20 years of neuromuscular electrical stimulation in COPD

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Shareable abstract (@ERSpublications)
Limb muscle dysfunction is a systemic consequence of COPD. NMES is an alternative limb training modality that does not cause dyspnoea. Although meta-analysis shows weak evidence, NMES is a way to enhance quadriceps strength and exercise capacity in COPD. https://bit.ly/49259hO

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Abstract

Although a lung disease, COPD is also associated with extrapulmonary manifestations including, among others, limb muscle dysfunction. Limb muscle dysfunction is a key systemic consequence of COPD that impacts patients' physical activity, exercise tolerance, quality of life and survival. Deconditioning is the main mechanism underlying the development of limb muscle dysfunction in COPD, which can be partially improved with exercise. However, some patients may not be able to tolerate exercise because of incapacitating breathlessness or unwillingness to undertake whole-body exercise. Alternative training modalities that do not give rise to dyspnoea, such as neuromuscular electrical stimulation (NMES), are urged. Over the past 20 years, NMES in COPD has presented conflicting conclusions in meta-analysis. In this review, we try to understand the reason for this result by analysing possible biases and factors that brought conflicting conclusions. We discuss the population (the intervention group, but also the control group), the outcome measures, the frequency of stimulation, the rehabilitation protocol (*i.e.* NMES alone *versus* standard care/rehabilitation or NMES plus conventional exercise training *versus* conventional exercise training alone or NMES *versus* sham treatment) and the trial design. The main reason for this discrepancy is the lack of dedicated guidelines for NMES. Further research is urged to determine the optimal parameters for an NMES programme. Despite this, NMES appears to be an effective means of enhancing quadriceps strength and exercise capacity in COPD with the potential to break the vicious circle induced by the disease and COPD patients' lifestyle.

Introduction

COPD is the third leading cause of death worldwide, causing 3.23 million deaths in 2019 [1]. COPD is not only an important cause of morbidity and mortality worldwide, but also a significant economic and social burden [2]. Although it is a chronic lung disease characterised by emphysema and/or chronic inflammation in the airways [2], COPD is also associated with extrapulmonary manifestations, all contributing to the overall clinical picture of the disease and the decreased quality of life [3]. The extrapulmonary manifestations comprise cardiovascular disease [4], osteoporosis [5], depression [6] and limb muscle dysfunction [7, 8]. Limb muscle dysfunction is a key systemic consequence of COPD that impacts patients' physical activity, exercise tolerance, quality of life and even survival. Deconditioning is the main mechanism underlying the development of limb muscle dysfunction in COPD. Other potential contributors to limb muscle dysfunction in COPD are inflammation, malnutrition, oxidative stress and hypoxaemia [8] (figure 1). Limb muscle atrophy, weakness [9] and poor oxidative capacity [10] are independent predictors of morbidity, mortality and increased healthcare resource utilisation in COPD [11]. Neuromuscular electrical stimulation (NMES) was first proposed in 2002 for limb muscle dysfunction in COPD. However, the potential benefit of NMES for COPD is still under debate. Even a meta-analysis that combined the results of the scientific studies on NMES in COPD patients did not come to a defined conclusion. This review aims to elucidate these contrasting results by critically analysing the meta-analysis published on NMES in COPD patients to understand possible bias or other factors responsible for such inconclusiveness.

