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 highly 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 favorable effects of a rehabilitation program.

Forty-six patients followed a three-month high-intensity exercise training program. Exercise capacity, quadriceps force and quality of life were measured before and after the program. Exercise training-induced quadriceps contractile fatigue was assessed after one month of rehabilitation with magnetic stimulation. A ≥15% fall in quadriceps force 15 minutes after training was considered as significant fatigue.

Twenty-nine out of 46 patients (63%) developed significant fatigue. Patients with fatigue had a higher increase in six-minute walking distance (+57[+47,+103] vs. +17[-7,+46] m, p=0.0023) and Chronic Respiratory Disease Questionnaire score (+22±12 vs. +14±12 points, p=0.028) after the training program 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.

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Exercise therapy; exercise tolerance; muscle, skeletal; quality of life; rehabilitation
Introduction

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

Some patients with COPD do improve exercise performance to a lesser extent in response to an exercise training program\textsuperscript{5}. In general, patients with muscle weakness and low baseline exercise tolerance who show less ventilatory limitation experience greater improvements in their exercise capacity\textsuperscript{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\textsuperscript{8-10}. We speculated that the onset of contractile muscle fatigue during exercise is a marker of muscle overload. A proportion of patients does not develop contractile fatigue of the quadriceps after whole-body\textsuperscript{11,12} or single muscle\textsuperscript{13} endurance exercise performed up to exhaustion. It is currently unknown whether contractile fatigue occurs during exercise training, which typically consists of several submaximal bouts of exercise. In the absence of muscle overload, training effects could be less pronounced.

In the present study we hypothesized that the occurrence of contractile fatigue of the quadriceps after a training session in patients with COPD would be associated to a more favorable outcome after an exercise training program. 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 multicenter cohort study conducted in Leuven (Belgium) and Québec (Canada). Some of the results of this study have been previously reported in the form of an abstract\textsuperscript{14}.

Methods

Subjects

A convenience sample of fifty-seven patients that were referred for outpatient pulmonary rehabilitation at University Hospital Gasthuisberg, Leuven, Belgium (n=49) and at Institut Universitaire de cardiologie et de pneumologie de Québec, Québec, Canada (n=8) were enrolled in the study. All patients had a primary diagnosis of COPD. 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 three-month multidisciplinary pulmonary rehabilitation program, including three weekly exercise training sessions. Before and after the training program, patients underwent an evaluation of lung function, respiratory
and peripheral muscle force, maximal exercise capacity, six-minute walking 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. Maximum voluntary quadriceps strength (MVC) and potentiated twitch force (TWq_{pot}) using magnetic stimulation were assessed after one week, one month and 3 months of rehabilitation. Muscle assessments were performed before, 15 minutes and 40 minutes after the exercise training session. A more than 15% fall in TWq_{pot} 15 minutes 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 one month of rehabilitation, when patients were fully familiarized with the training program. Both centers 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 45mm figure-of-eight coil powered by a double Magstim stimulator (Magstim Co Ltd., Whitland, Dyed, Wales, UK). The strain-gauge signal was transformed by an analogue force transducer (DS Europe 546QD), amplified (Model 811A amplifiers; Hewlett-Packard) 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 5 isometric maximal voluntary contractions for three seconds.

- **Potentiated Quadriceps Twitch contraction**

The potentiated quadriceps twitch force ($TW_{q_{pot}}$) was systematically measured three seconds 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 $1.2\pm4.3$ N (median 0N) or $0.5\pm2\%$ of the MVC (median 0%), suggesting a truly reliable maximum effort during MVC in strongly encouraged patients.

