Does quadriceps contractile fatigue influence rehabilitation outcomes in COPD–chronic respiratory failure patients?

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Shareable abstract (@ERSpublications)
The presence of quadriceps peripheral muscular fatigue predicts greater improvement in effort tolerance following pulmonary rehabilitation in COPD patients with chronic respiratory failure, suggesting it could be an important evaluation target https://bit.ly/416z6wn

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Abstract

Background In patients with moderate COPD, response to pulmonary rehabilitation including exercise training varies according to the presence of peripheral muscle fatigue (pMF) of quadriceps. This study investigates the role of pMF in predicting pulmonary rehabilitation outcomes in more severe COPD patients who have already developed chronic respiratory failure (COPD–CRF).

Methods A *post hoc* analysis of a prospective randomised controlled trial was performed at Istituti Clinici Scientifici Maugeri Lumezzane (Brescia, Italy), involving 30 COPD–CRF patients undergoing a pulmonary rehabilitation programme comprising 20 endurance training sessions. Pre-to-post assessment included a 6-min walk test (6MWT), Fatigue Severity Scale (FSS), Barthel dyspnoea index, and quality-of-life questionnaires. We assessed the contractile pMF of quadriceps *via* electrical nerve stimulation pre-to-post a cycling fatiguing task, using the change in potentiated quadriceps twitch for pMF.

Results At baseline, 12 (40%) patients developed pMF (pMF group), while 18 (60%) did not (no-pMF group). The pMF group had a lower baseline 6-min walk distance (6MWD) with greater FSS and lower quadriceps thickness. After pulmonary rehabilitation, no change in contractile pMF was found in the overall group, but pMF ameliorated only in the pMF group. The pMF group had a greater increase in 6MWD (71.67±53.64 m *versus* 35.28±36.01 m, $p<0.05$) and was more likely to exceed the minimal clinically important difference in 6MWD (OR 6.25, 95% CI 1.05–37.07; p=0.044). Other pulmonary rehabilitation outcomes improved similarly between groups.

Conclusion Baseline quadriceps pMF predicted greater improvement in the 6MWT in COPD–CRF patients, suggesting it may be a new target for predicting pulmonary rehabilitation outcomes and optimising training protocols.

Introduction

Pulmonary rehabilitation including exercise training is a crucial and effective treatment for COPD patients [1], but improvements in exercise performance vary across patients: those with muscle weakness, low exercise tolerance, and ventilatory limitations generally show greater gains in effort tolerance [2, 3]. Physiological changes in muscle characteristics and effort tolerability occur when exercise targets critical intensity and consequently muscle stress [4]. Typically, endurance training is utilised for pulmonary rehabilitation in patients with COPD; however, many of these patients struggle to achieve sufficient training intensity due to dyspnoea, lung mechanics, gas exchange issues and haemodynamic limitations, leading to early cessation of exercise and leaving the skeletal muscles insufficiently stressed to derive appropriate training adaptations [5–8].

Muscle fatigue is a reversible reduction in maximal voluntary muscle contraction force (MVC) during tasks like constant load exercise, with further stratification in central (reduced voluntary muscle activation

(MVA%)) and peripheral contractile muscle fatigue (pMF) [9]. Interestingly, only some COPD patients develop pMF after endurance exercise [10–12]. In a recent study of severe COPD patients with chronic respiratory failure (COPD–CRF), only 37% exhibited pMF after a constant-load cycling task to exhaustion [13]. The mechanisms underlying this phenomenon remain under debate: the main hypothesised causes range from ventilatory limitation to different muscle fibre phenotypes [10–13].

Recent studies in moderate COPD without CRF [14, 15] found that patients developing pMF after cycling had greater improvements in walking capacity and quality of life after endurance-based pulmonary rehabilitation. However, no studies have investigated this aspect in severe COPD patients with CRF.

CRF patients are a highly represented cluster in the field of pulmonary rehabilitation [16], are burdened by a high level of healthcare resource utilisation [17] and are characterised by continuous use of oxygen therapy, which may have implications for exercise tolerance [18], rehabilitation response and disease impact [16, 19].

Of note, as exposed previously, advanced ventilatory limitation may prevent CRF patients from developing pMF during exercise. In this context, we hypothesised that pMF, if present, may serve as a predictor for successful pulmonary rehabilitation outcomes in severe COPD patients with CRF. We examined, in COPD–CRF patients undergoing endurance training, 1) the role of baseline pMF in predicting pulmonary rehabilitation outcomes (dyspnoea, exercise tolerance, quality of life) and 2) the change in muscle fatigue (central and peripheral) induced by rehabilitative exercise training.

