

1 Word Count Text: 1,422

2 **INSPIRATORY MUSCLE TRAINING IMPROVES BREATHING PATTERN DURING EXERCISE IN COPD**
3 **PATIENTS**

4 Running Head: Exercise breathing pattern after IMT

5 Noppawan Charususin, [PT, MSc]^{1,2,3}, Rik Gosselink, [PT, PhD]^{1,2}, Alison McConnell, [PhD]⁴, Heleen
6 Demeyer, [PT, MSc]^{1,2}, Marko Topalovic, [MSc]¹, Marc Decramer, [MD, PhD]¹ and Daniel Langer, [PT,
7 PhD]^{1,2}

8 Affiliations:

9 ¹ Respiratory Rehabilitation and Respiratory Division, University Hospital Leuven, Belgium.

10 ² Faculty of Kinesiology and Rehabilitation Sciences, KU Leuven, Leuven, Belgium.

11 ³ Department of Physical Therapy, Thammasat University, Pathumthani, Thailand

12 ⁴ Department of Human Sciences & Public Health, Faculty of Health and Social Sciences, Bournemouth
13 University, United Kingdom

14

15 Correspondence:

16 Dr. Daniel Langer: daniel.langer@faber.kuleuven.be.

17 Department of Rehabilitation Sciences, KU Leuven, Tervuursevest 101, 3001 Leuven, Belgium.

18

19 **Conflict of interest:** Dr McConnell acknowledges a beneficial interest in the POWERbreathe® inspiratory
20 muscle trainers in the form of a share of royalty income to the University of Birmingham and Brunel
21 University. She has also provided consultancy services to POWERbreathe International Ltd.

1 **Support statements:** Dr Langer is a postdoctoral fellow of Research Foundation Flanders. The sponsor had
2 no role in the design of the study, the collection and analysis of the data, or the preparation of the
3 manuscript.

4 **Key words:** COPD; inspiratory muscle training; pulmonary rehabilitation; breathing pattern; maximal
5 incremental cycle ergometry test

6 **Take home message**

7 The addition of IMT to a PR program for selected COPD patients resulted in changes in breathing pattern
8 during exercise.

1 **To the Editor:**

2 Dyspnoea is typically the main symptom limiting exercise capacity in patients with chronic obstructive
3 pulmonary disease (COPD) [1-3]. Exertional dyspnoea has been linked to dynamic hyperinflation (DH),
4 when lung expansion critically encroaches upon the inspiratory reserve volume (IRV) [4]. Consequently,
5 patients develop a rapid and shallow breathing pattern, which is energetically opposite to the pattern
6 required to minimise the work of breathing [5]. Furthermore, the restriction of tidal volume (V_T) expansion
7 has recently been linked to daily physical activity limitation [6].

8 Besides mechanical factors, the limitation on V_T expansion might also be related to an imbalance between
9 the load / capacity relationship of the inspiratory muscles. The inspiratory muscles are functionally
10 weakened by DH during exercise. Furthermore, they are also forced to contract at higher velocities, whilst
11 working against elevated elastic loads [7,8]. These factors might exacerbate restriction of V_T expansion
12 and exacerbate exertional dyspnoea.

13 Inspiratory muscle training (IMT) is applied in COPD patients during pulmonary rehabilitation (PR) to
14 improve inspiratory muscle function, exertional dyspnoea, and exercise tolerance [9,10]. Wanke et al.
15 previously studied the effects of mechanical threshold loading IMT (MTL-IMT) in addition to general
16 exercise training and observed additional improvements in exercise capacity and larger V_T expansion at
17 peak exercise in the IMT group [10]. We have reported recently that high intensity tapered flow resistive
18 loading IMT (TFRL-IMT) resulted in significantly larger increases in respiratory muscle strength and
19 endurance, as well as changes in breathing pattern during loaded breathing, compared with conventional
20 MTL-IMT [11]. We were led to speculate that the specific characteristics of TFRL-IMT might result in
21 beneficial changes in breathing pattern during whole body exercise [11].