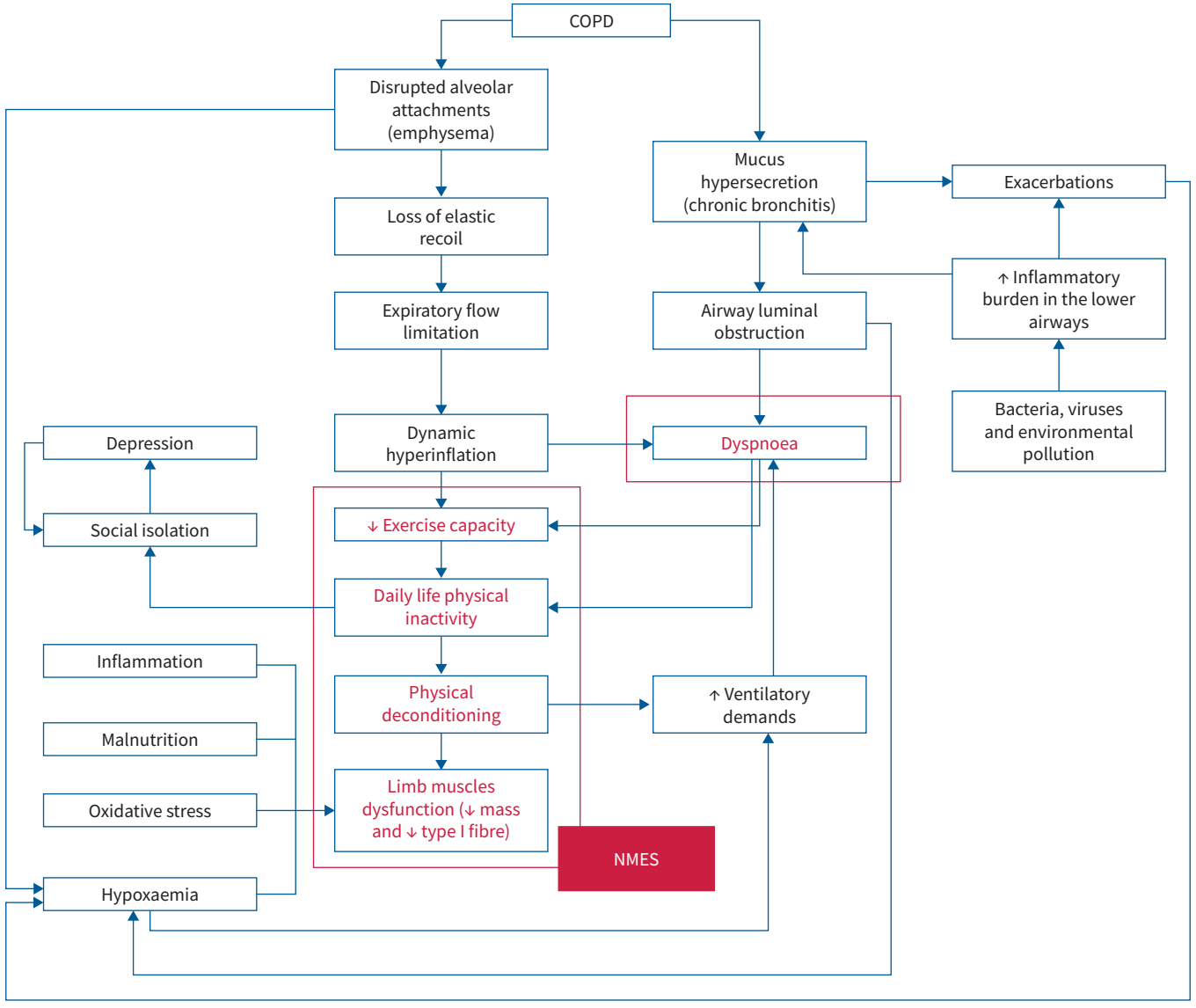

FIGURE 1 Flow diagram summarising the most important issues of the pathophysiology of COPD, with the direct impact of neuromuscular electrical stimulation (NMES) on it highlighted in red. ↑: increment; ↓: decrement.

NMES in COPD

Structural alterations of limb muscle occur in COPD, with fibre type distribution of the quadriceps shifting from type I fibres in favour of type IIx fibres (figure 1). Changes in capillarisation may occur, in terms of reduced capillary density and reduced number of capillaries per muscle fibre. Mitochondrial function is also altered in COPD muscle. Abnormal limb muscle bioenergetics, low mechanical efficiency and high resting energy expenditure can be important features of limb COPD muscles [8]. Limb muscle dysfunction can be partially improved with exercise training [7]; however, some patients with severe disease may not be able to tolerate exercise training. This may be due to incapacitating breathlessness or unwillingness to undertake whole-body exercise, for example, in bedridden patients receiving (or not receiving) mechanical ventilation during severe acute exacerbations of COPD. In these clinical situations, classical rehabilitation strategies are limited. Alternative training modalities that do not give rise to dyspnoea are urged. One of these is transcutaneous NMES. Although the use of NMES declined in the past, mainly because of the discomfort caused by the stimulation, new technologies allow painless strong muscle contractions. NMES enables more efficient muscle activation than that likely to be achieved with exercise. NMES activates large fast-twitch motor units with glycolytic fibres. This activation could potentially prevent (and treat) chronic diseases associated with muscle atrophy that ultimately lead to bedridden conditions [12, 13].