Methods

Study design

This *post hoc* analysis of a prospective randomised controlled trial, funded by the Ministry of Italian Health through a 5×1000 project [20], was conducted at Istituti Clinici Scientifici Maugeri Lumezzane (Brescia, Italy) from August 2019 to June 2023. Written informed consent was obtained from all participants; the study was approved by the ethics committee (CE 2288, 9 April 2019); and all procedures followed the Declaration of Helsinki.

Subjects

We evaluated a convenience sample of COPD–CRF patients referred to our centre for inpatient pulmonary rehabilitation, including those with high-quality pre-to-post quadriceps muscle fatigue measures. Inclusion criteria were a COPD diagnosis, presence of CRF (arterial oxygen tension (P_{aO_2}) <60 mmHg) with the prescription of 24-h oxygen therapy for ⩾3 months [21], forced expiratory volume (FEV_1) <50%, stable clinical condition (pH >7.35, no recent changes in therapy, no exacerbations or hospitalisations in the past 3 months), and absence of orthopaedic, neurological, cardiac or cognitive impairments. Patients received oxygen (O_2) *via* nasal prongs as liquid oxygen during rest and from portable cylinders during activities. O_2 was prescribed based on arterial blood gas (ABG) analysis to achieve P_{aO_2} >60 mmHg at rest and monitored with a saturimeter to maintain arterial oxygen saturation >91% during exercise.

Pulmonary rehabilitation and exercise training programme

The pulmonary rehabilitation programme was an inpatient multidisciplinary intervention involving pulmonologists, physiotherapists, psychologists, nutritionists and nurses. The core component was exercise training, focusing on endurance with either continuous or interval cycle ergometer sessions, as described in Vitacca *et al.* [20]. Patients exercised once daily, 6/7 days a week, for 40 min. The total workload was similar across training modalities. Progression was tailored to individual heart rate, peripheral oxygen saturation (S_{pO_2}) (maintained >91%), and the Maltais protocol [22] for assessing dyspnoea and fatigue. Each session was supervised by experienced physiotherapists, with clinical staff blinded to fatigue measurements.

Measures

Anthropometric data, complexity and severity of comorbidities by Cumulative Illness Rating Scale (CIRS1 and CIRS2) [23] were collected. At baseline, static and dynamic lung volumes were measured by spirometer (Spirolab; CareFusion, Germany) according to the European Respiratory Society guidelines [24]. The amount of oxygen and carbon dioxide in the blood at rest was assessed by ABG analysis (ABL90 series; Radiometer Medical APS, Denmark) and respiratory muscle strength by maximal inspiratory pressure and maximal expiratory pressure (MicroRPM; CareFusion, Basingstoke, UK).

The thigh volume of the dominant leg was indirectly based on leg circumferences (three locations: distal, central and proximal), thigh length and skinfold measurements [25], and the rectus femoris thickness was assessed by an echo scan (Logiq Q V2; General Electric, Solingen, Germany) [26].

Before (t_0) and after (t_1) the training programme, functional exercise capacity was assessed by

- 6-min walk test (6MWT) [27]; and
- cycloergometer incremental exercise test (CIET) to determine peak power output (peak W). The incremental exercise test was performed on an electromagnetically braked cycle ergometer (Ergoline 800; Sensor Medics, Anaheim, CA, USA) with ramp load increments of 10 $W \cdot min^{-1}$ up to the limit of tolerance, with the patients maintaining a cadence of 60 rpm.

In addition, we evaluated the following.

- Perceived dyspnoea using the Barthel dyspnoea index [28], which assesses breathlessness during activities of daily living: score from 0 (no dyspnoea) to 100 (maximum dyspnoea).
- Perceived fatigue in daily life using the Italian version of the Fatigue Severity Scale (FSS) [29] and according to the classification proposed by KRUPP *et al.* [30]: non-fatigue if the score is ⩽4.0; borderline fatigue if the score ranges between 4.0 and 5.0; fatigue if the FSS score is >5.0.
- Health-related quality of life as defined by the Maugeri Respiratory Failure (MRF) questionnaire [31].
- Impact of the disease, as described by the COPD Assessment Test score [32].

At the end of each training session, the following parameters were recorded: work (in joules), volume of work (workload in watts), S_{pO_2} and inspiratory oxygen fraction (F_{iO_2}).