1 We hypothesised that the addition of TRFL-IMT to a PR program would have the following effects: 1)
2 enhancement of inspiratory muscle function might result in improvements in V_T expansion, by providing
3 a training stimulus within the range of IRV, and 2) enhancement of the velocity of shortening of the
4 inspiratory muscles against high resistances might enable patients to shorten their inspiratory time and
5 leave more time for expiration.

6 This historically controlled study was approved by the University Hospital Leuven's Institutional Review
7 Board (Approval Number ML7489) and registered at www.clinicaltrials.gov (NCT02186340). Twenty-five
8 clinically stable COPD patients with inspiratory muscle weakness ($P_{I\max} < 100\%$ predicted) gave their
9 written informed consent, and were offered IMT during the final 8 weeks of a 12-week multidisciplinary
10 PR program. A historical control group including patients who participated in an *identical* PR program
11 without IMT was recruited from the PR database of the University Hospital Leuven. These patients were
12 individually matched to the participants of the combined intervention for the following baseline
13 characteristics upon entry into the program: age, gender, pulmonary function, $P_{I\max}$, and exercise
14 capacity.

15 Patients performed daily high intensity TRFL-IMT (POWERbreathe® KH1, HaB International Ltd., Southam,
16 UK) consisting of two cycles of 30 breaths at the highest tolerable intensity according to a recently
17 published protocol [11].

18 All repeated measures analyses of changes in breathing pattern at different levels of ventilation were
19 performed in SAS, release 9.3. Levels of ventilation were defined as percentages of baseline maximal
20 ventilation ($V_{E\max}$) (40, 60, 80, and 100% of peak ventilation of the baseline cycling test). Outcomes

1 between groups were compared with a mixed models analysis. The Tukey method was used to correct
2 post-hoc comparisons between groups at cut-off levels of V_E for multiple testing.

3 **Changes in inspiratory muscle function.** Patients in the IMT group exhibited significantly larger
4 improvements in $P_{I_{max}}$ in comparison to the control group ($+29\pm 15$ vs. $+1\pm 12$ cmH₂O, $p<0.001$). The IMT
5 group completed $94\pm 5\%$ of sessions (based on data stored by the TFRL devices) and increased their
6 training load from $45\pm 2\%$ to $81\pm 4\%$ of their baseline $P_{I_{max}}$ ($p<0.001$).

7 **The effects of adjunctive IMT on exercise capacity and dyspnoea sensation.** A significantly larger increase
8 in peak exercise cycle capacity was observed in the IMT group, which is consistent with a previous study
9 [10]. Significantly higher levels of peak V_E ($+3\pm 6$ vs. -2 ± 7 L/min, $p=0.013$) and peak work rate ($+13\pm 14$ vs.
10 $+2\pm 12$ Watts, $p=0.004$) were obtained in the IMT group, but dyspnoea intensity at peak exercise was not
11 different between groups.

12 **The effects of adjunctive IMT on breathing pattern at identical levels of ventilation (iso- V_E).** At 80% and
13 100% of baseline $V_{E_{max}}$, significant differences in the interaction effects of group*ventilation were found
14 between groups for both V_T and f_R , between post-intervention and baseline ($p=0.047$ and $p=0.004$,
15 respectively) (Figure 1). However, the deeper and slower breathing pattern adopted only by participants
16 in the TFRL-IMT group was not accompanied by changes in inspiratory flow rates. The V_T/T_i remained
17 constant, with inspiratory (T_i) and expiratory (T_e) time increasing proportionately, leaving duty cycle
18 (T_i/T_{tot}) unchanged.

19 In the IMT group, there were significant correlations between changes in $P_{I_{max}}$ and changes in breathing
20 pattern (V_T ($r=0.448$, $p=0.001$), and f_R ($r= -0.417$, $p=0.003$)) at 80% of baseline $V_{E_{max}}$. This supports a

1 possible causal link between inspiratory muscle weakness and breathing pattern. In contrast with Wanke
2 et al. (1994) who observed changes in breathing pattern only at at peak exercise, we also observed
3 changes in breathing pattern at iso-ventilation [10]. The larger improvements in breathing pattern that
4 we found at iso-ventilation after IMT, did not however translate into larger improvements in breathing
5 pattern at peak exercise. Improvements in peak exercise capacity were comparable between studies.

