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Early View

Original research article

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Effects of inspiratory muscle training on exertional breathlessness in patients with unilateral diaphragm dysfunction: a randomized trial

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"Take home" message: Inspiratory muscle training is a well-tolerated conservative treatment option for people with unilateral diaphragm dysfunction that yields meaningful benefits in activity-related dyspnea and exercise tolerance.

ABSTRACT

Unilateral diaphragm dysfunction (UDD) is an underdiagnosed cause of dyspnea. Inspiratory muscle training (IMT) is the only conservative treatment for UDD, but the mechanisms of improvement are unknown. We characterized the effects of IMT on dyspnea, exercise tolerance, and respiratory muscle function in people with UDD.

Fifteen people with UDD (73%male, 61±8yrs) were randomized to 6-months of IMT (50% maximal inspiratory mouth pressure ($P_{I,max}$), n=10) or sham training (10%$P_{I,max}$, n=5) (30 breaths 2x/day). UDD was confirmed by phrenic nerve stimulation and persisted throughout the training period. Symptoms were assessed by the Transitional Dyspnea Index (TDI) and exercise tolerance by constant-load cycle tests performed pre- and post-training. Esophageal (P_{es}) and gastric (P_{ga}) pressures were measured with a dual-balloon catheter. Electromyography (EMG) and oxygenation (near-infrared spectroscopy) of respiratory muscles were assessed continuously during exercise.

The IMT group (from 45±6%$P_{I,max}$ to 62±23%$P_{I,max}$) and sham group (no progression) completed 92% and 86% of prescribed sessions, respectively. $P_{I,max}$, TDI scores, and cycle endurance time improved significantly more after IMT *vs.* sham (mean between-group differences: 28[95%CI:13-28]cmH_2O, 3.0[95%CI:0.9-5.1]points, and 6.0[95%CI:0.4-11.5]minutes, respectively). During exercise at iso-time, P_{es}, P_{ga}, and EMG of the scalene muscles were reduced and oxygen saturation index of the scalene and abdominal muscles higher post-training *vs.* pre- only in the IMT group (all $p<0.05$).

The effects of IMT on dyspnea and exercise tolerance in UDD were not mediated by improvement in isolated diaphragm function, but may reflect improvements in strength, coordination, and/or oxygenation of the extra-diaphragmatic respiratory muscles.

INTRODUCTION

Diaphragm dysfunction is an important yet underdiagnosed cause of dyspnea [1]. One (unilateral) or both (bilateral) sides of the diaphragm can exhibit partial to complete loss of function, with the left hemidiaphragm more commonly involved in unilateral diaphragm dysfunction (UDD) than the right [2, 3]. People with UDD are typically asymptomatic at rest, but often experience dyspnea on exertion, when lifting heavy objects, performing any overhead activity, bending forward, or lying down [2]. This can likely be explained by a worsening paradoxical response of gastric pressure with exertion and a compensatory recruitment of extra-diaphragmatic respiratory muscles [4]. The prognosis of UDD varies depending on the etiology, with spontaneous recovery more frequently reported in cases of traumatic cause relative to neuropathy [5, 6].

Treatment options for UDD and related symptoms are limited. A weak hemidiaphragm can be surgically immobilized (plication) to improve lung volumes, symptoms, and ability to perform activities of daily living [7]. However, plication has no direct effect on diaphragm contractility and surgery is not appropriate for all patients [8]. Inspiratory muscle training (IMT) is currently the only conservative treatment option for UDD. Three case studies and an RCT reported improvements in lung volumes, respiratory muscle strength, diaphragm motility, symptoms, and participation in activities of daily living after IMT in people with unilateral or bilateral diaphragm dysfunction [9-12]. It was suggested that these benefits from IMT reflected improvements in non-diaphragmatic respiratory muscle function [9]. Studies with larger sample sizes, monitoring of training adherence, and more specific measurements of diaphragmatic function (*e.g.*, magnetic stimulation) are still needed to assess the clinical utility and mechanisms of change after IMT in this population.

The purpose of this single blind, parallel group, randomized controlled trial was to comprehensively characterize the effects of a six-month IMT program on exertional dyspnea, exercise tolerance, and respiratory muscle function (both at rest and during exercise) in people with UDD. We hypothesized that IMT would improve exertional dyspnea and exercise tolerance with attendant increases in strength of the extra-diaphragmatic inspiratory muscles.

METHODS

Participants. Adults with UDD were recruited at the University Hospital Gasthuisberg from January, 2018 to January, 2022 within 12 months of diagnosis (**Figure 1**). Individuals with a Baseline Dyspnea Index (BDI) score ≤9, an elevated hemidiaphragm on a chest radiography, paradoxical movement during a sniff maneuver on a chest fluoroscopy, and either a seated vital capacity (VC) <75%predicted, a reduction in forced vital capacity (FVC) >15% when supine *vs.* seated, or a MIP <70%predicted were eligible. Individuals with malignancy; psychiatric or cognitive disorders; progressive neurological, neuromuscular, or vestibular disorders; cardiac or respiratory disease that could contribute to dyspnea; or severe orthopedic problems that could impair exercise performance were excluded (n=47).

Study design. This study (NCT04563468) was approved by the Ethics Committee Research of University Hospitals Leuven (S60754). All participants provided written informed consent prior to enrollment in accordance with the Declaration of Helsinki. Participants were allocated into an intervention group (IMT) or a control group (sham training) in a 2:1 ratio, respectively, by a study team member using block randomization and sequentially numbered

opaque sealed envelopes [13]. Pre- and post-training assessments were made two days prior to starting the training program and two days after cessation. Participants trained at home and kept a diary of the external load. During one supervised monthly session at the research center, patient's maximal inspiratory mouth pressure ($P_{I,max}$) was assessed and the training program adapted. The supervising study team member was aware of the group allocation, but participants were blinded.

Intervention training protocol. The IMT group followed a strength program consisting of two sessions daily for six months using an electronic tapered flow resistive loading (TFRL) device (POWERbreathe® KH1; HaB International Ltd., UK). Each session consisted of 30 breaths against an external load of approximately 50%$P_{I,max}$. At monthly supervised study visits, the load was increased to the highest possible that allowed average inspiratory volumes ≥75%VC throughout each training session and a perceived inspiratory effort of 4-5 on the 0-10 category ratio scale.

Sham training protocol. Participants in the control group received a placebo program that was presented as an endurance IMT program. Control group participants were also instructed to perform two "training" sessions daily, each consisting of 30 breaths ≥75%VC against an external load of approximately 10%$P_{I,max}$, which was fixed throughout the intervention period.

Symptoms. The influence of dyspnea on activities of daily living was assessed using the BDI (first study visit), and the pre-to-post-training change was captured using the Transitional Dyspnea Index (TDI; final study visit) [14].

