Skeletal muscle structure and function in response to electrical stimulation in moderately impaired COPD patients

Simone Dal Corsoa,1, Lara Nápolisb, Carla Malagutia, Ana Cristina Gimenesa, André Albuquerquea, Cristiano Rabelo Nogueiraa, Marcelo Bicalho De Fuccioa, Roberto D.B. Pereirab, Acari Bulleb, Niall McFarlanec, Luiz E. Nerya, J. Alberto Nederab,*

aPulmonary Function and Clinical Exercise Physiology Unit (SEFICE), Division of Respiratory Diseases, Department of Medicine, Federal University of São Paulo (UNIFESP), São Paulo, São Paulo, Brazil
bNeuromuscular Division, Federal University of São Paulo (UNIFESP), São Paulo, São Paulo, Brazil
cInstitute of Biomedical and Life Sciences, University of Glasgow, Glasgow, Scotland, UK

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KEYWORDS
Chronic obstructive pulmonary disease; Electrical stimulation; Skeletal muscle; Rehabilitation; Strength

Summary
Study objective: To determine the structural and functional consequences of high-frequency neuromuscular electrical stimulation (hf-NMES) in a group of moderately impaired outpatients with chronic obstructive pulmonary disease (COPD).

Design: A prospective, cross-over randomized trial.

Setting: An university-based, tertiary center.

Patients and materials: Seventeen patients (FEV1 = 49.6 ± 13.4% predicted, Medical Research Council dyspnoea grades II–III) underwent 6-weeks hf-NMES (50 Hz) and sham stimulation of the quadriceps femoris in a randomized, cross-over design. Knee strength was measured by isokinetic dynamometry (peak torque) and leg muscle mass (LMM) by DEXA; in addition, median cross-sectional area (CSA) of type I and II fibres and capillary–fibre ratio were evaluated in the vastus lateralis. The 6-min walking distance (6MWD) was also determined.

Abbreviations: COPD, chronic obstructive pulmonary disease; CSA, cross-sectional area; DEXA, dual-energy X-ray absorptiometry; DLCO, carbon monoxide diffusing capacity; FEV1, forced expiratory volume in 1s; FFM, fat-free mass; FVC, forced vital capacity; LMM, leg muscle mass; MHC, myosin heavy chain; 6MWD, six-min walking distance; NMES, neuromuscular electrical stimulation; PaO2, arterial oxygen partial pressure; RV, residual volume; TLC, total lung capacity.

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*Corresponding author. Tel.: +55 11 5571 8384; fax: +55 11 55 75 2843.
E-mail address: abneder@pneumo.epm.br (J.A. Neder).

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Results: At baseline, patients presented with well-preserved functional capacity, muscle strength and mass: there was a significant relationship between strength and type II CSA ($P<0.05$). NMES was not associated with significant changes in peak torque, LMM or 6MWD as compared to sham ($P>0.05$). At micro-structural level, however, electrical stimulation increased type II, but decreased type I, CSA; no change, however, was found in the relative fibre distribution or capillary:fibre ratio ($P>0.05$). There was no significant association between individual changes in structure and function with training ($P>0.05$). Post-NMES increase in type II CSA was inversely related to baseline mass and strength ($P<0.05$).

Conclusion: NMES may promote a modest degree of type II muscle fibre hypertrophy in COPD patients with well-preserved functional status. These micro-strutural changes, however, were not translated into increased volitional strength in this sub-population.

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Introduction

Exercise intolerance is a hallmark of advanced chronic obstructive pulmonary disease (COPD). Although much attention has been paid to the pulmonary-mechanical abnormalities which actually characterize the disease, new evidence has demonstrated that skeletal muscle impairment is centrally related to patients’ functional capacity. In particular, several reports have described significant reductions on muscle mass and strength which responded variably to selected interventions. In this context, we, and others, have showed that high-frequency neuromuscular electrical stimulation (hf-NMES) might improve peripheral muscle function with beneficial consequences on physical capacity in severely-disabled patients. Interestingly, marked changes in strength after hf-NMES were found in some of them—despite a training duration that is not commonly associated with a substantial degree of muscle hypertrophy (6–8 weeks). These findings raise the question of whether the changes on strength after hf-NMES would, or not, be related to enhanced muscle mass. The authors reasoned that by answering this question we would bring new light on the controversy about the relationship between muscle structure and function in this patient population.

