Differences of ventilatory muscle recruitment and work of breathing in COPD and interstitial lung disease during exercise: a comprehensive evaluation

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Limitation of exercise capacity in chronic respiratory diseases is characterised by early and excessive use of the respiratory muscles. Consequently, there is a neuromechanical dissociation with impact on the work of breathing and higher dyspnoea. https://bit.ly/3HVrsuh

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Abstract

Introduction COPD and interstitial lung disease (ILD) are significant chronic respiratory disorders, impacting quality of life. Respiratory muscle roles and differences remain not entirely clear. The objective of the present study was to evaluate the degree of recruitment of the respiratory muscles and the work of breathing in COPD and ILD during exercise.

Methods We compared the sensory–mechanical relationships in COPD, ILD and healthy controls (n=20 each). They performed pulmonary function, noninvasive and invasive respiratory muscle strength, surface electromyography and work-of-breathing assessments.

Results COPD and ILD did not show lower static muscle strength compared to controls, but did show poor performance in the exercise test with increased transdiaphragmatic pressure (P_{di}). In ILD, there was a higher increase in oesophageal pressure and a lower gastric pressure (P_{ga}) on inspiration; in COPD, there was a significant increase in P_{ga} on inspiration. In ILD, there is greater recruitment of accessory inspiratory muscles, whereas in COPD, there is marked use of both inspiratory and expiratory muscles. The neuromechanical inefficiency (increased neural respiratory drive without the corresponding tidal volume) was found in both diseases. In COPD, there is a considerable increase in elastic work to overcome intrinsic positive end-expiratory pressure ($PEEP_i$) and expiratory work of breathing, whereas in ILD, non-$PEEP_i$ elastic work of breathing is the highest part of the total work of breathing.

Conclusions Early and increased activity of the respiratory muscles and work-of-breathing components significantly contribute to dyspnoea, exercise intolerance and neuromechanical inefficiency of ventilation in COPD and ILD. The mechanisms of P_{di} generation were different between diseases.

Introduction

Chronic respiratory diseases are among the most disabling conditions for patients, leading to significant impairment in quality of life and intense dyspnoea during daily activities. COPD and interstitial lung disease (ILD) are the most common chronic respiratory diseases.

During exercise, both diseases are marked by excess ventilation, even at submaximal intensities. In COPD, there are more studies highlighting the relevance of respiratory mechanical constraint, with an intense increase of dyspnoea when the inspiratory reserve volume is close to 0.5 L or when the tidal volume (V_T) begins to plateau despite the continuing increase of ventilation [1, 2]. Due to dynamic hyperinflation, there

is a progressive increase of end-expiratory lung volume, enabling the inspiratory muscles, which are possibly overloaded at rest, to overcome a high-pressure gradient (intrinsic positive end-expiratory pressure ($PEEP_i$)) to initiate a new respiratory cycle. Thus, patients have increased elastic work related to $PEEP_i$ in association with the consequent elevation of elastic mechanical constraint (non-$PEEP_i$) in the work of breathing [3, 4].

In ILD, the early and intense drop in oxygen saturation during exercise is clearly a contributor to high dyspnoea [5], mainly resulting in higher ventilatory drive; as a consequence, the mechanical restriction is even more intensified, with operating lung volumes that are reduced at all moments of exercise (owing to augmented elastic recoil even at rest) [6, 7]. Differently to COPD, ILD patients do not have to overcome $PEEP_i$ to generate inspiratory flow, but the pathological high lung elastic recoil forces the ventilatory muscles, particularly the inspiratory muscles, to generate higher pleural pressure gradients in order to obtain an efficient V_T [8, 9]. With respect to the work of breathing during exercise, they also have increase in the total work, with overload in the elastic (non-$PEEP_i$) component.

In both COPD and ILD, there is the neuromechanical inefficiency characterised by increased neural respiratory drive and increased recruitment of inspiratory muscles to generate higher ventilation, but a noncorresponding tidal (alveolar) volume. This concept is directly related to higher dyspnoea in both respiratory diseases.

Faisal *et al.* [10] have shown these different patterns of lung mechanics during exercise, and found increased work of breathing in COPD and ILD patients compared to healthy individuals. One interesting finding was the relationship between dyspnoea and diaphragmatic demand in the face of a high inspiratory neural drive. This study provides a strong reference for the mechanism of dyspnoea in both respiratory diseases, but some questions remain to be answered. The inspiratory accessory muscles have not been evaluated, nor have the possible differences in the mechanism to generate P_{di} between ILD and COPD.

Thus, we performed comprehensive monitoring of ventilatory muscle recruitment during maximal exercise in COPD, ILD and healthy controls. Our objective was to evaluate the dynamic patterns of responses in association with exercise performance and dyspnoea among these groups.

Methods

Subjects

20 patients with ILD (total lung capacity (TLC) <80% predicted; forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ⩾0.7) and 20 patients with COPD (FEV_1/FVC <0.7 post-bronchodilator, history of smoking) were recruited from the chronic pulmonary disease outpatient department of a tertiary university hospital (Hospital das Clínicas, São Paulo, Brazil). 20 healthy volunteers were recruited as the control group (aged >18 years, normal lung function test, nonsmokers). Exclusion criteria were the presence of asthma, moderate/severe cardiovascular impairment (New York Heart Association >2), use of oxygen therapy and limitations that prevented the test from being performed.

Study design

This cross-sectional study was approved by the local ethics committee (CAPPesq) (protocol number 0835/11), and all subjects provided written informed consent.

All assessments were performed during a single visit. Assessment of dyspnoea, pulmonary function and maximal muscle strength was performed at the baseline. Metabolic, cardiovascular and respiratory variables were evaluated during a maximum incremental cardiopulmonary exercise test (CPET) on a cycle, with continuous measurement of respiratory mechanics and surface electromyography (EMG) of the inspiratory and expiratory muscles.

Measurements at rest

Spirometry was performed using a calibrated pneumotachograph (Medical Graphics Corporation (MGC), St Paul, MN, USA), whereas lung volumes and diffusing capacity of the lung for carbon monoxide (D_{LCO}) were obtained on a body plethysmograph (Elite Dx, Elite Series; MGC) according to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines [11–13]. The predicted values were derived for the Brazilian population [14–16].

The subjects answered a dyspnoea questionnaire (modified Medical Research Council (mMRC)), indicating how much shortness of breath affects their functionality [17]. In addition, they answered a quality-of-life questionnaire (St George's Respiratory Questionnaire (SGRQ)) [18].