Contractile muscular fatigue evaluation

Muscle fatigue assessment (global fatigue, central and peripheral components) was measured before (∼5 min) and 5 min after a constant-load cycling test (CLCT) as follows: subjects were seated in an upright position with back support and a seat belt was applied to the pelvis. The knee was flexed at 90° and the ankle of the dominant leg was attached to the force transducer (DBBSE 100 kg, A2829; Applied Measurements, Aldermaston, UK), by a strap and a rigid steel bar. The output from the force transducer was amplified (INT2- L; London Electronics Limited, Sandy, UK) and recorded using a PowerLab-16/35 data acquisition system (ADI Instruments, Dunedin, New Zealand). Electrical stimuli were delivered after positioning self-adhesive electrodes (50×90 mm, MyoTrode PLUS; Globus G0465, Codognè, Italy) with the cathode positioned over the femoral triangle, 3–5 cm below the inguinal ligament, and the anode placed over the posterior iliac crest. Each test procedure began with the determination of the maximal M-wave and potentiated resting quadriceps twitch (Qtwpot) responses in the resting quadriceps muscle (*i.e.* peripheral component). Briefly, the current intensity was progressively increased (+20 mA each time) starting from 25 mA to the value beyond which there was no further increase in M-wave peak-to-peak amplitude and resting quadriceps twitch. The 125% of the intensity was chosen to evoke the individual maximum M-wave response. The Qtwpot was evoked in the resting muscle by electrical stimulation consisting of single square-wave pulses of 1 ms duration at 350 V, delivered by a constant current stimulator (Digitimer mod. DS7HA, Digitimer, Welwyn Garden City, UK). The Qtwpot was elicited 2 s after a 5-s MVC (*i.e.* global fatigue) of the quadriceps before and after a fatiguing CLCT task. Voluntary muscle activation (%MVA) of the quadriceps muscle during the MVCs was assessed using the superimposed twitch technique. The force produced during a single twitch superimposed on the MVC was compared with the force produced by the electrically evoked twitch produced, at rest, 2 s after the MVC.

The evaluation was repeated at least three times and the mean data of MVC, Qtwpot and %MVA were used. The interval between the MVCs was 30 s. Therefore, it should be noted that the Qtwpot was assessed in the potentiated state [13]. pMF was assessed using the percentage change in Qtwpot after the fatiguing CLCT task, calculated as:

$$(\text{Qtwpot post} - \text{Qtwpot pre})/(\text{Qtwpot pre}) \times 100$$

To better describe the phenomenon, we clustered the recruited subjects in two subgroups: pMF, representing the subjects who developed pMF, and no-pMF, indicating the patients who did not. The cut-off of the pMF was a Qtwpot reduction >15% after the fatiguing task [14].

Fatiguing task

A CLCT at 80% peak power output was used to induce muscle fatigue, performed on an electromagnetically braked cycle-ergometer (Ergoline 800; Sensor Medics). Time to exhaustion was recorded in seconds, with patients exercising as long as possible with continuous encouragement. The test ended when dyspnoea/muscle fatigue perception became intolerable, or the cadence (60 rpm) was not maintained for >10 s. Dyspnoea and leg rate of perceived exertion were recorded every 60 s using the modified Borg scale [33]. To assess

changes in muscle fatigue post-pulmonary rehabilitation, we repeated the CLCT after pulmonary rehabilitation, stopping at the initial exhaustion time (t_0) to ensure equivalent work volume.

Statistical analysis

All statistical analyses were performed using STATA 11.2 software (Stata, College Station, TX, USA). Data are presented as mean±SD. Differences between groups were assessed using an unpaired t-test for continuous data and a Chi-squared test for categorical and binary data. Pre-to-post assessments within the same group were analysed using paired t-tests. The Pearson's correlation coefficient (R) was used to evaluate relationships between variables. The minimal clinically important difference (MCID) for 6MWT was 30 m [27]. A p-value <0.05 was considered significant.

Results

Out of the 60 patients enrolled in the previous study [20], 30 were suitable for this subanalysis, with selection based on good-quality muscle fatigue measures available both before and after the intervention.

Before the pulmonary rehabilitation period, the fatiguing task was coupled with a decline of −8.45±7.74% in MVC (p<0.001), −5.00±11.06% in MVA (p<0.001) and −16.8±18.1% in Qtwpot (p<0.001), and in the whole population. Interestingly, 12 (40%) patients reached the threshold of pMF (Qtwpot reduction >15% in absolute value), while 18 (60%) did not.

Table 1 describes the characteristics of the population studied. Patients were predominantly male, with severe lung obstruction, severe static hyperinflation and impaired oxygen exchange. The level of dyspnoea was moderately high, with borderline levels of perceived fatigue. Patients showed severe exercise tolerance and moderate reduction in muscle strength. The pMF group walked a lower distance, had greater fatigue perception during the 6MWT, and reduced rectus femoris thickness, indicating a worse functional status.

Change in muscle fatigue induced by exercise training

After pulmonary rehabilitation, the whole group exhibited no differences in global fatigue (change in MVC% +1.5±12.26%, p=0.5081), pMF (change in ΔQtwpot% +4.35±18.95%, p=0.2353) and central component of muscle fatigue (change in ΔMVA% +4.276±11.72%, p=0.0599) at iso-volume of work after CLCT compared to baseline.

