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

Maurice J.H. Sillen [1], Frits M.E. Franssen [1], Jeannet M.L. Delbressine [1], Anouk W. Vaes [1], Emiel F.M. Wouters [1,2], and Martijn A. Spruit [1]

AFFILIATIONS

1. Department of Research & Education
   CIRO+, Centre of expertise for chronic organ failure
   Horn, the Netherlands
2. Department of Respiratory Medicine
   Maastricht University Medical Centre (MUMC+)
   Maastricht, the Netherlands

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).

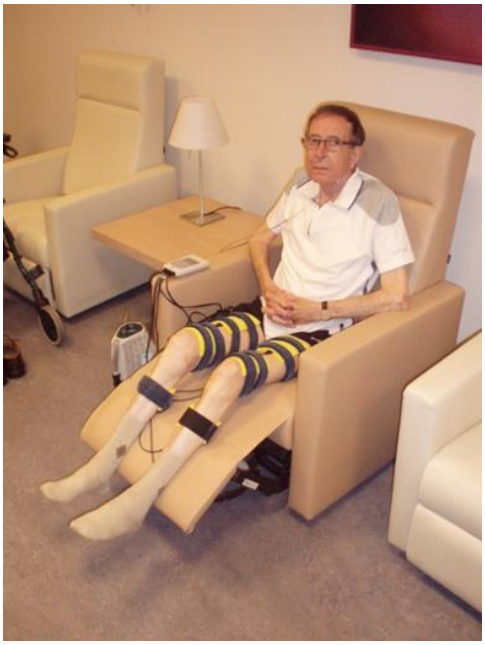

Figure E1. Transcutaneous neuromuscular electrical stimulation of a man with COPD GOLD IV Written consent was obtained for the use of this photograph.