Pulmonary function. Spirometry (sitting and supine), whole body plethysmography, single-breath diffusing capacity of the lungs for carbon monoxide (DL_{CO}), and a 10-second maximal voluntary ventilation (MVV) maneuver were performed according to established guidelines [15, 16] using a commercially available system (Vmax229d with Vs62j body plethysmograph; Duomed, BE) pre- and post-training. Values were expressed as absolute and as a percentage of predicted values [17].

Respiratory pressures. Respiratory muscle strength was assessed pre- and post-training. $P_{I,max}$ and maximal expiratory mouth pressure ($P_{E,max)}$ were assessed at residual volume and total lung capacity (TLC), respectively (MicroRPM; Micromedical, UK) [18]. Esophageal (P_{es}) and gastric (P_{ga}) pressures were measured using a dual-balloon esophageal catheter (Guangzhou Yinghui Medical Equipment Ltd., CN). The esophageal and gastric balloons were filled with 0.8 and 1.4ml of air, respectively Maximal voluntary P_{es} and P_{ga} were recorded during sniff and cough maneuvers, respectively. Maximal involuntary P_{es} and P_{ga} were also recorded during a supramaximal potentiated twitch elicited via magnetic phrenic nerve stimulation [19, 20]. Breifly, 45-mm figure-of-eight coils were used and powered by a double Magstim® stimulator (Magstim Co Ltd, UK). For unilateral stimulations, both stimulators powered one coil. For bilateral stimulations, each coil was powered by one stimulator. A ramping protocol was used to ensure supramaximality. Transdiaphragmatic pressure (P_{di}) was calculated as the difference between P_{es} and P_{ga} and compared to previously defined lower limit of normal (15cmH_2O) [21].

Esophageal, gastric, and transdiaphragmatic tidal pressure swings during exercise were defined as the difference between the average pressures generated during inspiration and expiration ($P_{es,av}$, $P_{ga,av}$, $P_{di,av}$, respectively). Gastric rise ($P_{ga,rise}$) was the difference between the maximal pressure generated during expiration and the average during expiration.

Phrenic nerve conduction. Phrenic nerve conduction was assessed by magnetic stimulation pre- and post-training as previously described [22]. Compound motor action potential

(CMAP) amplitude and latency from the affected side were used, with the non-affected side measured as a reference, and compared to previously defined normal values (<300microvolts and >8.1milliseconds, respectively) [23].

Exercise test protocol. Cardiopulmonary exercise tests (CPET) were performed pre- and post-training on an electronically-braked cycle ergometer (Ergoline 800s; Duomed). Incremental tests started at 20watts and increased by 20watts each minute thereafter until task failure. Peak work-rate was defined as the highest completed step. Constant load tests were subsequently performed after a 30-minute resting period at 80% of peak work-rate, also to task failure.

Metabolic and ventilatory responses were measured breath-by-breath (Vmax Vs229d; Duomed). Inspiratory capacity (IC) was measured at rest, every two minutes and at the end of the exercise tests. Iso-time was defined as the highest sub-maximal time a participant achieved on both the pre- and post-IMT exercise tests. Peak exercise was defined as the last 30 seconds of exercise.

Participants rated the intensity of dyspnea, unpleasantness of their breathing, and their leg discomfort using the 0-10 category-ratio scale before each CPET, every minute during exercise, and at peak exercise.

Respiratory muscle activation. The dual-balloon multi-pair esophageal electrode catheter was used to record electromyography of the crural diaphragm (EMG_{di}) [24]. Bipolar electrodes were placed on the sternocleidomastoid (EMG_{scm}) and scalene (EMG_{sca}) to record the surface electromyography of extra-diaphragmatic respiratory muscles (TeleMyo DDTS; Velamed GmbH, DE). These data were expressed as peak during inspiration relative to maximal activation recorded during an IC maneuver.

Respiratory muscle oxygenation saturation. Changes from rest in oxygenation saturation of the scalene, sternocleidomastoid, and rectus abdominus muscles were assessed by continuous-wave near-infrared spectroscopy (NIRO-200 NX; Hamamatsu, JP) [25].

Statistical analysis. Initial sample sizes of 16 (IMT) and 8 (control) were estimated to provide 80% power to detect a 4 and 3 Borg unit reduction in dyspnea, respectively, at iso-time with a standard deviation of 1 unit and an $\alpha<5\%$. [26]. Due to the COVID-19 pandemic, recruitment was limited and the trial was stopped before the intended sample size was reached. Exercise data were averaged over 1-minute epochs. A two-way repeated measures ANOVA was used to identify pre-to-post-training within-group differences during exercise at standardized submaximal timepoints. Significant main and interaction effects for each outcome variable were tested in relation to the assumption of sphericity (Mauchly) and were adjusted using the Greenhouse-Geisser correction if appropriate. In the case of a significant main effect, pairwise comparisons were made using a Bonferroni post hoc test for multiple comparisons. Paired t-tests were used to compare outcomes pre- and post-training within groups. Unpaired t-tests were used to compare the pre-to-post-training difference in outcomes between groups. Statistical significance was set to $p<0.05$.

RESULTS

Ten participants were randomized to IMT and five to control (**Figure 1**, **Table 1**). Causes of UDD in the IMT group were idiopathic (n=5), pneumonia (n=1), respiratory infection (n=1), cervical block before arthroscopic debridement (n=1), shoulder surgery (n=1), and thyroid surgery (n=1). Causes of UDD in the control group were idiopathic (n=3), secondary to COVID-19 (n=1), neuralgic amyotrophy caused by hepatitis E (n=1). Time from symptom onset to study

enrollment was 9±3 and 7±4 months in the IMT and control groups, respectively. A higher proportion of the control group were females relative to the IMT group. The IMT group had slightly better spirometry and diffusing capacity. Both groups experienced similar dyspnea during activities of daily living. Peak work-rate was within the normal range for both groups, but peak incremental dyspnea ratings were higher than peak leg discomfort ratings, which was also reflected in a greater relative contribution of breathing discomfort to leg discomfort in the reason(s) for stopping exercise across groups. The control group exhibited a greater degree of exercise induced arterial hypoxemia and ventilatory limitation at peak incremental exercise.

The IMT group completed an average of 321 sessions (89%) starting with an average load of 45±6%$P_{I,max}$ that increased to 62±23% of the baseline $P_{I,max}$ by the end of the six-month training period. The control group completed an average of 309 sessions (86%) with an average load of 6±2%$P_{I,max}$. Within-group pre- and post-training measurements as well as the between-group magnitude of change in (i) phrenic nerve conductance, TDI, exercise tolerance, pulmonary function, and respiratory muscle strength and are summarized in **Table 2**; (ii) and exercise responses at iso-time in **Table 3**.

Neither the latency or amplitude of the affected or unaffected side were different pre-to-post-training within or between groups, respectively. Outcomes were still abnormal. However, there was a trend towards a greater recovery in amplitude of the affected side in the control group.