Maximal inspiratory pressure (P_{Imax}) and maximal expiratory pressure (P_{Emax}) were measured using a digital manovacuometer (MicroRPM; CareFusion, Yorba Linda, CA, USA). The reference values for P_{Imax} and P_{Emax} were based on the Brazilian population [19–21].

We passed two filled latex balloon catheters (CooperSurgical, Trumbull, CT, USA) to measure the oesophageal pressure (P_{oes}), gastric pressure (P_{ga}) and transdiaphragmatic pressure (P_{di}) [22, 23]. We have described the complete technique of passing the catheter previously [24]; these techniques are in accordance with the ATS/ERS statement on respiratory muscle testing [25].

Maximal volitive respiratory strengths were measured during a maximal sniff manoeuvre (P_{oes} sniff, P_{ga} sniff and P_{di} sniff). P_{di} was also measured during a nonvolitional diaphragmatic contraction through bilateral magnetic stimulation of the phrenic nerve (P_{di} twitch).

Measurements during exercise

All subjects performed an incremental CPET limited by exhaustion on a cycle ergometer (Corival; Lode, Groningen, the Netherlands). During the test, respiratory and metabolic variables were recorded (Vmax; CareFusion). Electrocardiography (CardioPerfect; Welch Allyn, Skaneateles Falls, NY, USA) and oxygen saturation (Onyx, model 9500; Nonin, Plymouth, MN, USA) were monitored continuously during the test.

The reference values for the stress test were based on the sedentary adult Brazilian population [26]. The inspiratory capacity (IC) and modified Borg Rating of Perceived Exertion Scale [27] were assessed at rest and every 2 min during exercise.

Continuous monitoring of respiratory pressures was performed in addition to surface EMG (EMG System, São José Campos, SP, Brazil) of the scalene, sternocleidomastoid and external oblique muscles.

The components of the work of breathing were quantified using pressure–volume loops (*i.e.* Campbell diagram) constructed from flow, pressure and volume data obtained during graded exercise [28–30]. Work of breathing during inspiration was composed of the resistive (elastic force to overcome $PEEP_i$ + work to overcome the inspiratory airway resistance) and non-$PEEP_i$ elastic to inflate the lungs, overcoming the respiratory elastance. Expiratory work was another component of the total work of breathing.

All measurements were performed breath-by-breath, and the mean cycle was generated based on the last 10 breaths of each exercise stage. We define the start and end of inspiration based on zero flow points. The onset of inspiration corresponds to the point where the airflow becomes positive, and the conclusion of inspiration is marked by the return of airflow. The respiratory pressures (P_{oes}, P_{ga} and P_{di}) during exertion were extracted from the inspiratory cycle. All signals used in the analysis were carefully selected and adjusted to remove specific interferences and maintain the integrity of signals relevant to the data analysis.

More technical details about data acquisition and analysis are provided in the supplementary material.

Statistical analysis

The normality of the distributions was tested using the Shapiro–Wilk test. Data are presented as mean±SD, mean±SEM for graphical presentations or median (interquartile range), as appropriate. A *post hoc* linear regression analysis was conducted to correct the possible effect of higher mean age in the COPD group compared to the other groups on static muscle strength measurements.

To analyse differences between variables with normal distribution during CPET, one-way analysis of variance (ANOVA) with *post hoc* Bonferroni test was used for isoworkload and isoventilation comparisons, and two-way ANOVA with *post hoc* Holm–Sidak test was used for contrast between stress test response patterns between groups. The significance level was set at 5% ($p<0.05$).

Results

Most COPD patients (n=13, 65%) had moderate/severe airflow obstruction (FEV_1 <50% pred), and all were ex-smokers. ILD patients already had fibrosing process findings on lung computed tomography, and the aetiologies were diverse: fibrosing interstitial pneumonitis (30%), hypersensitivity pneumonitis (35%), autoimmune diseases (25%), sarcoidosis (5%) and usual interstitial pneumonia (5%). The healthy controls were matched by sex, except for age, which was similar only to the ILD group. The COPD patients were older with a moderate degree of airflow obstruction, significant air trapping and lung hyperinflation. ILD patients had a similar drop in D_{LCO} compared to COPD patients but a more significant reduction in lung volume. Both groups presented with dyspnoea to moderate/mild activities in daily life (mMRC=2) (table 1).

TABLE 1 Subject characteristics, pulmonary function and respiratory muscle strength at rest

	Controls	COPD	ILD
Male:female	11:9	10:10	12:8
Age, years	48±15	60±6*	45±13.7#
BMI, kg·m^{-2}	27.1±8.3	25.6±6.3	26.4±3.2
mMRC dyspnoea scale (0–4)	0	2.0±1.17*	2.0±0.95¶
Pulmonary function			
FVC, L (% predicted)	3.92±1.24 (93.5±15.1)	2.91±0.99 (85.3±18.4)	2.36±0.73¶ (59.6±14.5#,¶)
FEV_1, L (% predicted)	3.19±1.06 (93.4±13.3)	1.25±0.58* (46.9±14.8*)	2.00±0.59#,¶ (62.5±14.8#,¶)
FEV_1/FVC, %	81.4±4	43±10.4*	85.6±6.2
MVV, % predicted	135.5±39.8	62.7±21.9*	90.8±22.8#,¶
V'_E/MVV, %	8.7±2.6	43.9±21*	16.9±6#,¶
IC, L (% predicted)	2.78±0.71 (103.9±16.8)	1.95±0.56* (77.8±13.5*)	1.45±0.58#,¶ (54.2±18.6#,¶)
SVC, L (% predicted)		2.99±1.03 (87.2±18.9)	2.50±0.77 (59.1±15.9#)
RV, L (% predicted)		3.38±0.95 (178±55.4)	1.39±0.17# (90.3±30.3#)
TLC, L (% predicted)		6.51±1.33 (121.2±17.6)	3.79±0.85# (68.6±13.5#)
RV/TLC, %		52±12.1	38±8#
D_{LCO}, % predicted		56.4±35.4	45.2±14.7
Respiratory muscle strength			
P_{Imax}, cmH_2O (% predicted)	89.7±34.7 (87±24.8)	63.9±16.9* (70.6±20.8*)	90.3±31.2# (83.6±23.3)
P_{Emax}, cmH_2O (% predicted)	103.74±34.1 (98.4±36.9)	81.5±24.1 (87.2±47.6)	100.4±36.6 (90.2±28.9)
P_{oes} sniff, cmH_2O	−37.5±16.4	−32.8±25.8	−44.1±19.4
P_{ga} sniff, cmH_2O	31.4±15.7	22±14.9	25.9±16.5
P_{di} sniff, cmH_2O	69±24.1	59±23	70±29.5
P_{di} bilateral twitch, cmH_2O	15.7±8.5	15±16.3	14.7±8.2
P_{di} twitch/P_{di} sniff, cmH_2O	0.22±0.12	0.25±0.39	0.21±0.14
P_{ga} twitch T10, cmH_2O	20±14.5	21.68±13.11+	19.35±13.92

