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ORIGINAL RESEARCH

Effectiveness of neuromuscular electrical stimulation for the rehabilitation of moderate-to-severe COPD: a meta-analysis

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Purpose: Patients with COPD often experience skeletal muscle dysfunction. For those who are unable or unwilling to undertake physical training, neuromuscular electrical stimulation (NMES) may provide an alternative method of rehabilitation. The purpose of this meta-analysis was to investigate the controversial topic of whether this therapy is effective in patients with moderate-to-severe COPD.

Patients and methods: We pooled data from nine trials published between January 9, 2002 and January 4, 2016 across PubMed, Embase, Cochrane Central Register of Controlled Trials, Google Scholar, and relevant websites for randomized controlled trials. In these trials, patients with moderate-to-severe COPD were randomly allocated to receive NMES. Primary outcomes were quadricep strength and exercise capacity. The secondary outcome was health-related quality of life.

Results: We extracted data from 276 patients. NMES contributed to statistically improved quadricep strength (standardized mean difference 1.12, 95% confidence interval [CI] 0.64–1.59, I^2=54%; $P<0.00001$) and exercise capacity, including longer exercise distance (weighted mean difference 51.53, 95% CI 20.13–82.93, I^2=90%; P=0.001), and longer exercise endurance (standardized mean difference 1.11, 95% CI 0.14–2.08, I^2=85%; P=0.02). There was no significant difference in St George's Respiratory Questionnaire scores (weighted mean difference –0.07, 95% CI –2.44 to 2.30, I^2=56%; P=0.95).

Conclusion: NMES appears an effectual means of enhancing quadricep strength and exercise capacity in moderate-to-severe COPD patients. Further research is demanded to clarify its effect on other outcomes and determine the optimal parameters for an NMES program.

Keywords: neuromuscular electrical stimulation, chronic obstructive pulmonary disease, quadriceps muscle strength, exercise capacity

Introduction

COPD is a major cause of morbidity and mortality worldwide, and leads to a significant economic and social burden. It is predicted to become the third-leading cause of death in 2020.[1–3] It is now recognized that COPD is characteristic with inspiratory muscle fatigue and skeletal muscle deconditioning, which is associated with reduced quality of life and premature mortality.[4]

It has been well established that physical and respiratory muscle training is beneficial for patient rehabilitation in COPD, and physical training especially is considered one of the best treatments available for enhancing limb-muscle function.[1,5–7] A recent study showed that physical training may prevent cognitive decline and associated comorbidities in male patients with COPD.[8] Indeed, advanced-stage COPD

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patients may be too frail to tolerate physical training because of intense breathlessness at rest or on minimum exertion.[9] Neuromuscular electrical stimulation (NMES) is emerging as a new rehabilitation modality that does not evoke dyspnea to obtain a benefit in patients who are unable to participate in a traditional rehabilitation program. Also, it has been intensively applied in healthy people and athletes for curative care rehabilitation and preventing deconditioning.[10]

Previous studies[11–20] have not reached consistent conclusions, and a meta-analysis[21] published in 2014 draw equivocal findings on the effects of NMES in moderate-to-severe COPD. Also, there have been several larger-scale and higher-quality trials[22–28] published in recent years; therefore, we performed a meta-analysis to investigate the effects of NMES in these patients.

Patients and methods

Search strategy

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials, Google Scholar, and relevant websites to detect randomized controlled trials (RCTs) published up to June 2016 in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[29–31] Search terms were "chronic obstructive pulmonary disease", "neuromuscular electrical stimulation", and their corresponding Medical Subject Headings terms. Studies were filtered for human subjects and RCTs; only published trials written in English were included. We excluded studies of comparisons other than NMES and those with duplicated data.

Study selection

The inclusive selection criteria were RCTs investigating the role of NMES in patients with moderate-to-severe COPD, predefined program of NMES applied to the lower limbs, unstimulated or other treatment (ie, sham stimulation) defined as the control group, and primary outcome quadricep strength and exercise capacity, defined as moving distance and endurance time. The secondary outcome was St George's Respiratory Questionnaire (SGRQ) score.[32] The criteria complied with PICO (patient/problem/population, intervention, comparison/control/comparator, outcomes) principles. For articles reported in more than two publications, only the full version was used for meta-analysis. Abstracts published merely in academic conferences or website materials were excluded.

Data extraction

Two investigators (XL and LG) assessed the title or abstract for eligibility. In cases of discordance, a third investigator (BG) participated in discussion to reach a final consensus. For studies that met the inclusion criteria, full papers were obtained for further analysis. Information related to trial design, characteristics of the patients, and relevant results were noted according to a redesigned form. We recorded first author, year, patient numbers, age, sex, body mass index, forced expiratory volume in 1 second, stage of COPD, experimental and control interventions (ie, type of intervention, pulse duration, pulse frequency, duty cycle, intensity of current used, training intensity, session time, and duration in weeks), and outcome parameters and their results. When data were insufficient or inapplicable, we attempted to contact the authors by email or used a formula[29–31] to convert into available data.

