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

Michele R. Schaeffer [1], Zafeiris Louvaris[1], Antenor Rodrigues[1,2], Diego Poddighe [1], Ghislaine Gayan-Ramirez[3], Tin Gojevic[1], Linde Geerts[1], Elise Heyndrickx[1], Marine Van Hollebeke [1], Luc Janssens[1,4], Rik Gosselink [1], Dries Testelmans[3] and Daniel Langer [1,3]

[1]Department of Rehabilitation Sciences, Research Group for Rehabilitation in Internal Disorders, KU Leuven, Leuven, Belgium. [2]Keenan Centre for Biomedical Research, Li Ka Shing Knowledge Institute, Unity Health Toronto, Toronto, ON, Canada. [3]Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), Department of Chronic Diseases and Metabolism (CHROMETA), KU Leuven, Leuven, Belgium. [4]Department of Electrical Engineering, Faculty of Engineering Technology, KU Leuven, Leuven, Belgium.

Corresponding author: Daniel Langer (daniel.langer@kuleuven.be)

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Inspiratory muscle training is a well-tolerated conservative treatment option for people with unilateral diaphragm dysfunction that yields meaningful benefits in activity-related dyspnoea and exercise tolerance. https://bit.ly/3PhCS0a

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Abstract

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

Methods 15 people with UDD (73% male, 61±8 years) were randomised 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 twice per day). UDD was confirmed by phrenic nerve stimulation and persisted throughout the training period. Symptoms were assessed by the transitional dyspnoea index (TDI) and exercise tolerance by constant-load cycle tests performed pre- and post-training. Oesophageal (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.

Results The IMT group (from 45±6 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 *versus* 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) min, respectively). During exercise at iso-time, P_{es}, P_{ga} and EMG of the scalene muscles were reduced and the oxygen saturation indices of the scalene and abdominal muscles were higher post- *versus* pre-training only in the IMT group (all $p<0.05$).

Conclusion The effects of IMT on dyspnoea and exercise tolerance in UDD were not mediated by an 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 dyspnoea [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 dyspnoea 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 aetiology, 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 immobilised (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 a randomised controlled trial 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 nondiaphragmatic 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, randomised controlled trial was to comprehensively characterise the effects of a 6-month IMT programme on exertional dyspnoea, exercise tolerance and respiratory muscle function (both at rest and during exercise) in people with UDD. We hypothesised that IMT would improve exertional dyspnoea 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 dyspnoea index (BDI) score ⩽9, an elevated hemidiaphragm on a chest radiography, paradoxical movement during a sniff manoeuvre

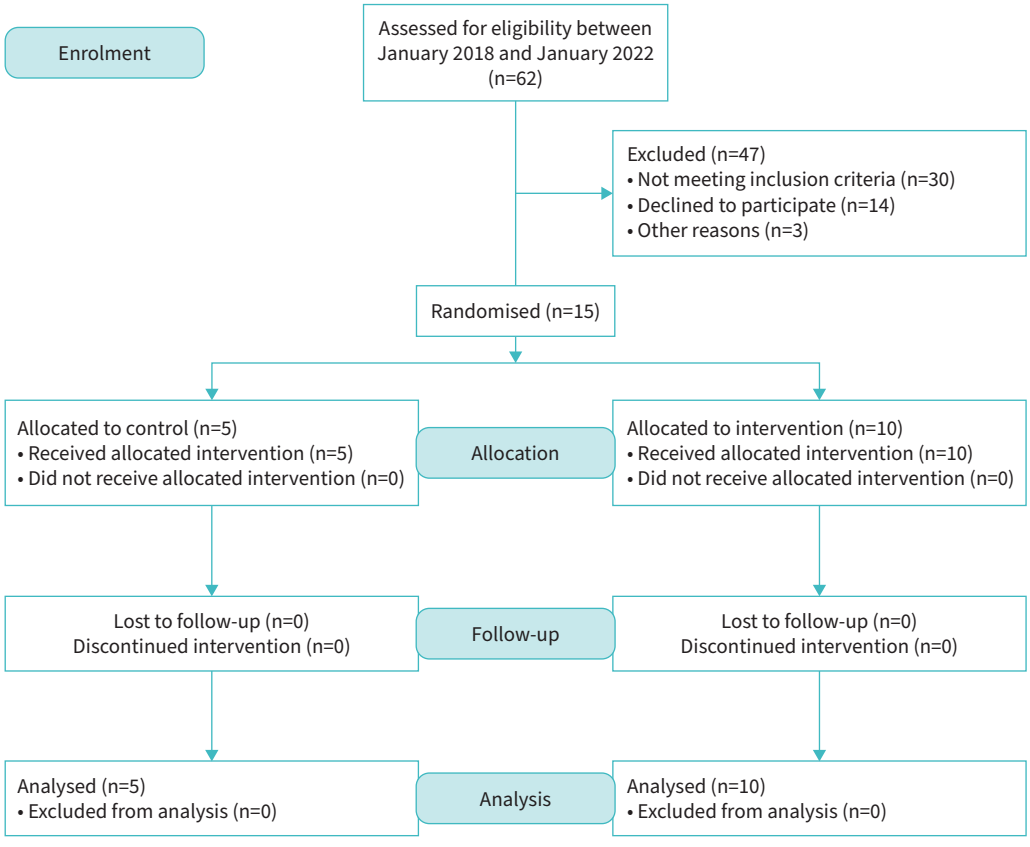

FIGURE 1 Enrolment and inclusion of study participants.