Data are presented as n or mean±SD. ILD: interstitial lung disease; BMI: body mass index; mMRC: modified Medical Research Council; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; MVV: maximal voluntary ventilation; V'_E: minute ventilation; IC: inspiratory capacity; SVC: slow vital capacity; RV: residual volume; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{Imax}: maximum inspiratory (mouth) pressure; P_{Emax}: maximum expiratory (mouth) pressure; P_{oes}: oesophageal pressure; P_{ga}: gastric pressure; P_{di}: transdiaphragmatic pressure; sniff: maximal sniff manouevre; bilateral twitch: magnetic stimulation of the phrenic nerve bilaterally; T10: 10th thoracic vertebra. *: p<0.05 for control subjects *versus* COPD; #: p<0.05 for COPD *versus* ILD; ¶: p<0.05 for control subjects *versus* ILD; +: p<0.05 for age-corrected as a covariate in *post hoc* regression.

The mean±SD SGRQ showed high and similar values (COPD 43.1±20.9 and ILD 39.2±22), indicating impairment of quality of life.

Only P_{Imax} showed a statistically significant difference in ventilatory strength for patients with COPD, while all other noninvasive and invasive measurements of static respiratory strength were similar to controls. The effect of age in the COPD group was a statistically significant covariate only for the P_{ga} twitch 10th thoracic vertebra measurement (table 1).

During the maximal CPET, both disease groups experienced a decrease in their exercise performance, with a more pronounced reduction observed in the COPD group. The results show that the V_T/IC ratio was highest in the ILD and COPD group, indicating a higher degree of mechanical restriction. The COPD group had a lower respiratory exchange ratio (RER) compared to the control group, indicating that they had a lower metabolic stress during exercise. This was due to their early and intense ventilatory limitation (higher V'_E/maximal voluntary ventilation (MVV)), characterised mainly by dynamic air trapping during exercise (higher decline of IC). ILD presented hyperventilation based on a tachypnoeic pattern (high respiratory frequency) and a marked oxygen desaturation with the most intense dyspnoea score (table 2).

Finally, the patients had greater dyspnoea during isoworkload and even during isoventilation (figure 1).

During exercise progression, respiratory patients already had higher values of P_{di} at lower workloads. At the peak of the exercise, the P_{di} values were similar between the three groups; however, the patients with respiratory diseases showed different patterns: higher P_{oes} in ILD, and higher P_{ga} in COPD (figure 2a,b,c). Although patients had generated higher values of P_{di}, they did not have higher V_T values (figure 2d). This

TABLE 2 Physiological parameters at peak exercise

	Controls	COPD	ILD
Work rate, W (% predicted)	174±73.2 (128±26)	44±13.9* (69±28*)	78±33.1#,¶ (66±36#)
V'_{O_2}, L·min^{-1} (% predicted)	2.17±0.89 (95±16)	0.99±0.50* (62±24*)	1.45±0.58#,¶ (86±31#,¶)
Heart rate, beats·min^{-1} (% predicted)	160±13 (89±21)	128±20* (80±12)	147±21.2¶ (84±9)
RER	1.09±0.09	0.94±0.11*	1.07±0.10¶
V'_E, L·min^{-1}	79±29.5	34.88±14.8*	62.23±19.9¶
V'_E/MVV, %	59±15	77±19*	68±16
f_R, breaths·min^{-1}	37±7	30±6*	52±13#,¶
V_T, L	2.12±0.54	1.14±0.41*	1.25±0.45#
IC, L	2.77±0.66	1.48±0.54*	1.54±0.57#
Δ IC from rest, L	0.08±0.46	−0.47±0.30*	0.08±0.17
V_T/IC, %	75±11	78±13	82±12
V'_E/V'_{CO_2}	34.53±4.42	41±10.58*	42.45±8.56#
EELV, L		1.20±0.45	2.30±0.48¶
P_{ETCO_2}, mmHg	33.7±3.75	33.08±5.90	30.7±4.70#
S_{pO_2}, %	94.8±2.8	92.3±4.2	88.4±6.1#,¶
Dyspnoea, Borg units	5.28 (0.5–9)	8.3 (3–9)*	8.55 (5–10)#
Leg discomfort, Borg units	7.40 (3–10)	6.80 (3–10)	6.15 (0–10)

Data are presented as mean±SD or median (interquartile range). ILD: interstitial lung disease; V'_{O_2}: oxygen consumption; RER: respiratory exchange ratio; V'_E: minute ventilation; MVV: maximal voluntary ventilation; f_R: respiratory frequency; V_T: tidal volume; IC: inspiratory capacity; Δ: change; V'_{CO_2}: carbon dioxide production; V'_E/V'_{CO_2}: ventilatory equivalent for carbon dioxide; EELV: end-expiratory lung volume; P_{ETCO_2}: partial pressure of end-tidal carbon dioxide; S_{pO_2}: oxygen saturation as measured by pulse oximetry. *: p<0.05 for control subjects *versus* COPD; #: p<0.05 for control subjects *versus* ILD; ¶: p<0.05 for COPD *versus* ILD.

inefficiency is pointed out by the decline of V_T/P_{di} at peak exercise in patients instead of the increase that happened in healthy controls (figure 2e,f). This increased effort and low ventilatory efficiency in both diseases were also demonstrated by a high percentage of P_{oes} activation in relation to the maximum P_{oes} generated (P_{oes}/P_{oesmax}) at rest and all exercise intensities (supplementary figure S1).

The increase in P_{oes} in ILD was correlated with a higher degree of dyspnoea in ILD (R=0.63; p<0.01), while higher inspiratory P_{ga} on exertion was associated with greater dyspnoea in COPD patients (R=0.65; p<0.01) (supplementary table S1).

Considering the inspiratory accessory muscles (EMG scalene and sternocleidomastoid), the patients with respiratory diseases showed higher recruitment compared to the control group (figure 3a,c). Regarding the expiratory muscles, the highest value of recruitment was achieved in COPD patients (figure 3e). When we evaluated the reserve of accessory muscles activated during exercise (% EMG from rest), it was observed that the greater baseline activation in respiratory diseases was responsible for a lower capacity for a percentage increase in EMG during exercise (figure 3b,d,f).