*Measurements before and after the rehabilitation program*

Static and dynamic lung volumes were measured according to the European Respiratory Society guidelines\textsuperscript{16,17}. Lung diffusion capacity was assessed by the single breath method\textsuperscript{18}. Maximal isometric voluntary contraction force of the quadriceps was measured as described in the previous paragraph. Maximal inspiratory pressure (PImax) was measured from residual volume (RPM, Micromedical, UK) and was compared with reference values\textsuperscript{19}. Functional exercise capacity was assessed using the 6MWD test. The best of two standardized tests was reported as percentage of the predicted value\textsuperscript{20}. Maximal exercise capacity was evaluated using an incremental cycle ergometer test (Ergometrics 900, Ergoline, Bitz, Germany). After two minutes of resting breathing, patients started a three-minute unloaded warm-up period. Subsequently work rate was increased by
10 watts per minute until the symptom limited peak work rate was reached\textsuperscript{21}. Oxygen consumption (\(\text{VO}_2\)), carbon dioxide production (\(\text{VCO}_2\)) and ventilation were measured breath by breath and averaged over 30 seconds (\(\text{Vmax series, SensorMedics, Anaheim, CA}\)). Maximal voluntary ventilation (MVV) was measured over 12 seconds.

The Chronic Respiratory Disease Questionnaire (CRDQ) was used to assess health-related quality of life\textsuperscript{22}. This 20-item questionnaire scores quality of life in four domains (dyspnea, mastery, emotional functioning and fatigue) and has been validated in the Dutch language\textsuperscript{23}. The total score can range from 20 to 140 with higher scores indicating better quality of life.

\textit{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 to 70\% of the maximal workload during the symptom-limited incremental cycle test. The target duration of cycling and walking increased from 10 minutes at week 2 to 16 minutes at week 12. The standard exercise modality was endurance training, but interval training (bouts of two minutes alternated with one-minute 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. The 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 increased gradually over time, using a Borg scale rating of four to six on perceived exertion or dyspnea 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 standardized 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 aiming to keep oxygen saturation above 90%. Patients attended $32 \pm 5$ the training sessions (adherence of $80 \pm 11\%$).

Statistical analysis

All statistical analyses were performed with SAS 9.1.3. Data were expressed as means $\pm$ standard deviations or medians [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 analyzed using paired t-tests, Wilcoxon signed-rank tests or repeated-measures ANOVA. Chi square 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, $VCO_2 = b \cdot (\exp(k \cdot VO_2) + a$, was constructed to describe the relationship between $VCO_2$ and $VO_2$ during the maximal exercise tests before and after the training program. The change in $VCO_2$ at iso-$VO_2$ ($VO_2$ max) after the training program was computed using this formula.

Results

Patient flow

Fifty-seven 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 one month because of a calcaneus fracture, leaving 46 patients for the final analysis. One patient did not perform the 6MWD test after three 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 program.

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=46)</th>
<th>Contractile fatigue (n=29)</th>
<th>No contractile fatigue (n=17)</th>
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<td>Age (yrs)</td>
<td>64 ± 8</td>
<td>63 ± 7</td>
<td>66 ± 9</td>
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<td>BMI (kg/m²)</td>
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<td>25 ± 5</td>
<td>26 ± 5</td>
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<td>FEV₁ (%pred)</td>
<td>42 ± 13</td>
<td>41 ± 13</td>
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<td>FRC (%pred)</td>
<td>164 ± 36</td>
<td>175 ± 36</td>
<td>145 ± 29</td>
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<td>TL₉,CO (%pred)</td>
<td>44 ± 16</td>
<td>41 ± 16</td>
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<td>6MWD (m)</td>
<td>409 ± 108</td>
<td>415 ± 103</td>
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<td>6MWD (%pred)</td>
<td>62 ± 18</td>
<td>62 ± 17</td>
<td>64 ± 19</td>
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<td>Borg Dyspnea 6MWD</td>
<td>6 ± 2</td>
<td>6 ± 3</td>
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<td>Borg Leg Fatigue 6MWD</td>
<td>4 ± 3</td>
<td>4 ± 3</td>
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<td>MVC (N)</td>
<td>285 ± 105</td>
<td>286 ± 103</td>
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<td>Twq₉ pot (N)</td>
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<td>109 ± 35</td>
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<td>VO₂ max (%pred)</td>
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<td>51 ± 17</td>
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<td>W max (%pred)</td>
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<td>VE/MVV (%)</td>
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<td>102 ± 19</td>
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<tr>
<td>Borg Dyspnea</td>
<td>8 ± 2</td>
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<td>8 ± 1</td>
<td>0.18</td>
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<td>Incremental exercise</td>
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<td>Borg Leg Fatigue</td>
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<td>CRDQ (points)</td>
<td>78 ± 16</td>
<td>75 ± 12</td>
<td>83 ± 19</td>
<td>0.13</td>
</tr>
</tbody>
</table>