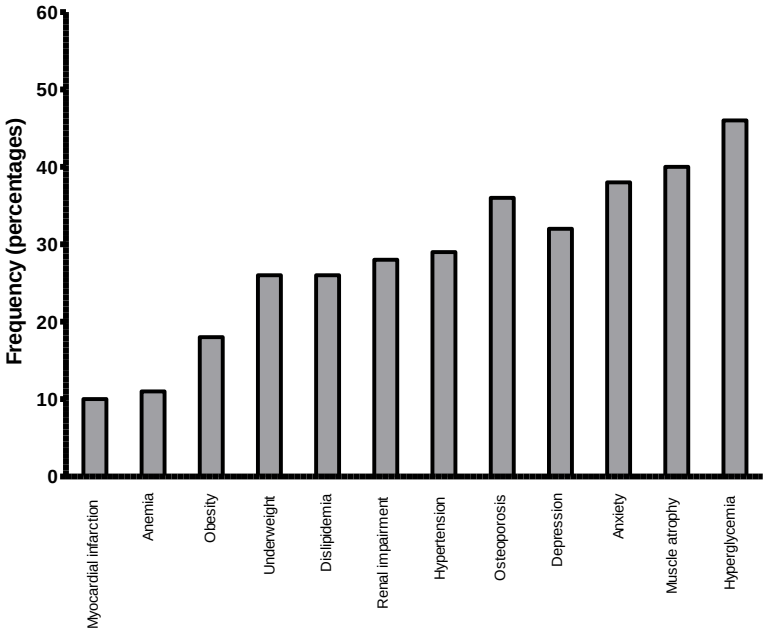

Figure E2. Comorbidities

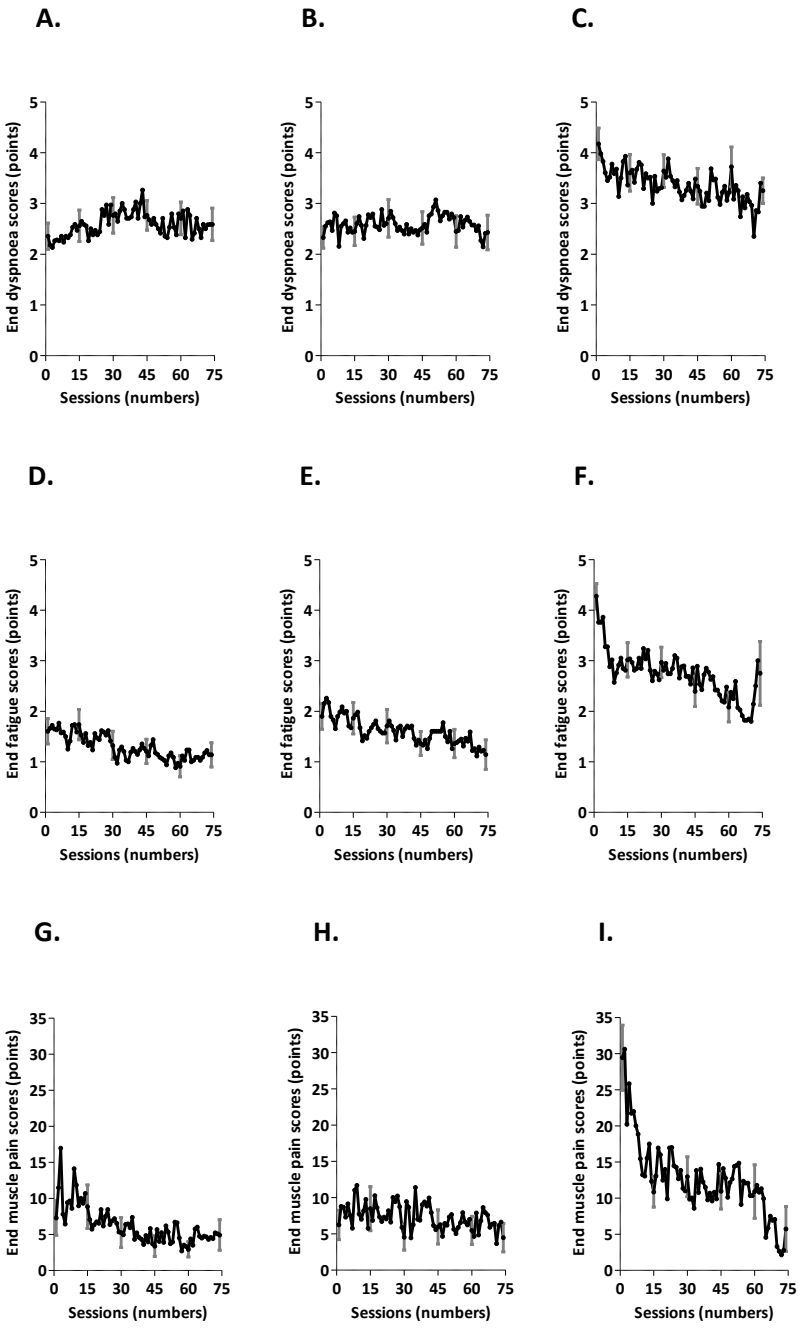

Figure E3. End dyspnoea scores (A. HF-NMES; B. LF-NMES; C. Strength training), end fatigue scores (D. HF-NMES; E. LF-NMES; F. Strength training) and end muscle pain scores (G. HF-NMES; H. LF-NMES; I. Strength training) directly after the interventions

REFERENCE LIST

1. Spruit MA, Vanderhoven-Augustin I, Janssen PP, et al. Integration of pulmonary rehabilitation in COPD. *Lancet*. 2008;371(9606):12-3. Epub 2008/01/08.
2. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176(6):532-55. Epub 2007/05/18.
3. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest*. 1988;93(3):580-6.
4. Borges O. Isometric and isokinetic knee extension and flexion torque in men and women aged 20-70. *Scand J Rehabil Med*. 1989;21(1):45-53.
5. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869. Epub 2010/03/25.
6. Wegmann H. The "new" Declaration of Helsinki. *Jouirnal of International Biotechnology Law*. 2009;6(4):173-6.
7. Sillen MJ, Franssen FM, Delbressine JM, et al. Heterogeneity in clinical characteristics and co-morbidities in dyspneic individuals with COPD GOLD D: findings of the DICES trial. *Respir Med*. 2013;107(8):1186-94. Epub 2013/05/28.
8. Spruit MA, Singh SJ, Garvey C, et al. An official american thoracic society/european respiratory society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-64. Epub 2013/10/17.
9. Revill SI, Robinson JO, Rosen M, et al. The reliability of a linear analogue for evaluating pain. *Anaesthesia*. 1976;31(9):1191-8. Epub 1976/11/01.
10. Vivodtzev I, Lacasse Y, Maltais F. Neuromuscular electrical stimulation of the lower limbs in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil Prev*. 2008;28(2):79-91. Epub 2008/03/25.
11. Vanderthommen M, Duchateau J. Electrical stimulation as a modality to improve performance of the neuromuscular system. *Exerc Sport Sci Rev*. 2007;35(4):180-5. Epub 2007/10/09.
12. Sillen MJ, Wouters EF, Franssen FM, et al. Oxygen uptake, ventilation, and symptoms during low-frequency versus high-frequency NMES in COPD: a pilot study. *Lung*. 2011;189(1):21-6. Epub 2010/11/17.
13. Feigenbaum MS, Pollock ML. Strength training: rationale for current guidelines for adult fitness programs. *The Physician and sportsmedicine*. 1997;25(2):44-63. Epub 1997/02/01.
14. Ratamess NA, Alvar BA, Evetoch TK, et al. Progression Models in Resistance Training for Healthy Adults. *Medicine & Science in Sports & Exercise*. 2009:687-708.
15. Spruit MA, Gosselink R, Troosters T, et al. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. *Eur Respir J*. 2002;19(6):1072-8. Epub 2002/07/11.
16. Mathur S, Makrides L, Hernandez P. Test-retest reliability of isometric and isokinetic torque in patients with chronic obstructive pulmonary disease. *Physiother Can*. 2004;56:94–101.