6 Our second hypothesis was that patients would be able to perform faster contractions with their
7 inspiratory muscles during exercise; resulting in reductions in inspiratory time and leaving more time for
8 expiration, which in turn might ameliorate DH. However, the previously observed increased capacity to
9 perform fast contractions, [11] did not result in significant between-group changes in inspiratory flow
10 rates during exercise. This is consistent with previous data from Petrovic et al [13], who reported a
11 similarly small *within* group difference (5% as compared to 7% in our study) in V_T/T_i , which also did not
12 result in a significant *between* group difference after 8 weeks of inspiratory flow resistive loading (IFRL)
13 [13]. It is possible that longer training durations are needed to achieve significance. Another possibility
14 might be that specific breathing retraining strategies, during exercise, in combination with IMT might be
15 needed to teach patients how to use their increased capacity to perform faster inhalations during exercise.
16 Collins et al. (2008) previously observed that the combination of ventilation-feedback (VF) and exercise
17 training changed T_i/T_{tot} , decreased exercise-induced DH, and increased exercise tolerance [14].

18 Based on the observed differences in results and differences in training methods in our study in
19 comparison with the studies of Wanke et al (1994) [10], and Petrovic et al (2012) [13], a prospective study
20 would be worthwhile comparing the specific effects of each training method on exercise capacity and
21 breathing pattern head-to-head. In contrast to Wanke et al. who used maximal isometric contractions at

1 RV and high intensity MTL training [10], both TFRL-IMT, and IFRL-IMT (used by us and by Petrovic and
2 colleagues, respectively) allow end-inspiratory lung volume (EILV) to enter the IRV, and permit higher
3 inspiratory flow rates (i.e. higher shortening velocities) at high training intensities (i.e. resistances
4 $>50\%P_{I\max}$) [11, 13]. According to muscle length (lung volume) and pressure-flow specificity of IMT, this
5 should provide a training stimulus that is more specific to the operating range and the contraction pattern
6 of the inspiratory muscles during exercise, since the largest improvements in function should occur at the
7 volumes over which IMT is performed and larger increases in inspiratory flow are expected with high
8 velocity training [12, 15].

9 The main limitation of this study is the study design. Since a historical group of patients who participated
10 in an identical PR program served as control subjects, a prospective randomised controlled study design
11 will be needed to corroborate our findings. It also remains uncertain whether our observed effects on
12 breathing pattern occurred due to a reduction in mechanical restriction on V_T expansion (reaching higher
13 EILV) or due to a reduction in DH (reducing EELV). However, it seems most likely that the higher V_T would
14 be due to higher EILV, and not to a lowering EELV, because T_i increased in proportion to T_e and T_i/T_{tot}
15 remained unchanged; however, more elaborate measurement techniques will be required to evaluate the
16 effects of IMT on operating lung volumes.

17 In conclusion, the addition of IMT to a PR program in COPD patients with inspiratory muscle weakness
18 resulted in a deeper and slower breathing pattern during exercise. Patients could achieve significantly
19 higher peak work rate and exercise ventilation without increasing dyspnea sensation. Our findings provide
20 encouraging preliminary evidence supporting an additional benefit of adjunctive TFRL-IMT on exercise
21 breathing pattern.

1 **Acknowledgements:**

2 *Author contributions:* DL had full access to all of the data in the study and takes responsibility for the
3 integrity of the data and the accuracy of the data analysis. DL and RG contributed substantially to the
4 study design. DL, NC and HD provided data collection. DL, NC, MT and contributed to the data analysis
5 and interpretation. DL, RG, and NC contributed to the writing of the manuscript. RG, AKM, and MD
6 contributed to the critical review of the manuscript.