The first articles about NMES and COPD were published in 2002, when Bourjeily-Habr *et al*. [14] and Neder *et al*. [15] tested the potentiality of NMES of the lower extremities in improving functional impairment (and the consequent disability) caused by COPD. Both results favoured NMES of peripheral muscles as a valuable adjunct to the comprehensive pulmonary rehabilitation of patients with COPD. In the 20 years that followed these first pieces of evidence, at least one study per year was published, sometimes with contrasting results or conclusions. The majority of the data proved NMES to improve muscle strength, and/or endurance, and/or whole-body exercise tolerance, and/or breathlessness during activities of daily living. However, some researchers did not find important beneficial effects to recommend the systematic use of NMES in COPD patients.

24 studies are considered in this review, describing a total of 591 patients (table 1).

Meta-analysis on NEMS in COPD patients

Meta-analysis is the statistical procedure of analysing and integrating the results from several similar independent studies. Meta-analysis plays a central role in evidence-based medicine since it provides a more precise estimate of the effects of healthcare than that derived from the individual studies included. By combining the results from more studies, a meta-analysis increases the statistical power. It quantifies the overall treatment effect (*i.e.* the gain or loss seen in the experimental group compared to the control group) that may be hard to gather from the individual studies. For this reason, interpreting a meta-analysis is an important skill for the clinician because it re-examines the effectiveness of treatment interventions by considering contrasting results while identifying patterns and sources of disagreement among different studies [38].

Seven meta-analysis studies were dedicated to NEMS and COPD [39–45]. The first meta-analysis on NMES and COPD was published in 2009. It included five studies and showed a modest effect of NMES in increasing muscle torque significantly (four studies included) and walk distance (three studies included) in the treated groups compared to control, sham or other treatment groups. In addition, patients with less severe COPD tended to show less improvement. The authors concluded that evidence was weak for the effectiveness of NMES in improving lower limb muscle function in COPD patients [39]. In 2013, Maddocks *et al*. [40] ran a meta-analysis concluding that NMES led to a statistically significant improvement in quadriceps muscle strength and mass, as well as in the 6-min walk test, compared to the control. However, they included randomised controlled trials in adults with advanced chronic respiratory disease, chronic heart failure, cancer and HIV/AIDS. COPD was represented by eight out of 11 studies and 126 out of 218 participants [40]. In 2016 [41], the same authors published an update of the previously published review, including 13 COPD studies (403 participants). The overall conclusions had not changed from the last publication. Therefore, the findings of this meta-analysis referred to adults with advanced disease, including (but not exclusively) COPD patients [40]. The lack of efficacy of NMES of the lower limbs in COPD patients was inferred the following year. Pan *et al*. [42] analysed eight trials involving 156 COPD patients, finding no association between NMES and significant changes in quadriceps strength for 6-min walk distance (6MWD). Additionally, NMES failed to improve the muscle fibre characteristics, but it did significantly improve dyspnoea. The authors attributed to small sample size and different measures for evaluating outcomes as the reason for their inconclusive results. In contrast to this, the effectiveness of NMES for the rehabilitation of moderate-to-severe COPD was shown in 2016. This meta-analysis was conducted on nine trials, including 276 moderate-to-severe COPD patients randomly allocated to receive NMES. The conclusions of this meta-analysis were in favour of NMES since it contributed to statistically improved quadriceps strength and exercise capacity, including longer exercise distance and longer exercise endurance, with no difference in St George's Respiratory Questionnaire scores [43]. The meta-analysis including the highest number of studies (n=16) was published by Hill *et al*. [44] in 2018. The 16 studies contributed data on 267 participants with COPD. Seven studies explored the effect of NMES *versus* standard care, and the remaining nine examined the effect of NMES plus conventional exercise training *versus* traditional exercise training alone. Six studies utilised sham stimulation in the control group. This meta-analysis provided many interesting results. When applied in isolation, NMES increased both peripheral muscle force and quadriceps endurance, with an unclear effect on thigh muscle size. The 6MWD and time to symptom limitation exercising at a submaximal intensity increased. The severity of leg fatigue on completion of an exercise test was reduced. However, unfortunately, the quality of this evidence was low or very low. The effect on peripheral muscle force was uncertain when NMES was combined with conventional exercise training. The number of studies was insufficient for a meta-analysis on the impact on quadriceps endurance or thigh muscle size. At the same time, 6MWD increased in favour of NMES combined with conventional exercise training. Finally, the authors also analysed the most debilitated patients (*i.e.* people admitted to an intensive care unit (ICU) or a high respiratory dependency centre). The addition of NMES may have accelerated the achievement of a functional milestone by

