ORIGINAL ARTICLE

Efficacy of lower-limb muscle training modalities in severely dyspnoeic individuals with COPD and quadriceps muscle weakness: results from the DICES trial

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ABSTRACT

Rationale Strength training and neuromuscular electrical stimulation (NMES) improve lower-limb muscle function in dyspnoeic individuals with chronic obstructive pulmonary disease (COPD). However, high-frequency NMES (HF-NMES) and strength training have never been compared head-to-head; and effects of low-frequency NMES (LF-NMES) have never been studied in COPD. Therefore, the optimal training modality to improve lower-limb muscle function, exercise performance and other patient-related outcomes in individuals with severe COPD remains unknown.

Objectives To study prospectively the efficacy of HF-NMES (75 Hz), LF-NMES (15 Hz) or strength training in severely dyspnoeic individuals with COPD with quadriceps muscle weakness at baseline.

Methods 120 individuals with COPD (FEV_1: 33±1% predicted, men: 52%, age: 64.8±0.8 years) were randomised to HF-NMES, LF-NMES or strength training as part of a comprehensive inpatient pulmonary rehabilitation programme. No treadmill walking or stationary cycling was provided.

Measurements and main results Groups were comparable at baseline. Quadriceps muscle strength increased after HF-NMES (+10.8 Newton-metre (Nm)) or strength training (+6.1 Nm; both p<0.01), but not after LF-NMES (+1.4 Nm; p=0.43). Quadriceps muscle endurance, exercise performance, lower-limb fat-free mass, exercise-induced symptoms of dyspnoea and fatigue improved significantly compared with baseline after HF-NMES, LF-NMES or strength training. The increase in quadriceps muscle strength and muscle endurance was greater after HF-NMES than after LF-NMES.

Conclusions HF-NMES is equally effective as strength training in severely dyspnoeic individuals with COPD and muscle weakness in strengthening the quadriceps muscles and thus may be a good alternative in this particular group of patients. HF-NMES, LF-NMES and strength training were effective in improving exercise performance in severely dyspnoeic individuals with COPD and quadriceps weakness.

Trial registration NTR2322

INTRODUCTION

Lower-limb muscle dysfunction is a prominent extrapulmonary feature in individuals with moderate-to-very severe chronic obstructive pulmonary disease (COPD).[1] It is related to exercise intolerance, increased healthcare use and mortality.[1] Physical inactivity is most probably its main underlying cause.[1] Therefore, exercise-based pulmonary rehabilitation should be part of the integrated care of individuals with COPD.[2]

Lower-limb muscle dysfunction occurs frequently in severely dyspnoeic individuals with COPD.[3] Therefore, there is great interest in effective rehabilitative modalities which do not evoke severe dyspnoea, such as strength training or transcutaneous neuromuscular electrical stimulation (NMES).[2] Indeed, the metabolic load on the impaired respiratory system is relatively low during strength training or NMES in individuals with COPD.[4 5]

Strength training or high-frequency NMES (HF-NMES; stimulation frequencies ≥50 Hz) increases quadriceps muscle function, exercise capacity and health status as compared with a non-exercise control group or sham NMES in individuals with COPD, respectively.[6 7] To date, a head-to-head comparison of strength training and HF-NMES has not been done in severely dyspnoeic individuals with COPD. Therefore, it remains unknown whether, and to what extent, these training modalities may have similar effects in individuals with COPD. A priori, no differences were expected between the groups.

Low-frequency NMES (LF-NMES, at 15 Hz) of lower-limb muscles increased exercise capacity in individuals with chronic heart failure.[8] To date, the effects of LF-NMES at 15 Hz have not been studied in individuals with COPD. However, it seems reasonable to hypothesise that quadriceps muscle endurance will improve to a greater extent after LF-NMES,[8 9] while quadriceps muscle strength will improve to a greater extent after HF-NMES.[10]

The aim of the DICES (Dyspnoeic Individuals with COPD: Electrical stimulation or Strength training) trial was to study the efficacy of HF-NMES, LF-NMES or strength training in severely dyspnoeic individuals with COPD with quadriceps muscle weakness at baseline.

METHODS

Please see online supplementary data for all details.

Participants

Individuals with COPD referred for a pulmonary rehabilitation programme at the Centre of

Expertise for Chronic Organ Failure (CIRO+) were screened for eligibility.[11] Inclusion criteria were primary diagnosis of COPD; baseline modified Medical Research Council (MRC) dyspnoea grade 3 or 4 and quadriceps weakness (peak torque ≤80% predicted).[12] Exclusion criteria were neuromuscular diseases; joint disorders in hip, leg and/or knee; metal implants in hip, leg and/or knee; cardiac pacemaker or internal cardiac defibrillator and/or outpatient pulmonary rehabilitation programme.

Design and procedures

A prospective, single-blind, randomised controlled trial was designed which was approved by the medical ethical committee of the Maastricht University Medical Centre+ (MEC 09-3-072). The DICES trial was registered at http://www.trialregister.nl (NTR2322) before enrolment of the first subject. All participants gave written informed consent to participate. Some baseline findings of the DICES trial have been published.[13]

Interventions

Participants were randomly assigned to HF-NMES, LF-NMES or strength training (8 weeks, twice a day, five times a week). All sessions were supervised by a physiotherapist. Symptom scores for dyspnoea, fatigue and muscle pain were assessed before and directly after each session.[14] The DICES trial was part of a regular 8-week inpatient pulmonary rehabilitation programme, including also non-exercising components such as occupational therapy, relaxation therapy, exacerbation management strategies, educational sessions and psychosocial counselling.[2] The interdisciplinary treatment was comparable among the groups. None of the participants underwent treadmill walking or stationary ergometry cycling.

NMES protocols

Quadriceps and calf muscles of both legs were stimulated electrically with a portable battery-operated electrical stimulator, using eight carbon-rubber electrodes (Tensmed S84, Enraf-Nonius, Rotterdam, the Netherlands) (see online supplementary figure E1).[5] After a continuous 3-min warm-up at 5 Hz, intensity was adjusted to individual toleration during each 18-min session. The frequencies used were 75 Hz (HF-NMES) or 15 Hz (LF-NMES).[5]

Strength training

Strength training consisted of bilateral leg extension and bilateral leg press exercises (Technogym SpA, Gambettola, Italy).[15] Both exercises started at 70% of one-repetition maximum, four sets of eight repetitions for each exercise with at least 2 min of recovery between each set. The training load was set to increase by 5% every 2 weeks.[15]

Outcomes

Primary outcome

The primary outcome was the change in isokinetic quadriceps muscle function (ie, peak muscle strength and endurance) using a Biodex (Biodex System 4 Pro, Biodex Medical Systems, Inc, New York, USA).[16] Participants performed 30 sequential volitional maximal contractions at an angular velocity of 90°/s, while seated upright and with the hip joint in 90° of flexion. Quadriceps muscle strength was defined as the highest peak torque (Newton-metre (Nm)). Quadriceps muscle endurance was defined as the total amount of delivered work (Joules (J)) during the set of 30 repetitions.[16] To minimise learning effects, the measurement was performed twice at the initial assessment. Best values were used for analyses.

Secondary outcomes

Functional exercise performance was measured with the 6-min walk test (6MWT), including a practice walk at initial assessment.[17] The best value was used for further analyses. The constant work-rate cycling endurance test (CWRT, expressed in seconds) was performed at 75% of the measured peak cycling work rate.[18] Dyspnoea and fatigue were assessed before and after exercise tests and at isotime during the postintervention CWRT. Anxiety and depression were assessed using the Hospital Anxiety Depression Scale.[19] Disease-specific health status was measured using the St George's Respiratory Questionnaire (SGRQ).[20] The Canadian Occupational Performance Measure (COPM), a semistructured interview performed by an occupational therapist, was used to assess problematic activities of daily life (ADLs),[21] and has been shown to be reliable in individuals with COPD.[22] Whole-body dual-energy x-ray absorptiometry scan was used to assess body mass index and fat-free mass index (FFMI).[23] A modified MRC dyspnoea scale was used to assess dyspnoea.[24] In addition, age, sex, height, weight, comorbidities,[25] pulmonary function parameters and arterial blood gases were collected at the initial assessment.[13]

Sample size calculation, randomisation, blinding and statistics

The DICES trial was powered to detect a significant difference in the change in maximal quadriceps strength between HF-NMES and LF-NMES of 9.2 kg on average.[26] Each intervention group needed to have 36 individuals with COPD. Adjusting for drop out and withdrawals, we aimed for a minimum of 40 individuals in each intervention group.

