Respiratory Muscle Fatigue following Exercise in Patients with Interstitial Lung Disease

Davide Elia^{a, b} Julia L. Kelly^a Dario Martolini^a Elisabetta A. Renzoni^a
Afroditi K. Boutou^a Alfredo Chetta^b Michael I. Polkey^a Nicholas S. Hopkinson^a

^aNIHR Respiratory Biomedical Research Unit at Royal Brompton and Harefield NHS Foundation Trust and Imperial College, Royal Brompton Hospital, London, UK; ^bCardiopulmonary Department, Unit of Respiratory Diseases, University Hospital, Padiglione Rasori, Parma, Italy

Key Words

Abdominal muscles • Diaphragm • Exercise • Fatigue • Interstitial lung disease • Magnetic stimulation

Abstract

Background: It is not known whether respiratory muscle fatigue occurs as a consequence of exercise in patients with interstitial lung disease (ILD) and, if so, to what extent it is related to changes in dynamic lung volumes. **Objectives:** To assess the development of respiratory muscle fatigue in patients with ILD and relate it to the respiratory pattern during exercise. **Methods:** Sixteen ILD patients (11 women) performed incremental, symptom-limited cycle ergometry with inspiratory capacity manoeuvres used to measure changes in end-expiratory lung volume (EELV). Twitch transdiaphragmatic pressure (TwPdi) and twitch gastric pressure (TwT₁₀Pga), in response to magnetic stimulation, were used to assess the development of fatigue. **Results:** TwPdi did not differ significantly before and after exercise (21.8 ± 8 vs. 20.2 ± 8 cm H₂O; $p = 0.10$), while TwT₁₀Pga fell from 28.6 ± 18 to 25.2 ± 14 cm H₂O ($p = 0.02$). EELV fell from 2.18 ± 0.65 to 1.91 ± 0.59 liters following exercise ($p = 0.04$). The fall in TwT₁₀Pga correlated with peak oxygen uptake at peak of exercise ($r = -0.52$, $p = 0.041$), increase in heart rate ($r = 0.53$,

$p = 0.032$) and with the decrease of EELV during exercise ($r = 0.57$, $p = 0.021$). Abdominal muscle fatiguers ($n = 9$, 56%), defined as having a $\geq 10\%$ fall in TwT₁₀Pga, had a fall in EELV of $22 \pm 22\%$ compared to $0.7 \pm 8\%$ in non-fatiguers ($p = 0.016$). **Conclusion:** Abdominal muscle fatigue develops during exercise in some ILD patients in association with increased expiratory muscle activity manifested by reduced EELV.

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Background

Interstitial lung diseases (ILD) include a diverse group of pulmonary disorders which mainly affect the pulmonary interstitium and are characterized by a reduction in lung compliance, an increase in elastic load and a reduction in lung volumes. Patients with ILD often experience dyspnoea and fatigue during daily activities. This results in significant physical limitation, often associated with reduced psychological wellbeing and social interaction. Exercise limitation in ILD has been associated with multiple factors, including O₂ diffusion limitation, ventilation/perfusion mismatch, pulmonary vascular bed ablation and abnormalities in ventilatory mechanics [1, 2]. Although pulmonary rehabilitation has recently been

shown to have a significant effect on improving the quality of life in ILD [3, 4], the role played by impaired respiratory skeletal muscle function in the limitation of activity has not been thoroughly studied so far [5].

Muscle fatigue is defined as a reversible loss of the ability to generate force, resulting from activity under load [6]. Fatigue may be measured as the time from the onset of the contraction to the time at which a target tension developed cannot be sustained [7]. In healthy subjects, diaphragm fatigue can be induced by volitional ventilatory efforts [8, 9] or by exercise, when this is performed at a high percentage of peak capacity [10–12]. It has previously been reported in patients with chronic obstructive pulmonary disease (COPD) that diaphragm fatigue does not occur after maximal voluntary ventilation [13], exhaustive treadmill exercise [14] or even during failed weaning from mechanical ventilation [15]. While this may, in part, be due to muscular adaptations [16, 17], we have also speculated that, as is the case with limb muscle [18], the diaphragm shortening inherent to hyperventilation in COPD exerts a protective effect [13]. For this reason, our previous observation that abdominal muscle fatigue occurs in patients with COPD (whereas diaphragm fatigue does not [19]) was consistent with this, since the abdominal muscles lengthen during hyperinflation.

