 ± 57*† |
| Pre-exercise resting IC | 104 ± 35 | 101 ± 43 | 125 ± 55 | 143 ± 65* |
| End-of-exercise IC | 144 ± 53 | 131 ± 35 | 149 ± 80 | 156 ± 75 |
| Highest exercise IC | 146 ± 52 | 131 ± 35 | 154 ± 78 | 173 ± 81*† |

Values are means ± SD. FRC, functional residual capacity; IC, inspiratory capacity; $Pi_{max}$, maximal inspiratory pressure measured at the mouth during an inspiratory occlusion; RV, residual volume. *$P < 0.05$, within-group difference pre- vs. postintervention by paired *t*-test; †$P < 0.05$ by unpaired *t*-test comparing treatment differences for IMT vs. control.

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## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

D.L., K.A.W., R.G., and D.E.O. conceived and designed research; D.L. and C.E.C. performed experiments; D.L., C.E.C., A.F., K.A.W., S.D., M.T., and A.I. analyzed data; D.L., C.E.C., A.F., K.A.W., J.A.N., R.G., S.D., M.T., A.I., and D.E.O. interpreted results of experiments; D.L. and K.A.W. prepared figures; D.L., K.A.W., and D.E.O. drafted manuscript; D.L., K.A.W., J.A.N., R.G., S.D., M.T., A.I., and D.E.O. edited and revised manuscript; D.L., C.E.C., A.F., K.A.W., J.A.N., R.G., and D.E.O. approved final version of manuscript.

## REFERENCES


1. **American Thoracic Society/European Respiratory Society.** ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 166: 518–624, 2002. doi:10.1164/rccm.166.4.518.
2. **Black LF, Hyatt RE.** Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 99: 696–702, 1969. doi:10.1164/arrd.1969.99.5.696.
3. **Blackie SP, Fairbarn MS, McElvaney GN, Morrison NJ, Wilcox PG, Pardy RL.** Prediction of maximal oxygen uptake and power during cycle ergometry in subjects older than 55 years of age. *Am Rev Respir Dis* 139: 1424–1429, 1989. doi:10.1164/ajrccm/139.6.1424.
4. **Borg GAV.** Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 14: 377–381, 1982. doi:10.1249/00005768-198205000-00012.
5. **Campbell EJ, Gandevia SC, Killian KJ, Mahutte CK, Rigg JR.** Changes in the perception of inspiratory resistive loads during partial curarization. *J Physiol* 309: 93–100, 1980. doi:10.1113/jphysiol.1980.sp013496.
6. **Carroll TJ, Riek S, Carson RG.** The sites of neural adaptation induced by resistance training in humans. *J Physiol* 544: 641–652, 2002. doi:10.1113/jphysiol.2002.024463.
7. **Charususin N, Gosselink R, McConnell A, Demeyer H, Topalovic M, Decramer M, Langer D.** Inspiratory muscle training improves breathing pattern during exercise in COPD patients. *Eur Respir J* 47: 1261–1264, 2016. doi:10.1183/13993003.01574-2015.
8. **Davenport PW, Friedman WA, Thompson FJ, Franzén O.** Respiratory-related cortical potentials evoked by inspiratory occlusion in humans. *J Appl Physiol (1985)* 60: 1843–1848, 1986. doi:10.1152/jappl.1986.60.6.1843.
9. **Decramer M.** Effects of hyperinflation on the respiratory muscles. *Eur Respir J* 2: 299–302, 1989.
10. **Dempsey JA.** New perspectives concerning feedback influences on cardiorespiratory control during rhythmic exercise and on exercise performance. *J Physiol* 590: 4129–4144, 2012. doi:10.1113/jphysiol.2012.233908.
11. **Doig GS, Simpson F.** Randomization and allocation concealment: a practical guide for researchers. *J Crit Care* 20: 187–191, 2005. doi:10.1016/j.jcrc.2005.04.005.