TABLE 1 Studies included in this review

First author [reference]	Year	Patients	FEV_1	MV, ICU, H	Exacerbations	Frequency of stimulation	Wave	Stimulation protocol	6MWD m	Muscles
Bourjeily-Habr [14]	2002	18	38% pred	No	No	50 Hz	Asymmetrical square wave pulse	20 min on each limb, 3 days per week for 6 continuous weeks	NA	Quadriceps, hamstring and calf muscles
Neder [15]	2002	15	38.0±13.3% pred	No	No	50 Hz	Symmetrical biphasic square pulsed current	(15 min in the first week and 30 min thereafter), in sequence, 5 times per week for 6 weeks (a total of 30 sessions)	NA	Quadriceps
Zanotti [16]	2003	12	NA	Yes	No	35 Hz	Bipolar, biphasic, asymmetric rectangular pulses	5 days per week for 4 weeks for 30 min	Bedridden	Quadriceps femoris and on vastus glutei
Vivodtzev [17]	2006	9	27±3% pred	No	No	35 Hz	Symmetrical, biphasic, square-pulsed current	4 times a week for >30 min for 4 weeks	185±93	Quadriceps
Dal Corso [18]	2007	17	49.6±13.4% pred	No	No	50 Hz		6 weeks, 5 times per week	489±78	Quadriceps femoris
Sillen [19]	2008	13	49 (33–57)% pred	No	No	75 Hz	Symmetrical biphasic square pulse	A session lasting 21 min	NA	Quadriceps femoris muscles
Abdellaoui [20]	2011	9	25 (17–41)% pred	Yes	Yes	35 Hz	Biphasic symmetric, constant current impulses	1 h per day, 5 days per week for 6 weeks	0 (0–135)	Quadriceps and hamstring muscles
Nápolis [21]	2011	30	49.7±13.4% pred	No	No	50 Hz	Symmetrical, biphasic, square-pulsed current	(15 min at a time the first week, 30 min at a time the second week and 60 min at a time thereafter) 5 times per week for 6 weeks	495.6±72.9	Lower limb
Sillen [22]	2011	17	45±16% pred	No	No	15 Hz *versus* 75 Hz	Symmetrical biphasic square pulse	1 session of 29 min at 15 Hz, 1 session of 21 min at 75 Hz	380±98	Quadriceps muscles: vastus medialis, rectus femoris muscle and vastus lateralis
Giavedoni [23]	2012	11	41.3± 5.6% pred	Yes	Yes	50 Hz	Asymmetrical biphasic pulse	14 consecutive days (1 session per day, 30 min session) within 48 h of admission completed after discharge	NA	Quadriceps and vastus medialis
Vivodtzev [24]	2012	12	34±3% pred	No	No	50 Hz	Symmetrical, biphasic, square-pulsed current	At home, 5 days per week for 6 weeks (35 min of the quadriceps and 25 min of the calf)	346±21	Quadriceps and calf muscles
Chaplin [25]	2013	20	39.8±26.7% pred	Yes	Yes	35 Hz *versus* 50 Hz	Symmetrical biphasic pulse	30-min daily for the length of the hospital stay		Both quadriceps
Sillen [26]	2014	120	33±1% pred	No	No	15 Hz *versus* 75 Hz	Symmetrical biphasic square pulse	8 weeks, twice a day, 5 times a week, 18-min session	322±8	Quadriceps and calf muscles
Vieira [27]	2014	11	61.9±20.1% pred	No	No	50 Hz	Symmetrical biphasic square	8 weeks, 5 days per week, twice per day, 45 min per session	334.1± 89.8	Quadriceps muscles