It is not known to what extent fatigue of the respiratory muscles occurs in patients with ILD. Static lung volumes are typically reduced in patients with ILD because of reduced lung compliance, but few data exist on dynamic lung volume changes in this group of conditions. In one study of 7 patients with ILD, lung volumes did not change significantly during exercise compared to resting values [20]. Thus, the aim of this study was to investigate whether the increased loading to which the respiratory muscles are subjected during exercise in ILD would lead to the development of respiratory muscle fatigue. This was assessed by magnetic nerve stimulation and relating this to changes in dynamic lung volumes.

Methods

Subjects

Patients with ILD were recruited from the Royal Brompton Hospital specialist ILD clinic. Sixteen ILD patients (11 women and 5 men) took part in the study. The diagnosis of ILD was based on clinical features including evidence from CT thorax, bronchoalveolar lavage, lung function and in some cases, lung biopsy. Baseline patient characteristics are given in table 1.

ILD patterns included 4 patients with idiopathic pulmonary fibrosis (2 confirmed by surgical lung biopsy), 3 with fibrotic hypersensitivity pneumonitis (confirmed by surgical biopsy) and 9

Table 1. Baseline data for all subjects and comparing those who did or did not develop abdominal muscle fatigue

	All (n = 16)	Fatiguers (n = 9)	Non-fatiguers (n = 7)	p
Age, years	59 ± 7	58 ± 10	60 ± 3	0.52
BMI	27 ± 4.86	25 ± 4.27	28 ± 5.23	0.18
FFMI	18 ± 2.7	18.5 ± 3.34	18.3 ± 1.58	0.91
FEV ₁ , litres	1.93 ± 0.52	1.85 ± 0.29	2.03 ± 0.59	0.51
FEV ₁ , % pred	76 ± 15	74 ± 16	79 ± 14	0.52
FVC, litres	2.36 ± 0.61	2.34 ± 0.61	2.39 ± 0.67	0.87
FVC, % pred	77 ± 15	77 ± 15	76 ± 15	0.79
FEV ₁ /FVC, %	82 ± 7	79 ± 6	85 ± 7	0.10
TLC, % pred	74 ± 12	70 ± 12	78 ± 8	0.20
TLco, % pred	48 ± 13	46 ± 14	49 ± 11	0.70
PI _{max} , cm H ₂ O	77 ± 21.7	82 ± 23.7	71 ± 19	0.36
PE _{max} , cm H ₂ O	84 ± 25.4	83.5 ± 27	84 ± 24	1.0
SNIP, cm H ₂ O	74 ± 16	68 ± 13	81 ± 19	0.33
SnPdi, cm H ₂ O	96 ± 25	86 ± 24	108 ± 22	0.12
Cdyn, litres·cm H ₂ O ⁻¹	0.06 ± 0.02	0.07 ± 0.02	0.06 ± 0.02	0.46
Cough Pga	163 ± 44	171 ± 54	153 ± 27	0.67

Cdyn = Dynamic compliance; Cough Pga = cough gastric pressure; FFMI = fat-free mass index; PE_{max} = maximal expiratory pressure; PI_{max} = maximal inspiratory pressure; SNIP = sniff nasal pressure; SnPdi = sniff transdiaphragmatic pressure; TLco = carbon monoxide diffusing capacity of the lung.

p values are for t tests comparing fatiguers and nonfatiguers.

with associated connective tissue disease (CTD). Of these, 3 had systemic sclerosis (SSc), 1 had an overlap between SSc and systemic lupus erythematosus, 1 had rheumatoid arthritis, 1 had mixed CTD and 2 had undifferentiated CTD. In the 11 patients whose diagnosis was not confirmed by lung biopsy, diagnosis of the ILD pattern was based on CT appearances, bronchoscopy, serological findings and other clinical data [21]. Of the patients with CTD, 7 had imaging features of fibrotic non-specific interstitial pneumonitis and 2 had overlap features between fibrotic non-specific interstitial pneumonitis and organizing pneumonia. The diagnosis of CTD was based on current rheumatological criteria. All patients were clinically stable at the time of study and were free from cardiovascular, musculoskeletal or neurological disease that could affect exercise performance. Patients were excluded if they required home oxygen therapy or if there were any clinical features suggesting the presence of myopathy/myositis (abnormal muscle enzymes, muscle pain or fatigue or the presence of anti-synthetase antibodies). All subjects were on low doses of oral prednisone (8.9 ± 4 mg/day) and 7 were on a second immunosuppressive drug (4 on azathioprine and 3 on mycophenolate).