12. **Donaldson AV, Maddocks M, Martolini D, Polkey MI, Man WD.** Muscle function in COPD: a complex interplay. *Int J Chron Obstruct Pulmon Dis* 7: 523–535, 2012.
13. **Elbehairy AF, Guenette JA, Faisal A, Ciavaglia CE, Webb KA, Jensen D, Ramsook AH, Neder JA, O'Donnell DE; Canadian Respiratory Research Network.** Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J* 48: 694–705, 2016. doi:10.1183/13993003.00077-2016.
14. **Faisal A, Alghamdi BJ, Ciavaglia CE, Elbehairy AF, Webb KA, Ora J, Neder JA, O'Donnell DE.** Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am J Respir Crit Care Med* 193: 299–309, 2016. doi:10.1164/rccm.201504-0841OC.
15. **Formiga MF, Campos MA, Cahalin LP.** Inspiratory muscle performance of former smokers and nonsmokers using the test of incremental respiratory endurance. *Respir Care* 63: 86–91, 2018. doi:10.4187/respcare.05716.
16. **Gagnon P, Bussières JS, Ribeiro F, Gagnon SL, Saey D, Gagné N, Provencher S, Maltais F.** Influences of spinal anesthesia on exercise tolerance in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 186: 606–615, 2012. doi:10.1164/rccm.201203-0404OC.
17. **Gandevia SC, Killian KJ, Campbell EJ.** The effect of respiratory muscle fatigue on respiratory sensations. *Clin Sci (Lond)* 60: 463–466, 1981. doi:10.1042/cs0600463.
18. **Gea J, Pascual S, Casadevall C, Orozco-Levi M, Barreiro E.** Muscle dysfunction in chronic obstructive pulmonary disease: update on causes and biological findings. *J Thorac Dis* 7: E418–E438, 2015.
19. **Gosselink R, De Vos J, van den Heuvel SP, Segers J, Decramer M, Kwakkel G.** Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J* 37: 416–425, 2011. doi:10.1183/09031936.00031810.
20. **Guenette JA, Chin RC, Cheng S, Dominelli PB, Raghavan N, Webb KA, Neder JA, O'Donnell DE.** Mechanisms of exercise intolerance in global initiative for chronic obstructive lung disease grade 1 COPD. *Eur Respir J* 44: 1177–1187, 2014. doi:10.1183/09031936.00034714.
21. **Guenette JA, Chin RC, Cory JM, Webb KA, O'Donnell DE.** Inspiratory capacity during exercise: measurement, analysis and interpretation. *Pulm Med* 2013: 956081, 2013. doi:10.1155/2013/956081.
22. **Häkkinen K, Newton RU, Gordon SE, McCormick M, Volek JS, Nindl BC, Gotshalk LA, Campbell WW, Evans WJ, Häkkinen A, Humphries BJ, Kraemer WJ.** Changes in muscle morphology, electromyographic activity, and force production characteristics during progressive strength training in young and older men. *J Gerontol A Biol Sci Med Sci* 53A: B415–B423, 1998. doi:10.1093/gerona/53A.6.B415.
23. **Hamilton AL, Killian KJ, Summers E, Jones NL.** Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med* 152: 2021–2031, 1995. doi:10.1164/ajrccm.152.6.8520771.
24. **Hart N, Hawkins P, Hamnegård CH, Green M, Moxham J, Polkey MI.** A novel clinical test of respiratory muscle endurance. *Eur Respir J* 19: 232–239, 2002. doi:10.1183/09031936.02.00247602.
25. **Huang CH, Martin AD, Davenport PW.** Effect of inspiratory muscle strength training on inspiratory motor drive and RREP early peak components. *J Appl Physiol (1985)* 94: 462–468, 2003. doi:10.1152/japplphysiol.00364.2002.