M = male, F=female, BMI = body mass index, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, FRC = functional residual capacity, TLC = total lung capacity, TL,CO = transfer factor of carbon monoxide, PImax = maximum inspiratory pressure, 6MWD = six-minute walking distance, MVC = maximal voluntary contraction of the quadriceps, TWqpot = potentiated magnetic quadriceps twitch force, VO₂ max = maximal oxygen consumption during an incremental cycle test, Wmax = maximal workload during an incremental cycling test, VE = peak ventilation during an incremental cycle test, MVV = maximal voluntary ventilation, CRDQ = Chronic Respiratory Disease Questionnaire.

Data are expressed as means ± standard deviation.

Contractile fatigue of the quadriceps after exercise

Compared to resting values, TWqpot decreased by 19±12% and 20±9% 15 and 40 minutes after the end of the training session, respectively (both p<0.05). Figure 1 shows that various levels of fatigue were observed. Twenty-nine out of 46 patients (63%) developed significant contractile fatigue (drop in TWqpot > 15%) 15 minutes after training. Patients with fatigue also had a more pronounced decrease in TWqunpot (-24±11% vs. -7±8%, p<0.0001) and MVC (-8±8% vs -1±7%, p=0.002) after training compared to patients without fatigue. The development of fatigue was consistent throughout the rehabilitation program (week 1, week 5 and week 12).

Patients with contractile fatigue had more baseline static hyperinflation compared to those who did not develop contractile fatigue (total lung capacity (TLC) 125±16 %pred. vs. 106±16 %pred., p<0.001 and functional residual capacity (FRC) 175±36 %pred. vs. 145±29 %pred., p<0.01 respectively; Table 1). No baseline 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 week 2, 5 and 12 of the training program 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 maximal workload 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 1-repetition maximum. Figure 2 shows that training intensities were similar between the two groups at these time points. Duration of the different training modalities was also comparable between groups. Dyspnea and fatigue Borg scores at the end of the cycling training were also similar (dyspnea 4±1 vs. 4±1, p=0.83; fatigue 4±1 vs. 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. Seventeen of 29 patients with fatigue (65%) trained with oxygen supplements compared with 11 of 17 patients without fatigue (59%, p=0.68). Adherence to training was also similar in patients with and without fatigue (30±5 vs. 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 (maximal workload +10 [+1,+20] Watt, p<0.0001; maximal oxygen consumption
(VO2 max) +113 [-50,+259] ml/min, p=0.0002), isometric quadriceps force (+20 [-6,+35] 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] vs. +17 [-7,+46] m, p=0.0023; Figure 3A). Seventy-one percent of patients with fatigue showed an improvement in 6MWD exceeding the proposed clinically important difference of 50m24, compared with 18% of patients without fatigue (odds ratio 11.7 [2.6 - 51.9], p=0.0005). Symptoms of dyspnea 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 vs. +14±12 points, p=0.028). This difference was reflected mainly in the dyspnea subdomain (+7.3±4.2 vs. +3.9±5.9 points, p<0.031; Figure 3B) whereas in the fatigue (+4.4±3.4 vs. +2.9±3.3, p=0.15), mastery (+4.5±3.6 vs. +3.3±3.5, p=0.31) or emotional functioning (+5.8±4.5 vs. +4.2±3.5, p=0.21) subdomains no significant difference was found between subgroups. Eighty-six percent of patients with contractile fatigue showed an increase exceeding the proposed clinically important difference (2.5 points)25 in the dyspnea score compared with 56% of patients without fatigue (odds ratio 4.7 [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] vs. +12 [-6,+34] N, p=0.70; Figure 3C) or maximal exercise capacity (maximal workload +10 [+1,+19] vs. +10 [+2,+20] Watts, p=0.94, Figure 3D; VO2 max +112 [-73,+248] vs. +126 [+23,+259] ml/min, p=0.79) were not statistically different between patients with or without fatigue. Symptoms of dyspnea and leg fatigue during incremental cycling did not change from baseline
Discussion
The present study indicates that patients who develop significant quadriceps contractile fatigue during an exercise training session have favorable 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 increase in six-minute walking distance and a decrease in symptoms of dyspnea during activities of daily living compared with patients who did not develop fatigue. Furthermore, a greater reduction in CO₂ production at iso-VO₂, an effort-independent marker of improvement, was seen in patients with more pronounced contractile fatigue. Based on these findings, we submit that contractile fatigue of the quadriceps is a likely 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 bouts of maximal single muscle exercise. This is in line with our findings that 60% of patients develop quadriceps contractile fatigue during an exercise training session consisting of several bouts of submaximal exercise.