Outcomes

Outcomes were assigned to categories according to comparable features and representation. The preestablished primary outcome was quadricep strength and exercise capacity. Quadricep strength was measured using various methods, including isokinetic quadricep peak torque, maximum voluntary contraction, and author-defined score. Exercise capacity was primarily 6-minute walk test (6MWT),[33] shuttle-walk test (SWT),[34,35] and constant-work test (CWT),[36] and we pooled exercise distance and endurance time from these tests. The prespecified secondary outcome was health-related life quality measured with the SGRQ.

Data analysis

Meta-analyses were done with RevMan 5.3 software (Cochrane Collaboration, London, UK). Weighted mean difference (WMD) or standardized mean difference (SMD) with 95% confidence interval (CI) was considered for summary statistics and derived for the comparison of NMES with other rehabilitation methods. SMD was utilized when studies reported different units or scales for the outcome. To account for between-trial differences, we used mixed-effect modeling with random effect for parameters of interest, because of the anticipated heterogeneity in NMES methodology, including different stimulating parameters, different durations of therapy, and diverse study designs and study populations. Heterogeneity across studies was tested using the I^2 statistic: I^2 values of less than 25%, 25%–50%, or more than 50% indicated low, moderate, or high heterogeneity, respectively.[37] Potential heterogeneity sources were identified by sensitivity analyses conducted by eliding one study successively and comparing the influence of each study on the overall pooled estimate if $I^2 > 50\%$. Funnel plots were not constructed, owing to the limited number (below 10) of studies included in the analysis. For another primary outcome of exercise capacity, subgroup analyses were performed based

on methods of exercise test: 6MWT, SWT, and CWT. Data are presented as means (±standard deviation), and a two-tailed *P*-value <0.05 was considered statistically significant. The overall treatment effect was compared with its minimum clinically important difference (MCID).

Evaluation of bias and quality assessment

Freedom from bias was evaluated for each study in accordance with the basis of methodological domains:[29–31] adequacy of random-sequence generation and allocation concealment, attrition bias, reporting bias, and other biases. Two authors (BG and XL) reviewed all the studies and assigned a value of "high", "low", or "unclear".

The methodological quality of the identified trials was scored independently using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system.[38,39] The GRADE system classifies four levels – high, moderate, low, and very low – in terms of the quality of evidence. This approach for book reviews on the quality of the evidence is based on five items: study limitations, inconsistency of the results, indirectness of evidence, imprecision, and reporting bias. For purpose of assessing the reliability of the grade, the quality classification of the selected articles was independently assessed by two investigators, with divergences resolved by a third investigator (GB).

Results

Articles retrieved and characteristics of included trials

Primary literature searches included 370 articles, of which 62 remained after exclusion of duplicates. Following screening of titles and abstracts, 20 studies were removed owing to unrelated content; 17 studies were not RCTs. Of 25 full-text citations, nine studies with 276 participants fulfilled inclusive criteria to be reviewed. For papers excluded from this analysis, eight were due to study design,[10,13,15,16,40–43] four were due to the fact that stimulation was acupuncture,[44–47] three[11,24,28] had insufficient or inapplicable data, and one[25] reported on the same group of participants as in another paper.[26] Figure 1 describes the different phase of the search process. The pooled articles were published between 2002 and 2016. By pooling data from these trials, 139 were assigned to NMES (intervention population) and 137 assigned to the control population. The characteristics of participants, interventions, and the main results extracted in corresponding studies are shown in Table 1. NMES was applied to the quadriceps and

