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Effectiveness of exercise training in patients with COPD: the role of muscle fatigue

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ABSTRACT: The improvement in exercise performance in response to exercise training varies greatly from one patient with chronic obstructive pulmonary disease to another. It is possible that in a portion of patients the muscle stimulus applied during exercise training is insufficient to elicit training effects. We investigated whether patients presenting quadriceps contractile fatigue after training have more favourable effects of a rehabilitation programme.

46 patients followed a 3-month high-intensity exercise training programme. Exercise capacity, quadriceps force and quality of life were measured before and after the programme. Exercise training-induced quadriceps contractile fatigue was assessed after 1 month of rehabilitation with magnetic stimulation. A fall in quadriceps force of $\geqslant$15%, 15 min after training was considered as significant fatigue.

29 (63%) out of 46 patients developed significant fatigue. Patients with fatigue had a higher increase in 6-min walk distance (median (interquartile range) 57 (47–103) m *versus* 17 (-7–46) m; p=0.0023) and Chronic Respiratory Disease Questionnaire score (mean±SD 22±12 points *versus* 14±12 points; p=0.028) after the training programme compared with patients without fatigue. Improvements in quadriceps force and maximal exercise capacity were similar in both subgroups.

Patients who develop quadriceps contractile fatigue during exercise training show greater training effects in terms of functional exercise capacity and health-related quality of life.

KEYWORDS: Exercise therapy, exercise tolerance, muscle, quality of life, rehabilitation, skeletal

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Pulmonary rehabilitation is an essential nonpharmacologic treatment option for patients with chronic obstructive pulmonary disease (COPD) [1, 2]. Comprehensive pulmonary rehabilitation reduces dyspnoea, increases exercise tolerance, improves health-related quality of life and reduces the use of healthcare resources [3, 4]. Although pulmonary rehabilitation is a multidisciplinary treatment, exercise training forms the basis of its effects [3].

In some patients with COPD, exercise tolerance improves to a lesser extent after an exercise training programme [5]. In general, patients with muscle weakness and low baseline exercise tolerance who show less ventilatory limitation experience greater improvements in their exercise capacity [5–7]. Only a limited amount of the variability in training response can be explained with these variables, leaving room for other potential predictors of the success of exercise training.

Skeletal muscle overload is an important training principle indicating that the level of the training load has to be sufficient to stress the muscle in order to obtain physiological training adaptations [8–10]. We speculated that the onset of contractile muscle fatigue during exercise is a marker of muscle overload. A proportion of patients do not develop contractile fatigue of the quadriceps after whole-body [11, 12] or single muscle [13] endurance exercise performed up to exhaustion. It is currently unknown whether contractile fatigue occurs during exercise training, which typically consists of several submaximal episodes of exercise. In the absence of muscle overload, training effects could be less pronounced.

In the present study we hypothesised that the occurrence of contractile fatigue of the quadriceps after a training session in patients with COPD would be associated with a more favourable outcome after an exercise training programme. As a result, the presence of contractile fatigue after a training session would be a marker of skeletal muscle overload during training.

We addressed this hypothesis through a multicentre cohort study conducted in Leuven (Belgium) and Quebec (Canada). Some of the results of this study have been previously reported in abstract form [14].

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METHODS

Subjects

A convenience sample of 57 patients that were referred for outpatient pulmonary rehabilitation at University Hospital Gasthuisberg, Leuven (n=49) and at Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec (n=8) were enrolled in the study. All patients had a primary diagnosis of COPD [15]. Exclusion criteria were diagnosis of cancer, significant cardiac disease, cerebral, neurological or neuromuscular disorders and severe arthrosis, arthritis or other musculoskeletal limitations that impaired the testing procedures or exercise training. Since magnetic stimulation of the femoral nerve was conducted, patients with right hip arthroplasty or arterial bypass surgery in the pelvic or abdominal region were excluded.

Written informed consent was obtained from all patients. The study protocol was approved by the ethics committee of both hospitals.