Patients with and without contractile fatigue after training

It is unclear why some patients do not develop contractile fatigue during training. A tempting 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 TLco 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 capillarization and earlier blood lactate accumulation during exercise. 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 of the low absolute exercise intensities. 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 program 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. This could explain why changes in six-minute walking distance (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, subtle changes in FEV1 over time could influence the change in VO2 max after rehabilitation. Looking at an effort-independent measure of the physiological training effect, the decrease in VCO2 at iso-VO2 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 program in both centres was conducted according to international guidelines\textsuperscript{1,31} and improvements of relevant clinical outcomes (six-minute walking distance, quality of life) were clinically relevant\textsuperscript{24,25} and consistent with changes seen after similar programs in the literature\textsuperscript{3,4}. The mean symptom score on the modified borg scale after cycling exercise (around 5) indicates that patients trained at an adequate intensity\textsuperscript{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\textsuperscript{12,33,34}. The definition of fatigue was based on measurements of potentiated twitch force. A fall in potentiated twitch force of more than 15\% has been used previously to define contractile fatigue\textsuperscript{11}. The present study renders some additional validity to this cut-off. We chose to perform the contractile fatigue measurement one month after inclusion in an exercise training program 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-none phenomenon and that some patients who did not exhibit a $>15\%$ fall in $\text{TW}_{q\text{pot}}$ 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 $\text{VCO}_2$ at iso-$\text{VO}_2$ 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. Second, 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. Thirdly, we defined patients with or without muscle fatigue based on the development of fatigue during a single training session after one month of rehabilitation. However, when performing the same analysis with fatigue results after one week and three months of training, similar results are found.

Clinical relevance

Our results emphasize the importance of developing fatigue of the quadriceps muscles during exercise training to optimize 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\textsuperscript{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 fatigue.
Acknowledgments

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Reference List


Figure legends

Figure 1. Individual changes in quadriceps potentiated twitch force 15 and 40 minutes after termination of exercise training (as percentage of the baseline value). Fifteen minutes after training, 29 out of 46 patients (63%) showed a more than 15% decrease in force (dashed line).

![Graph showing changes in quadriceps potentiated twitch force](image)

Figure 2. Training intensity at week 2, week 5 and week 12 during the three-month training program in patients with (white bars) and without (black bars) quadriceps contractile fatigue. Cycling intensity is expressed as percentage of maximal workload during the baseline incremental cycle test, walking intensity as percentage of the speed during the baseline six-minute walking test, leg extension as percentage of the one-repetition maximum, assessed during the first training session.
Figure 3. Individual changes in six-minute walking distance (6MWD; in meters; Figure 3A), dyspnea subdomain score of the chronic respiratory disease questionnaire (CRDQ; in points; Figure 3B), quadriceps force (as percentage of the baseline value, Figure 3C) and maximal workload during incremental exercise testing (as percentage of the baseline value, Figure 3D) after the training program in patients with and without quadriceps contractile fatigue. The solid lines represent the median score of each group. The dashed line in Figure 3A and 3B represents the estimated clinical important difference for this variable.

* p<0.05 between group; NS = not significant.