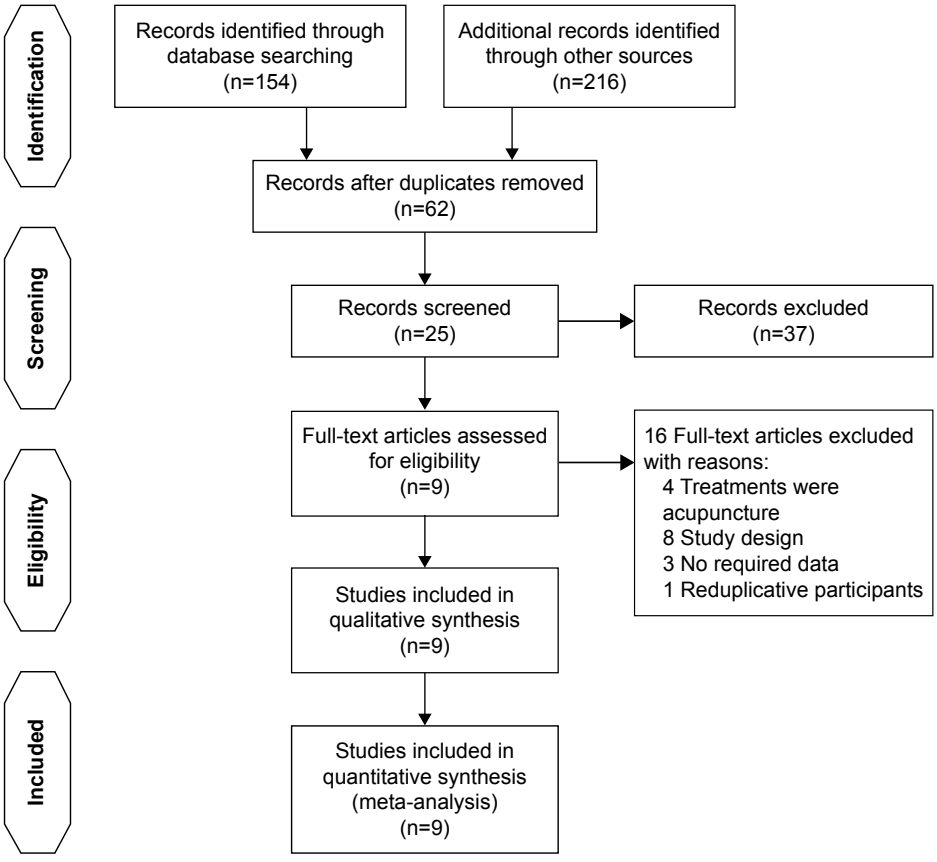

Figure 1 Study-selection flowchart.

Table 1 Characteristics of randomized controlled trials included in the meta-analysis

Study, year	Number of patients (m/f)	Grade	Stage	BMI, kg/m^2 (NMES/sham)	Age, years (NMES/sham)	FEV_1% (NMES/sham)	Study group (n)
Bourjeily-Habr et al,[19] 2002	18 (10/8)	Moderate-to-severe	Stable COPD	26.2/27.1	58.5/61.5	35.6/40.7	NMES (9); control (9)
Neder et al,[20] 2002	15 (9/6)	Moderate-to-severe	Stable COPD	24.8/25.6	66.6/65	38/39.5	NMES (9); control (6)
Zanotti et al,[18] 2003	24 (17/7)	NA	Stable COPD in ICU	24.5/22.4	66.2/64.5	NA	NMES + UR (12); UR (12)
Vivodtzev et al,[17] 2006	17 (11/6)	Severe	Stable COPD	18.1/18	59/68	27/34	NMES + UR (9); UR (8)
Vivodtzev et al,[12] 2012	20 (13/7)	Severe	Stable COPD	21/21	70/68	34/30	NMES (12); sham (8)
Sillen et al,[25,26] 2014	81 (43/38)	Severe	Stable COPD	24.1/24.9	64.4/64	33/33	HF-NMES (41); strength training (40)
Vieira et al,[27] 2014	20 (20/0)	Moderate-to-severe	Stable COPD	27.47/27.6	56.3/56.4	36.5/39.6	NMES (11); control (9)
Tasdemir et al,[23] 2015	27 (24/3)	Moderate-to-severe	Stable COPD	25.1/27.4	62.1/62.9	29/42.5	NMES + cPR (13); Sham + cPR (14)
Maddocks et al,[22] 2016	52 (21/31)	Severe	Stable COPD	25.7/27.8	70/69	30.8/30.7	NMES (25); placebo (27)

Notes: Data shown are mean ± SD unless otherwise indicated. (%), percentage predicted value.
Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; NMES, neuromuscular electrical stimulation; NA, not available; COPD, chronic obstructive pulmonary disease; UR, usual rehabilitation; HF-NMES, high frequency neuromuscular electrical stimulation; SWT, shuttle-walk test; 6MWT, 6-minute walk test; MVC, maximum voluntary contraction; SGRQ, St George's Respiratory Questionnaire; RCT, randomized controlled trial; ALMs, active limb mobilizations; M, male; F, female; ICU, intensive care unit; cPR, comprehensive pulmonary rehabilitation; MRC, Medical Research Council scale; I, intensive.

also to accessory respiratory muscles.[27] Stimulation-pulse duration was 250–400 μs, and stimulation frequency ranged from 8 to 120 Hz. Intensities ranged from 10 to 100 mA, and were gradually increased throughout the entire stimulation according to the patient's individual tolerance.

Risk-of-bias assessment and quality assessment

The risk-of-bias among studies is shown in Figure 2. Inadequate description of data on the randomization protocol or blinding strategy was reported in most of the RCTs, except for two,[22,26] which may have led to "unclear risk of bias". On the other hand, quality-assessment items are presented in Figures 3 and 4. Evidence based on RCTs is assumed to be high-quality evidence, unless there are some issues, which may reduce confidence in the study. These included limitations of study design, inconsistency, indirectness, imprecision, and publication bias.[48] For the pooled studies, we kept the original conclusion if the study quality was high and there was no violation of these criteria.[49]