However, the pMF group showed a significant amelioration of muscle pMF over time (change in ΔQtwpot% +18.93±14.01%, p=0.0007) which was greater (p<0.001) than in the no-pMF patients (change in ΔQtwpot% −5.32±13.93%, p=0.1235). Figure 1 shows the pre-to-post individual change in quadriceps peripheral muscle fatigue when performing a CLCT at iso-volume of work. There is a clear trend for all patients in the pMF group to decrease muscle fatigability, whereas no changes were observed in the no-pMF group. However, some patients in the no-pMF group even showed a tendency towards increased fatigability after pulmonary rehabilitation.

Role of quadriceps pMF in predicting rehabilitation outcomes

Table 2 describes the change in all rehabilitation outcomes in the whole population and according to pMF or no-pMF group. After the pulmonary rehabilitation programme, as expected, the whole group of patients showed a significant increase in effort tolerance, muscle strength, and improvement in the perception of dyspnoea and fatigue, impact of the disease and quality of life. The only difference between patients was 6-min walk distance (6MWD), which was greater in patients who developed fatigue than in those who did not (table 2). Figure 2 details the individual absolute value changes in 6MWD (figure 2a) and the percentage of patients who improved the distance above the MCID (figure 2b) [27] according to the subgroups of patients with and without peripheral muscle fatigue at t_0. Patients with pMF were more responsive to pulmonary rehabilitation (figure 2): the odds ratio for improving the 6MWD above the MCID in patients with pMF was 6.25 (95% CI 1.05–37.07, p=0.044).

Role of quadriceps pMF in training progression

All patients performed endurance training: 13 (43%) underwent continuous training and 17 (57%) underwent interval training. Figure 3 illustrates the mean workload, work volume (workload × time), blood oxygen saturation and F_{IO_2} over 20 sessions. No differences were found between groups, although there was a tendency for the no-pMF group to require less oxygen.

The workload increase was 9.97±10.31 W (pre-to-post p<0.001) in the total population, showing a change in mean workload of 6.41±9.60 W in the pMF group *versus* 12.33±10.35 W in the no-pMF group (p=0.1258).

TABLE 1 Patients' clinical characteristics, according to the presence or absence of quadriceps peripheral muscle fatigue (pMF)

	Overall	pMF group	No-pMF group	p-value
Subjects	30	12 (40)	18 (60)	
Male	19 (63.3)	8 (66.7)	11 (65.0)	0.9235
Age, years	65.3±8.2	65.17±10.07	65.39±7.07	0.9438
BMI, kg·m^{-2}	24.07±5.65	22.71±4.24	24.97±6.38	0.2904
CIRS1 score	1.72±0.41	1.63±0.33	1.78±0.45	0.3298
CIRS2 score	2.93±2.00	2.42±1.62	3.28±2.19	0.2547
FEV_1 % pred	30.93±13.59	29.92±10.93	31.61±15.38	0.7443
FVC % pred	64.80±14.91	62.25±17.39	66.50±13.27	0.4542
FEV_1/FVC	36.45±11.10	36.43±7.05	36.46±13.35	0.9955
RV % pred	199.33±54.50	188.37± 37.38	206.5±63.47	0.3871
P_{aO_2}/F_{IO_2} ratio	289.55±43.75	292.37±36.28	287.66±49.04	0.7786
F_{IO_2} %	22.27±2.39	21.67±1.61	22.67±2.76	0.2692
P_{aCO_2}, mmHg	44.88±7.80	44.33±9.39	45.25±6.81	0.7586
pH	7.42±0.03	7.43±0.03	7.41±0.03	0.2074
MIP, mmHg	57.56±19.78	62.67±21.53	54.69±18.83	0.3437
MEP, mmHg	85.2±34.36	81.44±37.89	87.31±33.31	0.6909
Barthel dyspnoea index	26.06±15.36	31.0±16.64	22.78±13.94	0.1541
MRF score	12.33±7.08	13.75±7.41	11.38±6.91	0.3807
FSS score	4.60±1.72	4.87±1.59	4.43±1.82	0.5026
CAT score	22.20±7.00	23.59±5.30	21.28±7.95	0.3865
6MWT				
6MWD, m	314.0±86.39	278.75±76.19	337.5±86.67	0.0670
6MWD, % pred	61.60±18.07	52.66±11.86	68.07±19.10	**0.0191**
Borg dyspnoea score	3.23±1.68	3.67±1.92	2.94±1.47	0.2542
Borg fatigue score	1.70±1.51	2.5±1.68.5	1.67±1.15	**0.0151**
CIET				
PPO, W	50.70±16.60	48.33±17.0	52.22±16.65	0.5389
Borg dyspnoea score	7.23±1.94	7.25±1.96	7.22±1.99	0.9702
Borg fatigue score	7.07±2.21	7.00± 2.45	7.11±2.11	0.8955
CLCT				
CLCT, s	268.23±169.54	279.58±199.82	260.67±151.81	0.7704
Borg dyspnoea score	7.77±1.19	8.08±0.67	7.56±1.44	0.2423
Borg fatigue score	6.87±2.34	6.92±2.61	6.83±2.29	0.9260
MVC, kg	27.39±8.15	26.87± 8.72	28.42±7.77	0.7650
Qtwpot, kg	5.59±4.94	5.46 ±3.68	5.68 ±5.73	0.9052
Thigh volume anthropometry, cm^3	5882.67±1858.16	5242.41±1766.54	6273.95±1850.37	0.1501
Rectus femoris thickness, cm	1.10±0.41	0.91±0.37	1.26±0.39	**0.0365**