7 *Other contributions:* The authors would like to acknowledge the physiotherapists V. Barbier, I. Muylaert,
8 and I. Coosemans for performing the pulmonary rehabilitation program and all measurements of included
9 patients as blinded outcome assessors. We would also like to thank Dr Hans Scheers from the Lung
10 Toxicology and Epidemiology Research Unit at the KU Leuven for providing statistical advice. Regarding
11 the access to the University Hospital Leuven rehabilitation database, we would like to thank Geert Celis
12 from Lung function Department, the University Hospitals Gasthuisberg (Leuven, Belgium).

References

- 1
2
3 (1) Vestbo J, Hurd SS, Agusti AG *et al.* Global strategy for the diagnosis, management, and prevention
4 of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*
5 2013; 187: 347-65.
- 6 (2) Parshall MB, Schwartzstein RM, Adams L *et al.* An official American Thoracic Society statement:
7 update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*
8 2012; 185: 435-52.
- 9 (3) Casaburi R, Rennard SI. Exercise limitation in chronic obstructive pulmonary disease. The
10 O'donnell threshold. *Am J Respir Crit Care Med* 2015; 191: 873-5.
- 11 (4) O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation. The
12 role of lung hyperinflation. *Am Rev Respir Dis* 1993; 148: 1351-7.
- 13 (5) Macklem PT. Therapeutic implications of the pathophysiology of COPD. *Eur Respir J* 2010; 35: 676-
14 80.
- 15 (6) Kortianou EA, Aliverti A, Louvaris Z *et al.* Limitation in tidal volume expansion partially determines
16 the intensity of physical activity in COPD. *J Appl Physiol* 2015; 118: 107-14.
- 17 (7) Langer D, Ciavaglia CE, Neder JA, Webb KA, O'Donnell DE. Lung hyperinflation in chronic
18 obstructive pulmonary disease: mechanisms, clinical implications and treatment. *Expert Rev*
19 *Respir Med* 2014; 8: 731-49.
- 20 (8) O'Donnell DE, Bertley JC, Chau LK, Webb KA. Qualitative aspects of exertional breathlessness in
21 chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med* 1997; 155:
22 109-15.
- 23 (9) Gosselink R, De Vos J, van den Heuvel SP *et al.* Impact of inspiratory muscle training in patients
24 with COPD: what is the evidence? *Eur Respir J* 2011; 37: 416-25.
- 25 (10) Wanke T, Formanek D, Lahrman H *et al.* Effects of combined inspiratory muscle and cycle
26 ergometer training on exercise performance in patients with COPD. *Eur Respir J* 1994; 7: 2205-11.
- 27 (11) Langer D, Charususin N, Jacome C *et al.* Efficacy of a novel method for inspiratory muscle training
28 in people with chronic obstructive pulmonary disease. *Phys Ther* 2015.
- 29 (12) Tzelepis GE, Vega DL, Cohen ME, McCool FD. Lung volume specificity of inspiratory muscle
30 training. *J Appl Physiol* 1994; 77: 789-94.

- 1 (13) Petrovic M, Reiter M, Zipko H, Pohl W, Wanke T. Effects of inspiratory muscle training on dynamic
2 hyperinflation in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 797-805.
- 3 (14) Collins EG, Langbein WE, Fehr L *et al.* Can ventilation-feedback training augment exercise
4 tolerance in patients with chronic obstructive pulmonary disease? *Am J Respir Crit Care Med*
5 2008; 177: 844-52.
- 6
7 (15) Tzelepis GE, Vega DL, Cohen ME, Fulambarker AM, Patel KK, McCool FD. Pressure-flow
8 specificity of inspiratory muscle training. *J Appl Physiol* 1994; 77: 795-801.
9

1 **Figure legends**

2 **Figure 1:** Changes in tidal volume (V_T) and breathing frequency (f_R) at the comparable percentages of baseline $V_{E_{max}}$
3 (40, 60, 80, 100 and peak ventilation) at baseline and after training in the IMT group (1A and 1B) and the control
4 group (2A and 2B). * $p < 0.05$ (baseline vs week 8) based on post-hoc tests from mixed model analysis, values
5 represented as mean \pm SEM.