on a chest fluoroscopy and either a seated vital capacity (VC) <75% predicted, a reduction in forced vital capacity (FVC) >15% when supine *versus* seated or a maximal inspiratory pressure <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 dyspnoea, or severe orthopaedic 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 enrolment 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 randomisation and sequentially numbered opaque sealed envelopes [13]. Pre- and post-training assessments were made 2 days prior to starting the training programme and 2 days after cessation. Participants trained at home and kept a diary of the external load. During one supervised monthly session at the research centre, the patient's maximal inspiratory mouth pressure ($P_{I,max}$) was assessed and the training programme 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 programme consisting of two sessions daily for 6 months using an electronic tapered-flow resistive-loading 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 programme that was presented as an endurance IMT programme. 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 dyspnoea 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 dyspnoea 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 and a 10 s maximal voluntary ventilation (MVV) manoeuvre 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]. Oesophageal (P_{es}) and gastric (P_{ga}) pressures were measured using a dual-balloon oesophageal catheter (Guangzhou Yinghui Medical Equipment Ltd., PR China). The oesophageal and gastric balloons were filled with 0.8 and 1.4 mL of air, respectively. Maximal voluntary P_{es} and P_{ga} were recorded during sniff and cough manoeuvres, respectively. Maximal involuntary P_{es} and P_{ga} were also recorded during a supramaximal potentiated twitch elicited *via* magnetic phrenic nerve stimulation [19, 20]. Briefly, 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 (15 cmH_2O) [21].

Oesophageal, gastric and transdiaphragmatic tidal pressure swings during exercise were defined as the difference between the average pressures generated during inspiration and expiration ($P_{es,av}$, $P_{ga,av}$ and $P_{di,av}$, 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 amplitude and latency from the affected side were used, with the nonaffected side measured as a reference and compared to previously defined normal values (<300 mV and >8.1 ms, respectively) [23].

Exercise test protocol

Cardiopulmonary exercise tests (CPETs) were performed pre- and post-training on an electronically braked cycle ergometer (Ergoline 800s; Duomed). Incremental tests started at 20 Watts and increased by 20 Watts 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-min 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 2 min 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 s of exercise.

Participants rated the intensity of dyspnoea, 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 oesophageal 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, Germany). These data were expressed as peak during inspiration relative to maximal activation recorded during an IC manoeuvre.

Respiratory muscle oxygenation

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

Statistical analysis

Initial sample sizes of 16 (IMT) and eight (control) were estimated to provide 80% power to detect a 4 and 3 Borg unit reduction in dyspnoea, respectively, at iso-time with a standard deviation of 1 unit and an $\alpha<5\%$. [26]. Due to the coronavirus disease 2019 (COVID-19) pandemic, recruitment was limited and the trial was stopped before the intended sample size was reached. Exercise data were averaged over 1-min epochs. A two-way repeated measures ANOVA was used to identify pre-to-post-training within-group differences during exercise at standardised 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

10 participants were randomised 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) and neuralgic amyotrophy caused by hepatitis E (n=1). Time from symptom onset to study enrolment was 9±3 and 7±4 months in the IMT and control groups, respectively. A higher proportion of the control group were female relative to the IMT group. The IMT group had slightly better spirometry and diffusing capacity. Both groups experienced similar dyspnoea during activities of daily living. Peak work rate was within the normal range for both groups, but peak incremental dyspnoea 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 hypoxaemia 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 6-month training period. The

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, $kg \cdot m^{-2}$	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
T_{LCO}, % 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, $beats \cdot min^{-1}$	130±47	127±62
Heart rate, % predicted	84±30	77±36
V'_{O_2}, $L \cdot min^{-1}$	2.0±0.6	2.5±1.4
V'_{O_2}, % predicted	89±13	107±49
V'_{O_2}, $L \cdot min^{-1}$	2.1±0.6	2.8±1.5
V'_E, $L \cdot min^{-1}$	63.4±17.9	74.2±38.5
V'_E/MVV, %	74±32	98±49
V'_E/V'_{CO_2}	30.9±3.6	27.1±12.3
RER	1.07±0.10	1.09±0.49
O_2 pulse, $ml \cdot beat^{-1}$	15.4±7.3	19.8±9.3
S_{pO_2}, %	95±40	91±41
Dyspnoea, 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±SD. BMI: body mass index; BDI: baseline dyspnoea index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; FRC: functional residual capacity; IC: inspiratory capacity; K_{CO}: carbon monoxide transfer coefficient; MVV: maximal voluntary ventilation; O_2 pulse: oxygen consumed per heart beat; $P_{E,max}$: maximal expiratory pressure; $P_{I,max}$: maximal inspiratory pressure; RER: respiratory exchange ratio; RV: residual volume; S_{pO_2}: peripheral oxygen saturation; TLC: total lung capacity; T_{LCO}: transfer factor for carbon monoxide; V'_{CO_2}: carbon monoxide production; V'_E: minute ventilation; V'_E/V'_{CO_2}: ventilatory equivalent for carbon dioxide; V'_{O_2}: oxygen consumption.