The research ethics committee of the Royal Brompton Hospital approved the study. All patients gave written informed consent. Spirometry, plethysmographic lung volumes and gas transfer were measured using a Compact Lab System (Jaeger, Germany) in accordance with ATS recommendations. Fat-free mass was

determined using bioelectrical impedance analysis (Bodystat 1500; Bodystat, Isle of Man, UK).

Respiratory Muscle Strength Assessment

Following the placement of oesophageal and gastric balloon catheters [22], the maximum inspiratory pressure, expiratory pressure [23], sniff nasal pressure, sniff transdiaphragmatic pressure [24] and cough gastric pressure [25] were determined. Pressure signals were amplified and passed to a computer running LabView 4.1 software (National Instruments, Austin, Tex., USA).

After performing the volitional tests, patients rested for 20 min without speaking to depotentiate their respiratory muscles. Diaphragm strength [transdiaphragmatic pressure at bilateral phrenic nerve twitch (TwPdi)] was assessed as the unpotentiated response elicited by bilateral, anterolateral, magnetic phrenic nerve stimulation, using a pair of 45-mm figure-of-eight coils each powered by a Magstim 200 monopulse unit delivering an output 100% of maximum with patients seated upright in a straight-backed chair [26]. Abdominal muscle strength [gastric pressure at twitch T10 nerve roots (TwT10Pga)] was assessed using the twitch gastric pressure response to stimulation delivered to the nerve roots supplying the abdominal muscles, at the level of the 10th thoracic vertebra, by a circular coil [19, 27]. Coil position was adjusted to produce the maximal response in gastric pressure and oesophageal pressure (Poes). Stimulations were performed at resting end expiration. Care was taken to ensure that patients were always in the same position when stimuli were delivered and the coil position was marked with indelible pen to ensure that this was constant.

The Poes method was used for the measurement of dynamic lung compliance. The patients were seated in an upright position and were connected to a bodyplethysmograph in order to measure lung volume and register the pressure/volume curves. Dynamic compliance was registered during quiet breathing with a respiratory rate between 10/min and 20/min.

Exercise Test

Subjects then performed an incremental exercise test on a cycle ergometer. The exercise protocol involved an initial 2 min of rest, 2 min of unloaded cycling followed by an increment of 10 W every minute. Breath by breath analysis of ventilatory parameters was performed using an Oxycon metabolic system (Jaeger). Poes was measured throughout the test and arterialized capillary blood gas sampling was performed before and after exercise. Patients performed an inspiratory capacity (IC) manoeuvre at the end of each minute to assess changes in dynamic lung volume, with end-expiratory lung volume (EELV) calculated by subtracting IC from TLC [28, 29]. Standardized encouragement was given. Exercise tests were symptom-limited with patients cycling until they felt unable to continue. Patients indicated their level of leg or breathing discomfort on a Borg scale before and after exercise and the reason for stopping was also documented.

After the end of the exercise test, patients again rested for 20 min to allow the muscle to depotentiate before the magnetic stimulations were repeated. On both occasions, the phrenic nerve stimulations were performed before the thoracic nerve-root stimulations.

Statistical Analysis

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) version 15 for Windows. Fatiguers

were defined a priori as individuals who had $\geq 10\%$ fall in TwT10Pga after exercise according to convention from previous work, with 10% being roughly twice the coefficient of variation for the test [19, 30]. Values before and after exercise were compared using the paired Student *t* test or the Wilcoxon signed-rank test and between groups using the Student *t* test or the Mann-Whitney *U* test. The Pearson (*r*) correlation coefficient or the Spearman rho were used to analyze correlations between parametric and non-parametric variables, respectively, as appropriate. Lung volumes at baseline and during the exercise were compared using ANOVA for repeated measures and the Dunnett post hoc test. Values are presented as mean $\pm$ SD, unless otherwise specified. A *p* value of <0.05 was considered significant.