Data are presented as n, n (%) or mean±SD, unless otherwise stated. Bold type represents statistical significance. BMI: body mass index; CIRS: Cumulative Illness Rating Scale; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; P_{aO_2}: blood oxygen tension; F_{IO_2}: inspiratory oxygen fraction; P_{aCO_2}: blood carbon dioxide tension; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; MRF: Maugeri Respiratory Failure questionnaire; FSS: Fatigue Severity Scale; CAT: COPD Assessment Test; 6MWT: 6-min walk test; 6MWD: 6-min walk distance; CIET: Cycloergometer Incremental Exercise Test; PPO: peak power output; CLCT: constant-load cycling test; MVC: maximal voluntary contraction; Qtwpot: quadriceps potentiated twitch.

Correlations

No statistical correlation was found between the anthropometric, clinical and functional variables and the possibility of developing pMF (Qtwpot change after CLCT) at baseline, except for the 6MWD at baseline (R=0.4540, p=0.0115), fatigue and dyspnoea during 6MWT assessed by the Borg scale (R= −0.3701, p=0.0441 and R= −0.3945, p=0.0310, respectively), indicating that patients with lower walking ability and more symptoms developed more fatigue during a high-intensity CLCT.

The change in pMF at iso-volume of work at CLCT after rehabilitative exercise training was found to be inversely related to the baseline muscle fatigue (R= −0.5380, p=0.0031), describing the possibility that training may directly affect muscle fatigability during cycling. In addition, the change in pMF after rehabilitative exercise training was related to high baseline volume of work (R= −0.4252, p=0.0270) and higher baseline perception of fatigue on the 6MWT (R=0.4152, p=0.0280), but not to dyspnoea (R=0.2130, p=0.2764).