TDI was different between groups (p=0.008), with a greater reduction in dyspnea observed in the IMT group. Exercise endurance time for constant work-rate cycling was higher post-training in the IMT group (p=0.01), but not control; the pre-to-post change in exercise endurance time was also different between groups (p=0.04).

Pre-to-post changes in pulmonary function were not different between groups. Forced expiratory volume in 1 second and MVV were higher post-training in the IMT group (p=0.01 and p=0.02, respectively). TLC was higher post-training in the control group (p=0.02). FVC and IC were similarly higher post-training in the IMT (p=0.003 and p=0.01, respectively) and control (p=0.049 and p=0.047, respectively) groups. There was a trend towards an improvement in the postural drop post-training in both groups, but it did not reach statistical significance.

$P_{I,max}$ was higher post-training in the IMT group (p=0.01), but not control; the pre-to-post change in $P_{I,max}$ was also different between groups (p=0.001). $P_{di,sniff}$ was higher post-training in the IMT group (p=0.01), but not control. The pre-to-post-change in $P_{di,sniff}$ was also different between groups (p=0.046). Neither $P_{E,max}$, $P_{di,tw}$ (affected, unaffected, or bilateral), or $P_{ga,cough}$ were different pre-to-post-training within or between groups, respectively. Only one participant in the IMT group had a $P_{di,tw}$ above the lower limit of normal at baseline (21.4 cmH_2O), and this value did not change post-training.

There was a main effect of training on dyspnea as well as an interaction between dyspnea and exercise time in the IMT group, but not control (**Figure 2**). Dyspnea was also lower at iso-time (p=0.02) and peak (p=0.04) post-training in the IMT group, but not control (**Figure 2A** and **D**). However, the pre-to-post change in dyspnea at iso-time was not different between groups. There was no main effect of training on leg effort observed for either group (**Figure 2B** and **D**). Leg effort ratings were not different at iso-time pre-to-post-training within or between groups, respectively.

There was a main effect of training on breathing frequency in the IMT group, but not control (**Figure 3B** and **E**); this difference was only observed at a submaximal exercise time of 2 minutes. There was no main effect of training on minute ventilation or tidal volume (**Figure 3A**,

C, **D**, and **F**). IC was similarly lower at iso-time post-training in both IMT (p=0.01) and control (p=0.01) groups, but not different pre-to-post-training between groups.

There was no main effect of training on $P_{es,av}$, $P_{ga,av}$, $P_{es,av}$, $P_{di,av}$, or $P_{ga,rise}$ (**Figure 4A-H**). $P_{es,av}$, $P_{ga,av}$, and $P_{ga,rise}$ were all significantly higher at iso-time post-training in the IMT group, but not control (p=0.04, 0.04, and 0.049, respectively). However, the pre-to-post change in these outcomes at iso-time were not different between groups. $P_{ga,av}$ was not different at iso-time pre-to-post-training within or between groups, respectively.

There was no main effect of training on $EMG_{di\%max}$, $EMG_{scm\%max}$, or $EMG_{sca\%max}$ (**Figure 4A-F**). While there was a difference in the pre-to-post change in $EMG_{scm\%max}$ between groups, $EMG_{scm\%max}$ was not different pre- *vs.* post-training in either group. $EMG_{di\%max}$ and $EMG_{sca\%max}$ were not different at iso-time pre-to-post-training within or between groups, respectively.

At iso-time, the change from rest in oxygen saturation ($StiO_2$) of the sternocleidomastoid and abdominal muscles were significantly lower post *vs.* pre-training only in the IMT group (p=0.03 and 0.01, respectively), with the change in $StiO_2$ of the sternocleidomastoid also significantly different between groups (p=0.004).

DISCUSSION

We showed that IMT in people with UDD: 1) reduces activity-related dyspnea with attendant improvements in exercise tolerance; 2) improves respiratory pressure generating capacity without changes in isolated diaphragm contractility; 3) decreases relative inspiratory muscle activation; and 4) improves both extra-diaphragmatic inspiratory and expiratory muscle oxygenation. Collectively, these findings suggest IMT could help manage symptoms in this patient population.

The IMT group in the present study achieved a larger reduction in exertional dyspnea compared to control. The observed change in TDI score was six-times the minimal clinically important difference (MCID) in the IMT group with a two-point average increase per subscale (moderate), and three-times the MCID in the control group with a one-point average increase per subscale (small) [14]. This suggests that IMT has a clinically relevant effect exceeding the natural evolution of function, including spontaneous recovery and related symptoms, observed in the control group. Additionally, dyspnea ratings were lower at every time point during CPET post-training in the IMT group, but not control, which likely contributed to the improved exercise endurance time unique to the IMT group. Lower symptoms in the context of exercise rehabilitation may increase exercise tolerance to higher intensities and/or longer durations, allowing for greater physiological training adaptations and subsequent improvements in quality of life.

Respiratory muscle strength improved in the IMT group but not control, without concomitant change in isolated involuntary diaphragm contractility or unilateral abnormality within or between groups. Importantly, both the diaphragm and the extra-diaphragmatic inspiratory muscles can contribute to maximal inspiratory mouth pressure and sniff pressures [9]. Thus, in the absence of change in more specific measurements (*e.g.*, electrical and magnetic stimulation), higher maximal voluntary pressures observed in the IMT group post-training in the present study likely reflected improvement in chest wall muscle function, extra-diaphragmatic muscle activation, and/or respiratory muscle coordination from the intervention *vs.* improvement in diaphragm function [27]. The increase in transdiaphragmatic pressure during maximal inspiratory sniff maneuvers in the IMT group is almost exclusively explained by an increase in

esophageal pressure, which is an index of global respiratory muscle effort and suggests increased ribcage muscle contribution. Previous studies have demonstrated a compensatory increase in extra-diaphragmatic respiratory muscle activation with diaphragm weakness or dysfunction [28-32]. Additionally, the magnitude of negative (*i.e.*, paradoxical) gastric pressure deflection during sniff maneuvers remained stable, indicating unchanged and/or potentially absent diaphragm contribution to maximal voluntary inspiratory pressure generation. These resting data are consistent with observed changes during exercise hyperpnea post-training where the IMT group achieved a similar tidal volume with less negative esophageal pressure during inspiration and a trend towards relatively lower activation and better oxygenation of the extra-diaphragmatic inspiratory muscles (*e.g.*, less respiratory muscle effort) post-training [33-35]. We speculate the more efficient breathing pattern adopted by the IMT-group post-training could be attributed to better strength and/or coordination (*i.e.*, timing and/or symmetry) of these muscles with the diaphragm during inspiration. Gastric pressure rise during expiration was also lower and oxygenation of the rectus abdominus muscles higher in the IMT group post-training, which could indicate withdrawal of the expiratory muscles as an inspiratory assist and an improved balance between ventilatory demand and respiratory muscle functional capacity [36]. Visualization of the diaphragm via ultrasound and other dynamic imaging techniques could also be useful to further elucidate the mechanisms of improvement [37].