Study design

All patients followed a 3-month multidisciplinary pulmonary rehabilitation programme, including three weekly exercise training sessions. Before and after the training programme, patients underwent an evaluation of lung function, respiratory and peripheral muscle force, maximal exercise capacity, 6-min walk distance (6MWD) and health-related quality of life (Chronic Respiratory Disease Questionnaire; CRDQ). The clinical staff who conducted these evaluations were blinded to the outcome of the fatigue measurement. Using magnetic stimulation, maximum voluntary contraction (MVC) and potentiated quadriceps twitch force (TWq_{pot}) were assessed after 1 week and 1 and 3 months of rehabilitation. Muscle assessments were performed before and 15 and 40 min after the exercise training session. A fall in TWq_{pot} of $>15\%$ 15 min after exercise training was defined as significant contractile fatigue [11]. The degree of quadriceps contractile fatigue induced by a single training session was reported after 1 month of rehabilitation, when patients were fully familiarised with the training programme. Both centres used the same equipment for all testing procedures.

Assessment of quadriceps strength

The right quadriceps force was evaluated using MVC and transcutaneous magnetic twitch stimulation of the femoral nerve. Subjects were sitting in a recumbent chair with hips extended at 120°, knees flexed at 90° and arms crossed in front of the chest. The following measures were performed in a fixed order to obtain a comprehensive assessment of skeletal muscle force.

Unpotentiated quadriceps twitch contraction

At rest, the femoral nerve was stimulated through a 45-mm, figure-of-eight coil powered by a double Magstim stimulator (Magstim Co Ltd, Whitland, UK). The strain-gauge signal was transformed by an analogue force transducer (546QD; CDS Europe, Milan, Italy), amplified (Biopac mp150; Biopac Systems, Goleta, CA, USA) and stored on a computer. Twitch forces were measured at 30, 50, 70, 80, 90, 95 and 100% of the maximum stimulator output to ensure supramaximality of the measurement.

Maximal voluntary contraction

Subjects performed five isometric MVC for 3 s.

Potentiated quadriceps twitch contraction

TWq_{pot} was systematically measured 3 s after the end of each MVC manoeuvre. The femoral nerve was stimulated with a twitch at 100% of power output of the stimulator. For analysis, the mean of the two highest values was calculated. Superimposed twitches were obtained during the preceding MVC to ensure maximal potentiation. The mean size of this superimposed twitch was 1.2 ± 4.3 N (median 0 N) or $0.5 \pm 2\%$ of the MVC (median 0%), suggesting a truly reliable maximum effort during MVC in strongly encouraged patients.

Measurements pre- and post-rehabilitation programme

Static and dynamic lung volumes were measured according to the European Respiratory Society guidelines [16, 17]. Diffusing capacity of the lung was assessed by the single breath method [18]. Maximal isometric voluntary contraction force of the quadriceps was measured as described previously. Maximal inspiratory pressure was measured from residual volume (MicroRPM; CareFusion, Basingstoke, UK) and was compared with reference values [19]. Functional exercise capacity was assessed using the 6MWD test. The best of two standardised tests was reported as percentage of the predicted value [20]. Maximal exercise capacity was evaluated using an incremental cycle ergometer (Ergometrics 900; Ergoline, Bitz, Germany). After 2 min of resting breathing, patients started a 3-min unloaded warm-up period. Subsequently work rate was increased by $10\ \mathrm{W \cdot min^{-1}}$ until the symptom limited peak work rate was reached [21]. Oxygen uptake (V'_{O_2}), carbon dioxide production (V'_{CO_2}) and ventilation were measured breath-by-breath and averaged over 30 s (Vmax series; SensorMedics, Anaheim, CA, USA). Maximal voluntary ventilation was measured over 12 s.

The CRDQ was used to assess health-related quality of life [22]. This 20-item questionnaire scores quality of life in four domains (dyspnoea, mastery, emotional functioning and fatigue) and has been validated in the Dutch language [23]. The total score can range from 20 to 140 with higher scores indicating better quality of life.