The three groups had similar values of total work of breathing at the peak of the exercise, but COPD and ILD increased significantly earlier than healthy individuals (figure 4a). This early increment is also present on the non-$PEEP_i$ elastic work of breathing in patients (mainly ILD), but COPD patients had an even steeper increase and achieved an early plateau at 20 W load (figure 4b).

COPD was characterised by higher inspiratory work of breathing (mainly $PEEP_i$ elastic+airway resistance) and expiratory work of breathing, in addition to $PEEP_i$, at all moments of exercise, including at rest (figure 4c,d,f). The respiratory pressure–time product was shown to be increased in respiratory diseases at rest, but mainly in exercise. This increase was even more striking in ILDs, and in COPD the increase was limited by poor exercise performance.

In healthy individuals, most of the work of breathing during exercise is due to a non-$PEEP_i$ elastic component (57–73% of total work of breathing), followed by stable ($PEEP_i$ + airway resistance) inspiratory work (20–23% of total work of breathing) and low expiratory work (3–7% of total work of breathing)

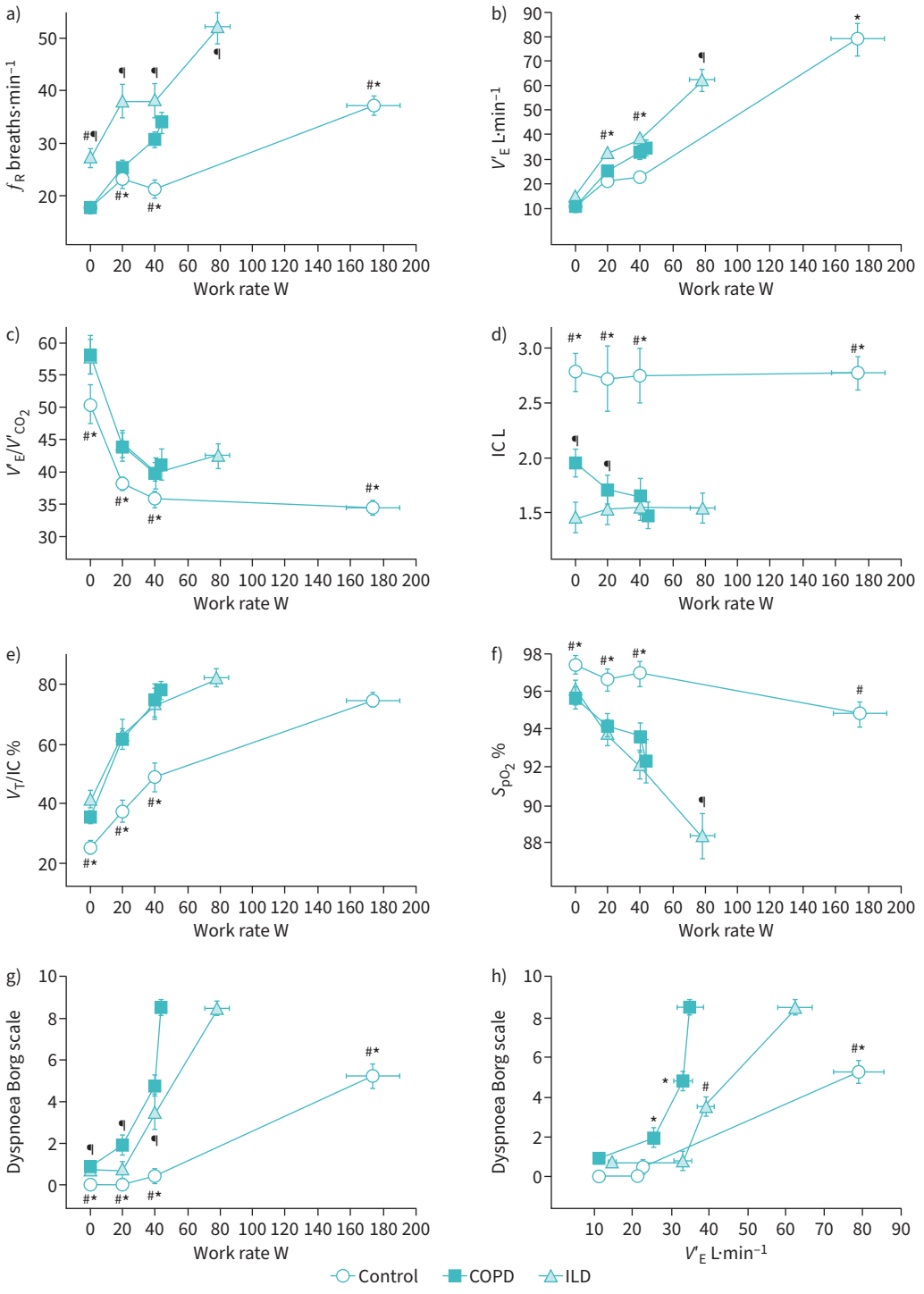

FIGURE 1 Metabolic and respiratory variables during incremental cycling exercise in patients with COPD, interstitial lung disease (ILD) and in a healthy control group. a) Respiratory frequency (f_R); b) minute ventilation (V'_E); c) ventilatory equivalent for carbon dioxide (V'_E/carbon dioxide production (V'_{CO_2})); d) inspiratory capacity (IC); e) tidal volume (V_T)/IC; f) oxygen saturation as measured by pulse oximetry (S_{pO_2}); g) dyspnoea *versus* work rate; h) dyspnoea *versus* V'_E. Data are presented as mean±SEM. *: p<0.05 for control subjects *versus* COPD; #: p<0.05 for control subjects *versus* ILD; ¶: p<0.05 for COPD *versus* ILD.