26. **Jensen D, O'Donnell DE, Li R, Luo YM.** Effects of dead space loading on neuro-muscular and neuro-ventilatory coupling of the respiratory system during exercise in healthy adults: implications for dyspnea and exercise tolerance. *Respir Physiol Neurobiol* 179: 219–226, 2011. doi:10.1016/j.resp.2011.08.009.
27. **Jolley CJ, Luo YM, Steier J, Rafferty GF, Polkey MI, Moxham J.** Neural respiratory drive and breathlessness in COPD. *Eur Respir J* 45: 355–364, 2015. doi:10.1183/09031936.00063014.
28. **Killian KJ, Gandevia SC, Summers E, Campbell EJ.** Effect of increased lung volume on perception of breathlessness, effort, and tension. *J Appl Physiol Respir Environ Exerc Physiol* 57: 686–691, 1984. doi:10.1152/jappl.1984.57.3.686.
29. **Killian KJ, Jones NL.** Respiratory muscles and dyspnea. *Clin Chest Med* 9: 237–248, 1988.
30. **Langer D, Charususin N, Jácome C, Hoffman M, McConnell A, Decramer M, Gosselink R.** Efficacy of a novel method for inspiratory muscle training in people with chronic obstructive pulmonary disease. *Phys Ther* 95: 1264–1273, 2015. doi:10.2522/ptj.20140245.
31. **Langer D, Jacome C, Charususin N, Scheers H, McConnell A, Decramer M, Gosselink R.** Measurement validity of an electronic inspiratory loading device during a loaded breathing task in patients with COPD. *Respir Med* 107: 633–635, 2013. doi:10.1016/j.rmed.2013.01.020.
32. **Leblanc P, Summers E, Inman MD, Jones NL, Campbell EJ, Killian KJ.** Inspiratory muscles during exercise: a problem of supply and demand. *J Appl Physiol (1985)* 64: 2482–2489, 1988. doi:10.1152/jappl.1988.64.6.2482.
33. **Lisboa C, Muñoz V, Beroiza T, Leiva A, Cruz E.** Inspiratory muscle training in chronic airflow limitation: comparison of two different training loads with a threshold device. *Eur Respir J* 7: 1266–1274, 1994. doi:10.1183/09031936.94.07071266.
34. **Loring SH, Garcia-Jacques M, Malhotra A.** Pulmonary characteristics in COPD and mechanisms of increased work of breathing. *J Appl Physiol (1985)* 107: 309–314, 2009. doi:10.1152/japplphysiol.00008.2009.
35. **Luo YM, Moxham J, Polkey MI.** Diaphragm electromyography using an oesophageal catheter: current concepts. *Clin Sci (Lond)* 115: 233–244, 2008. doi:10.1042/CS20070348.
36. **Macklem PT, Gross D, Grassino GA, Roussos C.** Partitioning of inspiratory pressure swings between diaphragm and intercostal/accessory muscles. *J Appl Physiol Respir Environ Exerc Physiol* 44: 200–208, 1978. doi:10.1152/jappl.1978.44.2.200.

37. **Mahler DA, Witek TJ Jr.** The MCID of the transition dyspnea index is a total score of one unit. *COPD* 2: 99–103, 2005. doi:10.1081/COPD-200050666.
38. **Moritani T.** Neuromuscular adaptations during the acquisition of muscle strength, power and motor tasks. *J Biomech* 26, *Suppl* 1: 95–107, 1993. doi:10.1016/0021-9290(93)90082-P.
39. **O'Donnell DE, Banzett RB, Carrieri-Kohlman V, Casaburi R, Davenport PW, Gandevia SC, Gelb AF, Mahler DA, Webb KA.** Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. *Proc Am Thorac Soc* 4: 145–168, 2007. doi:10.1513/pats.200611-159CC.
40. **O'Donnell DE, Hamilton AL, Webb KA.** Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. *J Appl Physiol (1985)* 101: 1025–1035, 2006. doi:10.1152/japplphysiol.01470.2005.