Exercise training

Exercise training included treadmill walking, quadriceps resistance exercise, stair climbing and cycling. The initial workload during walking was set at 75% of the mean walking speed during the 6MWD test. The initial workload during cycling was set at 60–70% of the maximal workload (W_{max}) during the symptom-limited incremental cycle test. The target duration of cycling and walking increased from 10 min at week 2 to 16 min at week 12. The standard exercise modality was endurance training, but interval training (2 min episodes of exercise alternated with 1-min resting periods) was used if necessary to provide the desired training intensity. Stair climbing consisted of climbing two steps up and two steps down at the patient's own pace. Resistance training on a leg press apparatus consisted of three series of eight repetitions, with an initial load of 70% of the one-repetition maximum. The training intensity was gradually increased over time, using a Borg scale rating of four to six on perceived exertion or dyspnoea as an indicator of adequate training intensity. Every training session was supervised by experienced and blinded physiotherapists who ensured an adequate training intensity. The sequence of the different exercises was standardised during the training session at which contractile fatigue was measured (*i.e.* walking, resistance exercise, stair climbing and cycling). Oxygen therapy was permitted during training to keep oxygen saturation >90%. Patients attended 32±5 training sessions (adherence of 80±11%).

Statistical analysis

All statistical analyses were performed with SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA). Data are expressed as mean±SD or median (interquartile range). The level of significance was 0.05 for all statistical tests. Between-group differences were evaluated using unpaired t-tests or Wilcoxon Mann–Whitney tests. Repeated measures were analysed using paired t-tests, Wilcoxon signed-rank tests or repeated-measures of ANOVA. Chi-squared tests and odds ratios (95% confidence interval) were used to compare proportions. Pearson or Spearman rank correlation coefficients were used to evaluate relationships between variables. An exponential function, $V'_{\mathrm{CO_2}} = b \times (\exp(k \times V'_{\mathrm{O_2}}) + a$, was constructed to describe the relationship between $V'_{\mathrm{CO_2}}$ and $V'_{\mathrm{O_2}}$ during the maximal exercise tests before and after the training programme. The change in $V'_{\mathrm{CO_2}}$ at iso-$V'_{\mathrm{O_2}}$ (maximal $V'_{\mathrm{O_2}}$ obtained in both tests) after the training programme was computed using this formula.

RESULTS

Patient flow

57 eligible patients agreed to participate in the study. Eight patients dropped out from rehabilitation because of lung transplantation (n=3) or serious respiratory (n=3) or cardiac (n=2) complications. Two patients withdrew their informed consent and one did not perform the muscle force protocol after 1 month because of a calcaneus fracture, leaving 46 patients for the final analysis. One patient did not perform the 6MWD test after 3 months and CRDQ score was not reliably assessed in two patients due to poor understanding of the questionnaire. Baseline characteristics are reported in table 1. No baseline differences were found between drop-outs and patients that completed the training programme.

Contractile fatigue of the quadriceps after exercise

Compared to resting values, 15 and 40 min after the end of the training session $\mathrm{TWq_{pot}}$ decreased by 19±12% and 20±9%, respectively (both $p<0.05$). Figure 1 shows that various levels of fatigue were observed. 29 (63%) out of 46 patients developed significant contractile fatigue (>15% decrease in $\mathrm{TWq_{pot}}$) 15 min after training. Patients with fatigue also had a more pronounced decrease in $\mathrm{TWq_{pot}}$ (-24±11% *versus* -7±8%; $p<0.0001$) and MVC (-8±8% *versus* -1±7%; $p=0.002$) after training compared to patients without fatigue. The development of fatigue was consistent throughout the rehabilitation programme (weeks 1, 5 and 12). Patients with contractile fatigue had more baseline static hyperinflation compared to those who did not develop contractile fatigue (total lung capacity 125±16% pred *versus* 106±16% pred ($p<0.001$), respectively; functional residual capacity 175±36% pred *versus* 145±29% pred ($p<0.01$), respectively) (table 1). No baseline