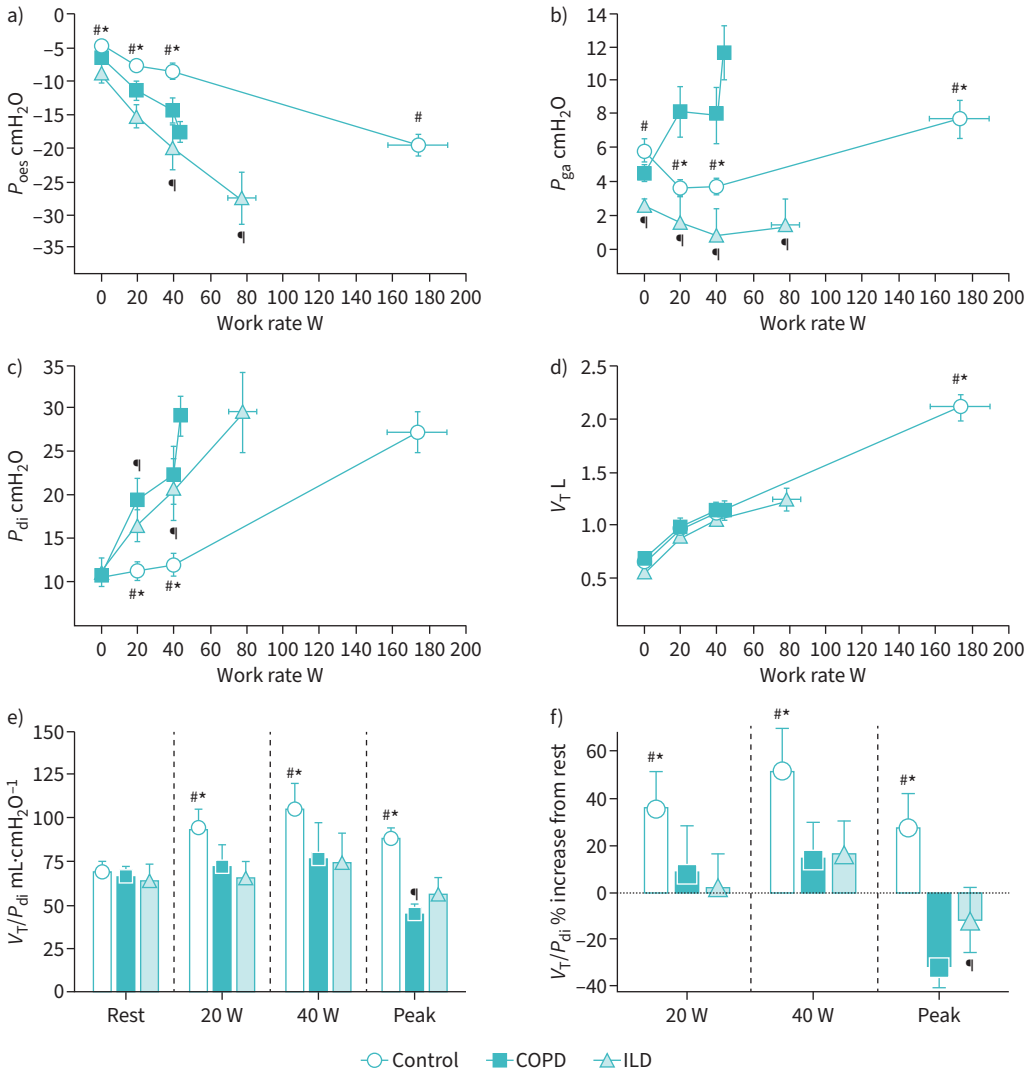

FIGURE 2 Measurements of a–c) respiratory pressures, d) tidal volume (V_T) and e,f) relationship between V_T and transdiaphragmatic pressure (P_{di}) during incremental cycling exercise in patients with COPD, interstitial lung disease (ILD) and in a healthy control group. Data are presented as mean±SEM. P_{oes}: oesophageal pressure; P_{ga}: gastric pressure. *: p<0.05 for control subjects *versus* COPD; #: p<0.05 for control subjects *versus* ILD; ¶: p<0.05 for COPD *versus* ILD.

(figure 5a). In COPD, there was an expressive increase of the inspiratory work of breathing $PEEP_i$ elastic + airway resistance (46–54% of total work of breathing), with a low and limited non-$PEEP_i$ elastic work (42–50% of total work of breathing) compared to the controls, and a stable and elevated expiratory work component (5–11%) (figure 5b). Finally, in ILD the non-$PEEP_i$ elastic component achieved the highest percentage at rest, declining during exercise (80% to 64% of total work of breathing, with a mild increase of inspiratory work of breathing $PEEP_i$ elastic + airway resistance (11–24%) and expiratory (1–10%) (figure 5c).

The pressure–volume loops of the Campbell diagram allow the visualisation of important respiratory mechanics data and the comparison of mechanical efficiency between respiratory diseases and healthy individuals. The diagram was constructed at rest and during exercise and placed on the same image for mechanical comparison of breathing among the three groups (figure 6). The COPD group has increased operating volumes even at rest, and reduced gain in V_T expansion. ILD patients have lower operating volumes and significant mechanical restriction.

In our study, dyspnoea in respiratory diseases was also correlated with the work of breathing and its components. In COPD, dyspnoea was correlated with total work of breathing at rest (R= −0.05; p=0.04)