A randomisation schedule was generated by the computer for participants with and without the use of long-term oxygen treatment; and with or without hospitalisation for a COPD exacerbation within <3 months of enrolment. The sequence was concealed. Analyses were performed using SPSS for Windows, V.17.0.1 (SPSS, Inc, Chicago, Illinois, USA). Differences within groups were analysed using paired t tests or Wilcoxon signed rank test. Groups were compared using one-way analysis of variance, χ^2 test, Fisher's exact test or Kruskal–Wallis one-way analysis of variance, as appropriate. The Bonferroni t test was used as post hoc test. Correlation analyses were done using Pearson's or Spearman's correlations. The level of significance was set at ≤0.05.

RESULTS

Participants' flow

Between September 2010 and November 2012, 120 individuals with COPD were included in the DICES trial (HF-NMES: n=41; LF-NMES: n=39; strength training: n=40). Ninety-one individuals (75.8%) were followed up at 8 weeks. The main reasons for dropping out were severe health problems, including hospital admission. Dropout rates were similar among intervention groups (figure 1).

Baseline characteristics

Participants generally had severe to very severe COPD, a poor diffusing capacity, explicit quadriceps muscle weakness, very severe dyspnoea, a poor functional and peak exercise performance and a poor health status (table 1). Participants used 10±1 types of medications (see online supplementary table E1) and

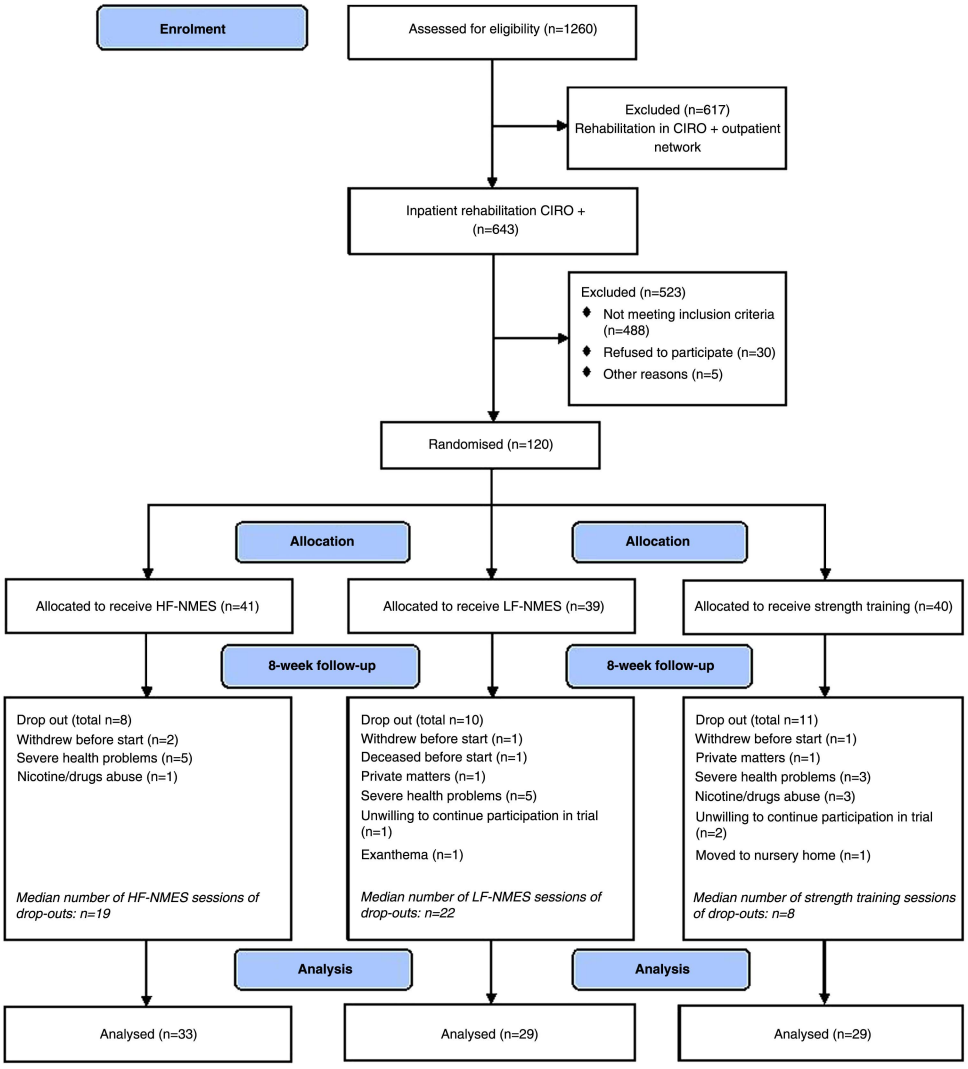

Figure 1 Flow diagram DICES trial (Dyspnoeic Individuals with COPD: Electrical stimulation or Strength training). CIRO, Centre of Expertise for Chronic Organ Failure; HF-NMES, high-frequency transcutaneous neuromuscular electrical stimulation; LF-NMES, low-frequency transcutaneous neuromuscular electrical stimulation.

had 3.2±0.1 objectified comorbidities (see online supplementary figure E2). The 29 individuals who dropped out and the 91 participants who completed the 8-week intervention had similar baseline characteristics (see online supplementary table E2).

Course of the 8-week NMES or strength training

The 91 participants who completed the programme attended 76 ±3 HF-NMES sessions, 74±1 LF-NMES sessions, or 68±2 strength training sessions (both NMES interventions vs strength training, p<0.001). Exacerbations requiring antibiotics and/or corticosteroid treatment occurred frequently during all three interventions: 58% of the HF-NMES participants; 41% of the LF-NMES participants and 41% of the strength training participants (p=0.254). During exacerbations of COPD which did not require hospital admission, NMES sessions (HF and LF) were continued. Strength training sessions were not always possible during exacerbations. The mean numbers of training sessions did not differ between the patients with and without one or more exacerbations (p=0.564).

HF/LF-NMES current intensities and strength training loads increased significantly over time (figure 2). All training modalities were safe. No side effects, such as acute dyspnoea or muscle pain, were reported (see online supplementary figure E3 for all details).

Efficacy

Quadriceps muscle function

Isokinetic quadriceps peak torque increased significantly after HF-NMES (10.8±2.9 Nm; p<0.01) or strength training (6.1 ±2.0 Nm; p<0.01), but not after LF-NMES (1.4±1.8 Nm; p=0.43). Improvement in isokinetic quadriceps peak torque was significantly higher after HF-NMES compared with LF-NMES (p=0.01; figure 3A). Isokinetic total work increased significantly in all groups (HF-NMES: 285±51 J; LF-NMES: 101 ±45 J; strength training: 192±51 J; all p<0.03). Again, the improvement after HF-NMES was significantly higher than with LF-NMES (p=0.03; figure 3B). Gains in peak muscle strength correlated with the increase in muscle endurance (HF-NMES: r=0.689; LF-NMES: r=0.581 and strength training: r=0.689, all p<0.001).

Six-minute walk test

Six-minute walk distance improved in all groups (HF-NMES: 66±14 m; LF-NMES: 51±15 m; strength training: 29±12 m;

Table 1 General characteristics

Characteristics	Total group (n=120)	HF-NMES (n=41)	LF-NMES (n=39)	Strength training (n=40)	p Value
Sex (M/F)	62/58	24/17	19/20	19/21	0.555
Age (years)	64.8±0.8	64.4±1.3	66.2±1.3	64.0±1.3	0.440
Pulmonary function					
FEV_1 (L)	0.85±0.03	0.87±0.04	0.87±0.07	0.80±0.05	0.578
FEV_1 (% predicted)	33±1	33±2	35±2	33±2	0.645
FEV_1/VC max (%)	32±1	31±1	31±2	33±2	0.545
TLCO (% predicted)	41±1	39±2	43±2	42±3	0.558
LTOT (%)	51	56	54	43	0.429
GOLD classification (I/II/III/IV)	0/12/36/72	0/5/12/24	0/2/14/23	0/5/10/25	0.942
GOLD classification (new) (A/B/C/D)	0/3/0/117	0/2/0/39	0/0/0/39	0/1/0/39	0.380
BMI (kg/m^2)	24.8±0.5	24.1±0.8	25.5±0.8	24.9±0.8	0.441
FFMI (kg/m^2)	16.5±0.2	16.3±0.3	16.6±0.3	16.6±0.4	0.688
Isokinetic quadriceps muscle function	n=120	n=41	n=39	n=40	
Peak torque (Nm)	76.2±2.4	78.7±4.4	76.1±4.1	73.4±4.1	0.682
Peak torque (% predicted)	54±1	54±3	55±2	53±3	0.812
Total work (J)	1175±44	1189±87	1164±67	1175±76	0.975
6-Min walk test	n=120	n=41	n=39	n=40	
6MWD (m)	322±8	311±16	315±14	337±14	0.412
6MWD (% predicted)	52±1	48±3	52±3	54±3	0.204
Cardiopulmonary exercise test	n=104	n=35	n=33	n=36	
Peak load (W)	44±1	45±2	45±2	44±2	0.984
Peak load (% predicted)	40±2	33±3	44±3	44±5	0.083
Peak VO_2 (mL/min)	820±21	831±37	829±43	806±30	0.858
Peak VO_2 (% predicted)	58±5	46±5	57±6	68±11	0.179
Peak VE (%MVV)	94±4	91±6	93±6	97±7	0.790
Peak HR (% predicted)	75±1	74±1	75±3	75±1	0.830
Constant work-rate cycling endurance test	n=96	n=33	n=30	n=33	
Cycle time (s)	191±10	199±20	188±15	185±14	0.836
Hospital Anxiety and Depression Scale	n=112	n=39	n=37	n=36	
Anxiety (points)	8.9±0.4	7.3±0.7	9.7±0.7	9.8±0.6	0.018
Depression (points)	8.4±0.4	8.1±0.5	8.0±0.7	9.1±0.7	0.436
St George's Respiratory Questionnaire	n=109	n=38	n=36	n=35	
Symptoms (points)	66.3±1.6	66.9±2.5	67.0±2.9	65.0±3.1	0.850
Activity (points)	81.7±1.6	84.4±2.2	80.9±3.0	79.6±2.9	0.431
Impact (points)	53.1±1.7	50.8±2.4	52.8±3.4	55.9±3.0	0.462
Total score (points)	63.9±1.3	63.6±1.7	63.7±2.6	64.6±2.3	0.932

