Inspiratory muscle training improves breathing pattern during exercise in COPD patients

To the Editor:

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

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

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

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

This historically controlled study was approved by the University Hospital Leuven's Institutional Review Board (Approval Number ML7489) and registered at www.clinicaltrials.gov (NCT02186340). 25 clinically stable COPD patients with inspiratory muscle weakness (maximal inspiratory pressure (P_{Imax} <100% predicted) gave their written informed consent, and were offered IMT during the final 8 weeks of a 12-week multidisciplinary PR programme. A historical control group including patients who participated in an *identical* PR programme without IMT was recruited from the PR database of the University Hospital Leuven. These patients were individually matched to the participants of the combined intervention for the following baseline characteristics upon entry into the programme: age, sex, pulmonary function, P_{Imax}, and exercise capacity.

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

All repeated measures analyses of changes in breathing pattern at different levels of ventilation were performed in SAS 9.3 Software (SAS, Cary, NC, USA). Levels of ventilation were defined as percentages of baseline maximal ventilation (V'_{Emax}) (40, 60, 80, and 100% of peak ventilation of the baseline cycling test). Outcomes between groups were compared with a mixed models analysis. The Tukey method was used to correct *post hoc* comparisons between groups at cut-off levels of minute ventilation (V'_E) for multiple testing.

Patients in the IMT group exhibited significantly larger improvements in P_{Imax} in comparison to the control group (29±15 *versus* 1±12 cmH$_2$O, p<0.001). The IMT group completed 94±5% of sessions (based on data stored by the TFRL devices) and increased their training load from 45±2% to 81±4% of their baseline P_{Imax} (p<0.001).

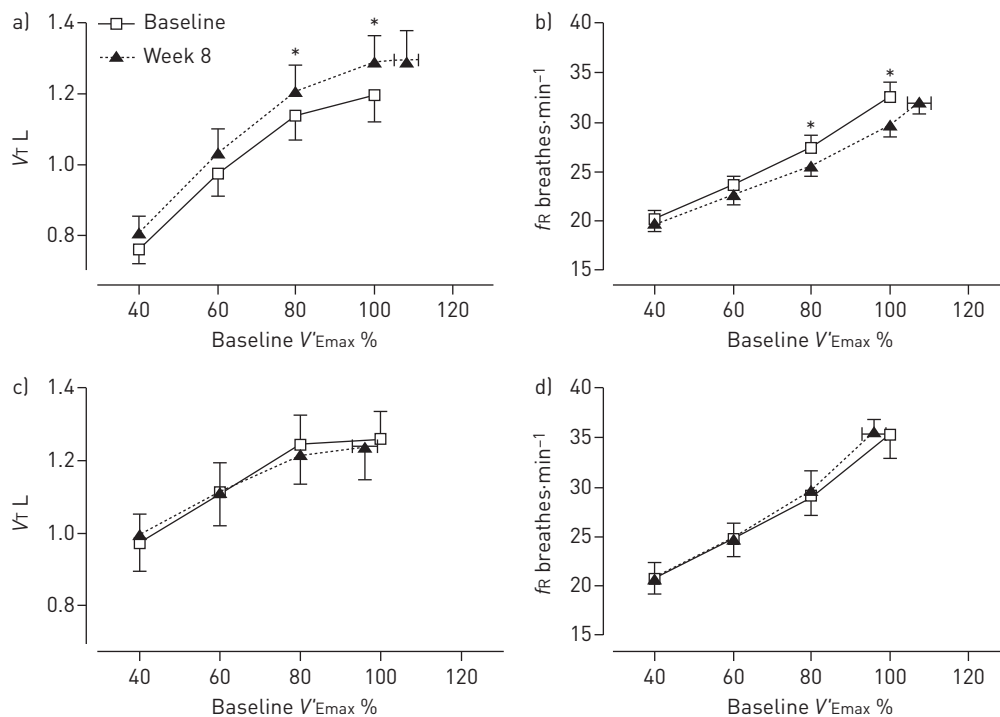FIGURE 1 Changes in tidal volume (V_T) and respiratory frequency (f_R) at comparable percentages of baseline maximal ventilation (V'_{Emax}) (40, 60, 80, 100 and peak ventilation) at baseline and after training in a) and b) the inspiratory muscle training group and c) and d) the control group. *: p<0.05 (baseline *versus* week 8) based on *post hoc* tests from mixed model analysis, values represented as mean±SEM.

A significantly larger increase in peak exercise cycle capacity was observed in the IMT group, which is consistent with a previous study [10]. Significantly higher levels of peak V'_E (3±6 *versus* −2±7 L·min⁻¹, p=0.013) and peak work rate (13±14 *versus* 2±12 W, p=0.004) were obtained in the IMT group, but dyspnoea intensity at peak exercise was not different between groups.

At 80% and 100% of baseline V'_{Emax} significant differences in the interaction effects of group by ventilation interaction were found, between groups for both V_T and f_R, between post intervention and baseline (p=0.047 and p=0.004, respectively) (figure 1). However, the deeper and slower breathing pattern adopted only by participants in the TFRL-IMT group was not accompanied by changes in inspiratory flow rates. The V_T/inspiratory time (t_I) remained constant, with t_I and expiratory time (t_E) time increasing proportionately, leaving duty cycle (t_I/period of respiratory cycle (t_{TOT})) unchanged.