NMES group			Control group	Study design
Training protocol	NMES parameters	Outcomes		
6 week ×3 sessions/week; 20 min/per session	Frequency: 50 Hz; pulse duration: NA; intensity: 56.7–95 mA; duty cycle: 0.2 s on/1.3 seconds off	SWT; quadriceps strength (isokinetic peak torque)	Control: sham NMES (same instruction and electrode position, but no stimulation)	RCT, double-blind
6 week ×5 sessions/week; 15 min in the 1st week and 30 min thereafter	Frequency: 50 Hz; pulse duration: 300–400 us; intensity: 10–20 mA to 100 mA; duty cycle: 2 s on/18 s off to 10 s on/30 s off	Quadriceps strength (peak torque), exercise endurance	Usual care	RCT, double-blind
4 week ×5 sessions/week; 30 min/per session	Frequency: 8–35 Hz; pulse duration: 250–350 us; intensity: NA; duty cycle: NA	Peripheral muscle strength	ALM	RCT, double-blind
4 week ×4 sessions/week; 30 min/per session	Frequency: 35 Hz; pulse duration: 400 us; intensity: max tolerable (21–46 mA); duty cycle: 47%	Quadriceps strength (MVC); 6MWT; dyspnoea	4 days per week of ALMs	RCT, single-blind
6 week ×5 sessions/week; 35 min of stimulation of the quadriceps followed by 25 min of stimulation of the calf	Frequency: 50 Hz; pulse duration: 400 us; intensity: max tolerable (20–31 mA); duty cycle: 2 s on/16 s off	Quadriceps strength; exercise endurance; SWT; dyspnoea	Sham: Frequency: 5 Hz, pulse duration =100 us	RCT, double-blind
8 week ×5 sessions/week; 18 min/per session	Frequency: 75 Hz; pulse duration: 400 us intensity: max tolerable; duty cycle: NA	Quadriceps muscle strength (isokinetic quadriceps muscle strength); 6MWT; exercise endurance; dyspnoea; SGRQ	Strength training	RCT, single-blind
8 week ×5 sessions/week; 60 min/per session	Frequency: 50 Hz; pulse duration: 300–400 us; intensity: max tolerable (15–20 mA to 100 mA); duty cycle: 2 s on/18 s off to 10 s on/30 s off	6MWT; dyspnoea; exercise endurance; SGRQ	Sham NMES (same instruction and electrode position, but no stimulation)	RCT, double-blind
10 week ×2 sessions/week; 20 min/per session	Frequency: 50 Hz; pulse duration: 300 us; intensity: max individual tolerance (29.43–35.81 mA); duty cycle: 10 s on/20 s off	SWT; dyspnoea; quadriceps muscle strength; exercise endurance; MRC; SGRQ	cPR: mainly exercise training Sham: NMES (Intensive: 5 mA), insufficient to elicit a tetanic muscular contraction	RCT, double-blind
6 week ×7 sessions/week; 30 min/per session	Frequency: 50 Hz; pulse duration: 350 us; intensity: max tolerable; duty cycle: 2 s on/15 s off to 10 s on/15 s off	6MWT; quadriceps muscle strength (MVC); SGRQ	Placebo NMES (I: 0–20 mA), insufficient to elicit a tetanic muscular contraction	RCT, double-blind

Primary outcomes

Results from nine RCTs (n=276) were obtained to assess the effects of NMES on patients with moderate-to-severe COPD. Aggregate analyses showed that the application of NMES was linked to significantly enhanced quadricep strength (SMD 1.12, 95% CI 0.64–1.59, I^2=54%; P<0.00001) (Figure 5). There was also a benefit of NMES in improving exercise capacity, evaluated as longer exercise distance traveled (WMD 51.53, 95% CI 20.13–82.93, $I^2_{overall}$ =90%, $I^2_{subgroup\ differences}$ =0; P=0.001) (Figure 6) or longer exercise endurance time (SMD 1.11, 95% CI 0.14–2.08, $I^2_{overall}$ =85%, $I^2_{subgroup\ differences}$ =81.6%; P=0.02) (Figure 7). We failed to draw funnel plots to explore the potential source of heterogeneity, because the number of RCTs included was fewer than 10. We further carried out subgroup analyses to investigate the impact of NMES on exercise capacity with different exercise tests. For 6MWT, walking distance was significantly improved (WMD 37.27, 95% CI 31.82–42.73, I^2=0; P<0.00001). For CWT, endurance time also increased significantly (SMD 1.78, 95% CI 1.16–2.40, I^2=35%; P<0.00001). For SWT, there