Values are expressed as mean±SEM.
Cycle tests were not performed by all subjects; major reasons were unstable blood gases or a severely disabled condition.
The major reasons for not performing questionnaires were technical problems.
Please see online supplementary data repository tables E3 and E4 for more details.
BMI, body mass index; FEV_1, forced expiratory volume in one second; FFMI, fat free mass index; GOLD, Global initiative for chronic Obstructive Lung Disease; HF-NMES, high-frequency transcutaneous neuromuscular electrical stimulation; HR, heart rate; LF-NMES, low-frequency transcutaneous neuromuscular electrical stimulation; LTOT, long-term oxygen therapy; TLCO, carbon monoxide transfer factor; VC max, maximum vital capacity; VE, minute ventilation; VO_2, oxygen uptake; MVV, maximal voluntary ventilation; 6MWD, 6-min walk distance.

all $p<0.03$; no differences between groups). Interestingly, symptoms at the end of the 6MWT were significantly lower than baseline after HF-NMES (dyspnoea: 6.9±0.4 vs 5.7±0.4 points; fatigue: 5.2±0.5 vs 3.4±0.4 points; both $p<0.014$) or LF-NMES (dyspnoea: 6.4±0.4 vs 5.4±0.5 points; fatigue: 4.9 ±0.5 vs 2.8±0.5 points; both $p<0.032$). Symptoms at the end of the 6-min walk test remained unchanged after strength training (dyspnoea: 5.6±0.4 vs 5.2±0.4 points; fatigue: 4.1±0.5 vs 3.3±0.5 points; both $p>0.11$).

Constant work-rate test

Endurance time during the CWRT improved in all groups (HF-NMES: 171±58 s; LF-NMES: 167±46 s; strength training: 69±30 s; all $p<0.03$; no differences between groups). At isotime, symptoms of dyspnoea were lower after both NMES protocols, and fatigue was lower after all three interventions compared with the initial CWRT (HF-NMES: Δ dyspnoea isotime: −1.8±0.6 points ($p=0.005$), Δ fatigue isotime: −2.6 ±0.6 points ($p<0.001$); LF-NMES: −1.9±0.6 points ($p=0.005$) and −1.4±0.5 points ($p=0.01$), respectively; and strength training: 0.4±0.4 points ($p=0.361$), −1.7±0.5 points, ($p=0.003$), respectively. Moreover, symptoms of fatigue at the end of the CWRT were significantly lower than at baseline after HF-NMES (6.3±0.5 vs 4.7±0.6 points), LF-NMES (5.8±0.5 vs 5.0±0.6 points) or strength training (6.1±0.5 vs 4.8±0.5 points; all $p<0.05$). Symptoms of dyspnoea at the end of the cycle endurance test did not change (data not shown).

Body composition

Body mass index and FFMI did not change significantly compared with baseline in any of the groups. Lower-limb FFM increased in all groups (HF-NMES: 0.58±0.18 kg; LF-NMES:

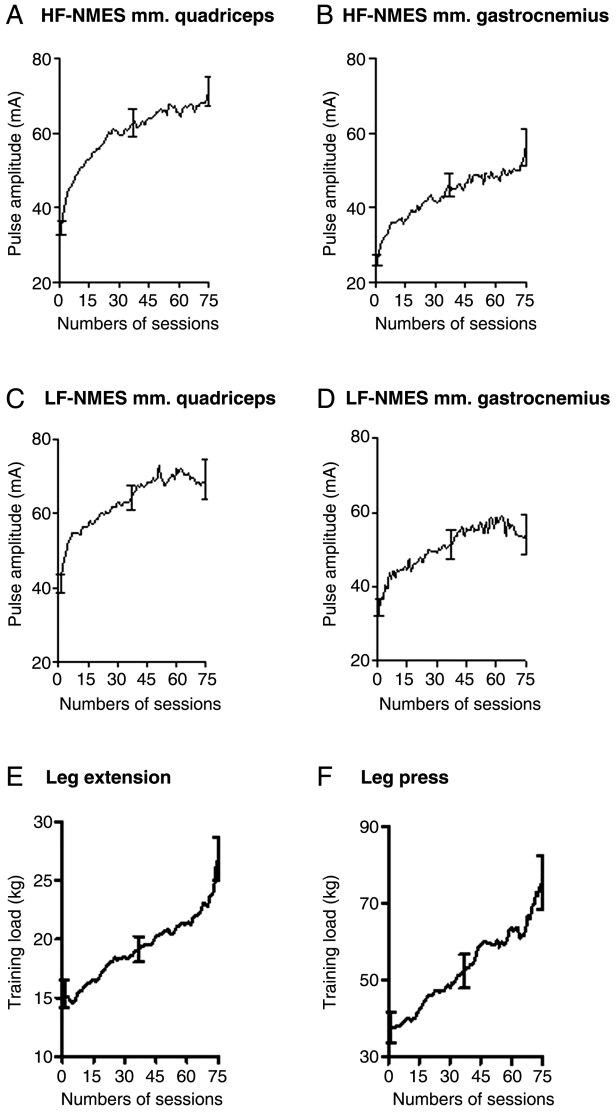

Figure 2 Course in NMES pulse amplitude and strength training load. Data are shown as mean±SEM. HF-NMES, high-frequency transcutaneous neuromuscular electrical stimulation; LF-NMES, low-frequency transcutaneous neuromuscular electrical stimulation.

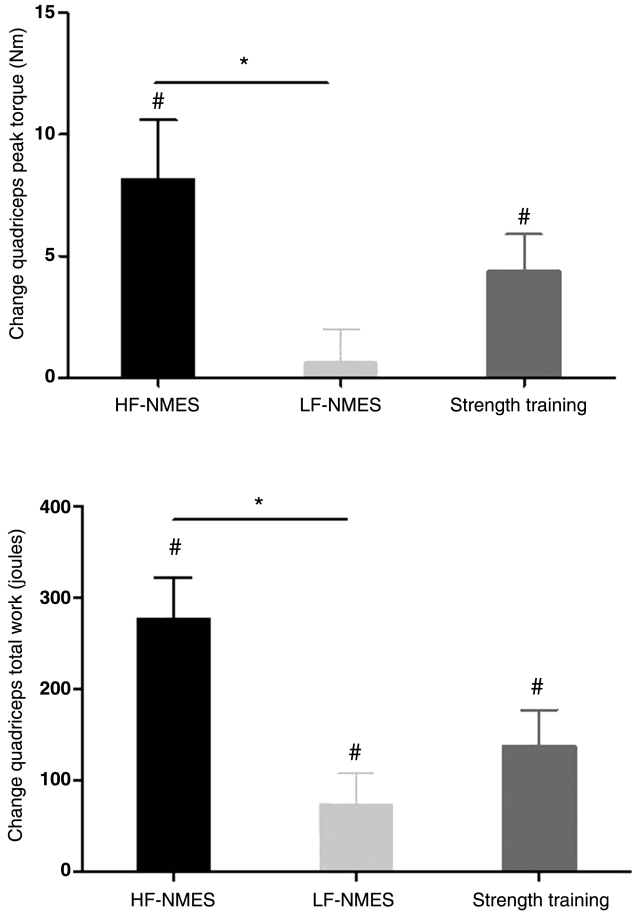

Figure 3 Change in quadriceps muscle strength and endurance. Data are shown as mean±SEM. *p≤0.05; #p≤0.05 compared with baseline. HF-NMES, high-frequency transcutaneous neuromuscular electrical stimulation; LF-NMES, low-frequency transcutaneous neuromuscular electrical stimulation.