The high level of adherence across study groups without any related adverse events suggests that IMT is well tolerated in people with UDD. Since both groups appeared equally motivated by the intervention and demonstrated meaningful improvements in TDI, we believe that our inclusion of a control group was adequate to rule out impact of a placebo effect.

Limitations and considerations. This study is limited by the single-center design and small sample size. While power to detect differences in certain outcomes may therefore be limited, we believe that the findings are novel and advance our understanding in this area of interest. We cannot discount spontaneous recovery occurring within the six-month training window. However, there was equal probability in both study groups that was likely accounted for by randomization. Additionally, there was greater evidence of recovery in the control group observed with electrical phrenic nerve stimulation. We also did not objectively measure physical activity during the intervention period. It is possible that those in the intervention group, especially those who experienced less exertional dyspnea at baseline, engaged in more daily activity, which could have also contributed to observed improvements in exercise capacity. Future work is still needed to determine precise mechanisms of improvement and most effective training protocols.

Conclusions. IMT is a well-tolerated treatment option that yields clinically meaningful reductions in dyspnea and improvement in exercise tolerance in people with UDD, likely via improvements in strength, coordination, and/or oxygenation of the extra-diaphragmatic respiratory muscles.

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Table 1. Baseline participant characteristics.

	IMT (n=10)	**Control** (n=5)
Demographics		
Male, n (%)	7 (70)	4 (80)
Age, years	63 ± 6.6	56.6 ± 10.8
Weight, kg	89 ± 21.2	93.2 ± 16.4
Height, cm	175 ± 10.3	177 ± 12.6
BMI, kg/m^2	28.8 ± 3.6	29.5 ± 1.4
BDI score, 0-12 scale	6.5 ± 1.8	7.6 ± 1.7
Left side paralysis, n (%)	4 (40)	4 (80)
Pulmonary function		
FVC, %predicted	72 ± 7	65 ± 9
FEV_1, %predicted	66 ± 5	58 ± 8
FEV_1/FVC, ratio	0.71 ± 0.08	0.74 ± 0.09
FVC_{supine}-FVC_{seated}, %dif	-29 ± 9	-24 ± 8
IC, %predicted	81 ± 14	66 ± 32
TLC, %predicted	79 ± 38	75 ± 35
RV, %predicted	107 ± 54	105 ± 49
FRC, %predicted	83 ± 41	76 ± 34
TL_{CO}, %predicted	84 ± 44	55 ± 25
K_{CO}, %predicted	117 ± 61	97 ± 43
Respiratory muscle strength		
$P_{I,max}$, %predicted	80 ± 20	83 ± 16
$P_{E,max}$, cmH_2O, %predicted	169 ± 72	143 ± 65
Peak incremental exercise		
Work-rate, watts	134 ± 40	163 ± 64
Work-rate, %predicted	95 ± 19	101 ± 19
Heart rate, beats/min	130 ± 47	127 ± 62
Heart rate, %predicted	84 ± 30	77 ± 36
$\dot{V}O_2$, l/min	2.0 ± 0.6	2.5 ± 1.4
$\dot{V}O_2$, %predicted	89 ± 13	107 ± 49
$\dot{V}CO_2$, l/min	2.1 ± 0.6	2.8 ± 1.5
$\dot{V}_E$, l/min	63.4 ± 17.9	74.2 ± 38.5
$\dot{V}_E$/MVV, %	74 ± 32	98 ± 49
$\dot{V}_E/\dot{V}CO_2$	30.9 ± 3.6	27.1 ± 12.3
RER	1.07 ± 0.10	1.09 ± 0.49
O_2 pulse, ml/beat	15.4 ± 7.3	19.8 ± 9.3
SpO_2, %	95 ± 40	91 ± 41
Dyspnea, 0-10 scale	8.0 ± 1.7	9.8 ± 0.4
Leg effort, 0-10 scale	7.6 ± 1.9	6.2 ± 3.9
Reasons for stopping, n (%contribution)		
Breathing discomfort	7 (70)	3 (60)
Leg discomfort	1 (10)	1 (20)
Combination	2 (20)	1 (20)

Values represented number (percent) or mean ± standard deviation.

BMI, body mass index; BDI, baseline dyspnea index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; IC, inspiratory capacity, TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; TL_{CO}, transfer factory for carbon monoxide; K_{CO}, carbon monoxide transfer coefficient; $P_{I,max}$, maximal inspiratory pressure; $P_{E,max}$, maximal expiratory pressure; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon monoxide production; $\dot{V}_E$, minute ventilation; MVV, maximal voluntary ventilation; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; RER, respiratory exchange ratio; O_2 pulse, oxygen consumed per heart beat; SpO_2, peripheral oxygen saturation.

Table 2. Pre- and post- training assessments.

	IMT		Control		Between	
	pre-	*post-*	*pre-*	*post-*	*mean dif*	*95% CI*
TDI, score		6.2 ± 1.2		3.2 ± 2.6	3.0†	0.9 to 5.1
Exercise endurance time, min	6.4 ± 2.8	12.4 ± 6.4†	7.2 ± 4.7	7.2 ± 3.4	6.0*	0.4 to 11.5
Pulmonary function						
FEV_1, l	2.1 ± 0.5	2.5 ± 0.8*	2.2 ± 0.7	2.4 ± 0.8	0.1	-0.2 to 0.5
FVC, l	3.0 ± 0.5	3.6 ± 0.8†	3.1 ± 1.1	3.4 ± 1.1*	0.3	-0.2 to 0.8
FVC_{supine}-FVC_{seated}, %dif	-29 ± 9	-23 ± 6	-24 ± 8	-18 ± 4	-12	-24 to 1
MVV, l	89 ± 44	108 ± 58*	78 ± 17	85 ± 18	8	-36 to 52
IC, l	2.6 ± 0.5	3.1 ± 0.8†	2.5 ± 0.9	3.1 ± 1.3*	-0.1	-0.6 to 0.5
TLC, l	5.4 ± 2.7	5.9 ± 2.6	5.2 ± 2.7	5.4 ± 2.8*	0.7	-2.6 to 4.0
RV, l	2.3 ± 1.2	2.3 ± 1.0	2.1 ± 1.0	2.1 ± 1.0	0.2	-1.3 to 1.7
TGV, l	3.0 ± 1.5	3.3 ± 1.5	2.6 ± 1.2	2.9 ± 1.4	0.3	-1.5 to 2.2
Respiratory muscle strength						
$P_{I,max}$, cmH_2O	79 ± 27	103 ± 19†	88 ± 23	84 ± 21	28†	13 to 43
$P_{E,max}$, cmH_2O	221 ± 96	219 ± 81	198 ± 103	190 ± 92	4	-44 to 53
$P_{es,sniff}$, cmH_2O	-53 ± 20	-66 ± 22‡	-52 ± 16	-54 ± 20	-10	-22 to 1
$P_{ga,sniff}$, cmH_2O	-4 ± 7	-6 ± 6	-3 ± 2	-5 ± 6	0	-6 to 7
$P_{di,sniff}$, cmH_2O	49 ± 17	60 ± 22†	53 ± 27	52 ± 28	12*	0 to 23
$P_{ga,cough}$, cmH_2O	208 ± 33	212 ± 26	202 ± 98	197 ± 96	9	-15 to 32
$P_{di,tw}$ affected, cmH_2O	1 ± 1	3 ± 3	3 ± 3	6 ± 4	0	-4 to 4
$P_{di,tw}$ unaffected, cmH_2O	9 ± 7	9 ± 5	8 ± 2	8 ± 5	3	-3 to 8
$P_{di,tw}$ bilateral, cmH_2O	10 ± 6	10 ± 7	9 ± 2	9 ± 3	-1	-6 to 4
Phrenic nerve conductance						
Latency, ms						
Affected	14.3 ± 7.7	13.4 ± 7.1	10.5 ± 5.9	10.2 ± 5.6	0.9	-3.4 to 5.3
Unaffected	8.6 ± 1.6	8.8 ± 1.8	8.0 ± 3.8	8.9 ± 4.1	-0.6	-5.0 to 3.8
Amplitude, μV						
Affected	143 ± 150	182 ± 163	100 ± 55	300 ± 217	-39	-255 to 178
Unaffected	495 ± 221	630 ± 200	450 ± 321	575 ± 472	35	-305 to 375