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 1) phrenic nerve conductance, TDI, exercise tolerance, pulmonary function and respiratory muscle strength are summarised in table 2 and 2) exercise responses at iso-time in table 3.

Neither the latency nor 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.

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

Values represent mean±SD or mean difference and the lower to upper limit of the 95% confidence interval. dif.: difference; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; IC: inspiratory capacity; IMT: inspiratory muscle training; MVV: maximal voluntary ventilation; $P_{di,sniff}$: transdiaphragmatic pressure during a sniff manoeuvre; $P_{di,tw}$: transdiaphragmatic pressure during a supramaximal potentiated twitch; $P_{E,max}$: maximal expiratory pressure; $P_{es,sniff}$: oesophageal pressure during a sniff manoeuvre; $P_{ga,sniff}$: gastric pressure during a sniff manoeuvre; $P_{ga,cough}$: gastric pressure during a cough manoeuvre; $P_{I,max}$: maximal inspiratory pressure; RV: residual volume; TDI: transition dyspnoea index; TGV: thoracic gas volume; TLC: total lung capacity. *: p<0.05; **: p<0.01; ***: p<0.001.

TDI was different between groups (p=0.008), with a greater reduction in dyspnoea 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 s 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 the control group; the pre-to-post change in $P_{I,max}$ was also different between groups (p=0.001). Transdiaphragmatic pressure during a sniff manoeuvre ($P_{di,sniff}$) was higher post-training in the IMT group (p=0.01), but not in the control group. 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) nor gastric pressure during a cough manoeuvre 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.

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						
Dyspnoea, 0–10 scale	7.4±2.0	5.1±3.0*	7.4±2.1	7.6±2.4	−2.6	−5.7–0.6
Leg effort, 0–10 scale	7.1±1.7	6.1±2.9	5.2±4.1	5.0±3.8	−0.8	−3.2–1.6
Breathing pattern						
V'_E, L·min^{-1}	52.4±21.2	53.5±22.6	69.0±38.1	66.4±36.5	3.8	−3.4–11.0
f_B, breaths·min^{-1}	34±12	30±11	33±18	28±15	2	−6–10
V_T, L	1.6±0.6	1.8±0.9	2.2±1.2	2.5±1.4	0	−0.6–0.5
T_i/T_{tot}, %	45±15	46±15	45±25	47±26	0	−6–6
PEFR, L·s^{-1}	2.6±1.0	2.7±1.1	3.4±1.9	3.2±1.7	0.2	−0.3–0.7
IC, L	2.3±0.4	2.8±0.7**	2.6±0.9	2.9±1.0*	0.3	−0.2–0.6
Respiratory mechanics						
P_{es}, cmH_2O	−21±12	−15±7*	−21±11	−20±11	6	−2–14
$P_{ga,av}$, cmH_2O	−14±9	−9±4*	−13±7	−11±7	4	−3–11
$P_{di,av}$, cmH_2O	7±5	6±4	8±5	9±7	−2	−6–2
$P_{ga,rise}$, cmH_2O	24±17	16±8*	21±12	20±14	−7	−19–5
EMG_{di}, % max	60±25	54±24	67±9	60±5	2	−7–11
EMG_{scm}, % max	27±15	18±9	21±13	25±12	−13*	−25–−1
EMG_{sca}, % max	47±26	35±20	31±18	35±19	−16	−40–8
Respiratory muscle tissue oxygenation						
Δ $S_{tiO_2,scm}$, %	−13.5±8.5	−6.1±4.2*	−5.6±7.8	−11.4±9.0	13.3*	0.2±26.4
Δ $S_{tiO_2,sca}$, %	−6.9±2.8	−8.4±5.8	−6.4±5.9	−8.2±10.6	0.3	−11.0±11.6
Δ $S_{tiO_2,abd}$, %	−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. Δ $S_{tiO_2,abd}$: change in tissue oxygenation index of the rectus abdominus from rest to iso-time; Δ $S_{tiO_2,sca}$: change in tissue oxygenation index of the scalene from rest to iso-time; Δ $S_{tiO_2,scm}$: change in tissue oxygenation index of the sternocleidomastoid from rest to iso-time; f_B: breathing frequency; EMG_{di}: electromyography of the diaphragm; EMG_{sca}: electromyography of the scalene; EMG_{scm}: electromyography of the sternocleidomastoid; IC: inspiratory capacity; PEFR: peak expiratory flow rate; $P_{di,av}$: average transdiaphragmatic pressure during inspiration; $P_{es,av}$: average oesophageal pressure during inspiration; $P_{ga,av}$: average gastric pressure during inspiration; $P_{ga,rise}$, average increase in gastric pressure during expiration; T_i/T_{tot}: ratio of inspiratory time for one breath to total time of one breath; V'_E: minute ventilation; V_T: tidal volume. *: p<0.05; **: p<0.01.