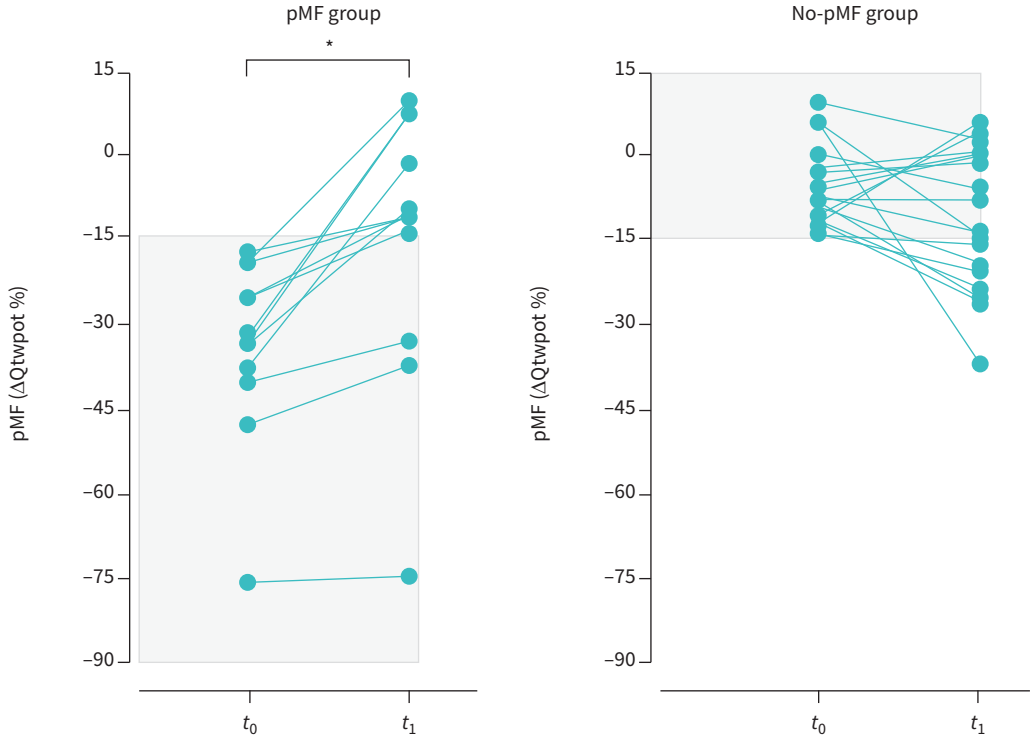

FIGURE 1 Individual change in quadriceps peripheral muscle fatigue (pMF) (measured as change in quadriceps potentiated twitch (ΔQtwpot%)) at iso-volume of work at constant-load cycling test after pulmonary rehabilitation (t_1), according to a) being fatigued (pMF) or b) not fatigued (no-pMF) at the beginning of the intervention (t_0). *: p<0.05 pre-to-post difference (paired t-test).

The change in 6MWD was directly related to the presence of fatigue perception after the test (R=0.3781, p=0.0394), and inversely related to the rectus femoris thickness (R= −0.4444, p=0.0296).

Discussion

The present study shows that COPD–CRF patients with higher pMF of quadriceps at baseline during high-intensity constant-load exercise initially had a worse functional status, characterised by shorter walking distance, greater fatigue perception during the 6MWT, and reduced rectus femoris thickness. Moreover, according to our hypothesis, this group has a more favourable exercise training response in

TABLE 2 Change (Δ) in rehabilitation outcomes in the overall population and according to the presence/absence of quadriceps peripheral muscle fatigue (pMF) at baseline

	Overall[#]	pMF group	No-pMF group	Between-group p-value
Subjects	30	12	18	
Δ6MWD, m	49.83±46.78	71.67±53.64	35.28±36.20	**0.0343**
ΔCIET, W	6.00±10.70	7.50±10.55	5.00±10.98	0.5401
ΔCLCT, s	578.83±587.89	464.25±449.44	655.22±665.91	0.3928
ΔMVC, kg	0.41±6.35	−0.29±7.19	0.89±5.90	0.6278
ΔBarthel dyspnoea index	−6.60±10.01	−9.17±11.66	−4.89±8.68	0.2587
ΔFSS score	−0.52±1.25	−0.99±1.13	−0.14±1.25	0.0783
ΔCAT score	−5.97±7.45	−8.33±8.08	−4.39±8.68	0.1591
ΔMRF score	−1.82±2.97	−2.58±2.39	−1.25±3.30	0.2469

Data are presented as n or mean±SD, unless otherwise stated. Bold type represents statistical significance. 6MWD: 6-min walk distance; CIET: Cycloergometer Incremental Exercise Test; CLCT: constant-load cycling test; MVC: maximal voluntary contraction; FSS: Fatigue Severity Scale; CAT: COPD Assessment Test; MRF: Maugeri Respiratory Failure questionnaire. [#]: all overall pre-to-post comparisons were p⩾0.05.

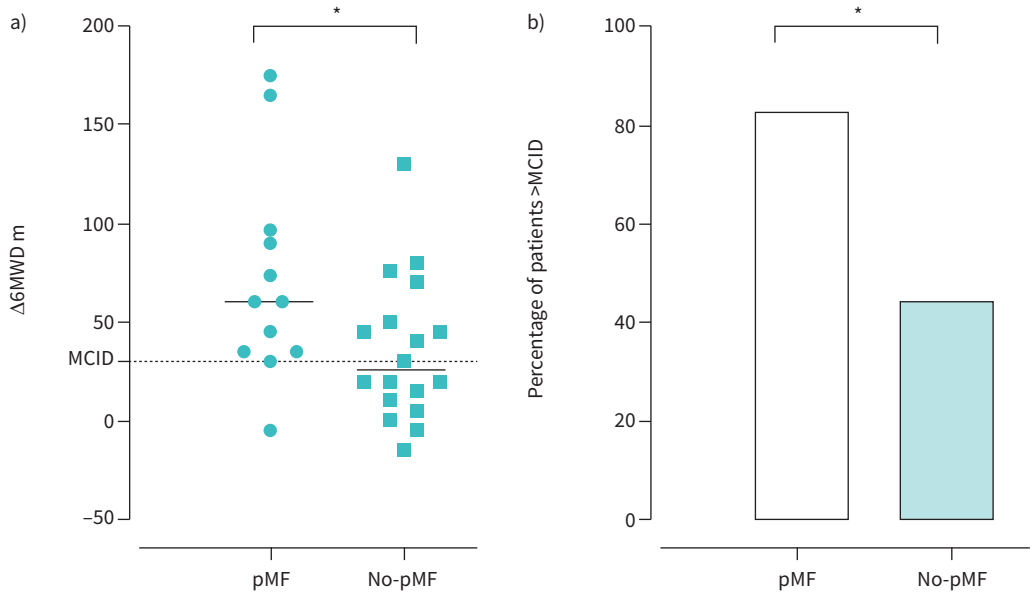

FIGURE 2 Individual changes (Δ) in a) 6-min walk distance (6MWD) and b) percentage of patients reaching the minimal clinically important difference (MCID), according to the presence/absence of quadriceps peripheral muscle fatigue (pMF) at baseline. *: p<0.05.