Values represent mean ± standard deviation or mean difference and the lower to upper limit of the 95% confidence interval.
TDI, transition dyspnea index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MVV, maximal voluntary ventilation; IC, inspiratory capacity, TLC, total lung capacity; RV, residual volume; TGV, thoracic gas volume; $P_{I,max}$, maximal inspiratory pressure; $P_{E,max}$, maximal expiratory pressure; $P_{es,sniff}$, esophageal pressure during a sniff maneuver; $P_{ga,sniff}$, gastric pressure during a sniff maneuver; $P_{di,sniff}$, transdiaphragmatic pressure during a sniff maneuver; $P_{ga,cough}$, gastric pressure during a cough maneuver; *, $p<0.05$; †, $p<0.01$; ‡, $p<0.001$.

Table 3. Exercise responses at iso-time during constant work-rate exercise pre- and post- training.

	IMT		Control		Between	
	pre-	*post-*	*pre-*	*post-*	*mean dif*	*95% CI*
Perceptual ratings						
Dyspnea, 0-10 scale	7.4 ± 2.0	5.1 ± 3.0*	7.4 ± 2.1	7.6 ± 2.4	-2.6	-5.7 to 0.6
Leg effort, 0-10 scale	7.1 ± 1.7	6.1 ± 2.9	5.2 ± 4.1	5.0 ± 3.8	-0.8	-3.2 to 1.6
Breathing pattern						
$\dot{V}_E$, l/min	52.4 ± 21.2	53.5 ± 22.6	69.0 ± 38.1	66.4 ± 36.5	3.8	-3.4 to 11.0
f_b, breaths/min	34 ± 12	30 ± 11	33 ± 18	28 ± 15	2	-6 to 10
V_T, l	1.6 ± 0.6	1.8 ± 0.9	2.2 ± 1.2	2.5 ± 1.4	0.0	-0.6 to 0.5
T_i/T_{tot}, %	45 ± 15	46 ± 15	45 ± 25	47 ± 26	0	-6 to 6
PEFR, l/s	2.6 ± 1.0	2.7 ± 1.1	3.4 ± 1.9	3.2 ± 1.7	0.2	-0.3 to 0.7
IC, l	2.3 ± 0.4	2.8 ± 0.7†	2.6 ± 0.9	2.9 ± 1.0*	0.3	-0.2 to 0.6
Respiratory mechanics						
P_{es}, cmH_2O	-21 ± 12	-15 ± 7*	-21 ± 11	-20 ± 11	6	-2 to 14
$P_{ga,av}$, cmH_2O	-14 ± 9	-9 ± 4*	-13 ± 7	-11 ± 7	4	-3 to 11
$P_{di,av}$, cmH_2O	7 ± 5	6 ± 4	8 ± 5	9 ± 7	-2	-6 to 2
$P_{ga,rise}$, cmH_2O	24 ± 17	16 ± 8*	21 ± 12	20 ± 14	-7	-19 to 5
EMG_{di}, %max	60 ± 25	54 ± 24	67 ± 9	60 ± 5	2	-7 to 11
EMG_{scm}, %max	27 ± 15	18 ± 9	21 ± 13	25 ± 12	-13*	-25 to -1
EMG_{sca}, %max	47 ± 26	35 ± 20	31 ± 18	35 ± 19	-16	-40 to 8
Respiratory muscle tissue oxygenation						
$\Delta StiO_{2,scm}$, %	-13.5 ± 8.5	-6.1 ± 4.2*	-5.6 ± 7.8	-11.4 ± 9.0	13.3*	0.2 ± 26.4
$\Delta StiO_{2,sca}$, %	-6.9 ± 2.8	-8.4 ± 5.8	-6.4 ± 5.9	-8.2 ± 10.6	0.3	-11.0 ± 11.6
$\Delta StiO_{2,abd}$, %	-7.1 ± 3.5	-3.4 ± 3.5*	-5.2 ± 1.2	-3.4 ± 3.1	1.2	-3.4 ± 5.8

Values represent mean ± standard deviation or mean difference and the lower to upper limit of the 95% confidence interval.

f_b, breathing frequency; V_T, tidal volume; $\dot{V}_E$, minute ventilation; Ti/Ttot, ratio of inspiratory time for one breathe to total time of one breath; PEFR, peak expiratory flow rate; IC, inspiratory capacity; $P_{es,av}$, average esophageal pressure during inspiration; $P_{ga,av}$, average gastric pressure during inspiration; $P_{di,av}$, average transdiaphragmatic pressure during inspiration; $P_{ga,rise}$, average increase in gastric pressure during expiration; EMG_{di}, electromyography of the diaphragm; EMG_{scm}, electromyography of the sternocleidomastoid; EMG_{sca}, electromyography of the scalene; $\Delta StiO_{2,scm}$, change in tissue oxygenation index of the sternocleidomastoid from rest to iso-time; $\Delta StiO_{2,sca}$, change tissue oxygenation index of the scalene from rest to iso-time; $\Delta StiO_{2,abd}$, change tissue oxygenation index of the rectus abdominus from rest to iso-time; *, $p<0.05$; †, $p<0.01$.