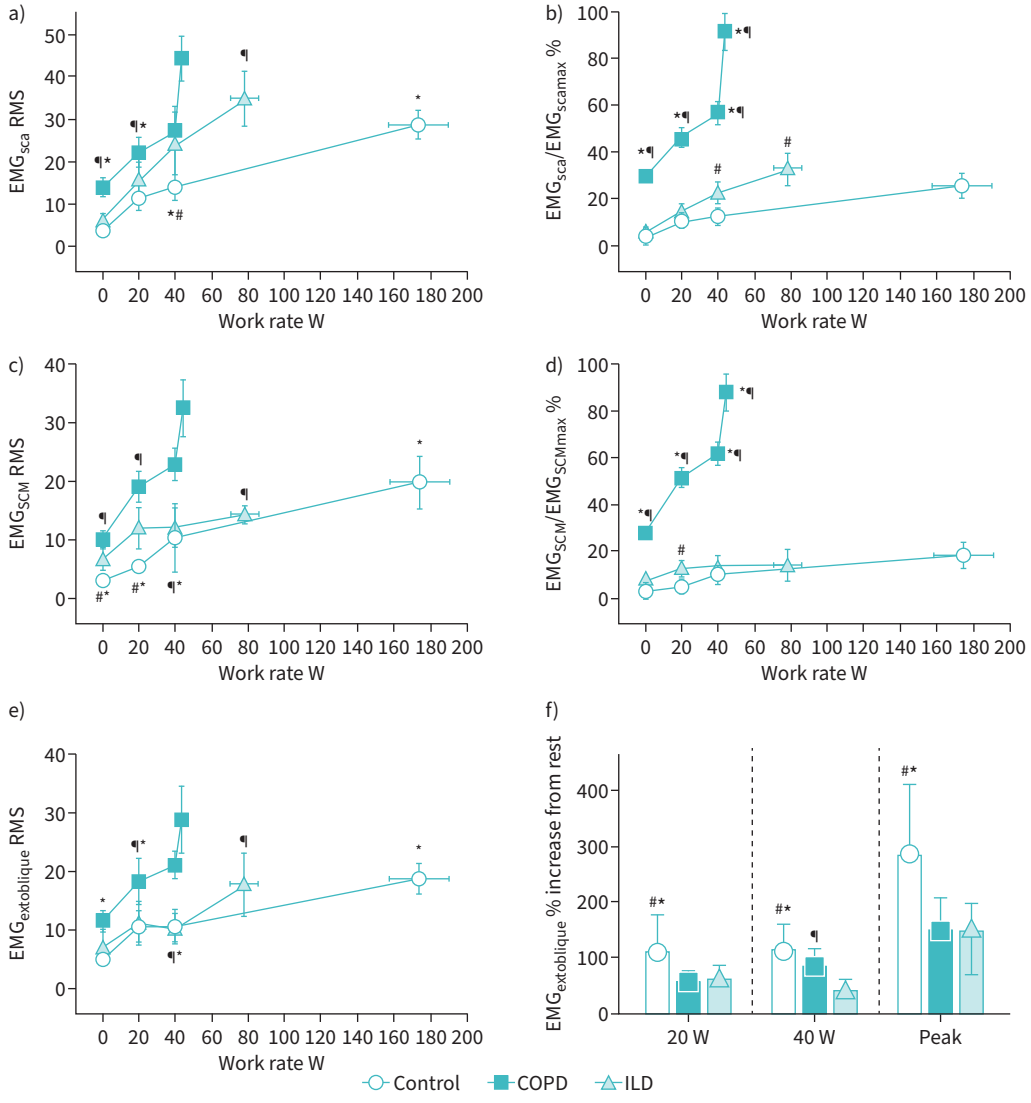

FIGURE 3 Surface electromyography (EMG) measurements of the a–d) inspiratory (scalene (EMG_{sca}) and sternocleidomastoid (EMG_{SCM})) and e,f) expiratory (external oblique ($EMG_{extoblique}$) accessory respiratory muscles during incremental cycling exercise in patients with COPD, interstitial lung disease (ILD) and in a healthy control group. RMS: root-mean-square value. Data are presented as mean±SEM. *: p<0.05 for control subjects *versus* COPD; #: p<0.05 for control subjects *versus* ILD; ¶: p<0.05 for COPD *versus* ILD.

and peak exercise (R=0.49; p=0.04), in addition to an association with expiratory work of breathing at rest (R=0.64; p=0.04). In ILD, dyspnoea was associated with total work of breathing at peak exercise (R=0.46; p=0.05) (supplementary table S1). The high energy cost of ventilation measured by the oesophageal pressure–term product (PTP) and ventilatory inefficiency (V_T/P_{di}) was correlated with a higher degree of dyspnoea at rest and in all stages of exercise (supplementary figure S2).

Discussion

This study used a comprehensive monitoring of respiratory muscles and lung mechanics. In both COPD and ILD, patients were able to generate ventilatory strength, but there was neuromechanical inefficiency.

Our innovative contributions were mainly related with clarifying the different mechanisms of diaphragmatic strength generation, the relevance of early recruitment of inspiratory accessory muscles, and a better understanding of the correlation between the work of breathing, muscle activity and dyspnoea in

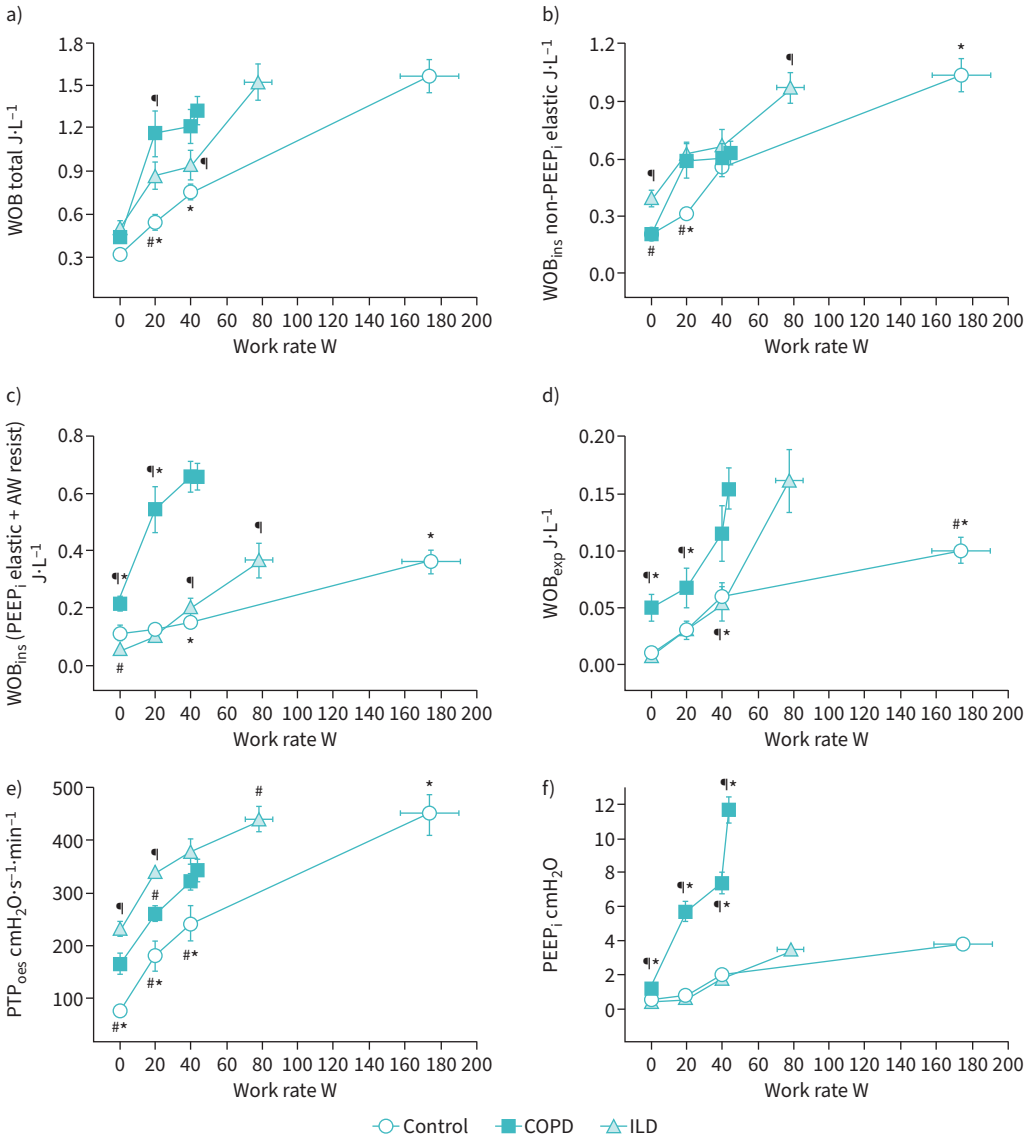

FIGURE 4 a–d) Work of breathing (WOB) and its components, e) oesophageal pressure–time product (PTP_{oes}) and f) intrinsic positive end-expiratory pressure ($PEEP_i$) during incremental cycling exercise in patients with COPD, interstitial lung disease (ILD) and in a healthy control group. AW resist: airways resistance; WOB_{ins}: inspiratory work of breathing; WOB_{exp}: expiratory work of breathing. Data are presented as mean±SEM. *: p<0.05 for control subjects *versus* COPD; #: p<0.05 for control subjects *versus* ILD; ¶: p<0.05 for COPD *versus* ILD.

respiratory diseases. Although FAISAL *et al.* [10] found these correlations in COPD and ILD, the inspiratory accessory muscles and the mechanism to generate P_{di} in both respiratory diseases have not yet been evaluated.