TABLE 1 Baseline characteristics of study participants

	All patients	Contractile fatigue	No contractile fatigue	p-value
Subjects	46	29	17	
Male/female	35/11	21/8	14/3	0.50
Age yrs	64±8	63±7	66±9	0.25
BMI kg·m^{-2}	25±5	25±5	26±5	0.49
$\mathrm{FEV_1}$ % pred	42±13	41±13	44±14	0.51
FRC % pred	164±36	175±36	145±29	**0.0056**
$T_{\mathrm{L,CO}}$ % pred	44±16	41±16	48±14	0.18
6MWD m	409±108	415±103	415±103	0.75
6MWD % pred	62±18	62±17	64±19	0.74
Borg dyspnoea				
6MWD	6±2	6±3	5±2	0.55
Incremental exercise	8±2	8±2	8±1	0.18
Borg leg fatigue				
6MWD	4±3	4±3	5±3	0.27
Incremental exercise	6±2	6±3	6±2	0.84
MVC N	285±105	286±103	282±111	0.91
$\mathrm{TWq_{pot}}$ N	113±37	109±35	121±39	0.29
$V'_{\mathrm{O_2,max}}$ % pred	49±17	49±18	51±17	0.66
$W_{\max}$ % pred	45±18	46±19	44±17	0.64
V'_{E}/MVV %	99±18	97±17	102±19	0.35
CRDQ points	78±16	75±12	83±19	0.13

Data are presented as n or mean±SD, unless otherwise stated. BMI: body mass index; $\mathrm{FEV_1}$: forced expiratory volume in 1 s; % pred: % predicted; FRC: functional residual capacity; $T_{\mathrm{L,CO}}$: transfer factor of the lung for carbon monoxide; 6MWD: 6-min walk distance; MVC: maximum voluntary contraction; $\mathrm{TWq_{pot}}$: potentiated quadriceps twitch force; $V'_{\mathrm{O_2,max}}$: maximal oxygen uptake; $W_{\max}$: maximal workload; V'_{E}: minute ventilation; MVV: maximal voluntary ventilation; CRDQ: Chronic Respiratory Disease Questionnaire. Bold signifies statistical significance.

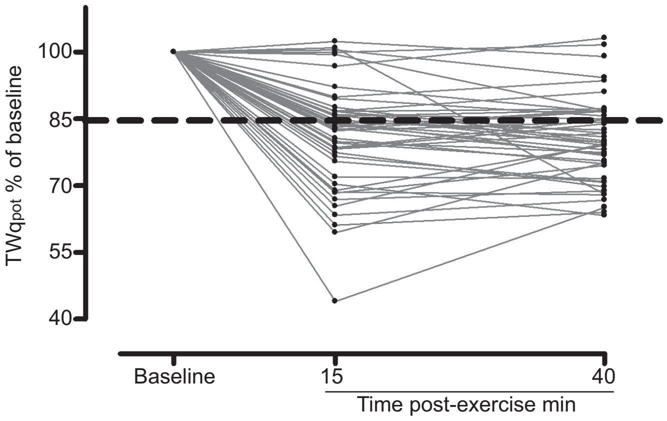

FIGURE 1. Individual changes in quadriceps potentiated twitch force (TWq_{pot}) 15- and 40-min post-exercise training. 15 min after training, 29 (69%) out of 46 patients showed a >15% decrease in force (- - - -).