Continued

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TABLE 1 Continued

First author [reference]	Year	Patients	FEV_1	MV, ICU, H	Exacerbations	Frequency of stimulation	Wave	Stimulation protocol	6MWD m	Muscles
Vivodtzev [28]	2014	20	54±14% pred	No	No	50 Hz	Symmetrical, biphasic, square-pulsed current	8 sessions of 45 minutes (2 supervised: 1 for teaching and 1 for evaluation), followed by 5 at home for training and 1 final directly supervised session	366±146	Quadriceps
Tasdemir [29]	2015	13	1.0±0.4 L	No	No	50 Hz	Biphasic symmetric constant current impulses	20 min per day, 2 days per week, for 10 weeks	257.6±99.7	Quadriceps femoris muscle
Kaymaz [30]	2015	50	26% pred	No	No	50 Hz	Symmetrical biphasic waveform	15 mins, 10 weeks (2 days a week)	Not reported	Quadriceps and deltoid muscles
Azevedo [31]	2016	13	48.0±9.6% pred	No	No	50 Hz	Pulsed, biphasic symmetric rectangular current	Once	Not reported	Quadriceps femoris of the right leg
Maddocks [32]	2016	25	30.8±11.1% pred	No	No	50 Hz	Current fixed	6-week programme consisting of 30 min of daily bilateral NMES	209.2 (98.6)	Quadriceps
Kucio [33]	2016	30	1.66±0.69 L	No	No	35 Hz	Commutative, symmetric rectangular current	3 weeks	397.2±70.65	Quadriceps and gastrocnemius muscles
Akar [34]	2017	30	NA	Yes	Yes	50 Hz	Symmetrical biphasic square waves with 6 s duration of contraction, 1.5 s of increase and 0.75 s of decrease	5 days per week for a total of 20 sessions	NA	Deltoid and quadriceps muscle
Latimer [35]	2019	13	45.5±19.3% pred	No	No	50 Hz	Biphasic impulse	30 min	NA	Quadriceps
Lopez-Lopez [36]	2020	21	36.58±16.79% pred	Yes	Yes	35 Hz	Biphasic symmetric, constant current impulses	(Once a day) during the hospitalisation period for a total of 5–7 sessions	NA	Quadriceps
Meys [37]	2020	62	~30% pred	No	Yes and no	35 Hz *versus* 50 Hz	Symmetrical biphasic stimulation	8 weeks, twice per day, 5 times per week, 18 min per section	326 (261–385)	Quadriceps and calf muscles

Data are presented as n, mean±SD or median (interquartile range), unless otherwise stated. FEV_1: forced expiratory volume in 1 s; MV: mechanical ventilation; ICU: intensive care unit; H: hospitalisation; 6MWD: 6-min walk distance; NA: not available; NMES: neuromuscular electrical stimulation.

reducing the time taken for participants to first sit out of bed. However, these patients showed no risk difference for mortality or minor adverse events [44]. The last meta-analysis on NMES dealt with critically ill COPD patients by investigating the effect of NMES on the duration of mechanical ventilation. The rationale of this analysis is that NMES might affect respiratory muscles through its systemic effects, similar to exercise training. Three studies (106 COPD patients) were included, and neuromuscular and functional electrical stimulations were considered. The stimulation may slightly reduce invasive mechanical ventilation duration [45].