ILD and COPD were characterised by significant limitations in daily activities (mMRC and SGRQ). Although our patients were younger than those in previous studies [9, 10], the degree of impairment of lung function (TLC and D_{LCO}) was similar, and our patients had worse exercise performance, denoting greater disease severity. Except for P_{Imax} in COPD, there was no reduction in the maximal inspiratory and expiratory strengths in patients in volitional and nonvolitional tests when compared to the values obtained from healthy controls. In accordance with other studies [31–34], the measurement of maximal static strength did not show significant inspiratory impairment in either respiratory disease. However, it is important to point out that these tests only assess the ability to generate static force, and not the dynamic ability to maintain that force, such as during exercise. Our values of invasive ventilatory strength were

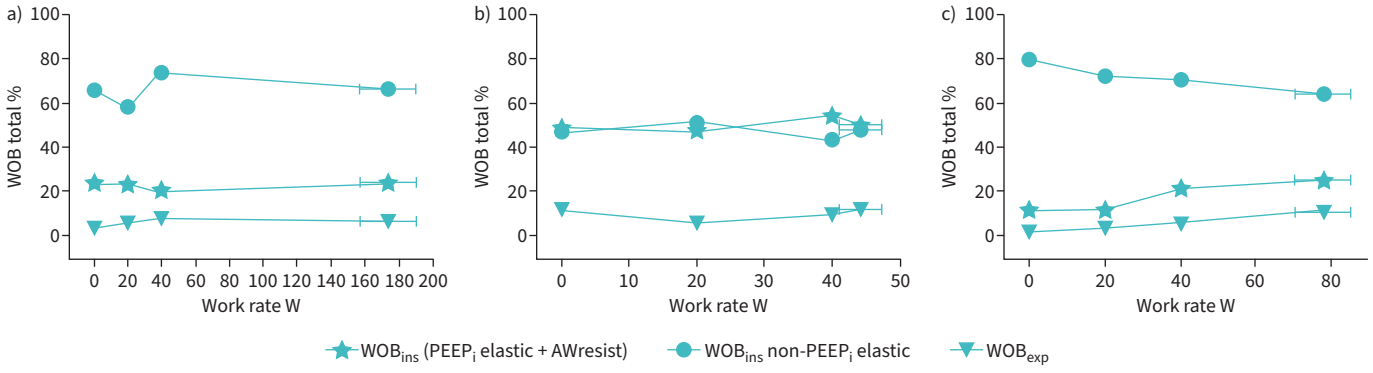

FIGURE 5 Participation of the components of the work of breathing (WOB) in the total work during incremental cycling exercise in a) a healthy control group; b) patients with COPD and c) patients with interstitial lung disease. AWresist: airways resistance; WOB_{ins}: inspiratory work of breathing; $PEEP_i$: intrinsic positive end-expiratory pressure; WOB_{exp}: expiratory work of breathing. Date are presented as mean±SEM.

lower than some previously reported as a reference [35], which is probably related not only to technical differences (catheter balloons and pressure transducers), but also to age and different populations. STEIER *et al.* [35] found values from different diseases (neuromuscular, dyspnoea of unknown origin and others) with a wide range of values. The mean values of respiratory muscle strength obtained in physiological studies, which generally have a small sample size, should be interpreted with caution, as individual and population variabilities can have a significant impact on the averages obtained. SPIESSHOEFER *et al.* [36] demonstrated that twitch P_{di} values obtained by bilateral cervical stimulation were age-dependent. In the same study, the authors analysed previous values and found that many participants were young and male.

Exercise performance was reduced in both respiratory groups. COPD patients had the lowest workload and ended up with a high metabolic reserve (RER <1.05) due to early ventilatory limitation: hyperventilation, high V'_E/MVV, oxygen desaturation and decline in IC. Patients with ILD had reduced performance characterised by ventilatory limitation, with hyperventilation, tachypnoeic pattern and oxygen desaturation. All of them had increased and early dyspnoea, not only at isoworkloads, but even when corrected to the same ventilation. This means that hyperventilation alone is not a determinant of higher dyspnoea.

During exercise, patients achieved high values of P_{di}. O'DONNELL and co-workers [2, 9] confirmed the capacity of COPD and ILD to generate high values of diaphragmatic strength during exercise. However, we found differences in the generation of P_{di} between the patients. ILD achieved the highest inspiratory P_{oes} values, while P_{ga} on inspiration decreased during exercise progression. In contrast, COPD patients exhibited elevated and increasing values during exercise for both P_{oes} and P_{ga} on inspiration. These

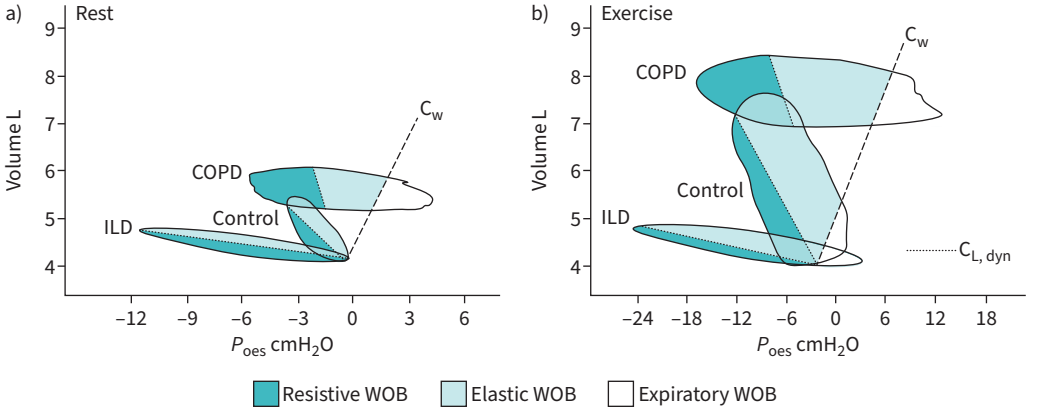

FIGURE 6 Campbell diagram at a) rest and b) peak exercise in patients with COPD, interstitial lung disease (ILD) and in a healthy control group. Resistive work of breathing (WOB) is unrelated to intrinsic positive end-expiratory pressure. C_w: rib cage compliance; $C_{L,dyn}$: dynamic lung compliance; P_{oes}: oesophageal pressure.