This study was therefore performed to investigate: (i) whether 6-weeks of NMES would increase isokinetic peak torque and (ii) the association between hf-NMES-induced changes in peripheral muscle strength and total and differential muscle fibre cross-sectional areas in moderately impaired patients with COPD.

Methods

Patients

Seventeen patients (16 males, aged 57–80) with COPD according to the GOLD criteria were referred from the COPD outpatient clinics of the São Paulo Hospital (Federal University of São Paulo, Brazil) for study participation. Subjects presented with moderate-to-severe ventilatory impairment (FEV$_1<$60% predicted in all but one patient).

Inclusion criteria were: dyspnoea on activities of daily living (Medical Research Council grades II–III), absence of associated locomotor or neurological conditions, arterial partial pressure for oxygen at rest ($\text{PaO}_2$)>60 mmHg, and disease stability as indicated by no change in medication dosage or exacerbation of symptoms in the preceding 12 weeks. Exclusion criteria were: use of pacemakers, malignancy, cardiac failure, distal arteriopathy, recent surgery, α-antiprotease deficiency, severe endocrine, hepatic or renal disorder, and use of anticoagulant medication. All patients were optimized in terms of standard medical therapy: maintenance medication included long- and short-acting β$_2$-agonists, theophylline, and inhaled steroids. No patient was receiving oral steroids or chronic domiciliary oxygen therapy; in addition, they have never been submitted to NMES or pulmonary rehabilitation. Informed consent (as approved by the Institutional Medical Ethics Committee) was obtained from all patients.

Design and procedures

This was a prospective, cross-over, single-blinded, randomized, and controlled trial (Fig. 1). After study enrollment, patients were randomly allocated to receive hf-NMES before sham stimulation or vice-versa: each treatment sequence lasted for 6 weeks. Pulmonary function, segmental (leg) body composition, peripheral muscle strength, and 6-min walking distance (6MWD) were determined at baseline. These tests were repeated after hf-NMES; post-sham analysis, however, was restricted to lung function, muscle strength, and 6MWD evaluations. For ethical reasons, peripheral muscle biopsy (vastus lateralis) was performed pre- and post-NMES only.

Electrical stimulation protocols

NMES and sham stimulation were delivered by a portable, four-channel NME stimulator (Dualpex 961™, Quark, Brazil). The electrical current was applied via two self-adhesive surface electrodes, which were placed longitudinally to the quadriceps femoris on the motor points. During the stimulation sessions, patients were sitting with legs...
semiflexed (knee joint at 150–160°): patients were told not to perform an active voluntary contraction in pace with the stimulation. During the home-based, 6-weeks, 5 times/week hf-NMES program, wave frequency and pulse duration were kept constant (50 Hz and 400 μs, respectively). Stimulation intensity was individually set to elicit a visible contraction of the quadriceps (ranging from 10 to 25 mA): this was increased weekly by approximately 5 mA according to the patient’s tolerance. The duty cycle (on:off time, %) was adjusted as follows: week 1 = 2 s:10 s (16%), i.e., 2/12 for 15 min/leg, week 2 = 5 s:25 s (16%) for 30 min/leg, weeks 3–4 = 10 s:30 s (25%) for 1 h/leg, and weeks 5–6: 10 s:20 s (33%) for 1 h/leg. The patients returned to the clinic to adjust hf-NMES parameters (intensity and duty cycle) once a week. During the 6-week, 5 times/week sham stimulation period, the following parameters were used: 10 Hz frequency, pulse duration of 50 μs and a current intensity of only 10 mA. We also certified that these settings were not sufficiently high to elicit an effective muscle contraction in all patients.

In order to familiarize the patients with the equipment and to detect possible side-effects, the hf-NMES training protocol was initially applied under the guidance of a qualified and experienced physiotherapist (first week). A family member was present at the end of this week: he/she was asked to monitor the training and to secure that the family member was present at the end of this week: he/she was asked to monitor the training and to secure that the family member was present at the end of this week. During the 6-week, 5 times/week sham stimulation period, the following parameters were used: 10 Hz frequency, pulse duration of 50 μs and a current intensity of only 10 mA. We also certified that these settings were not sufficiently high to elicit an effective muscle contraction in all patients.