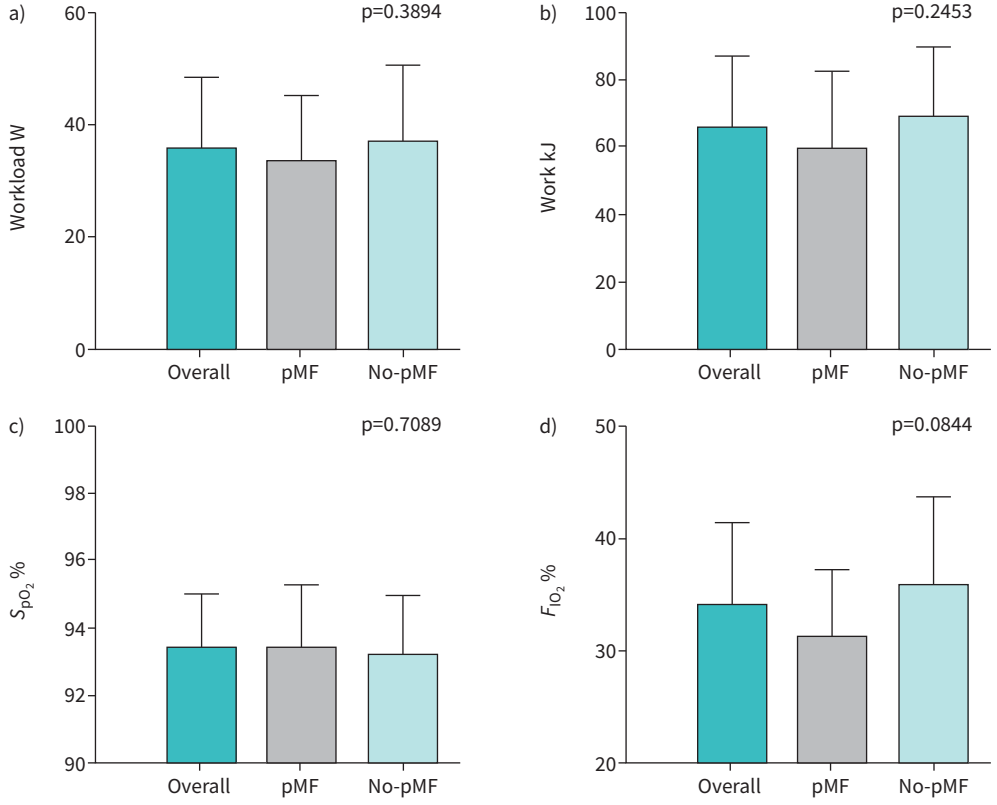

FIGURE 3 a) Mean workload, b) volume of work (workload × time), c) blood oxygen saturation (S_{pO_2}) and d) fraction of inspired oxygen (F_{IO_2}) over 20 sessions for the overall population and for the peripheral muscle fatigue (pMF) and no-pMF groups.

terms of walking exercise capacity and pMF than those without, showing a clear trend to decrease muscle fatigability after training.

Contractile muscular fatigue after cycling exercise

When small muscle mass is involved in the effort, muscle fatigue is more prevalent in COPD patients with CRF than in those with COPD alone or healthy controls [9]. However, consistent with our previous findings [13], less than half of these patients developed pMF during high-intensity constant load cycling.

The reason why some patients don't experience pMF remains unclear. Both fatigued and non-fatigued patients had similar levels of static hyperinflation and dyspnoea at baseline, similar symptoms at the exhaustion of CIET, and experienced higher leg muscle fatigue symptoms at the end of 6MWT.

Unfortunately, we did not assess dynamic hyperinflation and chest wall constraint during exercise [34], which could have better explained our data; in this direction, Vogiatzis *et al.* [35] demonstrated how interval training, a type of exercise that stimulates higher peripheral muscle involvement, is more effective in prolonging patient's exercise capacity by reducing dynamic hyperinflation.

Regarding differences in lung function, Mador *et al.* [11] found that patients who developed quadriceps pMF had better lung function and stronger quadriceps muscles compared to those without pMF. However, our sample was more severe, with a very narrow range of flow limitation (FEV_1 30.93±13.59%), which may have limited the ability to detect differences in spirometry parameters.