Results

The patients exercised for a mean of 9.6 ± 2.15 min achieving a peak workload of 80 ± 22.3 W ($76 \pm 21\%$ predicted). Peak oxygen uptake at peak of exercise (VO_2) was 1.32 ± 0.27 l/min or 19.9 ± 4.9 ml/kg/min, ($78 \pm 14.8\%$ predicted). The maximal heart rate was 137 ± 20 beats/min ($84 \pm 9\%$ predicted) and the peak exercise ventilation was 53 ± 12.7 l/min ($72 \pm 14\%$ predicted). Ten patients reported that they had stopped because of leg fatigue, 2 because of breathlessness and 4 because of a combination of the two. Median (25th, 75th centile) Borg dyspnoea score at the end of the exercise was 5 (4.5, 6.5) and Borg leg discomfort was 15 (15, 17).

Following exercise, TwT10Pga fell from 28.6 ± 18 cm H_2O to 25.2 ± 14 cm H_2O ($p = 0.02$) (fig. 1). This fall remained significant even if the patient with the largest fall in pressure was excluded from analysis ($p = 0.04$). In 9 patients (56%), 6 female and 3 male, it fell by more than 10% from baseline; these patients were defined as abdominal fatiguers. Two of them were affected by idiopathic pulmonary fibrosis, 1 by fibrotic hypersensitivity pneumonitis and 6 showed an ILD pattern of CTD. Of these, 2 had SSC, 1 had an overlap between SSC and systemic lupus erythematosus, 1 had mixed CTD and 1 had undifferentiated CTD. In the remaining 7 (5 female and 2 males) 2 were affected by idiopathic pulmonary fibrosis, 2 by fibrotic hypersensitivity pneumonitis, 1 had rheumatoid arthritis, 1 had SSC and 1 had mixed CTD. By contrast, TwPdi did not change significantly following exercise – before: 21.8 ± 8 cm H_2O and after: 20.2 ± 8 cm H_2O ($p = 0.10$).

During exercise there was a significant fall in EELV from 2.18 ± 0.65 litres at rest, to 1.91 ± 0.59 litres ($p = 0.04$) at peak exercise (fig. 2). The Poes achieved during IC manoeuvres did not change from the beginning to the end of exercise, suggesting that there was no reduction in

Fig. 1. TwPdi (a) and TwT10Pga (b) pressure before and after exercise.

Table 2. Exercise responses in all patients and those who did or did not develop abdominal muscle fatigue

	All	Fatiguers	Non-fatiguers	p
Peak VO_2 , l/min	1.32 ± 0.27	1.37 ± 0.3	1.24 ± 0.22	0.35
Peak VO_2 , %	78 ± 15	78 ± 18	79 ± 11	0.94
Peak work load, W	83 ± 22	83 ± 26	76 ± 16	0.24
Peak work, % pred	76 ± 21	69 ± 25	85 ± 11	0.14
VE peak, l/min	53 ± 12.7	55.3 ± 2.8	49.5 ± 1.5	0.8
IRV rest, litres	1.11 ± 0.4	1.08 ± 0.4	0.67 ± 0.5	0.78
IRV peak, litres	0.63 ± 0.5	1.14 ± 0.4	0.57 ± 0.6	0.72
EELV rest, litres	2.18 ± 0.65	2.08 ± 0.47	2.3 ± 0.45	0.96
EELV peak, litres	1.91 ± 0.59	1.56 ± 0.42	2.27 ± 0.66	0.008*
Δ EELV, % basal	-11 ± 17	-22 ± 22	-0.68 ± 8	0.016*
Poes peak, % Poes max	55 ± 17	65 ± 16	44 ± 12	0.014*
TwPdi before, cm H_2O	21.8 ± 8.0	17.8 ± 6.2	27.0 ± 7.3	0.02*
TwPdi after, cm H_2O	20.2 ± 8.0	17.6 ± 7.6	23.6 ± 7.6	0.14
Δ TwPdi, %	1.6 ± 3.7	-3.2 ± 15.7	-12.8 ± 16.1	0.9
TwT10Pga before, cm H_2O	28.6 ± 18.0	29.3 ± 22.0	27.6 ± 12.5	0.71
TwT10Pga after, cm H_2O	25.2 ± 14.1	22.6 ± 15.8	28.6 ± 11.8	0.17
Δ TwT10Pga, %	-9.8 ± 14.7	-21.2 ± 5.9	4.9 ± 7.1	$<0.0001^*$

IRV = Inspiratory reserve volume; VE peak = ventilation at peak of exercise.