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**Measurements**

**Body composition**

Total and segmental (right leg) body composition was assessed by dual energy X-ray absorptiometry (DEXA—Lunar Radiation Corporation, Madison, WI, USA): leg muscle mass (LMM, kg) was established according to the differential degree of photon attenuation at two levels of energy.15

**Pulmonary function tests**

Spirometric tests were performed by using the CPF System™ (Medical Graphics Corporation—MGC, St. Paul, MN, USA) with airflow being measured by a calibrated pneumotachograph. The subjects completed at least three acceptable maximal forced expiratory manoeuvres before and after 400 μg of inhaled salbutamol. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were recorded. A computer-based automated system (PF-DX System; Medical Graphics) was used to measure static lung volumes (total lung capacity and residual volume—TLC and RV, respectively) by the “breath-by-breath” N2 wash-out technique.16 Carbon monoxide diffusing capacity (DLCO) was measured by the modified Krogh technique (single breath): the subjects performed two acceptable and reproducible tests, with the results being within 10% or 3 mL CO/min/mmHg.17

**Peripheral muscle strength**

Concentric contractions of the quadriceps femoris (knee extension) of the right leg were evaluated using an isokinetic dynamometer (Con-Trex™, Cybex, Chattanooga, NY, USA). After mild warm-up exercise (typically walking around the room), positioning and stabilization of the subjects were standardized. The mechanical axis of rotation of the lever arm was aligned to the axis of rotation of the knee. The resistance pad at the end of the lever arm was strapped to the distal part of the tibia: the exact position varied according to the patients’ leg length. Correction for the effect of gravity was made. All patients performed a maximum isokinetic strength test with 2 trials of 5 movements tested at an angular velocity of 60′s separated by 2 min rest (peak torque, Nm). The highest value was selected for analysis.

**Muscle biopsy**

Open muscle biopsies of the right vastus lateralis were obtained from its central region, 10–15 cm above the patella at mid-thigh level. Biopsy sites were anaesthetized previously with 2% lidocaine and 1.5–2.0 cm skin incisions were made.19 Muscle samples (5–10 g) were divided into two parts. One was embedded in OCT compound, frozen in isopentane and cooled in liquid nitrogen for use in fibre-typing procedures. The other was immediately allocated in a tube, frozen and stored at −70 °C until needed. Muscle sections were obtained in a cryostat and type I and II fibres were identified using the standard adenosine triphosphatase stain at different pHs. At least 100 fibres were counted and measured in each case: median fibre cross-sectional areas (CSA) were individually measured by a single investigator. In addition, capillaries around fibres were counted and the mean was recorded as capillary contacts.

**Six-min walking distance**

Functional exercise capacity was measured by the 6-min walking distance test (6MWD) in a 50 m in-hospital corridor. Technical procedures were those recommended by the American Thoracic Society:20 oxyhaemoglobin saturation was checked at the end of the walking by pulse oximetry. Tests were performed in duplicate and the highest value was recorded: reference values were those proposed by Enright and Sherrill.21

**Statistical analysis**

After certification of data normality (Kolmogorov–Smirnov test), values are expressed as means ± standard deviation (sd); otherwise, medians and the interquartile range were used. Repeated measures analysis of variance was used to investigate the effects of NMES and sham stimulation taking into consideration the treatment sequence.
Product–moment correlation (Pearson) or Spearman’s correlation coefficient were used to define association between variables with symmetrical or asymmetrical distributions, respectively. The probability of a type I error was established at 0.05 ($P<0.05$).

Results

Pre-NMES evaluation

At baseline, patients presented with moderate-to-severe airflow obstruction and increased static lung volumes (Table 1). Eleven patients were classified as GOLD stage III: the remaining 6 patients were on stage II. Using the previously recommended criteria for fat-free mass (FFM) depletion in COPD (FFM index <15 and 16 kg/m$^2$ for males and females, respectively), only 5 patients were considered as "FFM-depleted". Patients also had well-preserved functional exercise capacity and muscle strength (Table 1).