Our data show that the patients who improved the most had worse functional walking endurance (assessed by 6MWT) and muscle function (assessed by muscle fatigue at 6MWT and quadriceps thickness).

The development of pMF may result from multiple factors affecting muscle contraction pathways, including neuromuscular junction functionality, excitation–contraction coupling and oxygen delivery [36, 37]. Patients with higher glycolytic enzyme activity, lower muscle capillarisation and earlier lactate accumulation are more prone to fatigue [38], with intrinsic muscle changes leading to early failure despite low exercise intensities [15]. Evaluating our results, we can assume that the pMF group could reach a sufficient muscle stress threshold to promote physiological adaptation. This aspect suggests the probable existence of a defined phenotype, in which both central and peripheral limitations contribute to define the best candidate to be considered a responder to treatment. However, due to the extreme complexity of the phenomenon, there is a need for further elucidation in future specific physiological studies.

pMF and training response

Our study aligns with previous findings in less-severe COPD patients [14, 15]. Quadriceps peripheral fatigue during constant-load cycling correlated with improvements in 6MWD post-training, but not with maximal cycling capacity or quadriceps strength changes. Like the 6MWD, submaximal endurance tests are more sensitive to aerobic metabolism changes than maximal tests [39]. COPD patients show higher P_{aO_2} during cycling, reducing oxyhaemoglobin desaturation compared to walking, where reduced capacity is linked to higher ventilatory demand [40, 41]. This suggests that improvements in pMF are more evident in tasks with greater ventilatory demands. Most of the work investigating the issue of quadriceps fatigue in COPD has been carried out using cycle ergometry [42], as the quadriceps are intensely recruited during this form of exercise, revealing a high prevalence of contractile quadriceps fatigue. Interestingly, Gagnon *et al.* [42] also described that fatigue after walking was only visible in the distal leg muscle groups (dorsiflexors, plantar flexors) and not in the quadriceps, highlighting the important involvement of the former muscles during walking. Alternatively, the significant improvement observed in our patients in the 6MWT, but not in the cycling test, may be due to greater quadriceps fatigue during the cycling task, which may have masked the differences in the endurance time response between the groups.

We found a similar trend in work volume per session between the pMF and no-pMF groups, consistent with Burtin *et al*. [14]. Our study is the first to describe muscle fatigue changes post-training using a constant load test with iso-work as the fatiguing task. Unlike Zghal *et al*. [43], who observed increased pMF after endurance training in healthy populations, we found no significant change in muscle fatigue in the whole group. However, patients with a larger decline in pMF showed marked improvements in this parameter, with a strong inverse correlation (R=−0.5380, p=0.0031) and greater 6MWD improvements.

Clinical implication

A deeper understanding of the modulators and characteristics of fatigue is essential to advance the development of targeted and effective interventions in both clinical and rehabilitation settings. One of the

most promising implications of our findings is the potential to introduce a new indicator of contractile muscle fatigue after the CLCT that could serve as a predictive tool. The presence of pMF during CLCT may identify COPD–CRF patients who achieve the correct target of peripheral exercise intensity according to current exercise training guidelines, possibly explaining their improved responses. If true, patients without pMF development may require alternative training strategies. This personalised approach could include alternative exercise modalities, adjustments in intensity, duration or progression, or the use of external supports such as mechanical ventilation or high-flow oxygen therapy during rehabilitation exercise training.

Limitations of the study

The study has several limitations. First, the *post hoc* evaluation is primarily descriptive with a small sample size, which may have limited the detection of significant differences. A future study with adequate sample size calculation is needed. Second, we used a whole-body task (CLCT) without a local muscle endurance test or detailed skeletal muscle fibre assessment, which could have provided more direct insights into muscle metabolism. In addition, our fatigue task is similar, but not identical, to those used in previous studies in this area [14, 15], which could lead to an error in the interpretation of the test response. Third, the lack of spirometry and gas exchange measurements during exercise limits conclusions about dynamic hyperinflation and metabolic impairment. Finally, oxygen therapy was administered to maintain saturation >91%, and different targets might have yielded different results.

Conclusion

This study shows that COPD–CRF patients with a higher baseline pMF of quadriceps during high-intensity constant-load exercise have a more favourable pulmonary rehabilitation response in terms of walking exercise capacity and pMF reduction compared to those with a lower baseline pMF. This suggests that assessment of contractile muscle fatigue may be an element to consider in guiding the selection of the best candidate for exercise training and in differentiating patients who may require alternative interventions. Further studies are needed to better characterise nonresponders and identify the most appropriate intervention.

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