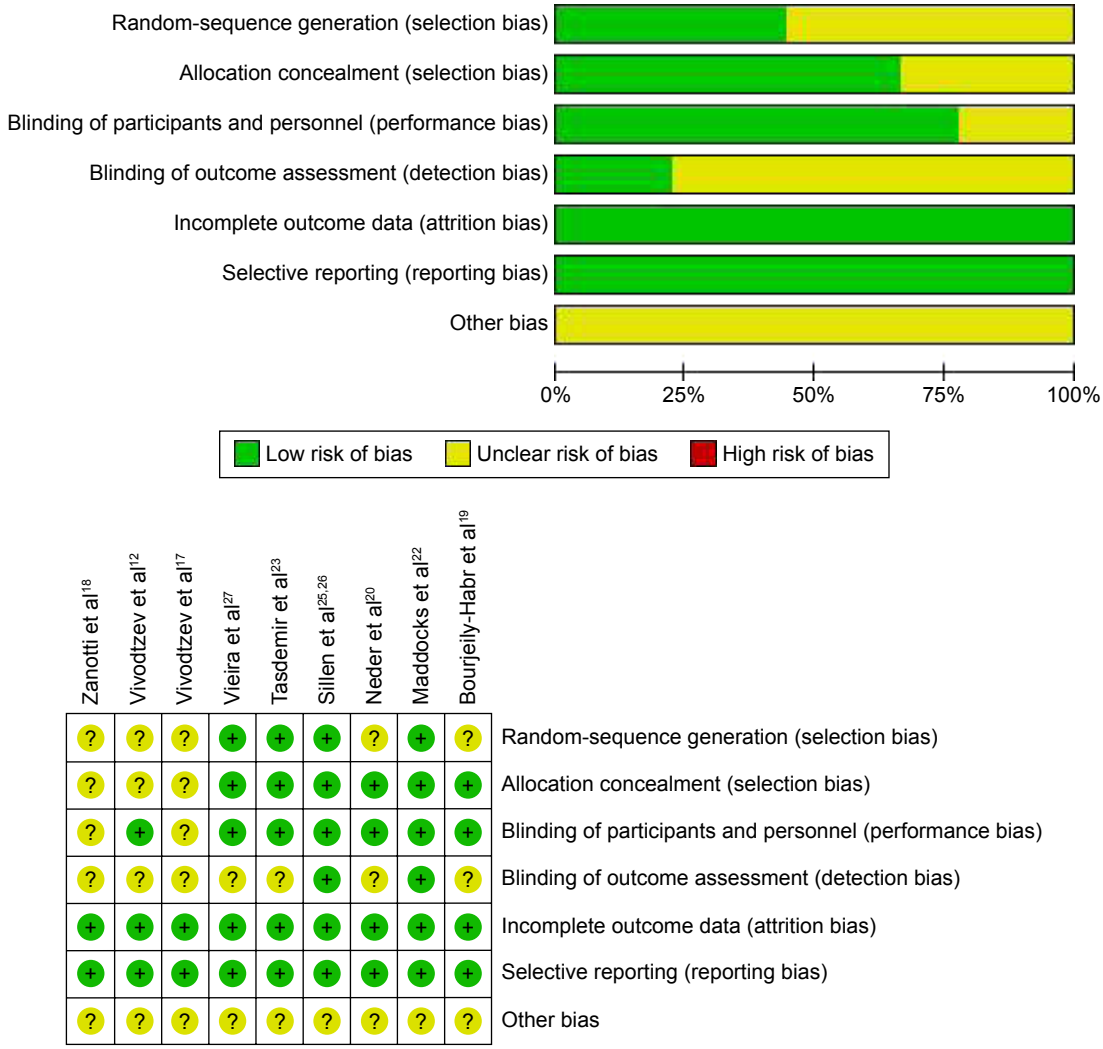

Figure 2 Risk-of-bias analysis.

was no significant improvement in distance (WMD 68.06, 95% CI −50.7 to 186.83, I^2=96%; P=0.26) or endurance time (SMD 0.28, 95% CI −0.82 to 1.38, I^2=70%; P=0.62).

Secondary outcomes

For health-related quality of life, the results demonstrated that NMES did not improve SGRQ scores (WMD −0.07, 95% CI −2.44 to 2.30, I^2=56%; P=0.95) (Figure 8). We did not perform sensitivity analyses to explore potential sources of heterogeneity, because only three RCTs were included.

Discussion

This pooled analysis of data from nine RCTs indicated several meaningful findings for NMES for severe COPD. The main findings of this meta-analysis are that NMES improved patients' quadricep strength and exercise capacity, particularly across a range of the subgroups, but no statistically significant improvement in the degree of health-related quality of life.

To our knowledge, our meta-analysis involved the largest numbers of patients with nine RCTs so far.[12,17–20,22,23,26,27] The strength and quality of this meta-analysis should be better than those with fewer patients and RCTs reported in the literature. Compared with the equivocal results of Pan et al's review[21] on the efficacy of NMES, our conclusion is contradictory. On the premise of including larger numbers and most high-quality trials, we performed subgroup analysis to classify the evaluation methodology on the outcomes. In addition, we use the GRADE system for the meta-analysis, which has advantages over other rating systems[48] for evaluating the methodological quality of pooled trials. As such, we consider our meta-analysis more convincing and providing evidence in favor of NMES.