0.44±0.18 kg; strength training: 0.37±0.13 kg; all p<0.03; no differences between groups).

Dyspnoea

Modified MRC dyspnoea scores improved in all groups (HF-NMES: −0.9±0.2 points; LF-NMES:

−0.7±0.2 points; strength training: −0.8±0.2 points; all p<0.005; no differences between groups).

Mood status

Symptoms of depression improved in all groups (HF-NMES: −1.8±0.6 points; LF-NMES: −2.2±0.5 points; strength training: −1.6±0.7 points; all p<0.04), while symptoms of anxiety only improved after LF-NMES (−1.8±0.6 points; p=0.004). Changes in symptoms of anxiety or depression were similar between groups (p>0.46).

Health status

Total SGRQ scores improved in all groups compared with baseline (HF-NMES: −10.2±2.4 points; LF-NMES: −10.5±3.0 points; strength training: −11.4±2.5 points; all p<0.003). Changes in health status scores were similar between groups (p=0.948). See online supplementary table E5 for the significant changes in the SGRQ domain scores.

Problematic activities of daily living (ADL)

COPM total scores for problematic ADL improved in all groups compared with baseline (HF-NMES: performance: 2.7±0.2 points, satisfaction: 3.5±0.2 points; LF-NMES: performance 2.5±0.2 points, satisfaction 2.9±0.3 points; strength training: performance 2.3±0.2 points, satisfaction 2.8±0.3 points; p<0.05), with no significant differences between groups (see online supplementary tables E6 and E7 for details).

DISCUSSION

As far as we know, this is the first trial comparing the effects of HF-NMES, LF-NMES and strength training as the sole supervised muscle training modality during an 8-week pulmonary rehabilitation programme in severely dyspnoeic individuals with COPD and quadriceps weakness at baseline. Lower-limb muscle strength increased in the HF-NMES group and the strength training group compared with baseline. Exercise performance, exercise-induced symptoms of dyspnoea and fatigue improved significantly compared with baseline in all three lower-limb training modalities. Only the increase in isokinetic quadriceps

muscle strength and endurance were higher after HF-NMES than after LF-NMES. Moreover, the DICES trial also showed that symptoms of depression, health status and problematic activities of daily living improved after an interdisciplinary pulmonary rehabilitation programme without treadmill walking or stationary cycling.

Lower-limb muscle function

Isokinetic quadriceps muscle strength improved after HF-NMES or strength training. This is in line with previous studies.[6 7] Interestingly, no significant differences were found between HF-NMES and strength training. Therefore, HF-NMES may be a preferential muscle training modality in patients with COPD with severe dyspnoea and muscle weakness, as the metabolic load on the impaired cardiorespiratory system is significantly lower than with strength training.[4] Moreover, HF-NMES recruits motor units in a non-selective, spatially fixed and temporally synchronous pattern,[27] contrary to the activation order according to the size principle involving activation of the slower (lower force-producing) motor units before the faster (higher force-producing) units.[28] In COPD, atrophy of fast-twitch muscle fibres is consistently reported.[29] It can be hypothesised that at least some of these fibres can be trained by HF-NMES, whereas these fibres might otherwise be activated only by high-force voluntary efforts.[30]

As expected from studies in healthy subjects,[31] quadriceps muscle strength did not improve after LF-NMES. Indeed, the change in isokinetic quadriceps muscle strength was significantly higher in the HF-NMES group than in the LF-NMES group. Comparable results were found in a study comparing HF-NMES (50 Hz) with LF-NMES (15 Hz) in healthy volunteers and in individuals with chronic heart failure.[10] The above-mentioned results might be obtained because the increase in muscle strength is proportional to the stimulation frequency: higher frequencies produce higher torques, which probably result in a greater increase in muscle strength.[32] Besides the peripheral pathway, HF-NMES can also produce muscle contractions by central recruitment through the electrically evoked sensory volley, in contrast to LF-NMES.[33] During HF-NMES, the recruitment of motor units through central pathways can augment contractions generated through peripheral pathways, leading to the development of greater torques.[34] While HF-NMES and LF-NMES had differential effects on muscle function in this study, the observed increase in lower-limb muscle mass was comparable, indicating that muscle dysfunction in COPD is not only related to the bulk of muscle.

Exercise performance

This trial shows that lower-limb muscle training modalities improve exercise performance significantly, while it is known that the load on the cardiorespiratory system is rather low.[4 5] Indeed, the mean improvement in 6-min walk distance exceeded the minimal important differences of 25 m in all three intervention groups.[35] Even though quadriceps muscle strength and endurance improved to a greater extent after HF-NMES than with LF-NMES, improvements in exercise performance were similar. This might be due to the fact that patients were still limited owing to their dyspnoea at the end of the exercise tests, while fatigue symptom scores were clearly lower at the end of the 6MWT or CWRT compared with baseline tests.

Dyspnoea, mood status, health status and problematic ADL

Both strength training and HF-NMES have a positive impact on health status in individuals with COPD.[7] Unfortunately, the design of our study does not allow us to distinguish between the impact of the muscle training modalities and the non-exercising parts of the pulmonary rehabilitation programme. The significant improvements in mood, health and problematic ADLs, however, were very encouraging as clinically relevant thresholds were exceeded, which is also true for walking and/or cycling-based pulmonary rehabilitation programmes.[2]

Strengths and methodological considerations

The DICES trial has several strengths. This is the largest randomised controlled trial studying the efficacy of HF-NMES, LF-NMES or strength training in severely dyspnoeic individuals with COPD and a considerable number of comorbidities. The number of participants provided sufficient statistical power to detect possible differences in changes in isokinetic quadriceps muscle function between HF-NMES, LF-NMES and strength training. However, the DICES trial is probably underpowered to detect statistically significant differences between HF/LF-NMES and strength training for changes in exercise performance, which did exceed minimal important differences. Isokinetic quadriceps muscle function was assessed twice at the initial assessment to minimise a learning effect. Outcome assessors were blinded for group allocation. They were not (in)directly involved in the delivery of the interventions. This places greater credence on the results.[36] Individuals randomly assigned to HF-NMES of LF-NMES were also blinded for the stimulation frequency applied. This is the first trial studying the efficacy of LF-NMES in individuals with COPD. All participants with baseline and outcome assessments were analysed, irrespective of the number of completed sessions or exacerbation treatment with antibiotics and/or corticosteroids during the intervention period.

The DICES trial also had some methodological limitations. The trial design did not include a control group, as strength training or HF-NMES had been proved to be beneficial compared with a non-exercise control group or sham NMES in individuals with COPD, respectively.[6 7 37] Twenty-nine participants (24.2%) did not complete the DICES trial. Dropping out appeared to be random across the DICES study sample as baseline characteristics were similar between participants who did and did not undergo outcome assessment (see online supplementary table E2). We believe that the drop-out rates are acceptable, as the DICES sample consisted of severely dyspnoeic individuals with COPD, who had muscle weakness and multiple coexisting morbidities. Moreover, our drop-out rate is comparable to drop-out rates in peer-reviewed COPD strength training trials (range: 11–38%).[6] The generalisability of our findings is limited owing to the strict inclusion and exclusion criteria. This approach, however, is in line with the philosophy of personalised medicine, in which healthcare is tailored to the individual patient or subgroups of patients.[38]

CONCLUSIONS

This study shows that HF-NMES is as effective as strength training in severely dyspnoeic individuals with COPD and quadriceps weakness in partially reversing quadriceps muscle dysfunction. HF-NMES may be a good alternative for strength training in this specific patient group. LF-NMES is not effective in improving muscle strength. HF-NMES, LF-NMES and strength training are effective training modalities, improving exercise performance, lower limb fat-free mass and health status in severely dyspnoeic individuals with COPD and quadriceps weakness.

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Contributors Trial concept and design: MJHS, EFMW and MAS; acquisition of data: MJHS, JMLD, AWV; analysis and interpretation of data, drafting the article: MJHS, FMEF and MAS; revising it critically for important intellectual content and final approval of the version to be published: all authors. MJHS had full access to all trial data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethics approval Medical ethical committee of the Maastricht University Medical Centre+, Maastricht, the Netherlands.

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Online data repository

Efficacy of lower-limb muscle training modalities in severely dyspnoeic individuals with chronic obstructive pulmonary disease and quadriceps muscle weakness: results from the *DICES* trial

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Trial registration: NTR2322

METHODS

Participants

Individuals with COPD referred for an inpatient interdisciplinary pulmonary rehabilitation programme at CIRO+, centre of expertise for chronic organ failure in Horn (the Netherlands) were screened for eligibility.[1] Inclusion criteria were: (i) primary diagnosis of COPD;[2] (ii) baseline modified MRC dyspnoea grade 3 ("*I stop for breath after walking 100 yards or after a few minutes on the level*") or 4 ("*I am too breathless to leave the house or breathless when dressing or undressing*");[3] and (iii) quadriceps weakness (peak torque ≤80% predicted). [4] Exclusion criteria were: (i) neuromuscular diseases; (ii) joint disorders in hip, leg and/or knee; (iii) metal implants in hip, leg and/or knee; (iv) cardiac pacemaker or internal cardiac defibrillator; and/or (v) outpatient pulmonary rehabilitation program.