different patterns are likely to be related to distinct mechanisms of the disease. In ILD, non-$PEEP_i$ elastic work of breathing was the most demanding and was associated with reduced lung volumes (low compliance), which certainly resulted in a higher challenge for the diaphragm to increase abdominal pressure and lung expansion into the abdominal compartment during inspiration. Using respiratory inductive plethysmography, we have shown that thoracoabdominal asynchrony with reduced lung expansion into the abdomen is frequent during exercise in fibrotic ILD and is related to the severity of disease, recruitment of inspiratory accessory muscles and dyspnoea [37].

Patients with COPD had to handle increased inspiratory work of breathing characterised by an elevated iPEEP that should be overcome before inspiratory flow could begin. During exercise progression and tachypnoea, dynamic hyperinflation increases iPEEP even more and results in elevated elastic work of breathing related to the over recruitment of inspiratory muscles [38, 39]. Consequently, the P_{di} increases substantially at the onset of exercise and persists until exhaustion. Interestingly, the P_{di} values were significantly higher even when corrected for ventilation (supplementary figure S1), showing high work over the diaphragm. Following this elevated demand, inspiratory accessory muscles are overrecruited very early as well. A higher P_{ga} during inspiration helps the lungs expand into the abdominal compartment, which occurs despite the anatomical disadvantage of the flattening diaphragm facing dynamic air trapping during exercise. The COPD group had high activation of the expiratory muscles from rest; this greater activation is believed to be a compensatory mechanism, helping to keep the diaphragm at its best tension/length ratio [40].

Increased activation of the inspiratory muscles has been associated with dyspnoea in populations with COPD [41, 42]. Faisal *et al.* [10] found greater diaphragmatic activation (PTP_{di}) during exercise in patients with ILD, as well as greater expiratory abdominal activation ($PTP_{gastric}$) in patients with COPD. Interestingly, PTP_{di} did not show an increase, but EMG_{di} exhibited a significant intensification in COPD compared to healthy individuals [10]. This discrepancy may be attributed to the fact that PTP involves inspiratory time, which is reduced in COPD, and the disadvantage of the diaphragm related to dynamic hyperinflation during exercise mainly in patients with more severe disease.

Some characteristics during exercise are similar and outstanding in both groups of patients: 1) inspiratory muscles are overworked very early and can increase strength; and 2) although there is a progressive increase in inspiratory strength, the gain in volume is not proportional, confirming the concept of neuromechanical inefficiency. Therefore, dyspnoea sets in very early, and patients are not able to keep this overwork of respiratory muscles for longer times.

The increased recruitment of inspiratory muscles without significant gain in V_T is the milestone of neuromechanical inefficiency and it is illustrated in figure 6. Even at rest, the disadvantage of higher increment of P_{oes} and reduced V_T expansion in both respiratory diseases is clear, when contrasted against healthy individuals. Furthermore, COPD has gone to high operating volumes (due to dynamic hyperinflation) and persisted in the restriction of gain volume. These patients have high elastic work just to overcome $PEEP_i$, findings that have been shown by Sliwinski *et al.* [43]. ILD had lower operating volumes with even higher increments of P_{oes}, but no significant inspiratory volume expansion. In contrast to both respiratory diseases, healthy individuals were characterised by low increment of P_{oes} and high gain in volume, confirming an efficient neuromechanical pattern at rest and intense exercise.

Proposals for a nonpharmacological approach to reduce dyspnoea in patients with chronic respiratory diseases are still needed. Therefore, inspiratory muscle training (IMT) is a promising strategy. Although individuals with pulmonary diseases often do not present with muscle weakness, as demonstrated in this study, IMT can bring benefits to the dyspnoea reported by patients. In 2018, Langer *et al.* [44] demonstrated in patients with moderate/severe COPD that an 8-week IMT programme reduced the diaphragmatic neural drive, resulting in less dyspnoea during exercise testing. In 2021, Hoffman *et al.* [45] evaluated the effect of an 8-week IMT programme on a small cohort of patients with chronic lung diseases, with the majority having COPD and idiopathic pulmonary fibrosis. After the training period, the patients showed less exertion-related dyspnoea, and better quality of life.

Limitations

Our COPD patients were older than the healthy controls and patients with ILD, which may intensify the impairments in COPD. However, lung function and ventilatory strength did not differ between respiratory diseases. Although our invasive values of maximal static ventilatory strength were reduced compared to the other groups [35], it has probably been influenced by other components. Most previous studies evaluated COPD with a high or total predominance of males and less-severe impairment in FEV_1 [46–48].

The absence of measurements of lung volume expansion (*e.g.* optoelectronic plethysmography (OEP)) limits the proper confirmation of the possible differences in abdominal compartments between COPD and ILD. However, P_{ga} during inspiration is a good parameter that shows dynamic changes in the abdominal compartment. Moreover, it is almost unfeasible to use a complex monitoring OEP in conjunction with all the measurements we have performed.

Conclusion

Patients with chronic respiratory diseases have to generate increased inspiratory force very early during exercise. Our novel findings were 1) that this was made possible not only by diaphragm recruitment, but also by the additional and increased recruitment of the accessory inspiratory muscles; 2) furthermore, the P_{di} generation mechanism was different in respiratory diseases. In ILD, there was a high contribution from P_{oes} and a low capacity to increase P_{ga}, and in COPD, there was a high contribution from P_{ga}.

Patients with COPD have high inspiratory (mainly elastic component to overcome the $PEEP_i$) and expiratory work of breathing. Patients with ILD are characterised by high levels of non-$PEEP_i$ elastic work of breathing to overcome the augmented respiratory elastance. Components of work of breathing are correlated with dyspnoea.

Neuromechanical inefficiency of ventilation is a common feature of both diseases and associated with greater dyspnoea.

These findings play a relevant role in better understanding the main limiting mechanisms in COPD and ILD, helping to define appropriate interventions to improve quality of life and reduce exercise limitations.

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