Quadricep strength was enhanced significantly, as demonstrated by pooled data on isokinetic quadricep peak torque

Quadriceps muscle strengh for moderate to severe COPD

Patient or population: patients with moderate to severe COPD
Settings:
Intervention: Quadriceps muscle strengh

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Quadriceps muscle strengh	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
quadriceps muscle strengh Follow-up: 14 years		The mean quadriceps muscle strengh in the intervention groups was **1.06 standard deviations higher** (0.62 to 1.49 higher)		223 (7 studies)	⊕⊕⊕⊕ **high**	SMD 1.06 (0.62 to 1.49)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Exercise distance for moderate to severe COPD

Patient or population: patients with moderate to severe COPD
Settings:
Intervention: Exercise distance

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Exercise distance	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Distance subgroup Follow-up: 10 years		The mean distance subgroup in the intervention groups was **46.97 higher** (20.15 to 73.79 higher)		251 (8 studies)	⊕⊕⊕⊕ **high**	
Distance subgroup - 6MWT		The mean distance subgroup - 6mwt in the intervention groups was **36.7 higher** (31.34 to 42.05 higher)		186 (5)		
Distance subgroup - SWT		The mean distance subgroup - swt in the intervention groups was **68.06 higher** (50.7 lower to 186.83 higher)		65 (3)		

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Exercise endurance time for moderate to severe COPD

Patient or population: patients with moderate to severe COPD
Settings:
Intervention: Exercise endurance time

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Exercise endurance time	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Endurance time subgroup Follow-up: 13 years		The mean endurance time subgroup in the intervention groups was **1.14 standard deviations higher** (0.32 to 1.96 higher)		179 (6 studies)	⊕⊕⊕⊕ **high**	SMD 1.14 (0.32 to 1.96)
Endurance time subgroup - CWT		The mean endurance time subgroup - CWT in the intervention groups was **1.71 standard deviations higher** (1.19 to 2.22 higher)		132 (4)		SMD 1.71 (1.19 to 2.22)
Endurance time subgroup - SWT		The mean endurance time subgroup - SWT in the intervention groups was **0.28 standard deviations higher** (0.82 lower to 1.38 higher)		47 (2)		SMD 0.28 (-0.82 to 1.38)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Figure 3 Quality assessment of quadricep strength and exercise capacity.
Abbreviations: SMD, standardized mean difference; CWT, constant-work test; SWT, shuttle-walk test; 6MWT, 6-minute walk test.

in three trials,[19,20,25,26] maximum voluntary contraction in two studies[17,22] and author-defined score of a seventh report (Figure 5).[18] Compared with Pan et al's review,[21] we included more methods of evaluation of quadricep strength and high-impact articles[22,26] published shortly after Pan et al's paper. The baseline level of impairment of peripheral muscle function may have important impact on the outcome of NMES. As subjects with varying degrees of impairment of peripheral function were included in the study reports, we included only reports with peripheral muscle weakness. The inconsistent inclusion criteria would have contributed to high heterogeneity. The severity of COPD may also have an impact on the effects of NMES. In this meta-analysis, we focused on COPD patients with moderate-to-severe flow limitation. The study by Napolis et al[15] was excluded, because it included COPD patients with low-level flow limitation. Studies including patients with acute exacerbations of COPD were also excluded, as they might have greater improvement, as suggested by the

SGRQ for moderate to severe COPD

Patient or population: patients with moderate to severe COPD
Settings:
Intervention: SGRQ

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk SGRQ				
SGRQ Follow-up: 2 years		The mean SGRQ in the intervention groups was **0.07 lower** (2.44 lower to 2.3 higher)		179 (four studies)	⊕⊕⊕⊕ High	

*The basis for the **assumed risk** (eg, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Figure 4 Quality assessment of SGRQ.
Abbreviations: SGRQ, St George's Respiratory Questionnaire; CI, confidence interval; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation.

Study or subgroup	NMES Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Standardized mean difference IV, random, 95% CI
Bourjeily-Habr et al[19]	10.5	6.47	9	3.9	6.47	9	13.5	0.97 (–0.02 to 1.96)
Maddocks et al[22]	3.43	4.92	25	0.34	4.92	27	22.6	0.62 (0.06–1.18)
Neder et al[20]	27.4	19.5	9	5.2	19.5	6	11.6	1.07 (–0.05 to 2.20)
Sillen et al[25,26]	10.8	2.9	41	6.1	2	39	23.4	1.86 (1.33–2.39)
Vivodtzev et al[17]	97	71	9	36	35	8	12.9	1.01 (–0.01 to 2.04)
Zanotti et al[18]	2.16	1.02	12	1.25	0.75	12	15.9	0.98 (0.13–1.84)
Total (95% CI)			**105**			**101**	**100**	**1.12 (0.64–1.59)**
Heterogeneity: τ^2=0.18; χ^2=10.76, *df*=5 (*P*=0.06); I^2=54%								
Test for overall effect: *Z*=4.61 (*P*<0.00001)								

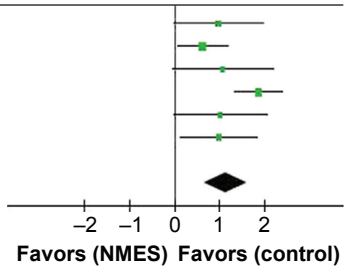

Figure 5 Meta-analysis of randomized controlled trials evaluating the effects of NMES on quadricep strength.
Abbreviations: NMES, neuromuscular electrical stimulation; SD, standard deviation; IV, inverse variance; CI, confidence interval.