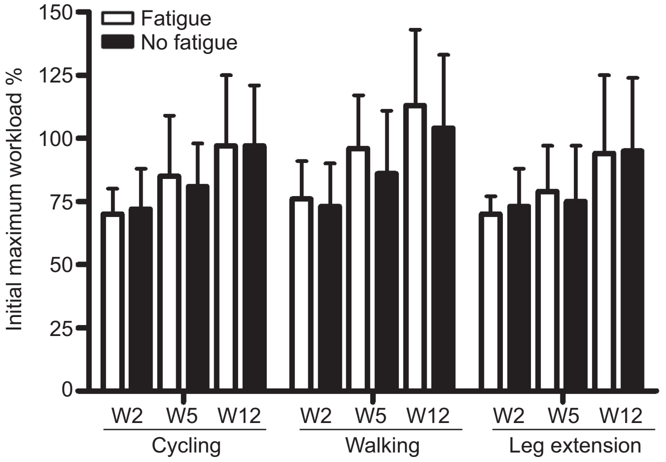

FIGURE 2. Training intensity at weeks (w) 2, 5 and 12 during the 3-month training programme in patients with and without quadriceps contractile fatigue. Cycling intensity is expressed as % of maximal workload during the baseline incremental cycle test, walking intensity as % of the speed during the baseline 6-min walk test, and leg extension as % of the one-repetition maximum, assessed during the first training session.

differences in spirometry data, diffusion capacity, anthropometric measures, muscle force, exercise capacity or quality of life were detected between patients with and without contractile fatigue (table 1). The training workload (intensity and duration) at weeks 2, 5 and 12 of the training programme was not different between groups. Figure 2 shows that training intensities were similar between the two groups at these time-points. Treadmill speed increased from 74±15% (week 2) to 109±29% (week 12) of the initial speed during the initial 6MWD test. Cycling workload increased from 70±12% (week 2) to 97±26% (week 12) of the W_{max} during the initial incremental cycle test. The workload of the quadriceps resistance exercise increased from 71±10% (week 2) to 94±30% (week 12) of the initial one-repetition maximum. Duration of the different training modalities was also comparable between groups. Dyspnoea and fatigue Borg scores at the end of the cycling training were also similar (dyspnoea 4±1 *versus* 4±1 ($p=0.83$) and fatigue 4±1 *versus* 4±1 ($p=0.33$) in patients with and without fatigue, respectively). When taking into account the highest of both symptom scores in each patient, mean symptom score at the end of cycling training was 5±2 in patients with fatigue and 5±1 in patients without fatigue. 17 (65%) out of 29 patients with fatigue trained with oxygen supplements compared with 11 (59%) out of 17 patients without fatigue ($p=0.68$). Adherence to training was also similar in patients with and without fatigue (30±5 *versus* 28±6 attended sessions, $p=0.56$).

Training effects

After 3 months of exercise training, the whole patient group showed a significant increase in 6MWD (50 (19–85) m, $p<0.0001$), maximal exercise capacity (W_{max} 10 (1–20) W, $p<0.0001$; maximal V'_{O_2} ($V'_{O_2,max}$) 113 (-50–259) $mL \cdot min^{-1}$, $p=0.0002$), isometric quadriceps force (20 (-6–5) N, $p=0.03$) and CRDQ score (19±12 points, $p<0.0001$).

Contractile fatigue and training effects

The increase in 6MWD was significantly larger in the patients who developed fatigue compared to those who did not (57 (47–103) *versus* 17 (-7–46) m, $p=0.0023$) (fig. 3a). 71% of patients with fatigue showed an improvement in 6MWD exceeding the proposed clinically important difference of 50 m [24], compared with 18% of patients without fatigue (OR 11.7 (95% CI 2.6–51.9), $p=0.0005$). Symptoms of dyspnoea and leg fatigue during the 6MWD test did not change from baseline and were similar in the two groups. Similarly the CRDQ score improved significantly more in the patients with fatigue (22±12 *versus* 14±12 points, $p=0.028$). This difference was mainly reflected in the dyspnoea subdomain (7.3±4.2 *versus* 3.9±5.9 points, $p<0.031$) (fig. 3b), whereas in the fatigue (4.4±3.4 *versus* 2.9±3.3, $p=0.15$), mastery (4.5±3.6 *versus* 3.3±3.5, $p=0.31$) or emotional functioning (5.8±4.5 *versus* 4.2±3.5, $p=0.21$) subdomains no significant difference was found between subgroups. 86% of patients with contractile fatigue showed an increase exceeding the proposed clinically important difference (2.5 points) [25] in the dyspnoea score compared with 56% of patients without fatigue (OR 4.7 (95% CI 1.1–19.9), $p=0.03$). Despite the significant improvement induced by training for the whole group, the increase in quadriceps force (24 (-6–35) N *versus* 12 (-6–34) N, $p=0.70$) (fig. 3c) or maximal exercise capacity (W_{max} 10 (1–19) W *versus* 10 (2–20) W, $p=0.94$; $V'_{O_2,max}$ 112 (-73–248) *versus* 126 (23–259) $mL \cdot min^{-1}$, $p=0.79$) (fig. 3d) were not statistically different between patients with or without fatigue. Symptoms of dyspnoea and leg fatigue during incremental cycling did not change from baseline and were similar in the two groups. The correlation between decrease in TWq_{pot} after exercise training and decrease in V'_{CO_2} at iso-VO_2 (baseline $V'_{O_2,max}$) after 3 months was 0.35 ($p=0.05$).