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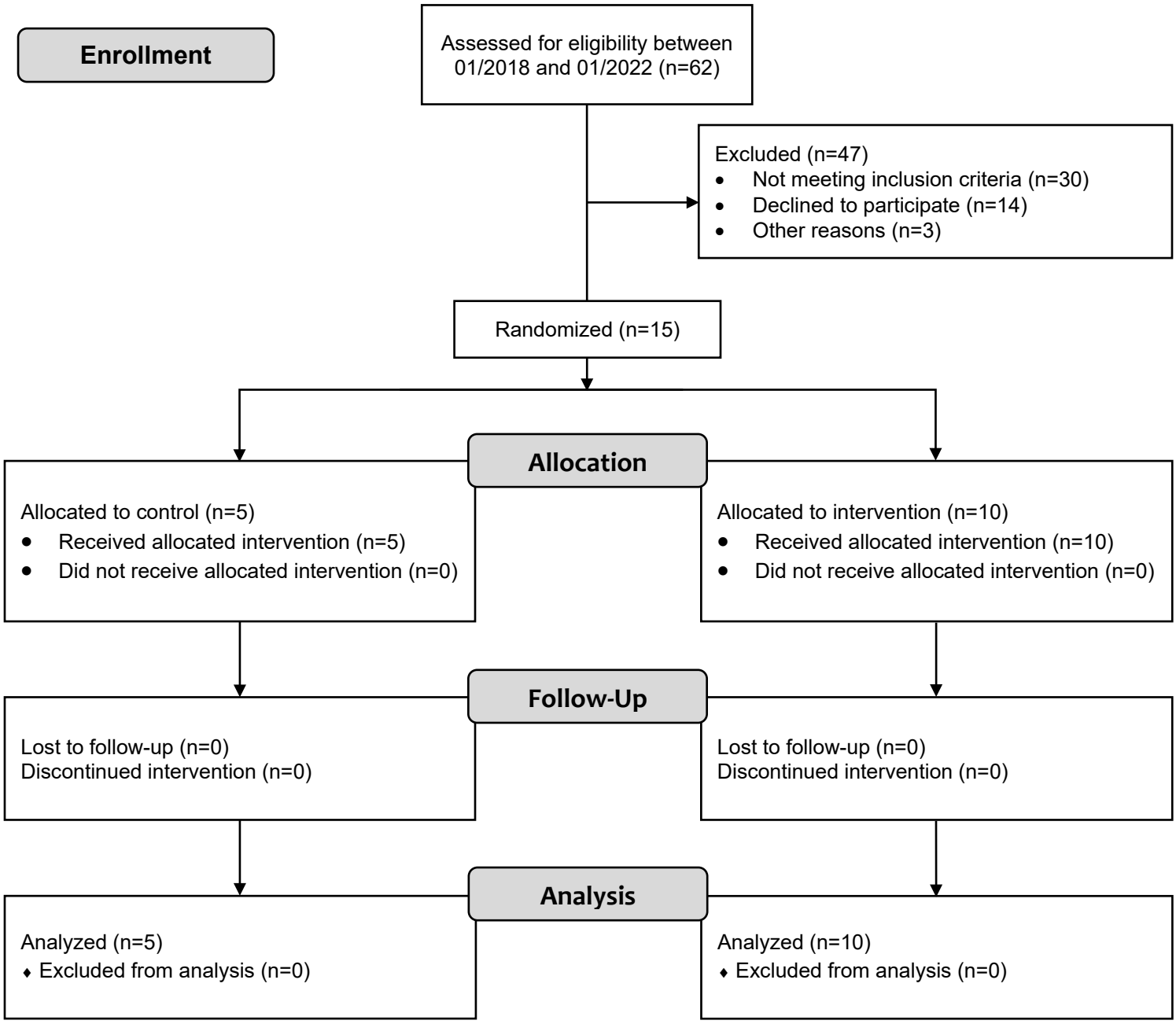
Figure 1. Enrollment and inclusion of study participants.



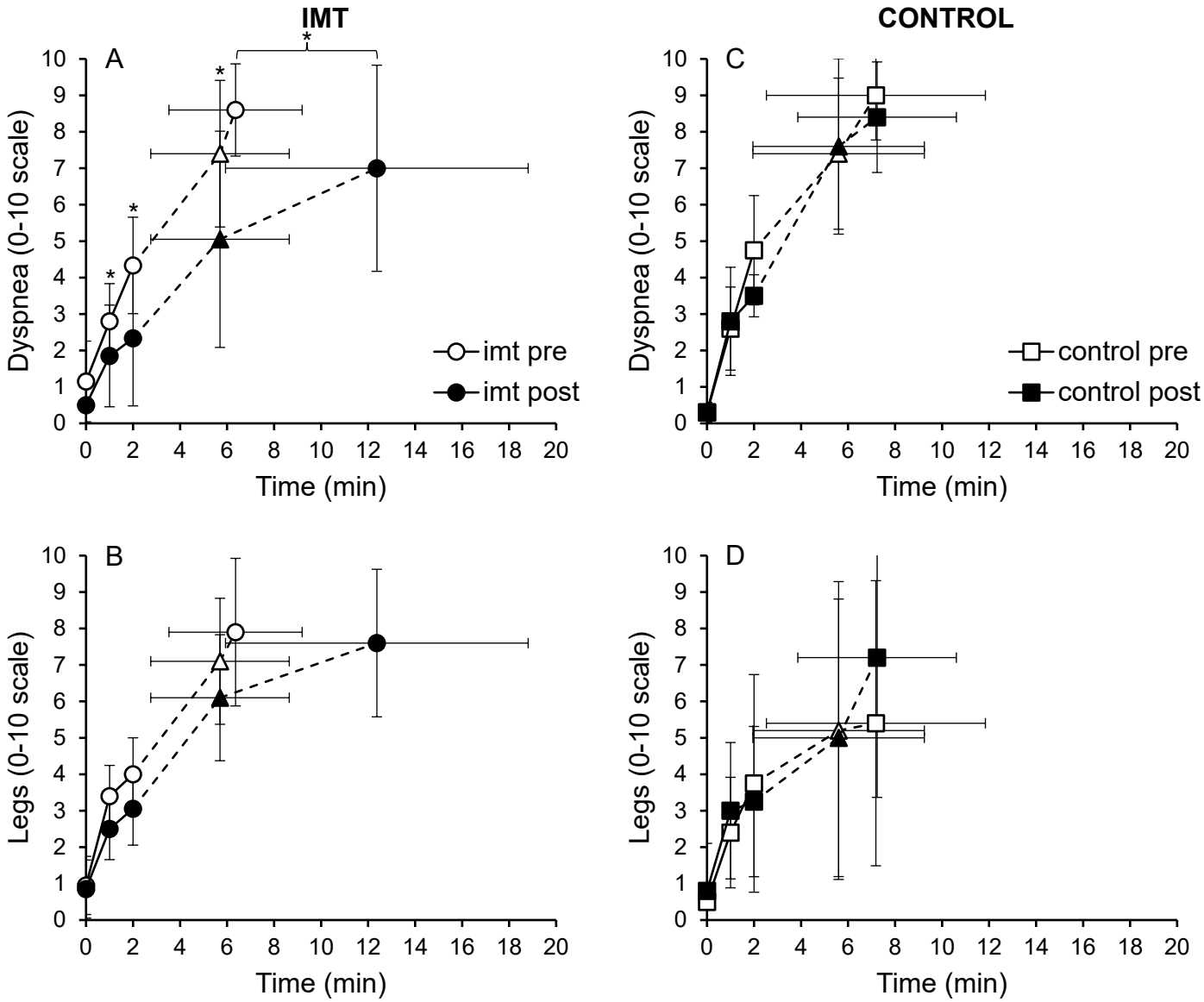


Figure 2. Perceptual ratings during constant work-rate exercise tests pre- and post- training for dyspnea (A, C) and leg fatigue (B, D).
Values represent mean ± standard deviation. Open symbols, pre-training; black symbols, post-training; triangles, iso-time; *, $p>0.05$.