Study or subgroup	NMES Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
6MWT								
Maddocks et al[22]	29.9	43.79	25	–5.7	43.79	27	15.8	35.60 (11.78–59.42)
Sillen et al[25,26]	66	14	41	29	12	39	17.3	37.00 (31.29–42.71)
Vieira et al[27]	75.7	57.89	11	0.8	57.89	9	11.9	74.90 (23.90–125.90)
Vivodtzev et al[17]	63	40	9	30	38	8	14.0	33.00 (–4.10 to 70.10)
Subtotal (95% CI)			**86**			**83**	**59.0**	**37.27 (31.82–42.73)**
Heterogeneity: τ^2=0.0; χ^2=2.17, *df*=3 (*P*=0.54); I^2=0								
Test for overall effect: *Z*=13.39 (*P*<0.00001)								
SWT								
Bourjeily-Habr et al[19]	68.8	47.21	9	0	47.21	9	13.0	68.80 (25.18–112.42)
Tasdemir et al[23]	38.4	41.8	13	69.2	33.6	14	15.2	–30.80 (–59.54 to –2.06)
Vivodtzev et al[12]	174	72	12	5	27	8	12.8	169.00 (124.17–213.83)
Subtotal (95% CI)			**34**			**31**	**41.0**	**68.06 (–50.70 to 186.83)**
Heterogeneity: τ^2=10,606.05; χ^2=56.73, *df*=2 (*P*<0.00001); I^2=96%								
Test for overall effect: *Z*=1.12 (*P*=0.26)								
Total (95% CI)			**120**			**114**	**100**	**51.53 (20.13–82.93)**
Heterogeneity: τ^2=1,476.62; χ^2=58.90, *df*=6 (*P*<0.00001); I^2=90%								
Test for overall effect: *Z*=3.22 (*P*=0.001)								
Test for subgroup differences: χ^2=0.26, *df*=1 (*P*=0.61); I^2=0								

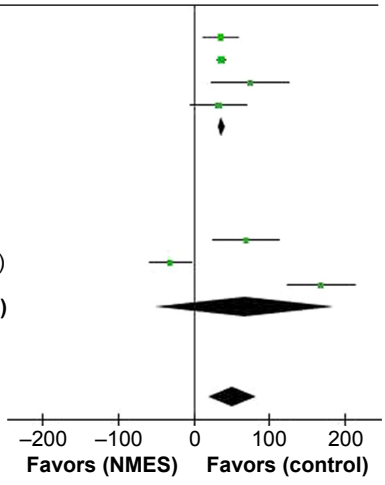

Figure 6 Meta-analysis of randomized controlled trials evaluating the effects of NMES on exercise distance.
Abbreviations: NMES, neuromuscular electrical stimulation; SD, standard deviation; IV, inverse variance; CI, confidence interval; 6MWT, 6-minute walk test; SWT, shuttle-walk test.

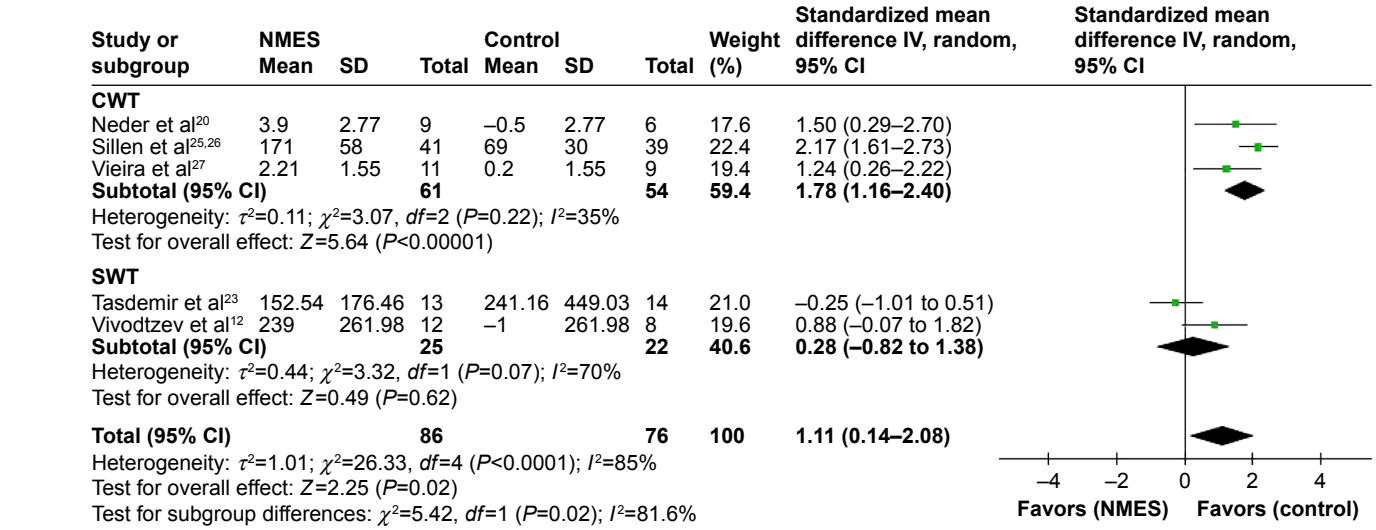

Figure 7 Meta-analysis of randomized controlled trials evaluating the effects of NMES on exercise endurance time.
Abbreviations: NMES, neuromuscular electrical stimulation; SD, standard deviation; IV, inverse variance; CI, confidence interval; CWT, constant-work test; SWT, shuttle-walk test.