* $p < 0.05$.

effort. Oxygen saturation fell significantly, from $96 \pm 0.9\%$ to $94 \pm 3.4\%$ ($p = 0.008$). During exercise, peak inspiratory Poes during tidal breathing became more negative (from -8.9 ± 7.2 cm H_2O to -20.9 ± 15 cm H_2O ; $p < 0.001$), and peak expiratory Poes became more posi-

tive (from -0.1 ± 4.5 cm H_2O to 6.9 ± 7 cm H_2O ; $p = 0.001$), indicating increasing expiratory muscle recruitment. Furthermore, Poes during tidal volume at peak of exercise in percentage of maximum Poes was $55 \pm 17\%$, suggesting significant inspiratory muscle loading during

Fig. 2. EELV (a), inspiratory reserve volume (IRV) (b), end-inspiratory lung volume (EILV) (c) and tidal volume (TV) (d) expressed as a percentage of predicted TLC during exercise (* $p < 0.05$; ** $p < 0.01$ vs. baseline).

exercise. Changes in Poes during exercise were not associated with peak exercise performance or with changes in TwPdi or TwT10Pga.

Change in TwT10Pga was associated with peak VO_2 ($r = -0.52$, $p = 0.041$), increase in heart rate ($r = -0.53$, $p = 0.032$) and with EELV at peak exercise ($r = 0.7$, $p = 0.021$) as well as with the change in EELV during exercise ($r = 0.57$, $p = 0.021$).

Abdominal fatiguers and non-fatiguers are compared in tables 1 and 2. There was no significant difference between the 2 groups in terms of baseline parameters except that TwPdi was lower in the abdominal fatiguers group ($p = 0.02$).

The peak workload and VO_2 achieved and the reason given for stopping did not differ between groups. EELV did not differ between groups at rest, but at the peak of

exercise it was significantly lower in the abdominal fatiguers; 1.56 ± 0.42 litres compared to 2.27 ± 0.66 litres in the non-fatiguers ($p = 0.008$) (fig. 2). The oxygen saturation was not significantly different between groups at rest. There was a significant drop in the fatiguers (from 97 to 93%, $p = 0.027$), but it did not change significantly in the non-fatiguers.

Discussion

We found that in patients with ILD, mean twitch gastric pressure, but not twitch transdiaphragmatic pressure, fell after symptom-limited cycle ergometry, indicating that low-frequency fatigue occurred in the abdominal muscles but not in the diaphragm. Abdominal muscle fa-

tigue was associated with a decrease in the EELV consistent with increased expiratory muscle recruitment and shortening and was also associated with a greater fall in oxygen saturations. These data suggest, at least for the abdominal muscles, that the presence of fatigue is more strongly related to contractile history and hypoxia than to length change.

Significance of Findings

Our results suggest that abdominal muscle fatigue may occur in patients with ILD and although the group in whom it occurs cannot be identified by their baseline characteristics, they do display a different pattern of ventilation during exercise with a fall in EELV. The association between the development of low-frequency fatigue of the abdominal muscles and fall in EELV is most readily explained as a consequence of the recruitment of expiratory muscles, driving down EELV to increase IC. Although not active during resting expiration in healthy subjects, the abdominal muscles play an important role during exercise, increasing expiratory flow rate and contributing to IC [31]. Moreover, expiratory muscles act as accessory muscles of inspiration, allowing them to produce force by improving their length-tension relationship and mechanical geometry [32] and thus help to overcome the elastic load that is present. Active contraction of the abdominal muscles shifts abdominal contents and diaphragm caudally. Abdominal relaxation allows these to fall, aiding inspiration.

In health, increase in minute ventilation is achieved by an increase in respiratory rate and tidal volume, with a fall in EELV and an increase in end-inspiratory lung volume. However, previous studies have not observed a fall in EELV in patients with ILD and, thus, differ from the data presented here [20, 33, 34]. This apparent discrepancy may be due to differences in the patient populations. In this study a milder group of patients was recruited, with those who required oxygen being excluded. The difference could be due to the relatively small sample sizes involved or because a different technique such as optoelectronic plethysmography was used [34]. The data suggest that the abdominal muscles are more susceptible to fatigue than the diaphragm, since the latter only fatigues at high levels of exercise in health and does not appear to fatigue in patients with ILD or COPD whereas abdominal muscle fatigue has now been shown to occur in both patient groups [19].