There was a main effect of training on dyspnoea as well as an interaction between dyspnoea and exercise time in the IMT group, but not in the control group (figure 2). Dyspnoea was also lower at iso-time (p=0.02) and peak (p=0.04) post-training in the IMT group, but not in the control group (figure 2a and d). However, the pre-to-post change in dyspnoea 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 in the control group (figure 3b and e); this difference was only observed at a submaximal exercise time of 2 min. 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 in the control group (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 5a–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- *versus* 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.

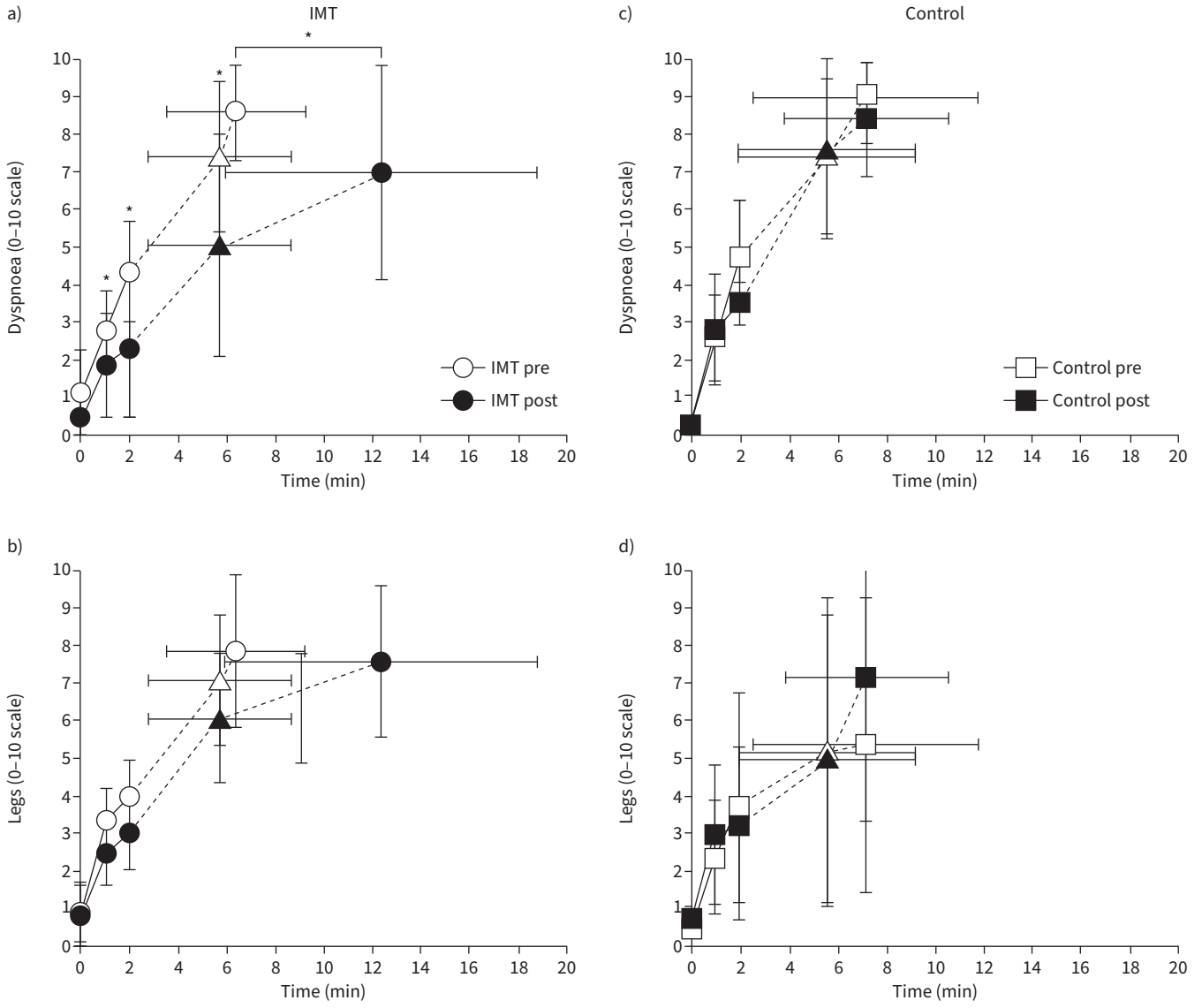

FIGURE 2 Perceptual ratings during constant work rate exercise tests pre- and post-training for a) and c) dyspnoea and b) and d) leg fatigue. Values represent mean±SD. Open symbols: pre-training; black symbols: post-training; triangles: iso-time. *: p>0.05.