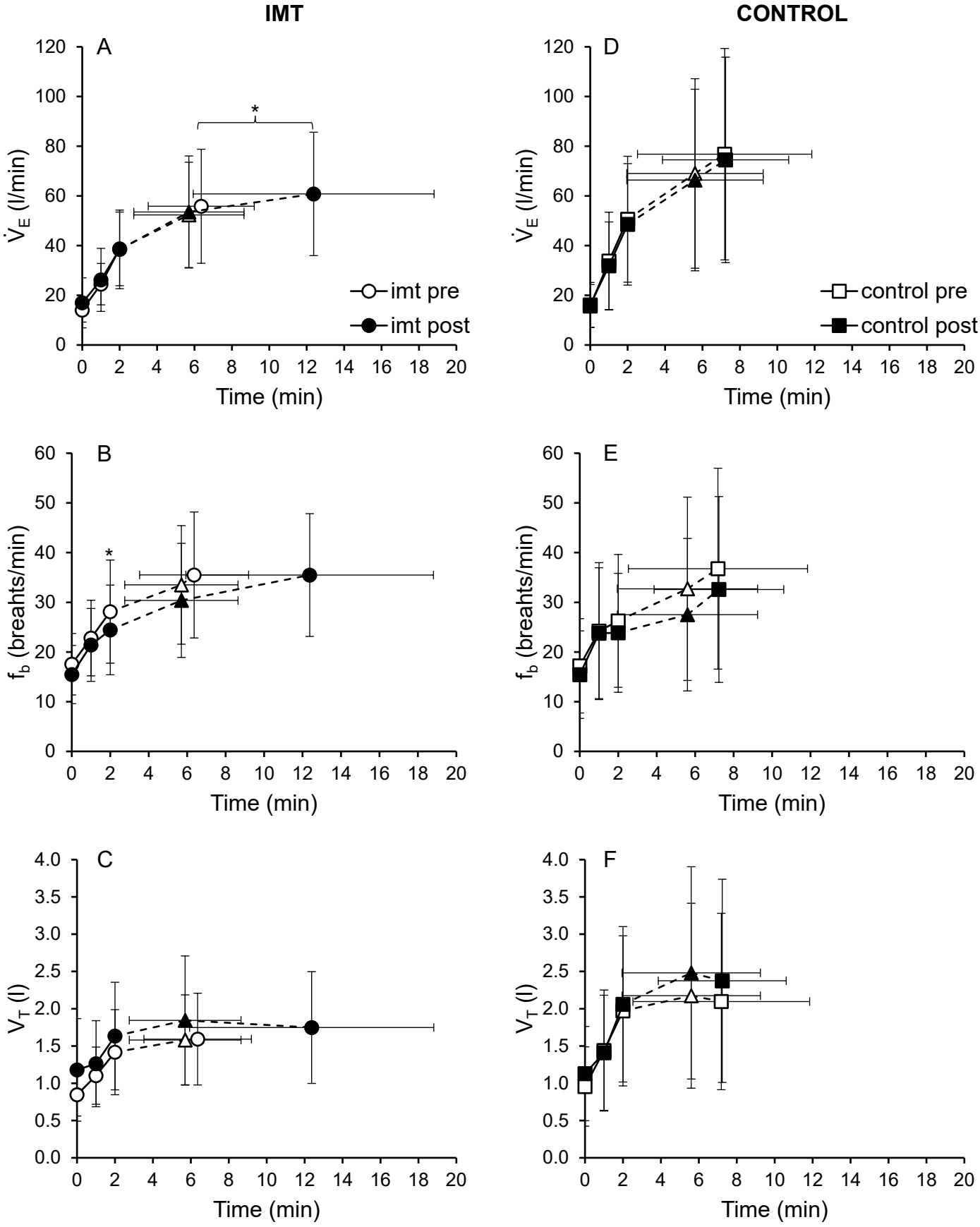


Figure 3. Ventilatory responses during constant work-rate exercise tests pre- and post- training. Values represent mean ± standard deviation. Open symbols, pre-training; black symbols, post-training; triangles, iso-time; $\dot{V}_E$, minute ventilation (A, E); f_b, breathing frequency (B, E); V_T, tidal volume (C, F); *, $p<0.05$.