Design and procedures

A prospective, single-blind, randomised controlled trial was set up according to the Consolidated Standards of Reporting Trials (CONSORT).[5] The ***DICES*** (***D***yspnoeic ***I***ndividuals with ***C***OPD: ***E***lectrical stimulation or ***S***trength training) trial protocol was approved by the Medical Ethical Committee of the Maastricht University Medical Centre+ (MEC 09-3-072) and conformed to the principles outlined in the World Medical Association declaration of Helsinki which is revised in Seoul.[6] Details of the ***DICES*** trial were registered at www.trialregister.nl (NTR2322) before first subject enrolment. All participants gave written informed consent to participate. Some baseline findings of the ***DICES*** trial have been published.[7]

Interventions

The ***DICES*** trial was part of a regular eight-week inpatient pulmonary rehabilitation program, including also non-exercising components like occupational therapy, exacerbation

management strategies, relaxation therapy, educational sessions, and psychosocial counselling.[8] The interdisciplinary treatment was comparable amongst groups. None of the participants underwent treadmill walking or stationary ergometry cycling.

Lower-limb muscle training existed of one of the following interventions: HF-NMES; LF-NMES; or strength training. The interventions took place in group sessions, twice per day, 5 times per week for 8 weeks. All sessions were supervised by a physiotherapist. Symptom scores for dyspnoea, fatigue, and muscle pain were assessed before and directly after each session.[9]

NMES protocols

NMES involves the application of an electrical current through electrodes placed on the skin over the targeted muscles, thereby depolarizing motor neurons and, in turn, inducing skeletal muscle contractions.[10, 11] Quadriceps and calf muscles of both legs were stimulated electrically with a portable battery-operated electrical stimulator (Tensmed S84, Enraf-Nonius, Rotterdam, the Netherlands) (figure E1). The output characteristics of the device have been checked on an oscilloscope. A total of eight carbon-rubber electrodes in moistened sponges were placed on the target muscles (four electrodes on each leg): two pairs of 8 x 12 cm on the quadriceps muscles and two pairs of 4 x 6 cm on the calf muscles. The electrodes on the quadriceps femoris muscles were placed transversally 5-10 cm distal to the inguinal fold and 4-8 cm proximal to the patella. The electrodes on the calf muscles were placed longitudinally on the belly of the gastrocnemii muscles. Both NMES protocols used a symmetrical biphasic square pulse with pulse duration of 400 μs. The contraction time was 6 seconds with 8 seconds relaxation excluding 1 second ramp-up and 1 second ramp-down. Thus, the total cycle length was 16 seconds. After a continuous warm-up of 3

minutes at 5 Hz, intensity was adjusted to individual toleration during each session lasting 18 minutes. The frequencies used were 75 Hz (HF-NMES) or 15 Hz (LF-NMES).[12]

Strength training

Strength training involves exercises that cause muscles to work or hold against an externally applied force or weight.[13] Strength training consisted of bilateral leg extension and bilateral leg press exercises (Technogym SpA, Gambettola, Italy).[14, 15] The 1RM was determined during the initial assessment to target the training load. Both exercises started at 70% of 1-repetition maximum (1RM), 4 sets of 8 repetitions per exercise with at least 2 minutes of recovery between each set. The training load was set to increase with 5% every two weeks.[15]

Outcomes

Primary outcome

The primary outcome parameter was the change in isokinetic quadriceps muscle function (i.e., peak muscle strength and muscle endurance), using a Biodex (Biodex System 4 Pro, Biodex Medical Systems, Inc., New York, USA). [16] The reliability of this method has been demonstrated previously in patients with COPD.[16] To avoid learning effects, the measurement was performed twice at the initial assessment. Best values were used for further analyses. During quadriceps muscle function testing, participants were seated upright on the chair of the dynamometer with support of the back and an angle of 90^0 of flexion in the hip joint. The participants were secured with straps. The lever arm was attached to the distal part of the tibia and its axis of rotation was aligned with the anatomical axis of the knee joint. Subjects were instructed to keep their hands on their thighs during testing and were asked to perform maximum strength. The participants performed thirty sequential volitional maximal contractions at an angular velocity of 90^0 per

second. They were strongly encouraged during this isokinetic test. Peak quadriceps muscle strength was defined as the highest peak torque (Newton-meter, Nm) and quadriceps muscle endurance as the total amount of delivered work (Joules, J) in this series of thirty contractions.[17]

Secondary outcomes

Functional exercise performance was measured with the 6-minute walk test (6MWT), including a practice walk at initial assessment.[18] The best value was used for further analyses. Moreover, the constant work-rate cycling endurance test (CWRT, expressed in seconds) was performed at 75% of the measured peak cycling work rate, which has a high reliability in individuals with COPD.[19] Symptoms scores for exercise-induced dyspnoea and fatigue were assessed before and after these exercise tests.

Symptoms of anxiety and depression were assessed using the Hospital Anxiety Depression Scale (HADS), with scores ranging from 0 (optimal) to 21 points (worst).[20] Disease-specific health status was measured using the St**.** George's Respiratory Questionnaire (SGRQ).[21]

The Canadian Occupational Performance Measure (COPM), a semi-structured interview performed by an occupational therapist, was used to assess problematic activities of daily life (ADLs),[22] and has been shown to be reliable in individuals with COPD.[23]

Whole-body dual-energy x-ray absorptiometry scan (DEXA scan) was used to assess body mass index and fat-free mass index.[24]

Modified MRC dyspnoea scale was used to assess shortness of breath.[3] In the modified MRC dyspnoea scale patients with COPD have to grade their self-perceived dyspnoea by using pre-defined statements.

Sample size

The ***DICES*** trial was powered to detect a significant difference between the muscle training modality groups of 9.2 kg on average.[25] Based on standard deviations of 14.6 kg in the intervention group and 13.1 kg in the control group, a significance level of 5% and a power of 80%, the number of patients in each intervention group needed to be 36. Adjusting for drop out and withdrawals from the trial, the minimum number of patients to be included in each group was set to be 40.

Randomisation

The randomisation schedule was generated by the computer for participants with and without the use of long-term oxygen therapy; and with or without a hospitalization for a COPD exacerbation <3 months of enrolment. MAS maintained the randomisation schedule centrally, and was not involved in the assessment and treatment of the participants. The sequence was concealed.

Blinding

Outcome assessors were blinded for treatment allocation. The investigators supervising the interventions (MJHS, AWV) were blinded for the initial results, and were not involved in the initial or outcome assessments. Participants were instructed to not divulge their group allocation. Participants randomly assigned to one of the NMES groups, were blinded for stimulation frequency.

Comorbidities

The following comorbidities were objectified, as described before:[7]

Body composition abnormalities

Body mass index (BMI, defined as body weight divided by squared height) and fat-free mass index (FFMI), defined as fat free mass divided by squared height) were determined, and classified as obesity (BMI $\geq$30 kg/m^2), underweight (BMI <21 kg/m^2), and/or muscle wasting (FFMI <14.62 kg/m^2 in women and FFMI <17.05 kg/m^2 in men).[26] In addition, bone mineral density (BMD of the hip, lumbar spine and whole body region, expressed as T-scores) were determined using dual-energy x-ray absorptiometry.[24] If the lowest of the three T-scores was <-2.5, the subject was defined as osteoporotic.[27]

Symptoms of anxiety and depression

Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS).[20] Scores can range from 0 (optimal) to 21 points (worst). A score of 10 points or more was defined as increased symptoms of anxiety and/or depression.[20, 28]

Hyperglycemia, anemia, dyslipidemia and systemic inflammation

Routinely, a post-absorptive venous blood sample was collected from the patients in the fasted state to analyse glucose, hemoglobin, triglycerides, high density lipoprotein (HDL) and creatinine.