Susceptibility to fatigue of the abdominal muscles may have been enhanced by a reduction in oxygen supply to the contracting muscles since it was associated with a

greater level of desaturation. Hypoxia has previously been shown to increase exercise-induced fatigue of the diaphragm [35]. The proportion of fast-twitch fibres, indeed, is higher in expiratory muscles than in the diaphragm [36], and so the oxidative capacity of the muscle is lower [37]. In addition, expiratory muscle endurance is lower than that of the inspiratory muscles during exercise [38]. Increased expiratory pressures may impede venous return and impair cardiac output which has been shown to be an important determinant of exercise capacity in ILD [1].

The length at which a muscle contracts has an important influence on its susceptibility to fatigue, although this has usually been evaluated in the context of shortening [18] and is thought to be related to impaired intracellular propagation of the depolarization [39]. A fall in EELV would be associated with expiratory muscle shortening and ought, therefore, to protect against fatigue. This is the reverse of the current data, although the effect of volume change on the contractile properties of the abdominal muscles has previously been investigated above rather than below functional residual capacity [40], unlike the inspiratory muscles [41]. Even so, we conclude that, at least for patients with ILD, contractile activity and hypoxia are more relevant determinants of the likelihood of fatigue.

Abdominal muscle fatigue was not associated with reduced exercise tolerance in ILD patients, but it might impact on symptom load by increasing the sensation of dyspnoea. Dyspnoea is known to increase after breathing against different expiratory loads [42], while specific training of the abdominal muscles has been demonstrated to reduce the feeling of breathlessness during exercise as well as the minute ventilation, as a consequence of a decrease of central respiratory drive [37]. Conversely, isolated unloading of the inspiratory muscles can reduce expiratory muscle activity [43]. However, we did not, in fact, find any association between abdominal muscle fatigue and breathlessness during exercise. The majority of the patients stopped because of leg fatigue alone or a combination of leg fatigue and breathlessness; however, both of those who stopped because of dyspnoea were abdominal fatiguers.

Expiratory muscle fatigue is related to limb muscle fatigue by an increase of sympathetic vasoconstrictor outflow [44], and it has been shown to compromise exercise tolerance because of an increase of leg discomfort and limb locomotor muscle fatigue in subjects exercising after undergoing an expiratory muscle fatiguing protocol [45]. This could therefore be a fruitful area for future research.

Methodological Issues

For reasons of tolerability, to reduce the number of stimulations that patients received we did not perform a formal stimulus response curve to confirm supramaximality of the stimulations. Supramaximality of magnetic phrenic nerve stimulation has been demonstrated in numerous previous studies [26, 46–50]. Care was taken to ensure that magnetic stimulation was performed with the patients and coils in the same positions. For thoracic nerve-root stimulation, a plateau in M-wave response has been observed by a number of authors [51], although we argued that thoracic nerve root stimulation cannot be supramaximal (because the coil does not anatomically cover all the nerve roots), though it is likely to be close to it. Nevertheless, the association of a fall in TwT10pga with increased expiratory muscle activity suggests that true fatigue was present [40].

We included only patients who were clinically stable and free from comorbidities that could affect exercise performance at the time of study. Patients were also excluded if they required home oxygen therapy. As a consequence, we studied patients with mild-to-moderate lung disease. It is possible that some had a degree of respiratory muscle involvement either as a consequence of their disease or their treatment, but this was not clinically apparent. TwPdi was lower in patients developing abdominal muscle fatigue, which raises the possibility that the pattern of breathing adopted reflects an increased ab-

dominal muscle contribution to ventilation to compensate for diaphragm dysfunction. However, it should be noted that maximum inspiratory pressures were in the normal range. Poes/Poes max was higher in abdominal fatiguers, suggesting that their inspiratory muscles were relatively more loaded.

We did not measure EMG during exercise to establish the presence or absence of high-frequency fatigue or sniff relaxation pressures immediately after exercise, which might have given further insight into the extent to which fatigue was limiting exercise and the degree to which the respiratory muscles were loaded.

Conclusions

Abdominal muscle fatigue occurs in patients with ILD after symptom-limited cycle-ergometry maximal exercise. Further work is needed to elucidate interactions with locomotor muscle fatigue.

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