Pre-NMES muscle biopsies revealed a paucity of type I fibres as compared to previously published data in normal subjects. In addition, there was a relative atrophy of type II fibres, i.e., median type II CSA was significantly lower than type I CSA ($P<0.05$) (Table 2). We also found a significant relationship between peak torque and fibre CSA: this finding was largely due to the high correlation between type II, but not type I, CSA and strength (Fig. 2). There was also a highly-significant correlation between LMM by DEXA with total muscle CSA (type I plus type II) and peak torque ($R = 0.85$ and $0.70$, $P<0.001$).

Effects of NMES on muscle structure and function

There were no relevant side effects (e.g., skin lesions or muscle pain) related to NMES application. Based on patient reports (diaries), the treatment was well-tolerated and accomplished by all participants. There was a substantial increase in the self-adjusted intensity of stimulation throughout the training period: as shown in Fig. 3, average current amplitude increased from 31 mA in the 1st week to 45 mA at the end of treatment (mean increase = 48.7%). Considering that the duty cycle also increased from 16% to 33% and the total session duration from 15 to 60 min/leg (i.e., effective stimulation time increased from ~2 to 20 min/session), there was a large increase in the training workload.

Repeated measures analysis of variance revealed that there were no significant effect of the treatment sequence (i.e., NMES before sham and vice-versa) on the main variables of interest ($P>0.05$). We therefore compared the effects of the interventions assuming the subjects as a single group: we found no statistically significant effects of NMES upon leg muscle mass, peak torque and 6MWD (Table 2). Similar results were found when the subjects were separated according to the presence ($N = 6$) or not of oxygen desaturation in the 6MWD ($\text{SpO}_2$ values ranging from 88% to 94%)($P>0.05$ for all variables). At the micro-structural level, however, there was a significant increase

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**Table 1** Baseline characteristics of the studied population ($n = 17$).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values (mean ± sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and body composition</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.9 ± 6.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.3 ± 13.3</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.64 ± 0.7</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>22.5 ± 3.9</td>
</tr>
<tr>
<td>Fat-free mass index (kg/m$^2$)</td>
<td>17.2 ± 1.9</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td></td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.91 ± 0.90</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>80.9 ± 19.9</td>
</tr>
<tr>
<td>FEV$_1$ (L)</td>
<td>1.43 ± 0.50</td>
</tr>
<tr>
<td>FEV$_1$ (% predicted)</td>
<td>49.6 ± 13.4</td>
</tr>
<tr>
<td>FVC/FEV$_1$</td>
<td>51.5 ± 20.4</td>
</tr>
<tr>
<td>TLC (% predicted)</td>
<td>114.2 ± 18.4</td>
</tr>
<tr>
<td>RV (% predicted)</td>
<td>193.4 ± 58.2</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>55.8 ± 11.1</td>
</tr>
<tr>
<td>DL$_{CO}$ (mmHg/L/min)</td>
<td>17.2 ± 5.8</td>
</tr>
<tr>
<td>DL$_{CO}$ (%)</td>
<td>54.5 ± 17.9</td>
</tr>
<tr>
<td>PaO$_2$ (mmHg)</td>
<td>68.7 ± 6.6</td>
</tr>
</tbody>
</table>

Definition of abbreviations: FVC = forced vital capacity, FEV$_1$ = forced expiratory volume in 1 s, TLC = total lung capacity, RV = residual volume, DL$_{CO}$ = lung diffusing capacity for carbon monoxide, PaO$_2$ = arterial partial pressure for oxygen.

**Table 2** Effects of sham stimulation and NMES on selected outcomes in patients with COPD ($n = 17$).

<table>
<thead>
<tr>
<th></th>
<th>Pre-sham</th>
<th>Post-sham</th>
<th>Pre-NMES</th>
<th>Post-NMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak torque</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (Nm)</td>
<td>100.6 ± 41.5</td>
<td>101.8 ± 37.7</td>
<td>93.8 ± 43.7</td>
<td>103.2 ± 50.6</td>
</tr>
<tr>
<td>% predicted</td>
<td>86.7 ± 38.1</td>
<td>87.3 ± 40.0</td>
<td>84.3 ± 35.3</td>
<td>88.1 ± 42.4</td>
</tr>
<tr>
<td>Muscle mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (kg)</td>
<td>7.19 ± 1.19</td>
<td>7.25 ± 1.37</td>
<td>7.31 ± 1.25</td>
<td>7.24 ± 1.48</td>
</tr>
<tr>
<td>% predicted</td>
<td>98.3 ± 17.8</td>
<td>99.0 ± 15.2</td>
<td>97.6 ± 18.9</td>
<td>99.7 ± 14.4</td>
</tr>
<tr>
<td>Walking distance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (Nm)</td>
<td>497 ± 75</td>
<td>500 ± 66</td>
<td>489 ± 78</td>
<td>502 ± 68</td>
</tr>
<tr>
<td>% predicted</td>
<td>98.3 ± 17.8</td>
<td>99.0 ± 15.2</td>
<td>97.6 ± 18.9</td>
<td>99.7 ± 14.4</td>
</tr>
</tbody>
</table>