DISCUSSION

The present study indicates that patients who develop significant quadriceps contractile fatigue during an exercise training session have favourable training response in terms of functional exercise capacity and health-related quality of life compared to those who do not. An appreciably higher fraction of patients with contractile fatigue after training showed a clinically relevant

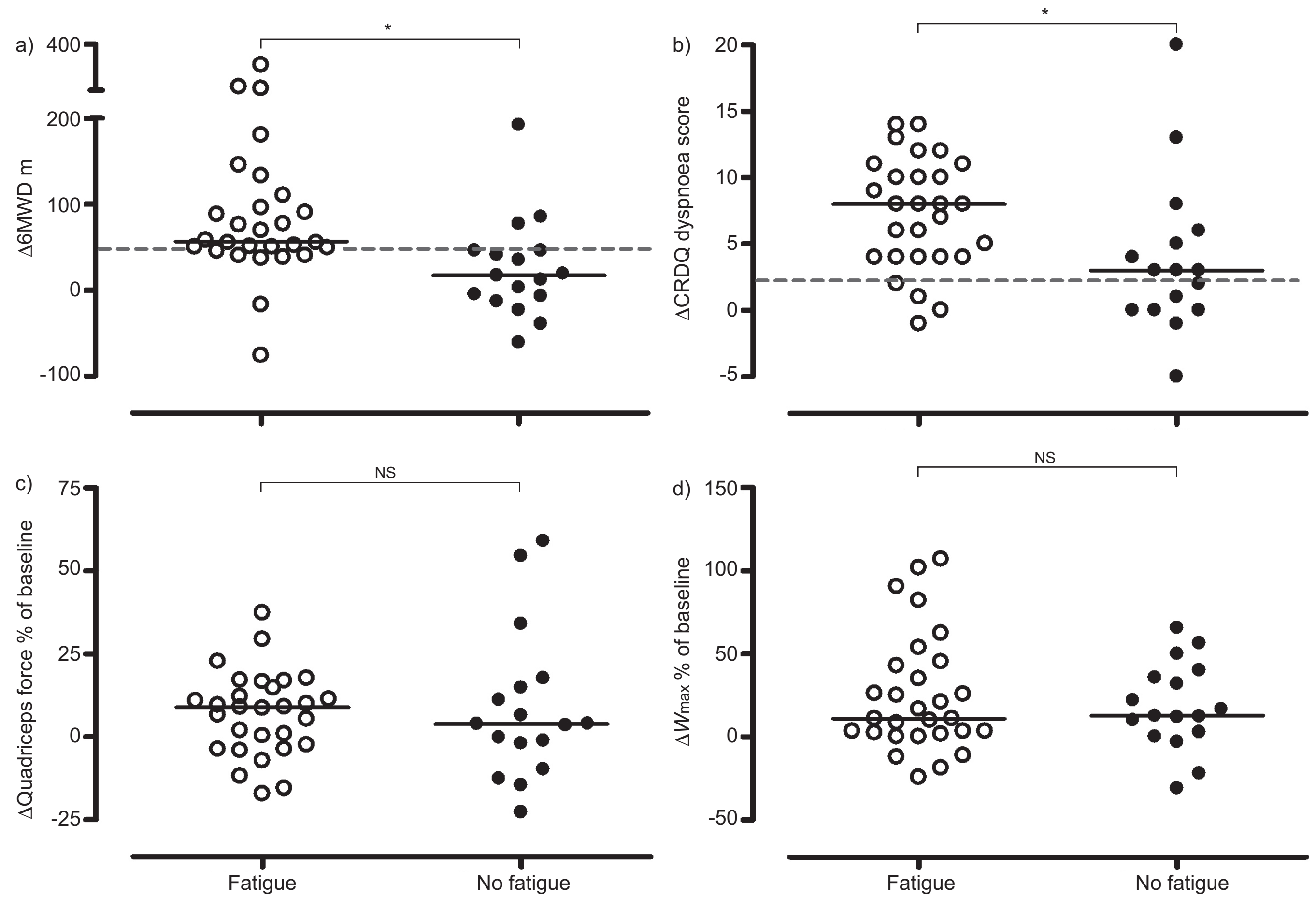

FIGURE 3. Individual change (Δ) in a) 6-min walk distance (6MWD), b) Chronic Respiratory Disease Questionnaire (CRDQ) dyspnoea score, c) quadriceps force, and d) maximal workload ($W_{\max}$) during incremental exercise testing after the training programme in patients with and without quadriceps contractile fatigue. ——: median score of each group; - - - -: estimated clinical important difference for this variable. NS: nonsignificant.*: $p<0.05$ between groups.

increase in 6MWD and a decrease in symptoms of dyspnoea during activities of daily living compared with patients who did not develop fatigue. Furthermore, a greater reduction in V'_{CO_2} at iso-V'_{O_2}, an effort-independent marker of improvement, was seen in patients with more pronounced contractile fatigue. Based on these findings, we report that contractile fatigue of the quadriceps is a probable marker of overload to the skeletal muscle. However, we could not identify simple clinical characteristics that could help predict the development of quadriceps fatigue. In addition the training intensity was high and not significantly different in both groups.

Contractile fatigue after exercise

The quadriceps muscle is more susceptible to develop early contractile fatigue in patients with moderate-to-severe COPD compared with healthy age-matched controls [12, 13]. The majority of patients with COPD develop quadriceps contractile fatigue during an endurance cycle test performed until symptom limitation [11, 12] or several episodes of maximal single muscle exercise [13]. This is in line with our findings that 60% of patients develop quadriceps contractile fatigue during an exercise training session consisting of several episodes of submaximal exercise.