41. **O'Donnell DE, McGuire M, Samis L, Webb KA.** General exercise training improves ventilatory and peripheral muscle strength and endurance in chronic airflow limitation. *Am J Respir Crit Care Med* 157: 1489–1497, 1998. doi:10.1164/ajrccm.157.5.9708010.
42. **O'Donnell DE, Elbehairy AF, Faisal A, Neder JA, Webb KA; Canadian Respiratory Research Network (CRRN).** Sensory-mechanical effects of a dual bronchodilator and its anticholinergic component in COPD. *Respir Physiol Neurobiol* 247: 116–125, 2018. doi:10.1016/j.resp.2017.10.001.
43. **Ottenheijm CA, Heunks LM, Sieck GC, Zhan WZ, Jansen SM, Degens H, de Boo T, Dekhuijzen PN.** Diaphragm dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 172: 200–205, 2005. doi:10.1164/rccm.200502-262OC.
44. **Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, O'Donnell DE; American Thoracic Society Committee on Dyspnea.** An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 185: 435–452, 2012. doi:10.1164/rccm.201111-2042ST.
45. **Petrovic M, Reiter M, Zipko H, Pohl W, Wanke T.** Effects of inspiratory muscle training on dynamic hyperinflation in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 7: 797–805, 2012. doi:10.2147/COPD.S23784.
46. **Polkey MI, Hamnegård CH, Hughes PD, Rafferty GF, Green M, Moxham J.** Influence of acute lung volume change on contractile properties of human diaphragm. *J Appl Physiol (1985)* 85: 1322–1328, 1998. doi:10.1152/jappl.1998.85.4.1322.
47. **Ramírez-Sarmiento A, Orozco-Levi M, Guell R, Barreiro E, Hernandez N, Mota S, Sangenis M, Broquetas JM, Casan P, Gea J.** Inspiratory muscle training in patients with chronic obstructive pulmonary disease: structural adaptation and physiologic outcomes. *Am J Respir Crit Care Med* 166: 1491–1497, 2002. doi:10.1164/rccm.200202-075OC.
48. **Ramsook AH, Molgat-Seon Y, Schaeffer MR, Wilkie SS, Camp PG, Reid WD, Romer LM, Guenette JA.** Effects of inspiratory muscle training on respiratory muscle electromyography and dyspnea during exercise in healthy men. *J Appl Physiol (1985)* 122: 1267–1275, 2017. doi:10.1152/japplphysiol.00046.2017.
49. **Redline S, Gottfried SB, Altose MD.** Effects of changes in inspiratory muscle strength on the sensation of respiratory force. *J Appl Physiol (1985)* 70: 240–245, 1991. doi:10.1152/jappl.1991.70.1.240.
50. **Rodrigues A, Da Silva ML, Berton DC, Cipriano G Jr, Pitta F, O'Donnell DE, Neder JA.** Maximal inspiratory pressure: does the choice of reference values actually matter? *Chest* 152: 32–39, 2017. doi:10.1016/j.chest.2016.11.045.
51. **Steier J, Kaul S, Seymour J, Jolley C, Rafferty G, Man W, Luo YM, Roughton M, Polkey MI, Moxham J.** The value of multiple tests of respiratory muscle strength. *Thorax* 62: 975–980, 2007. doi:10.1136/thx.2006.072884.
52. **Sundh J, Ekström M.** Persistent disabling breathlessness in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 11: 2805–2812, 2016. doi:10.2147/COPD.S119992.
53. **Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DM, López Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA, Agusti A.** Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2017 report: GOLD executive summary. *Eur Respir J* 49: 1700214, 2017. [Erratum in *Eur J Respir* 49: 1700214, 2017.] 10.1183/13993003.00214-2017.
54. **Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N.** Maintenance of inspiratory muscle training in COPD patients: one year follow-up. *Eur Respir J* 23: 61–65, 2004. doi:10.1183/09031936.03.00059503.