$P>0.05$ for all comparisons (repeated measures ANOVA).

Obs: Cross-over design: Post-NMES is pre-sham for 9 subjects and post-sham is pre-NMES for other 8 patients.
in type II, but a decrease in type I, CSA (median change (range) = 12.5% (−16.8% to 57.6%) vs. −9.8% (−40.8 to 36.6%), P < 0.05). In contrast, no significant changes were found on the relative proportion of fiber types or in the capillary:fiber ratio (Table 3).

In similarity with the pre-training analysis (Fig. 2), there was a significant, albeit weaker, correlation between post-training peak torque and type II CSA (R = 0.49, P = 0.04). More importantly, however, we were unable to find a significant correlation between % change with training in type II fiber CSA and % change in peak torque (Fig. 4, P > 0.05).

Predictors of improvement after NMES

We found that increase in muscle CSA with training, especially in type II, was inversely related to baseline mass and strength (Fig. 5, upper panels). On the contrary, baseline muscle CSA or strength did not relate to post-NMES improvement on peak torque (Fig. 5, lower panels).

Discussion

This seems to constitute the first study to evaluate the micro-structural effects of hf-NMES on the peripheral muscles and their relationships with functional changes in moderately impaired outpatients with COPD. The main original findings of the present study can be summarized as follows: (i) hf-NMES had no discernible effect on muscle strength, overall muscle mass or walking capacity; (ii) despite the lack of effect on the functional status, stimulation was associated with an increase in type II fibre CSA; and (iii) these micro-structural effects of hf-NMES were more clearly evident in those patients with diminished baseline muscle mass or strength. The main clinical message is that a hf-NMES training program, at least with the settings used in the present study, has a limited impact upon muscle.

Table 3 Baseline and post-NMES values for micro-structural variables in patients with COPD (n = 17).

<table>
<thead>
<tr>
<th></th>
<th>Pre-NMES</th>
<th>Post-NMES</th>
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<tbody>
<tr>
<td><strong>Muscle histology</strong></td>
<td></td>
<td></td>
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<tr>
<td>Type I fibres</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion (%)</td>
<td>36.6 (12.0)*</td>
<td>35.2 (9.3)*</td>
</tr>
<tr>
<td>Area (μm²)</td>
<td>4610 (1808)*</td>
<td>4009 (1329)*</td>
</tr>
<tr>
<td>Type II fibres</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion (%)</td>
<td>63.4 (12.0)</td>
<td>64.8 (9.3)</td>
</tr>
<tr>
<td>Area (μm²)</td>
<td>3786 (1294)</td>
<td>4119 (936)</td>
</tr>
<tr>
<td>Type I and II fibres</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area (μm²)</td>
<td>4003 (1294)</td>
<td>3905 (1026)</td>
</tr>
<tr>
<td>Capillary:fibre ratio</td>
<td>1.35 (0.95)</td>
<td>1.42 (1.11)</td>
</tr>
</tbody>
</table>

P < 0.05 (Wilcoxon test). Data are presented as median (interquartile range).

*Type I vs. Type II.

Pre-NMES vs. Post-NMES.
structure and function in outpatients with COPD with well-preserved functional capacity.