In the IMT group, there were significant correlations between changes in P_{Imax} and changes in breathing pattern (V_T (r=0.448, p=0.001), and f_R (r=−0.417, p=0.003)) at 80% of baseline V'_{Emax}. This supports a possible causal link between inspiratory muscle weakness and breathing pattern. In contrast with WANKE *et al.* [10] who observed changes in breathing pattern only at peak exercise, we also observed changes in breathing pattern at iso-ventilation. The larger improvements in breathing pattern that we found at iso-ventilation after IMT, did not, however, translate into larger improvements in breathing pattern at peak exercise. Improvements in peak exercise capacity were comparable between studies. Our second hypothesis was that patients would be able to perform faster contractions with their inspiratory muscles during exercise; resulting in reductions in inspiratory time and leaving more time for expiration, which in turn might ameliorate DH. However, the previously observed increased capacity to perform fast contractions [11], did not result in significant between-group changes in inspiratory flow rates during exercise. This is consistent with previous data from PETROVIC *et al.* [12], who reported a similarly small within group difference (5% as compared to 7% in our study) in V_T/t_I, which also did not result in a significant between group difference after 8 weeks of inspiratory flow resistive loading (IFRL). It is possible that longer training durations are needed to achieve significance. Another possibility might be that specific breathing retraining strategies, during exercise, in combination with IMT might be needed to teach patients how to use their increased capacity to perform faster inhalations during exercise. COLLINS *et al.* [13] previously observed that the combination of ventilation feedback and exercise training changed t_I/t_{TOT}, decreased exercise-induced DH, and increased exercise tolerance.

Based on the observed differences in results and differences in training methods in our study in comparison with the studies of WANKE *et al.* [10], and PETROVIC *et al.* [12], a prospective study would be worthwhile

comparing the specific effects of each training method on exercise capacity and breathing pattern head-to-head. In contrast to WANKE *et al.* [10] who used maximal isometric contractions performed at residual volume and high intensity MTL training, both TFRL-IMT, and IFRL-IMT (used by us and by PETROVIC *et al.* [12], respectively) allow end-inspiratory lung volume (EILV) to enter the IRV, and permit higher inspiratory flow rates (*i.e.* higher shortening velocities) at high training intensities (*i.e.* resistances >50% P_{Imax}) [11, 12]. According to muscle length (lung volume) and pressure-flow specificity of IMT, this should provide a training stimulus that is more specific to the operating range and the contraction pattern of the inspiratory muscles during exercise, since the largest improvements in function should occur at the volumes over which IMT is performed and larger increases in inspiratory flow are expected with high velocity training [14, 15].

The main limitation of this study is the study design. Since a historical group of patients who participated in an identical PR programme served as control subjects, a prospective randomised controlled study design will be needed to corroborate our findings. It also remains uncertain whether our observed effects on breathing pattern occurred due to a reduction in mechanical restriction on V_T expansion (reaching higher EILV) or due to a reduction in DH (reducing end-expiratory lung volume (EELV)). However, it seems most likely that the higher V_T would 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} remained unchanged; however, more elaborate measurement techniques will be required to evaluate the effects of IMT on operating lung volumes.

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

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The addition of IMT to a PR programme for selected COPD patients changes breathing pattern during exercise http://ow.ly/WWrFT

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Assessing small airway impairment in mild-to-moderate smoking asthmatic patients

To the Editor:

Asthma is characterised by airway inflammation throughout the bronchial tree, including the small airways. In asthma, small airway alterations are associated with poor clinical outcomes [1]. Cigarette smoke is known to induce peripheral airway abnormalities, asthmatic smokers exhibit a more rapid lung function decline, experience more frequent exacerbations and are more likely to be uncontrolled, even when the disease is managed as recommended [2]. The mechanisms accounting for poor responses to treatment in smoking asthmatic patients are currently unclear, although low accessibility to inhaled medications in the peripheral airways is considered a limiting factor for the efficacy of such treatments [3].

Currently, small-particle-size inhaled treatments (mass median aerodynamic diameter <2 μm), which feature increased peripheral deposition relative to standard formulations, are available [4]. A recent observational study reported the efficacy of inhaled small-particle-size formulations in comparison to standard formulations, with regard to the improvements in clinical outcomes in a population of smoking asthmatic patients [5]. Thereby, suggesting that targeting peripheral alterations might yield clinical benefits in this population.

In this study, we hypothesised that cigarette smoking aggravates small airway abnormalities in asthmatic patients. The primary study outcome was an assessment of small airway dysfunction in smoking asthmatics. In addition, we evaluated the effect of switching the pre-existing standard-size particle inhaled treatment to an equipotent small-particle-size inhaled formulation.

Cross-sectional phase and primary outcome. Stable asthmatic patients (*i.e.* no exacerbations and changes in inhaled treatments during the 3 months preceding the study) were consecutively screened at the Respiratory Department of the University of Ferrara (Ferrara, Italy). Never smokers or current smokers (10–20 pack-years) with mild-to-moderate asthma who ranged in age from 18 to 50 years, free from an exacerbation for a minimum of 2 months and treated for at least 3 months with low-dose standard-particle-size inhaled corticosteroids (ICS) (step 2) alone or together with long-acting β$_2$ agonists (LABA) (ICS/LABA, fixed-dose combination; step 3) [6] were included. We adopted a lower cut-off limit of 10 pack-years, a usual standard in clinical trials, to qualify smokers. The upper limit of 20 pack-years was arbitrarily chosen to reduce the inclusion of subjects with advanced/irreversible chronic obstructive pulmonary disease-like peripheral alterations. Patients were excluded if they had been treated with small-particle-size formulations before entering the study, had irreversible airflow limitation after inhaling 400 μg of albuterol (*i.e.* post bronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) <70%), or had an impaired diffusion capacity (predicted diffusing capacity of the lungs for carbon monoxide <80%).