At iso-time, the change from rest in oxygen saturation (S_{tiO_2}) of the sternocleidomastoid and abdominal muscles were significantly lower post *versus* pre-training only in the IMT group (p=0.03 and 0.01, respectively), with the change in S_{tiO_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 dyspnoea 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 dyspnoea compared to the control group. 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

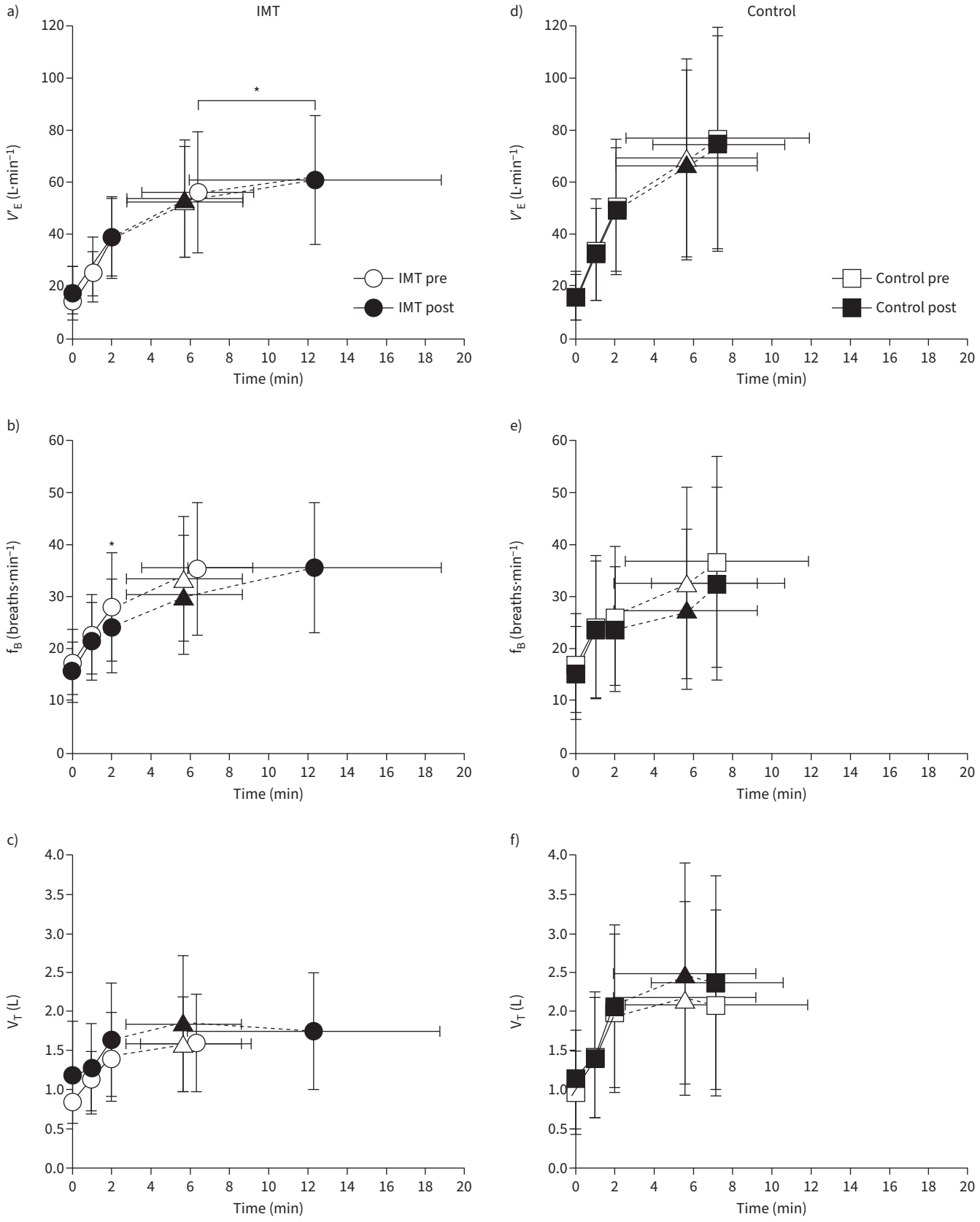

FIGURE 3 Ventilatory responses during constant work rate exercise tests pre- and post-training. Values represent mean±SD. Open symbols: pre-training; black symbols: post-training; triangles: iso-time; f_B: breathing frequency; V'_E: minute ventilation; V_T: tidal volume. *: p<0.05.