Abdellaoui et al.[14] Intensity might be the most important factor related to the efficacy of NMES on muscle strength.[12] Actually, stimulus intensity of the pooled studies differed greatly. However, it was defined as "maximal tolerance" in all trials. Therefore, stimulation intensity might be the most suitable and individualized dosage. We should emphasis the role of NMES itself firstly, instead of the dose-dependent response. The aggregate results suggested that regardless of the type of stimulation, significant increases in quadricep strength after NMES are easily achieved, in spite of the lack of an MCID for muscle strength in COPD patients, to assess whether these data are suggestive of clinically meaningful difference.[50,51] In summary, the overall results proved that quadricep strength was enhanced significantly after NMES.

The methodology of evaluation of exercise capacity may influence the outcome of the study. In Pan et al's review,[21] only the 6MWT was included in the pooled analysis. In this meta-analysis, three kinds of exercise capacity tests – 6MWT, SWT, and CWT – were included and subgroup analysis conducted. In order to minimize bias, WMD was used to pool walking distance and SMD to pool endurance time. Analogously, we excluded studies[14,15,21] to avoid variance in entry criteria. The aggregate random effect of NMES on walking distance was 51.53 m with a 95% CI of 20.13–82.93 (Figure 6), exceeding the MCID ranging of 25–33 m for 6MWT distance.[52] However, there was little information on methodological variations in performance of SWT and the lack of an MCID for SWT distance to be compared. The overall pooled SMD data for NMES on endurance time was 1.11 with a 95% CI of 0.14–2.08 (Figure 7), indicating that NMES resulted in a beneficial effect on exercise tolerance. We also observed high heterogeneity, which may have come from different SWT methodologies. Incremental SWTs were used in two trials and endurance SWT in another. The sensitivity, responsiveness, and reproducibility of these tests were not the same.[53,54] In the majority of the cases included, the increasing 6MWT and longer endurance made us consider effect sizes favoring NMES over control in exercise capacity.

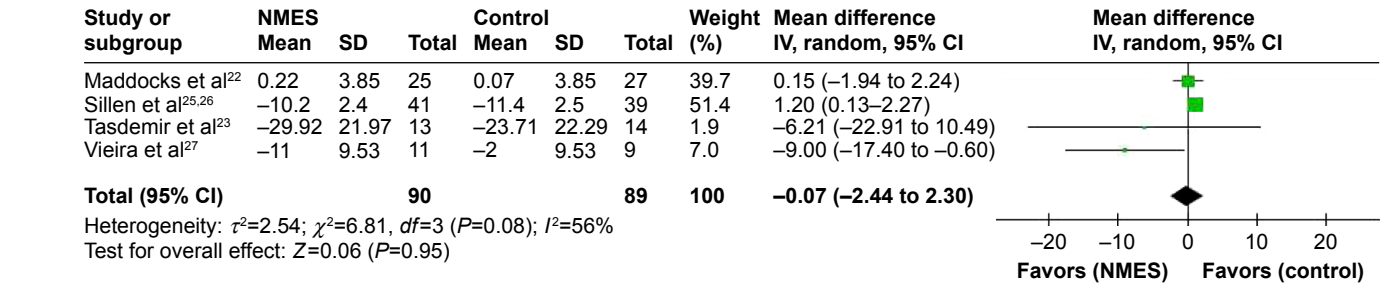

Figure 8 Meta-analysis of randomized controlled trials evaluating the effects of NMES on St George's Respiratory Questionnaire scores.
Abbreviations: NMES, neuromuscular electrical stimulation; SD, standard deviation; IV, inverse variance; CI, confidence interval.

However, from the result of our meta-analysis, NMES was not associated with health-related quality of life measured by the SGRQ. The actual value of NMES for health-related life quality is thus uncertain, probably due to the fact that the SGRQ is influenced by many other factors.[55] Further research is required to clarify its place in these outcomes.

This meta-analysis has several limitations. Firstly, the subgroup analysis with small sample size led to insufficient evidence. Secondly, the diversity of measurement could have led to heterogeneity correspondingly. Thirdly, NMES with different parameter settings or programs may lead to different physiological effects and outcomes. Therefore, further research needs to be done to standardize this technique.

In conclusion, NMES appears to be effective in enhancing quadricep strength and exercise capacity in moderate-to-severe COPD patients. Further research is needed to clarify its effect on other outcomes and determine the optimal use of NMES.

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Author contributions

LZ contributed to study conception and design, drafting the submitted article, and revising the draft critically for important intellectual content. RC revised the draft critically for important intellectual content, and provided final approval of the version to be published. XL contributed to acquisition, analysis, and interpretation of data, and drafting the submitted article. LG and BG contributed to acquisition, analysis, and interpretation of data. WW, ZZ, YH, and XC revised the draft critically for important intellectual content. All authors contributed at all stages of this study, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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