Patients with and without contractile fatigue after training

It is unclear why some patients do not develop contractile fatigue during training. One assumption would be that patients with a chronic lung disease who do not develop muscle fatigue during exercise do not achieve an adequate training intensity due to ventilatory constraints. Our findings do not confirm this hypothesis. The sensation of breathlessness during exercise was not related to the development of contractile fatigue during training. During maximal incremental cycle exercise the two subgroups of patients clearly reached their ventilatory limits at a comparable work rate. We did not perform measurements of inspiratory capacity during exercise to investigate the development of dynamic hyperinflation during exercise. However, in the absence of differences in transfer factor of the lung for carbon monoxide [26] and given the fact that more static hyperinflation was found in patients with contractile fatigue, it is unlikely that this group would have had less dynamic hyperinflation. Based on this information we have no evidence to assume a different ventilatory constraint during exercise training between groups.

Interestingly, the absolute and relative training load was not different between patients with and without significant contractile fatigue. This leads to the hypothesis that the susceptibility to develop contractile fatigue would be driven by muscle characteristics rather than the performed work.

The susceptibility to develop contractile fatigue during exercise is seen more often in patients with higher glycolytic enzyme activity in the muscle cytoplasm, lower muscle capillarisation and earlier blood lactate accumulation during exercise [27]. In these patients intrinsic muscle changes associated with early metabolite accumulation during exercise training may lead to early contractile failure of the working muscles, despite the low absolute exercise intensities [28]. Ventilatory limitations might prevent patients with better preserved oxidative metabolism from reaching a sufficient training intensity to induce a similar overload.