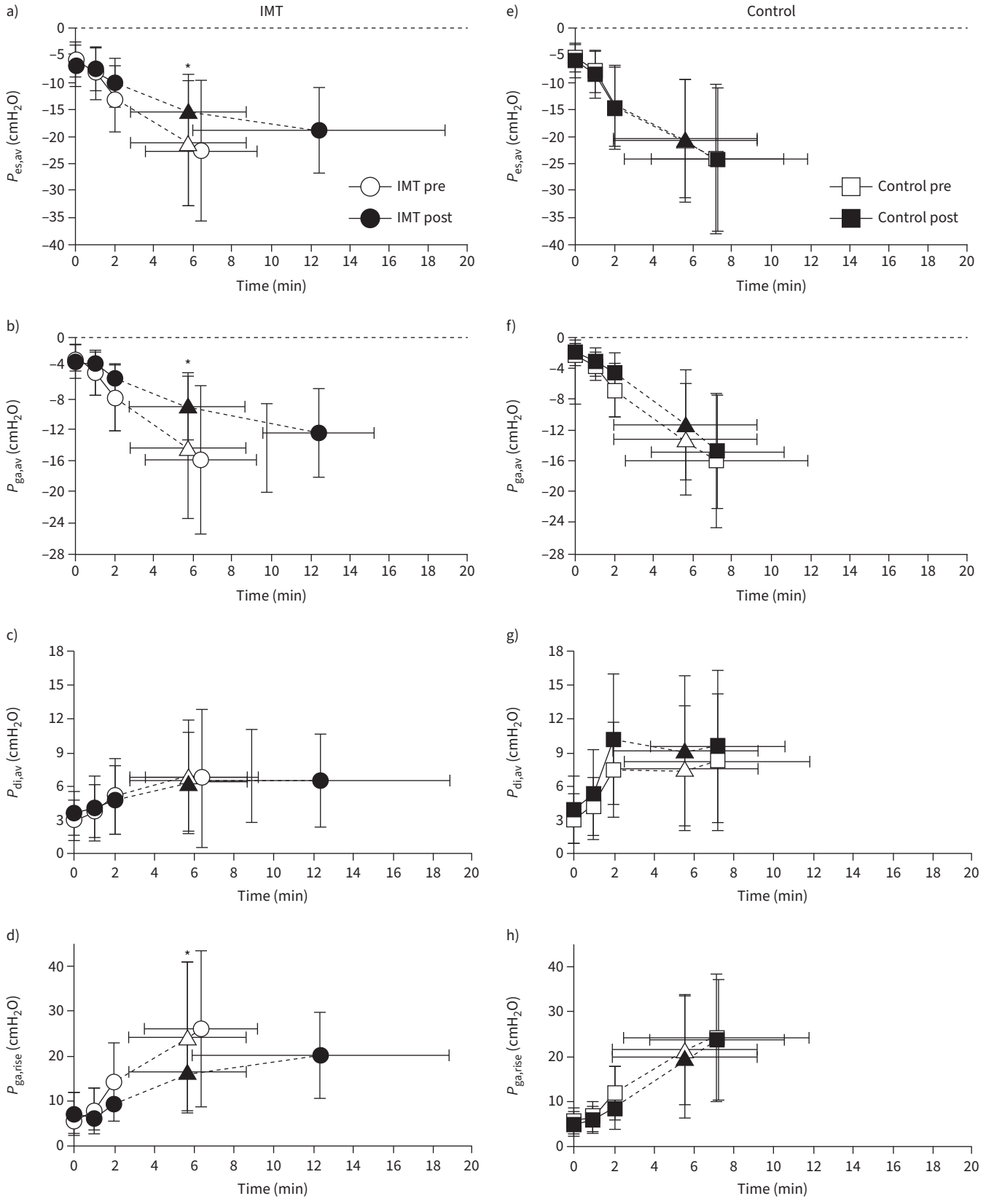

FIGURE 4 Respiratory pressures during constant work rate exercise tests pre- and post-training. Values represent mean±SD. Open symbols: pre-training; black symbols: post-training; triangles: iso-time; $P_{di,av}$: average transdiaphragmatic pressure during inspiration; $P_{es,av}$: average oesophageal pressure during inspiration; $P_{ga,av}$: average gastric pressure during inspiration; $P_{ga,rise}$: average increase in gastric pressure during expiration. *: p<0.05.