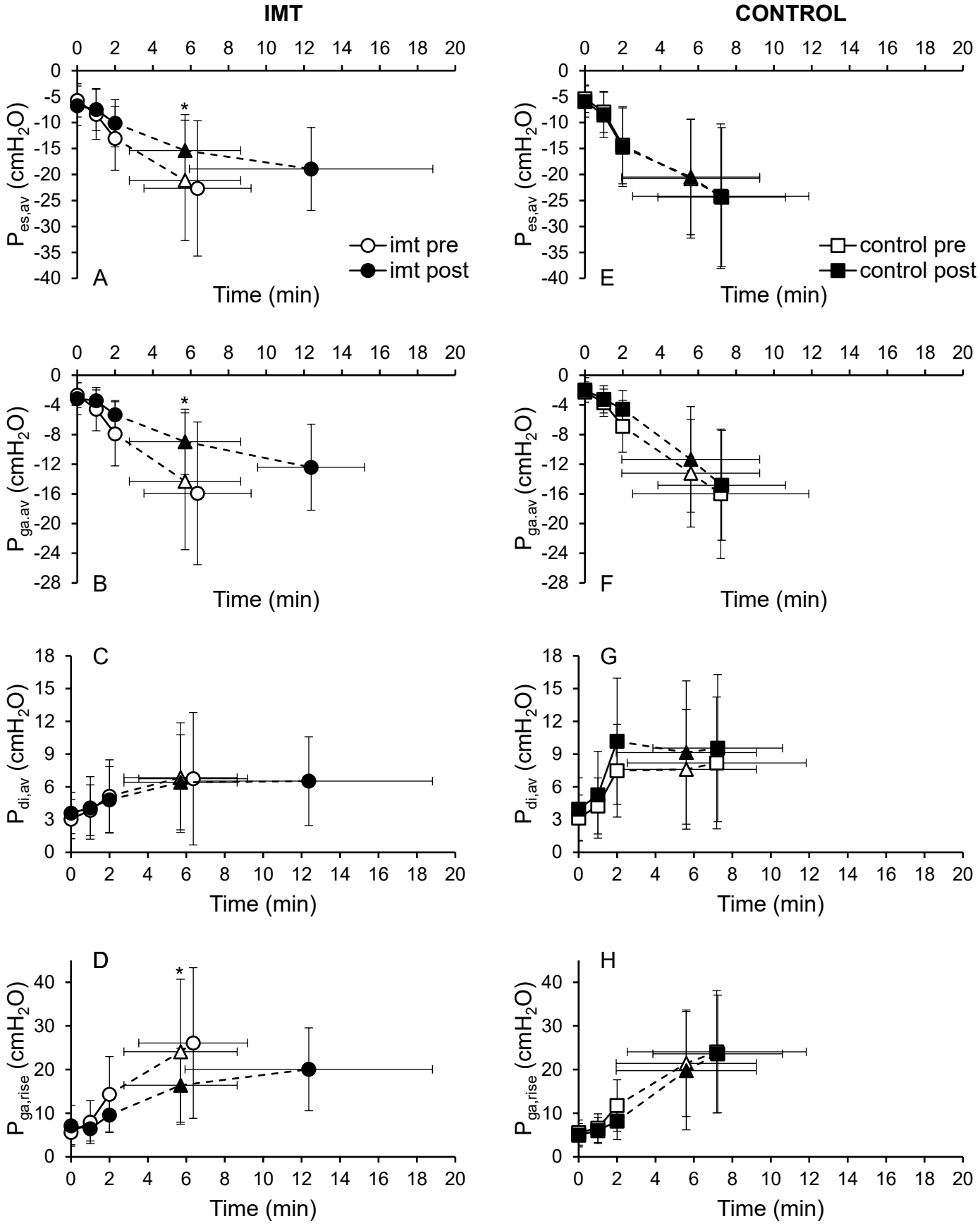


Figure 4. Respiratory pressures during constant work-rate exercise tests pre- and post- training. Values represent mean ± standard deviation. Open symbols, pre-training; black symbols, post-training; triangles, iso-time; $P_{es,av}$, average esophageal pressure during inspiration (A, E); $P_{ga,av}$, average gastric pressure during inspiration (B, F); $P_{di,av}$, average transdiaphragmatic pressure during inspiration (C, G); $P_{ga,rise}$, average increase in gastric pressure during expiration (D, H); *, $p<0.05$.

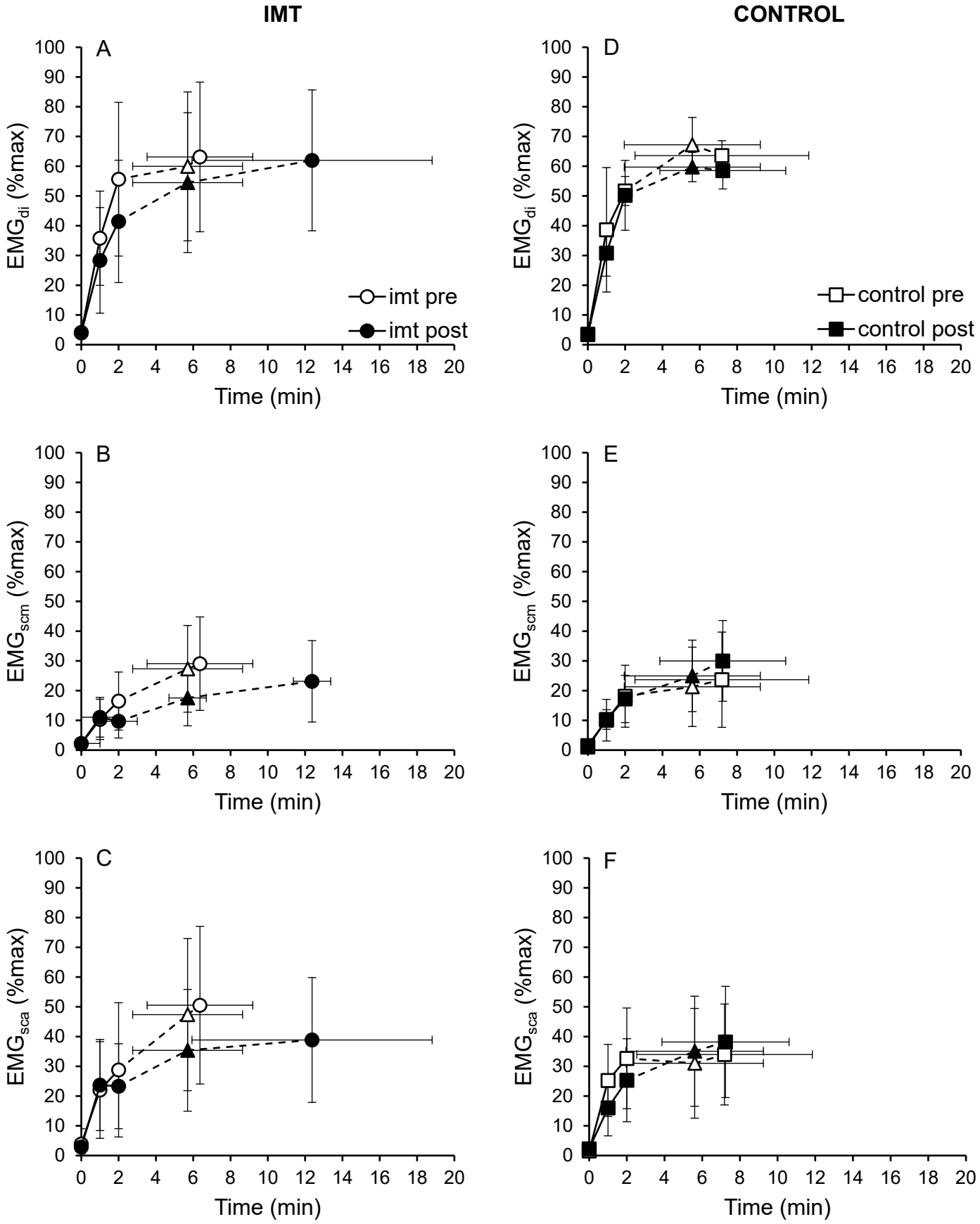


Figure 5. Respiratory muscle activity during constant work-rate exercise tests pre- and post- training. Values represent mean ± standard deviation. Open symbols, pre-training; black symbols, post-training; triangles, iso-time; EMG_{di}, electromyography of the diaphragm (A, D); EMG_{scm}, electromyography of the sternocleidomastoid (B, E); EMG_{sca}, electromyography of the scalene (C, F).