Contractile fatigue and training response

The development of contractile fatigue during exercise training was related to the magnitude of improvement in 6MWD and health-related quality of life following the training programme but not to the changes in maximal exercise capacity and isometric quadriceps force. In general, submaximal endurance exercise tests are more responsive to changes in aerobic metabolism than maximal exercise tests [29]. This could explain why changes in 6MWD (a submaximal exercise test) were related to muscle fatigue induced by exercise training while changes in maximal exercise capacity were not. As maximal exercise capacity is closely related to lung function [30], subtle changes in forced expiratory volume in 1 s over time could influence the change in $V'_{O_2\text{max}}$ after rehabilitation. Looking at an effort-independent measure of the physiological training effect, the decrease in V'_{CO_2} at iso-V'_{O_2} was correlated with the degree of muscle fatigue after exercise training.

No statistical difference was found in maximal isometric quadriceps force increase between patients with and without fatigue, even though the increase tended to be larger in the former group. Changes in maximal isometric muscle force reflect muscular and neuromuscular adaptations to exercise training which seem to be similar in both subgroups. The muscle stimulus that may lead to gains in plain muscle strength may not be adequately assessed by looking at muscle fatigue after training.

Methodological considerations

The multidisciplinary pulmonary rehabilitation programme in both centres was conducted according to international guidelines [1, 31] and improvements of relevant clinical outcomes (6MWD and quality of life) were clinically relevant [24, 25] and consistent with changes seen after similar programmes in the literature [3, 4]. The mean symptom score on the modified Borg scale after cycling exercise (~5) indicates that patients trained at an adequate intensity [32].

Supramaximal magnetic stimulation of the femoral nerve is an involuntary, well-tolerated and valid technique which is used to assess low-frequency quadriceps contractile fatigue in patients with COPD [12, 33, 34]. The definition of fatigue was based on measurements of TWq_{pot}. A fall in TWq_{pot} of >15% has been used previously to define contractile fatigue [11]. The present study renders some additional validity to this cut-off. We chose to perform the contractile fatigue measurement 1 month after inclusion in an exercise training programme because patients were fully accustomed to the training procedure at the time of the measurement. We acknowledge that muscle fatigue is not an all-or-nothing phenomenon and that some patients who did not exhibit a fall in TWq_{pot} of >15% after the training session may still have developed some degree of fatigue. This could lead to an underestimation of the differences between the two subgroups of patients, both in terms of baseline characteristics and training results. The correlation between the degree of change in V'_{CO_2} at iso-V'_{O_2} would support the idea.

Limitations of the study

First, we did not include a whole-body or local muscle endurance test or a skeletal muscle biopsy due to logistical restrictions. These tests would have provided more straightforward information on improvements in aerobic metabolism compared with an incremental cycle exercise test and a maximal isometric muscle test.

Secondly, we did not measure changes in inspiratory capacity during exercise training or testing. Consequently, we cannot make firm conclusions on the influence of dynamic hyperinflation on the ability to develop muscle fatigue.

Finally, we defined patients with or without muscle fatigue based on the development of fatigue during a single training session after 1 month of rehabilitation. However, when performing the same analysis with fatigue results after 1 week and 3 months of training similar results are found.

Clinical relevance

Our results emphasise the importance of developing fatigue of the quadriceps muscles during exercise training to optimise training effects in patients with moderate-to-severe COPD. Interestingly, a high relative training intensity is no guarantee to provide a significant stimulus to the muscle. It would be interesting to establish whether changes in training strategies (*e.g.* one-legged training [35]) could stimulate the development of contractile fatigue in patients who do not develop fatigue during the exercise training and whether this leads to improved training results in these patients.

Conclusion

Patients with COPD developing quadriceps contractile fatigue during exercise training showed larger training effects in terms of functional exercise capacity and health-related quality of life compared to those who did not develop fatigue.

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STATEMENT OF INTEREST

A statement of interest for M. Decramer can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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