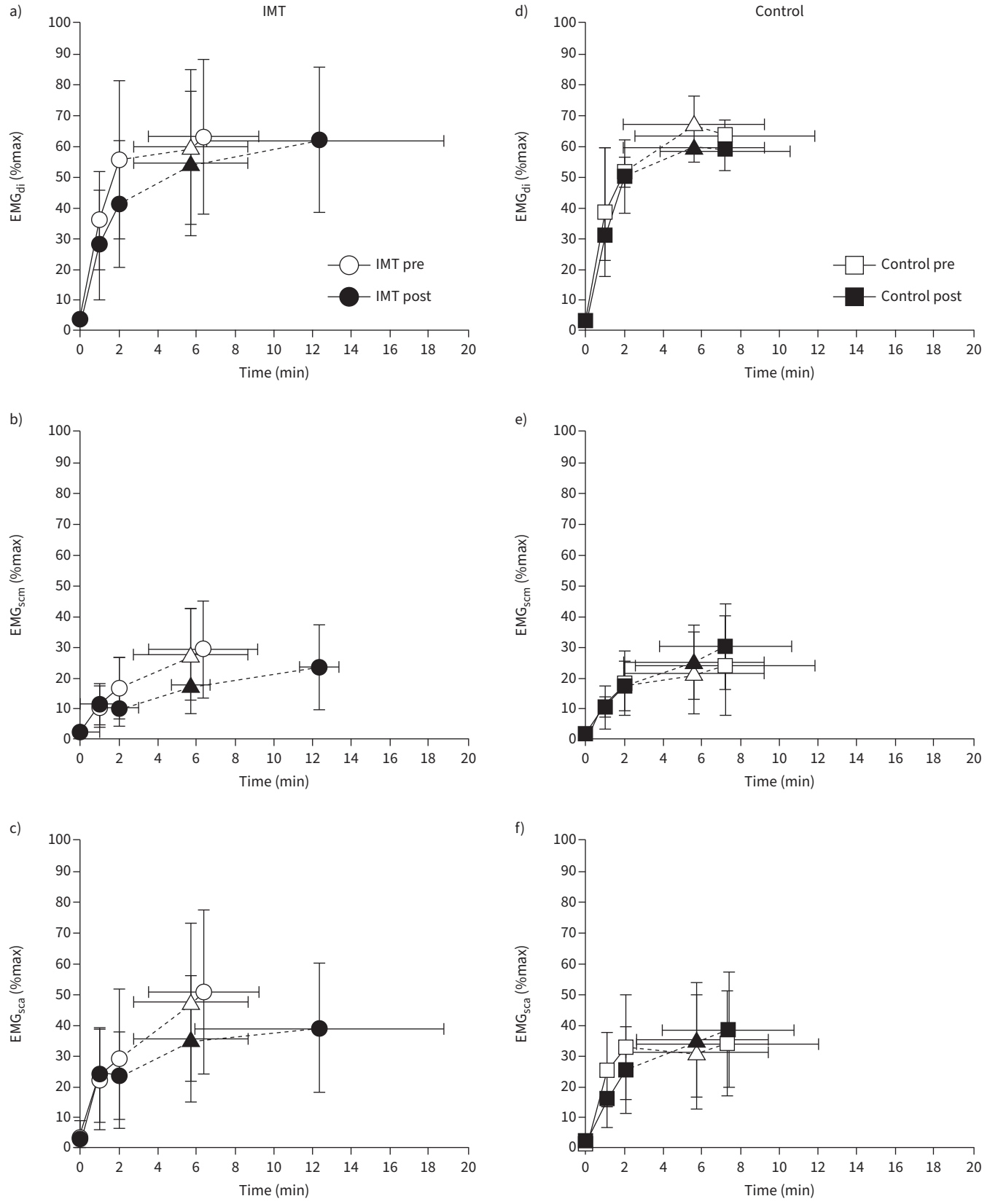

FIGURE 5 Respiratory muscle activity during constant work rate exercise tests pre- and post-training. Values represent mean±SD. Open symbols: pre-training; black symbols: post-training; triangles: iso-time; EMG_{di}: electromyography of the diaphragm; EMG_{sca}: electromyography of the scalene; EMG_{scm}: electromyography of the sternocleidomastoid.

IMT has a clinically relevant effect exceeding the natural evolution of function, including spontaneous recovery and related symptoms, observed in the control group. Additionally, dyspnoea ratings were lower at every time point during CPET post-training in the IMT group, but not in the control group, 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 in the control group, 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 *versus* improvement in diaphragm function [27]. The increase in transdiaphragmatic pressure during maximal inspiratory sniff manoeuvres in the IMT group is almost exclusively explained by an increase in oesophageal 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 manoeuvres 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 hyperpnoea post-training where the IMT group achieved a similar tidal volume with less negative oesophageal 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]. Visualisation 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-centre 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 6-month training window. However, there was equal probability in both study groups that was likely accounted for by randomisation. 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 dyspnoea 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 dyspnoea and improvement in exercise tolerance in people with UDD, likely *via* improvements in strength, coordination and/or oxygenation of the extra-diaphragmatic respiratory muscles.

Provenance: Submitted article, peer reviewed.

This study is registered at www.clinicaltrials.gov with identifier number NCT04563468. Individual deidentified participant data from this trial will not be shared.

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References

1 Puchongmart C, Nakornchai T, Leethotsarat K, *et al.* The incidence of diaphragmatic dysfunction in patients presenting with dyspnea in the emergency department. *J Ultrasound Med* 2023; 42: 1557–1566.
2 McCool FD, Manzoor K, Minami T. Disorders of the diaphragm. *Clin Chest Med* 2018; 39: 345–360.
3 Elefteriades J, Singh M, Tang P, *et al.* Unilateral diaphragm paralysis: etiology, impact, and natural history. *J Cardiovasc Surg* 2008; 49: 289–295.
4 Caleffi Pereira M, Cardenas LZ, Ferreira JG, *et al.* Unilateral diaphragmatic paralysis: inspiratory muscles, breathlessness and exercise capacity. *ERJ Open Res* 2021; 7: 00357-2019.
5 Efthimiou J, Butler J, Woodham C, *et al.* Diaphragm paralysis following cardiac surgery: role of phrenic nerve cold injury. *Ann Thorac Surg* 1991; 52: 1005–1008.
6 Hughes PD, Polkey MI, Moxham J, *et al.* Long-term recovery of diaphragm strength in neuralgic amyotrophy. *Eur Respir J* 1999; 13: 379–384.
7 Freeman RK, Van Woerkom J, Vyverberg A, *et al.* Long-term follow-up of the functional and physiologic results of diaphragm plication in adults with unilateral diaphragm paralysis. *Ann Thorac Surg* 2009; 88: 1112–1117.
8 Groth SS, Andrade RS. Diaphragm plication for eventration or paralysis: a review of the literature. *Ann Thorac Surg* 2010; 89: S2146–S2150.
9 Caleffi Pereira M, Dacha S, Testelmans D, *et al.* Assessing the effects of inspiratory muscle training in a patient with unilateral diaphragm dysfunction. *Breathe* 2019; 15: e90–e96.
10 Kodric M, Trevisan R, Torregiani C, *et al.* Inspiratory muscle training for diaphragm dysfunction after cardiac surgery. *J Thorac Cardiovasc Surg* 2013; 145: 819–823.
11 Petrovic M, Lahrmann H, Pohl W, *et al.* Idiopathic diaphragmatic paralysis–satisfactory improvement of inspiratory muscle function by inspiratory muscle training. *Respir Physiol Neurobiol* 2009; 165: 266–267.
12 Chatham K, Gelder CM, Lines TA, *et al.* Suspected statin-induced respiratory muscle myopathy during long-term inspiratory muscle training in a patient with diaphragmatic paralysis. *Phys Ther* 2009; 89: 257–266.
13 Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care* 2005; 20: 187–191.
14 Mahler DA, Witek TJ, Jr. The MCID of the transition dyspnea index is a total score of one unit. *COPD* 2005; 2: 99–103.
15 Graham BL, Steenbruggen I, Miller MR, *et al.* Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 2019; 200: e70–e88.
16 ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; 166: 518–624.
17 Hall GL, Filipow N, Ruppel G, *et al.* Official ERS technical standard: Global Lung Function Initiative reference values for static lung volumes in individuals of European ancestry. *Eur Respir J* 2021; 57: 2000289.
18 Laveneziana P, Albuquerque A, Aliverti A, *et al.* ERS statement on respiratory muscle testing at rest and during exercise. *Eur Respir J* 2019; 53: 1801214.
19 Polkey MI, Duguet A, Luo Y, *et al.* Anterior magnetic phrenic nerve stimulation: laboratory and clinical evaluation. *Intensive Care Med* 2000; 26: 1065–1075.