17. Franssen FM, Broekhuizen R, Janssen PP, et al. Limb muscle dysfunction in COPD: effects of muscle wasting and exercise training. *Med Sci Sports Exerc*. 2005;37(1):2-9. Epub 2005/01/06.
18. Hernandes NA, Wouters EF, Meijer K, et al. Reproducibility of 6-minute walking test in patients with COPD. *Eur Respir J*. 2011;38(2):261-7. Epub 2010/12/24.
19. Hul van 't A, Gosselink R, Kwakkel G. Constant-load cycle endurance performance: test-retest reliability and validity in patients with COPD. *J Cardiopulm Rehabil*. 2003;23(2):143-50. Epub 2003/04/02.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-70.
21. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med*. 1991;85 Suppl B:25-31; discussion 3-7. Epub 1991/09/01.
22. Annegarn J, Meijer K, Passos VL, et al. Problematic activities of daily life are weakly associated with clinical characteristics in COPD. *J Am Med Dir Assoc*. 2012;13(3):284-90. Epub 2011/04/01.
23. Sewell L, Singh SJ. The Canadian Occupational Performance Measure: is it a reliable measure in clients with chronic obstructive pulmonary disease? *Br J Occup Ther*. 2001;64:305-10.
24. Graat-Verboom L, Smeenk FW, van den Borne BE, et al. Progression of osteoporosis in patients with COPD: a 3-year follow up study. *Respir Med*. 2012;106(6):861-70. Epub 2012/03/01.
25. O'Shea SD, Taylor NF, Paratz JD. A predominantly home-based progressive resistance exercise program increases knee extensor strength in the short-term in people with chronic obstructive pulmonary disease: a randomised controlled trial. *Aust J Physiother*. 2007;53(4):229-37. Epub 2007/12/01.
26. Vestbo J, Prescott E, Almdal T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med*. 2006;173(1):79-83.
27. Graat-Verboom L, Wouters EF, Smeenk FW, et al. Current status of research on osteoporosis in COPD: a systematic review. *Eur Respir J*. 2009;34(1):209-18. Epub 2009/07/02.
28. Janssen DJ, Spruit MA, Uszko-Lencer NH, et al. Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. *Journal of palliative medicine*. 2011;14(6):735-43. Epub 2011/04/23.
29. Diagnosis and classification of diabetes mellitus. *Diabetes care*. 2010;33 Suppl 1:S62-9. Epub 2010/01/29.
30. Nutritional anaemias. Report of a WHO scientific group. *World Health Organization technical report series*. 1968;405:5-37. Epub 1968/01/01.
31. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet*. 2005;366(9491):1059-62. Epub 2005/09/27.
32. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41. Epub 1976/01/01.
33. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2007;49(2 Suppl 2):S12-154. Epub 2007/02/06.

34. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *Journal of hypertension*. 1999;17(2):151-83. Epub 1999/03/06.
35. Rautaharju PM, Warren JW, Jain U, et al. Cardiac infarction injury score: an electrocardiographic coding scheme for ischemic heart disease. *Circulation*. 1981;64(2):249-56. Epub 1981/08/01.