A fasting glucose level >5.6 mmol/L was defined as hyperglycemia;[29] anemia was defined as a hemoglobin level <13 g/dl (8.1 mmol/L, men) or <12 g/dl (7.5 mmol/L, women);[30] dyslipidemia was defined as a triglyceride level above 1.7 mmol/L or a HDL cholesterol level below 1.03 mmol/L (men) or below 1.29 mmol/L (women).[31]

Renal impairment

Renal function was established by the estimated glomerular filtration rate (eGFR), using the Cockroft-Gault formula.[32] Chronic kidney disease was defined as eGFR <60 ml/min, corresponding with stage 3 chronic kidney disease according to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) guidelines.[33]

Cardiovascular abnormalities

Peripheral blood pressure was measured three times with interval of 5 minutes, after 15 minutes of supine rest in early morning time. Mean values were calculated. Hypertension grade 1 or higher was based on cut-off values of >140 mm Hg for systolic blood pressure and >90 mm Hg for diastolic blood pressure.[34]

A resting ECG was obtained and the Cardiac Infarction Injury Score (CIIS) was scored by a cardiologist (NHMKU-L) blinded for medical history and outcome measures. CIIS is an ECG classification system that was developed as a diagnostic tool to determine the presence of myocardial infarctions. It is based on the power of certain electrocardiographic characteristics to discriminate between myocardial infarction patients and healthy individuals. These characteristics are weighted and combined into a single score.[35] Myocardial infarction was defined as a CIIS ≥ 20 [35].

Statistical analysis

Analyses were performed using SPSS for Windows, Version 17.0.1 (SPSS, Inc., Chicago, Il, USA). Descriptive statistics were presented as means with standard error of the means or numbers with percentages unless otherwise stated. All patients who had their outcome measures assessed were included in the analysis, regardless of the number of sessions they successfully completed. No imputations were made for missing data. Differences within

groups were analysed using paired T-tests or Wilcoxon signed rank test. Groups were compared using an analysis of variance (one-way ANOVA), χ^2 test, Fisher's exact test or Kruskal-Wallis one-way analysis of variance, as appropriate. The Bonferroni T-test was used as Post-Hoc test. Correlation analyses were done using Pearson's or Spearman's correlations. The level of significance was set at ≤0.05.

Results

Course of the 8-week NMES or strength training

The quadriceps muscle current intensity increased from 34±2 mA (in week 1) to 71±4 mA (in week 8) in the HF-NMES group ($p<0.001$); and from 41±3 mA to 69±5 mA in the LF-NMES group ($p<0.001$). The calf muscle current intensity increased also during the intervention, but at a lower level (HF-NMES: 26±1 to 56±5 mA; LF-NMES: 34±2 to 54±5 mA; both $p<0.001$). The leg extension training load increased from 15±1 to 27±2 kg; and the leg press training load from 38±4 to 75±7 kg (both $p<0.001$). The change in current intensity or training load did not differ between patients with or without exacerbations (all $p>0.07$).

Table E1. Numbers of patients using various categories of medications

Medication		N
1	SABA Short acting β2-agonists	62
2	SAMA Short-acting anticholinergics (SAAC)	13
3	SABA + SAMA Short-acting combinations (COMBI)	47
4	LABA Long-acting β2-agonists	26
5	LAMA Long-acting anticholinergics	95
6	ICS Inhaled corticosteroids alone	26
7	ICS + LABA Inhaled corticosteroids in combination with LABA	86
8	THEOLAIR	21
9	ORAL CORTICOSTEROIDS	58
10	ANTI-LEUKOTRIENES	3
11	ANTIHISTAMINICUM	8
12	NASAL CORTICOSTEROIDS	1
13	ACE OR ARB	32
14	BETA BLOCKERS	17
15	CALCIUM BLOCKERS	24
16	ANTI ARRYTHMICA	8
17	NITRATES	15
18	DIURETICS	41
19	ANTILIPAEMICA	39
20	ANTIAGGREGATES	36
21	COUMARINES	14
22	ORAL ANTIDIABETICA / INSULIN	11
23	CALCIUM SUPPLETION and/or VITAMIN D	34
24	BISFOSFONATES	39
25	ANTIDEPRESSIVES	24
26	ANXIOLYTICS and SLEEP MEDICATION	39
27a	PARACETAMOL	14
27b	NSAIDs	12
27c	MORPHINE	7
27d	CODEINE	10
27e	OTHER PAINKILLERS	0
28	PPI/ANTACIDA	73
29	ANTIBIOTICS	21
30	ACETYLCYSTEIN	32
31	OTHER MEDICATION	52

Table E2. Characteristics of analysed group and drop-outs

		Analysed group n=91	Drop out n=29	P-value
Gender	Male/Female	44/47	18/11	0.200
Age	years	64.3 ± 0.8	66.7 ± 1.8	0.163
FEV_1	litres	0.82 ± 0.03	0.95 ± 0.08	0.089
FEV_1	% predicted	33 ± 1	36 ± 3	0.315
FEV_1/VC max	%	32 ± 1	31 ± 2	0.721
DL_{CO}	%	41 ± 2	41 ± 3	0.960
RV	%	197 ± 6	203 ± 11	0.641
PaO_2	kPa	9.6 ± 0.2	10.0 ± 0.3	0.257
$PaCO_2$	kPa	5.7 ± 0.1	5.6 ± 0.2	0.913
SaO_2	%	95.2 ± 0.2	95.5 ± 0.5	0.845
Peak load	watts	44 ± 1	45 ± 2	0.773
Peak load	% predicted	42 ± 3	37 ± 3	0.367
Peak VO_2	ml/min	824 ± 25	811 ± 38	0.787
Peak VE	litres	34 ± 1	34 ± 2	0.837
Cycle time	seconds	194 ± 12	182 ± 16	0.593
6MWD	meters	320 ± 10	323 ± 16	0.879
6MWD	% predicted	52 ± 2	52 ± 2	0.983
Bodyweight	kg	69.8 ± 1.6	67.8 ± 2.5	0.517
BMI	kg/m^2	25.1 ± 0.5	23.9 ± 0.8	0.274
FFMI	kg/m^2	16.6 ± 0.2	16.2 ± 0.3	0.350
Peak torque	Nm	76.3 ± 2.9	77.8 ± 4.6	0.792
Peak torque	% predicted	55 ± 2	54 ± 3	0.810
Total work	Joules	1172 ± 52	1193 ± 85	0.837
HADS anxiety	points	8.8 ± 0.5	9.3 ± 0.9	0.624
HADS depression	points	8.6 ± 0.4	7.4 ± 0.7	0.168
SGRQ total score	points	65.0 ± 1.3	59.4 ± 3.6	0.081

Values expressed as mean ± SEM or numbers
Abbreviations: FEV_1=forced expiratory volume in one second; VC max=maximum vital capacity; DL_{CO}=diffusion capacity of the lung for carbon monoxide; RV=residual volume; PaO_2=resting arterial oxygen tension; $PaCO_2$=resting arterial carbon dioxide tension; SaO_2=resting arterial oxygen tension; peak VO_2=peak oxygen uptake; peak VE= peak minute ventilation; 6MWD=6-minute walk distance; : BMI=body mass index; FFMI=fat-free mass index; Nm=newtonmeter; kPa= kilopascal; ml/min=milliliter per minute; kg/m^2=kilogram per squared meter.

Table E3. General characteristics

	Total group n=120	HF-NMES n=41	LF-NMES n=39	Strength training n=40	P-value
Sex (M/F)	62/58	24/17	19/20	19/21	0.555
Age (years)	64.8 ± 0.8	64.4 ± 1.3	66.2 ± 1.3	64.0 ± 1.3	0.440
Pulmonary function					
FEV_1 (liters)	0.85 ± 0.03	0.87 ± 0.04	0.87 ± 0.07	0.80 ± 0.05	0.578
FEV_1 (% predicted)	33 ± 1	33 ± 2	35 ± 2	33 ± 2	0.645
FEV_1/VC max (%)	32 ± 1	31 ± 1	31 ± 2	33 ± 2	0.545
DL_{CO} (% predicted)	41 ± 1	39 ± 2	43 ± 2	42 ± 3	0.558
RV (% predicted)	198 ± 5	197 ± 9	194 ± 10	206 ± 9	0.590
Arterial blood gases					
PaO_2 (kPa)	9.7 ± 0.1	9.9 ± 0.3	9.7 ± 0.3	9.5 ± 0.2	0.852
$PaCO_2$ (kPa)	5.7 ± 0.1	5.6 ± 0.2	5.5 ± 0.2	5.8 ± 0.2	0.664
SaO_2 (%)	95.2 ± 0.2	95.6 ± 0.3	95.1 ± 0.4	95.1 ± 0.4	0.848
LTOT (%)	51	56	54	43	0.429
GOLD classification (I/II/III/IV)	0/12/36/72	0/5/12/24	0/2/14/23	0/5/10/25	0.942
GOLD classification (new) (A/B/C/D)	0/3/0/117	0/2/0/39	0/0/0/39	0/1/0/39	0.380
BMI (kg/m^2)	24.8 ± 0.5	24.1 ± 0.8	25.5 ± 0.8	24.9 ± 0.8	0.441
FFMI (kg/m^2)	16.5 ± 0.2	16.3 ± 0.3	16.6 ± 0.3	16.6 ± 0.4	0.688

Values expressed as mean ± SEM, percentages or numbers.
Abbreviations: HF-NMES=High-frequency transcutaneous neuromuscular electrical stimulation; LF-NMES=Low-frequency transcutaneous neuromuscular electrical stimulation; M=males; F=females; FEV_1=forced expiratory volume in one second; VC max=maximum vital capacity; DL_{CO}=diffusion capacity of the lung for carbon monoxide; RV=residual volume; PaO2=resting arterial oxygen tension; PaCO2=resting arterial carbon dioxide tension; SaO2=resting arterial oxygen tension; kPa= kilopascal; LTOT=long-term oxygen therapy; GOLD=Global Initiative for chronic Obstructive Lung Disease; BMI=body mass index; FFMI=fat free mass index; kg/m^2=kilogram per square meter.