20 Mills GH, Kyroussis D, Hamnegard CH, *et al.* Unilateral magnetic stimulation of the phrenic nerve. *Thorax* 1995; 50: 1162–1172.
21 Steier J, Kaul S, Seymour J, *et al.* The value of multiple tests of respiratory muscle strength. *Thorax* 2007; 62: 975–980.
22 Gayan-Ramirez G, Gosselin N, Troosters T, *et al.* Functional recovery of diaphragm paralysis: a long-term follow-up study. *Respir Med* 2008; 102: 690–698.
23 Chen R, Collins S, Remtulla H, *et al.* Phrenic nerve conduction study in normal subjects. *Muscle Nerve* 1995; 18: 330–335.
24 Luo YM, Moxham J, Polkey MI. Diaphragm electromyography using an oesophageal catheter: current concepts. *Clin Sci* 2008; 115: 233–244.
25 Louvaris Z, Rodrigues A, Dacha S, *et al.* High-intensity exercise impairs extradiaphragmatic respiratory muscle perfusion in patients with COPD. *J Appl Physiol* 2021; 130: 325–341.
26 Laveneziana P, Webb KA, Ora J, *et al.* Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. *Am J Respir Crit Care Med* 2011; 184: 1367–1373.
27 Nava S, Ambrosino N, Crotti P, *et al.* Recruitment of some respiratory muscles during three maximal inspiratory manoeuvres. *Thorax* 1993; 48: 702–707.
28 LoMauro A, Aliverti A, Perchiazzi G, *et al.* Physiological changes and compensatory mechanisms by the action of respiratory muscles in a porcine model of phrenic nerve injury. *J Appl Physiol* 2021; 130: 813–826.
29 Macklem PT. Respiratory muscles: the vital pump. *Chest* 1980; 78: 753–758.
30 Boyle KG, Mitchell RA, Ramsook AH, *et al.* The effect of diaphragm fatigue on the multidimensional components of dyspnoea and diaphragm electromyography during exercise in healthy males. *J Physiol* 2020; 598: 3223–3237.
31 Dres M, Dube BP, Goligher E, *et al.* Usefulness of parasternal intercostal muscle ultrasound during weaning from mechanical ventilation. *Anesthesiology* 2020; 132: 1114–1125.
32 Parthasarathy S, Jubran A, Laghi F, *et al.* Sternomastoid, rib cage, and expiratory muscle activity during weaning failure. *J Appl Physiol* 2007; 103: 140–147.
33 Turner LA, Tecklenburg-Lund SL, Chapman R, *et al.* The effect of inspiratory muscle training on respiratory and limb locomotor muscle deoxygenation during exercise with resistive inspiratory loading. *Int J Sports Med* 2016; 37: 598–606.
34 Van Hollebeke M, Poddighe D, Clerckx B, *et al.* High-intensity inspiratory muscle training improves scalene and sternocleidomastoid muscle oxygenation parameters in patients with weaning difficulties: a randomized controlled trial. *Front Physiol* 2022; 13: 786575.
35 Louvaris Z, Vogiatzis I, Habazettl H, *et al.* Improvement in respiratory muscle O_2 delivery is associated with less dyspnoea during exercise in COPD. *Clin Respir J* 2018; 12: 1308–1310.
36 Doorduin J, Roesthuis LH, Jansen D, *et al.* Respiratory muscle effort during expiration in successful and failed weaning from mechanical ventilation. *Anesthesiology* 2018; 129: 490–501.
37 Laghi FA, Jr, Saad M, Shaikh H. Ultrasound and non-ultrasound imaging techniques in the assessment of diaphragmatic dysfunction. *BMC Pulm Med* 2021; 21: 85.