Electrical stimulation of the locomotor muscles has been used for decades on different populations, ranging from elite athletes to bed-bound patients with cancer. Previous authors have found that either low frequency (lf) or hf-NMES can be effective in some, but not all, circumstances—as recently reviewed by Bax et al. More recently, there has been some renewed interest in establishing new muscle rehabilitative strategies for patients suffering from systemic disease states. In the present study, we were primarily interested in looking at the relationship between micro-structural and functional changes on the locomotor muscles after hf-NMES. In this sense, hf-NMES was used as a non-volitional, hypertrophic-type training to evaluate if potential changes on muscle mass would be proportionally related to increased strength. We chose hf-NMES since this stimulation paradigm has been found to be more effective than lf-NMES in promoting muscle hypertrophy. Our results showed that the small changes on the amount of contractile protein were largely restricted to type II fibres (Table 3) but this was not translated into increased strength (Table 2, Fig. 4).

All of the previous studies using NMES in COPD patients have evaluated severely- to very-severely disabled subjects. Although seems to be intuitive to consider passive exercise only for more frail and incapacitated patients, previous studies suggested that the baseline status of the skeletal muscle could modulate the effects of NMES, with...
better results found in subjects with well-preserved muscle apparatus.\textsuperscript{14,24,26} Unfortunately, however, our data showed that despite a positive effect on the amount of contractile protein in type II fibres, this selective hypertrophy was not sufficient to increase skeletal muscle strength.

Our data are at variance with previously published studies on the effects of NMES in COPD.\textsuperscript{6–9} We believe that the main reason for these discrepancies is related to differences on patients characteristics: as mentioned, this is the first study to have evaluated patients not severely disabled (Tables 1 and 2). Several hypotheses could be raised to explain why our patients did not respond as well as those evaluated in the previous studies:\textsuperscript{6–9} (i) higher stimulation intensity and/or longer treatment duration would be needed to promote a measurable effect in this sub-population, (ii) for moderately impaired patients, a concomitant volitional stimulus (i.e., active contraction) could have been more effective than NMES on isolation, and (iii) non-volitional techniques for strength assessment could have demonstrated a larger functional improvement after NMES. In addition, the lack of association between NMES-induced increase in type II fibre CSA and strength, despite a significant baseline and post-training correlation between them, may have been related to response heterogeneity in this relatively small sample.

We also found that muscle mass enhancement was inversely related to baseline values of either mass or strength (Fig. 5). We interpret these results as additional evidence that hf-NMES is likely to be more effective in more frail patients than those who were enrolled in the present study, e.g., such as those recovering from an acute exacerbation of COPD. This hypothesis, however, remains to be properly tested.

An interesting finding of the present study was the marked atrophy of type I fibres after hf-NMES (Table 3)—a finding that has been previously described in normal subjects.\textsuperscript{27} This could help explain the lack of a significant effect of hf-NMES on walking capacity; however, as discussed, it should be recognized that our patients—though referring dyspnea on daily life—were already relatively “well-trained” at muscular level (Table 2). In this context, it is intuitive to assume that a reduction on the area of the fatigue-resistant type I fibres would be associated with a reduction on the muscle oxidative capacity. However, the relationship between type I CSA and muscle oxidative potential is far from linear: future studies should evaluate the practical implications of a decrease on type I CSA after NMES on muscle oxidative profile. Also important is the notion that the size of type II fibres is more relevant for the muscle bulk and for strength generating capacity than type I CSA. Unfortunately, IF-NMES—which seems to be able to increase the expression of type I fibres\textsuperscript{28}—can induce a marked atrophy of type II fibres, with important implications for strength capacity.

This study presents a number of important limitations. Initially, it remains to be elucidated in which fibre II subtype the observed changes in mass were more relevant. For instance, there are convincing evidence that hf-NMES can increase the expression of myosine heavy chain (MHC) Ila in detriment of MHC-I and MHC-IIX.\textsuperscript{27} Similarly, we did not perform a detailed analysis of the myopathological features or the enzymatic profile of the fibres;\textsuperscript{27} it would be interesting to quantify, for example, the residual oxidative potential of the hypotrophic type I fibres after NMES.\textsuperscript{30} More importantly, however, the study could have be under-powered to unravel the effects of a training program in a population with well-preserved functional capacity at baseline (Table 2).

In conclusion, our data demonstrated that 6-weeks hf-NMES was ineffective in enhancing muscle strength and walking capacity in a group of moderately impaired COPD patients. Electrical stimulation, however, did increase the amount of contractile protein in type II fibers, i.e., muscle structural modifications were not directly translated into functional improvement.

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