Table E4. Baseline lower-limb muscle function, exercise performance, HADS and SGRQ.

	Total group	HF-NMES	LF-NMES	Strength training	P-value
Isokinetic quadriceps muscle function	n=120	n=41	n=39	n=40	
Peak torque (Nm)	76.2 ± 2.4	78.7 ± 4.4	76.1 ± 4.1	73.4 ± 4.1	0.682
Peak torque (% predicted)	54 ± 1	54 ± 3	55 ± 2	53 ± 3	0.812
Total work (joules)	1175 ± 44	1189 ± 87	1164 ± 67	1175 ± 76	0.975
6-minute walk test	n=120	n=41	n=39	n=40	
6MWD (meters)	322 ± 8	311 ± 16	315 ± 14	337 ± 14	0.412
6MWD (% predicted)	52 ± 1	48 ± 3	52 ± 3	54 ± 3	0.204
Dyspnoea, end (points)	6.4 ± 0.2	6.7 ± 0.4	6.5 ± 0.3	5.8 ± 0.3	0.126
Fatigue, end (points)	4.9 ± 0.2	5.2 ± 0.4	5.4 ± 0.5	4.0 ± 0.4	0.048
Saturation, end (%)	86.6 ± 0.6	87.3 ± 1.0	86.5 ± 1.1	86.1 ± 1.0	0.687
Cardiopulmonary exercise test	n=104	n=35	n=33	n=36	
Peak load (watts)	44 ± 1	45 ± 2	45 ± 2	44 ± 2	0.984
Peak load (% predicted)	40 ± 2	33 ± 3	44 ± 3	44 ± 5	0.083
Peak VO_2 (ml/min)	820 ± 21	831 ± 37	829 ± 43	806 ± 30	0.858
Peak VO_2 (% predicted)	58 ± 5	46 ± 5	57 ± 6	68 ± 11	0.179
Peak VE (liters)	34 ± 5	33 ± 2	34 ± 2	33 ± 2	0.993
Peak VE (%MVV)	94 ± 4	91 ± 6	93 ± 6	97 ± 7	0.790
Peak HR (bpm)	114 ± 1	114 ± 2	110 ± 3	117 ± 3	0.139
Peak HR (% predicted)	75 ± 1	74 ± 1	75 ± 3	75 ± 1	0.830
Dyspnoea, end (points)	7.3 ± 0.2	7.1 ± 0.3	7.4 ± 0.3	7.3 ± 0.3	0.794
Fatigue, end (points)	5.6 ± 0.3	5.6 ± 0.4	5.8 ± 0.5	5.3 ± 0.4	0.718
Saturation, end (%)	91.3 ± 0.4	91.3 ± 0.8	91.7 ± 0.7	91.0 ± 0.6	0.808
$\Delta tSaO_2$ (%)	-2.9 ± 0.3	-3.0 ± 0.6	-2.8 ± 0.6	-2.9 ± 0.5	0.901
Constant work-rate cycling endurance test	n=96	n=33	n=30	n=33	
Cycle time (seconds)	191 ± 10	199 ± 20	188 ± 15	185 ± 14	0.836
Dyspnoea, end (points)	7.1 ± 0.2	7.1 ± 0.3	7.2 ± 0.4	7.0 ± 0.3	0.900
Fatigue, end (points)	6.2 ± 0.2	6.3 ± 0.4	6.0 ± 0.4	6.2 ± 0.4	0.853
Saturation, end (%)	90.0 ± 0.4	90.2 ± 0.8	91.1 ± 0.7	88.8 ± 0.6	0.096
Hospital Anxiety and Depression Scale	n=112	n=39	n=37	n=36	
Anxiety (points)	8.9 ± 0.4	7.3 ± 0.7	9.7 ± 0.7	9.8 ± 0.6	0.018
Depression (points)	8.4 ± 0.4	8.1 ± 0.5	8.0 ± 0.7	9.1 ± 0.7	0.436
St. George's Respiratory Questionnaire	n=109	n=38	n=36	n=35	
Symptoms (points)	66.3 ± 1.6	66.9 ± 2.5	67.0 ± 2.9	65.0 ± 3.1	0.850
Activity (points)	81.7 ± 1.6	84.4 ± 2.2	80.9 ± 3.0	79.6 ± 2.9	0.431
Impact (points)	53.1 ± 1.7	50.8 ± 2.4	52.8 ± 3.4	55.9 ± 3.0	0.462
Total score (points)	63.9 ± 1.3	63.6 ± 1.7	63.7 ± 2.6	64.6 ± 2.3	0.932

Values expressed as mean ± SEM.
Cycle tests have not been performed by all subjects with as major reasons unstable blood gases or severe disabled condition.
The major reason for not performing questionnaires are technical problems.
Abbreviations: HF-NMES=High-frequency transcutaneous neuromuscular electrical stimulation; LF-NMES=Low-frequency transcutaneous neuromuscular electrical stimulation; FFM=fat free mass; 6MWD=6-minute walk distance; VO_2=oxygen uptake; $tSaO_2$=transcutaneous oxygen saturation; Nm=newton meter; ml/min=millilitres per minute; % MVV=percentage maximal voluntary ventilation; bpm=beats per minute.

Table E5. Health status

		HF-NMES			LF-NMES			Strength training		
		Baseline	End	P-value	Baseline	End	P-value	Baseline	End	P-value
SGRQ		n=31			n=29			n=29		
Symptoms	points	66.8 ± 3.0	56.4 ± 3.2	0.012	68.6 ± 2.7	62.6 ± 2.8	0.028	65.0 ± 3.1	54.2 ± 4.3	0.019
Activity	points	84.4 ± 2.4	76.0 ± 3.0	0.049	83.5 ± 2.9	75.9 ± 3.7	0.092	82.6 ± 2.2	73.1 ± 4.1	0.016
Impact	points	50.7 ± 2.8	38.3 ± 2.7	<0.001	55.2 ± 3.6	41.2 ± 3.5	0.001	56.3 ± 3.0	42.3 ± 3.1	0.001
Total score	points	63.4 ± 2.0	52.7 ± 2.0	<0.001	66.0 ± 2.6	55.6 ± 2.6	0.002	65.7 ± 2.1	53.6 ± 2.7	<0.001

Values expressed as mean ± SEM

Abbreviations: HF-NMES=high-frequency transcutaneous neuromuscular electrical stimulation; LF-NMES=low-frequency transcutaneous neuromuscular electrical stimulation; SGRQ=St. George's Respiratory Questionnaire.

Table E6. Canadian Occupational Performance Measure

		HF-NMES n=33			LF-NMES n=29			Strength training n=29		
		Baseline	End	P-value	Baseline	End	P-value	Baseline	End	P-value
Domain										
Self-care	P	4.2 ± 0.3	6.8 ± 0.2	<0.001	3.8 ± 0.3	6.3 ± 0.4	<0.001	4.1 ± 0.3	6.4 ± 0.3	<0.001
	S	3.4 ± 0.3	6.7 ± 0.3	<0.001	3.3 ± 0.4	6.4 ± 0.4	<0.001	2.8 ± 0.3	6.1 ± 0.5	<0.001
Mobility	P	3.4 ± 0.2	6.2 ± 0.3	<0.001	3.6 ± 0.3	6.2 ± 0.3	<0.001	3.3 ± 0.2	6.0 ± 0.3	<0.001
	S	2.6 ± 0.2	6.2 ± 0.4	<0.001	3.4 ± 0.3	6.3 ± 0.4	<0.001	2.9 ± 0.3	6.0 ± 0.4	<0.001
Productivity	P	3.8 ± 0.3	6.2 ± 0.4	<0.001	3.3 ± 0.3	5.7 ± 0.4	<0.001	3.4 ± 0.3	6.0 ± 0.4	<0.001
	S	2.9 ± 0.3	6.2 ± 0.4	<0.001	3.2 ± 0.4	5.8 ± 0.4	<0.001	3.2 ± 0.3	5.8 ± 0.4	<0.001
Leisure	P	2.4 ± 0.4	5.8 ± 0.5	<0.001	4.1 ± 0.5	5.8 ± 0.7	0.005	4.9 ± 0.7	6.3 ± 0.6	0.040
	S	2.1 ± 0.3	6.1 ± 0.4	<0.001	3.6 ± 0.5	6.0 ± 0.8	0.002	4.1 ± 0.7	5.4 ± 1.0	0.028
Total	P	3.5 ± 0.1	6.3 ± 0.2	<0.001	3.7 ± 0.2	6.0 ± 0.2	<0.001	3.6 ± 0.2	6.1 ± 0.2	<0.001
	S	2.8 ± 0.2	6.3 ± 0.2	<0.001	3.4 ± 0.2	6.1 ± 0.2	<0.001	3.0 ± 0.2	5.9 ± 0.2	<0.001

Values expressed as mean ± SEM.

Abbreviations: HF-NMES=high-frequency transcutaneous neuromuscular electrical stimulation; LF-NMES=low-frequency transcutaneous neuromuscular electrical stimulation; P=performance (points); S=satisfaction (points).

Table E7. Changes in COPM performance and satisfaction scores

		HF-NMES n=33	LF-NMES n=29	Strength training n=29	P-value
Domain					
Self care	P	2.6 ± 0.3	2.5 ± 0.4	2.4 ± 0.4	0.876
	S	3.3 ± 0.4	3.1 ± 0.5	3.4 ± 0.5	0.939
Mobility	P	2.8 ± 0.3	2.8 ± 0.4	2.5 ± 0.3	0.852
	S	3.6 ± 0.4	3.0 ± 0.4	2.8 ± 0.4	0.359
Productivity	P	2.3 ± 0.5	2.5 ± 0.4	2.6 ± 0.4	0.429
	S	3.1 ± 0.6	2.9 ± 0.5	2.8 ± 0.5	0.600
Leisure	P	3.1 ± 0.7	2.6 ± 0.5	1.9 ± 0.7	0.280
	S	3.7 ± 0.3	3.3 ± 0.6	2.1 ± 0.8	0.256
Total	P	2.7 ± 0.2	2.5 ± 0.2	2.3 ± 0.2	0.609
	S	3.5 ± 0.2	2.9 ± 0.3	2.8 ± 0.3	0.155

Values expressed as mean ± SEM.
Abbreviations: HF-NMES=high-frequency transcutaneous neuromuscular electrical stimulation; LF-NMES=low-frequency transcutaneous neuromuscular electrical stimulation; P=performance (points); S=satisfaction (points).

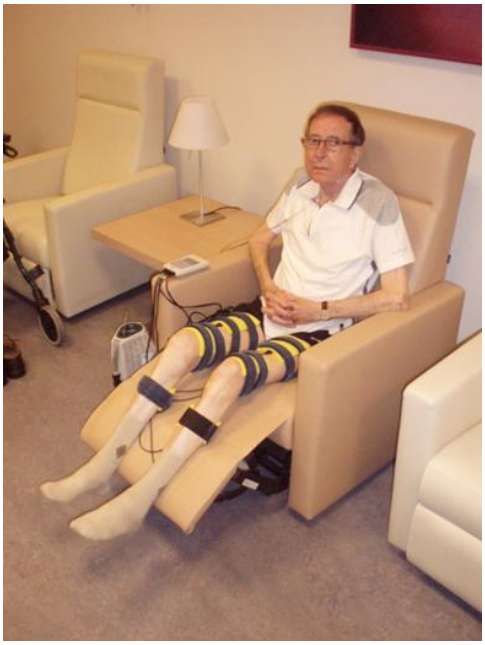

Figure E1. Transcutaneous neuromuscular electrical stimulation of a man with COPD GOLD IV Written consent was obtained for the use of this photograph.

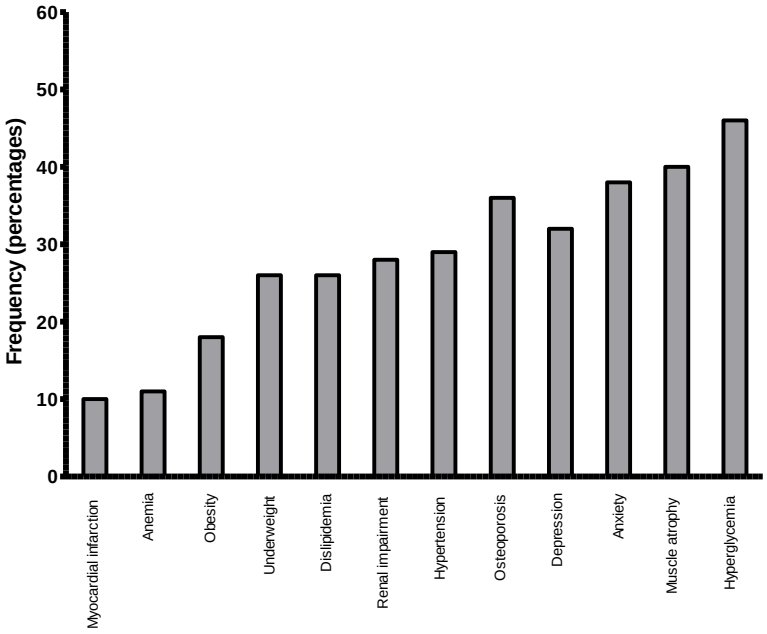

Figure E2. Comorbidities

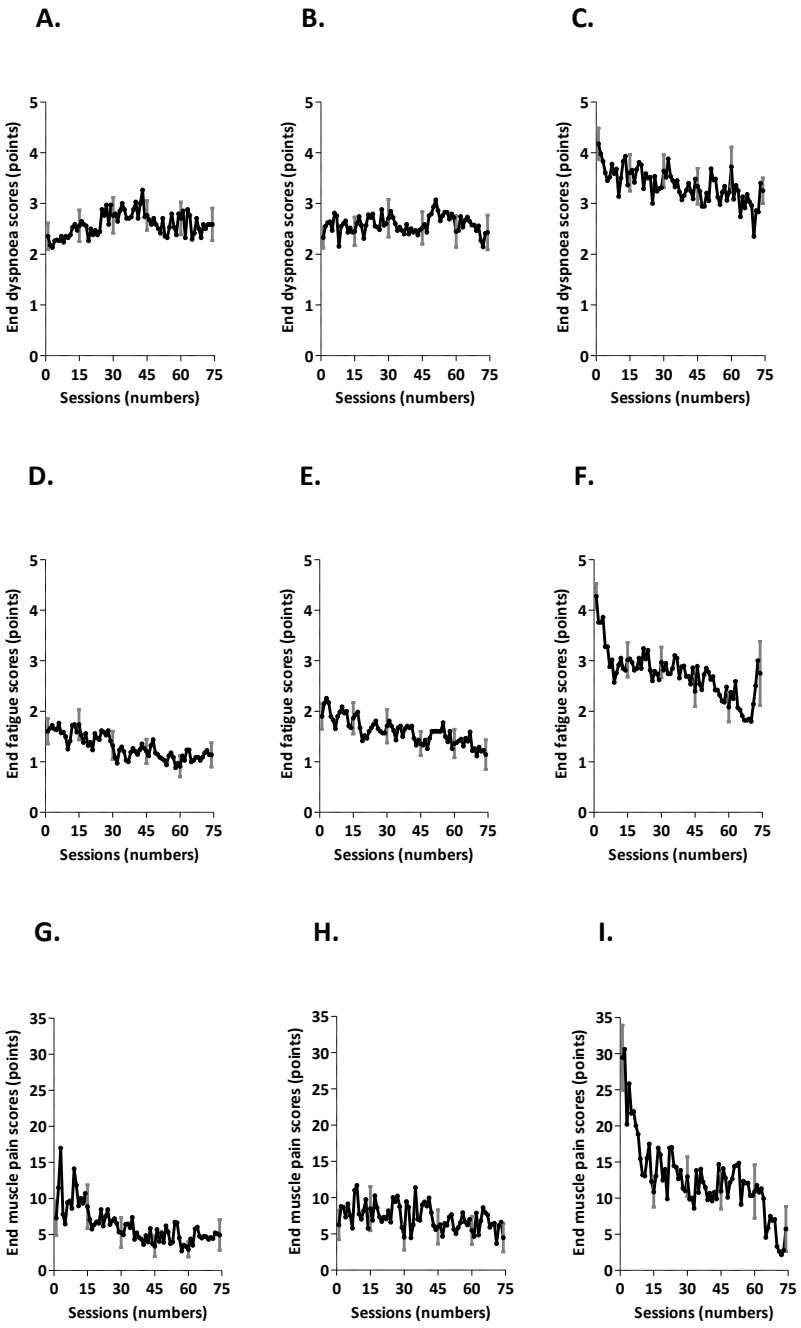

Figure E3. End dyspnoea scores (A. HF-NMES; B. LF-NMES; C. Strength training), end fatigue scores (D. HF-NMES; E. LF-NMES; F. Strength training) and end muscle pain scores (G. HF-NMES; H. LF-NMES; I. Strength training) directly after the interventions

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