Taken together, these meta-analyses still did not provide robust and conclusive evidence of the role of NMES as a component of, and in relation to, existing rehabilitation approaches for COPD patients.

However, all the authors recommend further research that would substantially impact on the confidence in estimating the effects of NMES in COPD. In some cases, the authors downgraded the quality of evidence ratings predominantly due to inconsistency among study findings and imprecision regarding estimated effects. In addition, most studies were conducted in a single centre with the risk of bias arising from a lack of participant or assessor blinding and a small study size. Therefore, more randomised controlled trials are advocated by all the authors, not only with a more significant number of participants, but with more homogeneous diseases and basal conditions and, above all, with an adequate methodological design.

The flow diagram in figure 1 summarises the most important issues of COPD pathophysiology with the most relevant effect of NMES training emphasised. The direct impact of NMES is to reverse limb dysfunction. Improved limb function would decrease the physical deconditioning of patients, improving their daily physical activity and, ultimately, exercise tolerance (also thanks to reduced dyspnoea). Indeed, NMES may be an adjuvant treatment that may enhance the strengthening effect of rehabilitative programmes or may significantly support COPD patients with muscle weakness or disabling dyspnoea who have difficulty engaging with existing services.

NMES is recommended by the official American Thoracic Society/European Respiratory Society statement on limb muscle dysfunction in COPD [8]. This means that the two most important respiratory societies consider NMES a valid tool for COPD. Therefore, it is essential to understand why meta-analysis failed to provide strong evidence of the efficacy of NMES in COPD. For this reason, in this review, we list and comment on some aspects that may have contributed to reducing the evidence of NMES efficacy. The heterogeneity in the responses of the different studies included in the meta-analysis should be identified clearly. Indeed, the heterogeneity is the most crucial parameter for meta-analysis to provide strong generalised conclusions.

Participants

The sample size of the studies varies from nine to 120 patients (table 1). The number of patients is not discussed in this review, considering that the appropriate sample size would be calculated based on the statistical principle. The sample size depends on the acceptable level of significance, the power of the study, the expected effect size, the underlying event rate in the population and the standard deviation in the population. In this way, bias in interpreting results is avoided, the results can be generalised to the population, and the study can detect the difference between test groups. True inferences about the population can therefore be made from the results obtained [46].

Similarly, homogeneous diseases and basal conditions should be basic assumptions while designing new protocols of measurements. Indeed, the literature covers many different levels of COPD, from mild-to-moderate to severe clinically stable forms [14, 15, 18, 19, 21, 22, 24–33, 35, 47] and severely ill patients requiring mechanical ventilation and/or during ICU staying due to exacerbation [16, 17, 20, 23, 34, 37, 48]. Such heterogeneity might affect the estimates of the effect, downgrading the evidence of NMES efficacy.

Other important factors contribute to heterogeneity of patients. These comprise the ability to tolerate high stimulation intensities, muscle mass, deconditioning and sarcopenia [49] or cachexia. Still, they are not deeply investigated or reported by the authors, although deserving attention. We can speculate that these factors may help to profile patients that are good/bad responders to NMES together with the expected effects of NMES.

We want to focus on another critical aspect that may alter the results: the control group. The purpose of having a control group is to rule out other factors that may influence the treatment results. Indeed, the difference between the control and the experimental group is that the independent variable (*i.e.* NMES efficacy) is changed only for the experimental group, while it is constant in the control group. In this way,

the independent variable's effects on the experiment are isolated, and alternative explanations of the experimental results are ruled out [50]. In paired-design studies, the same subject acts as both the intervention and the control; in this way, the number of patients recruited and the duration of the protocol are reduced. In one study, one leg was stimulated and the other was not [23]. However, if the stimulation works, asymmetry in leg function may occur, potentially affecting the outcome measures. In addition, comparing one stimulated leg to the nonstimulated one in one given individual is wrong, due to the central effect of NMES, as both neural and muscular adaptations occur. The former mainly occurred during the first 4 weeks of training, whereas changes in muscle mass and architecture became significant between weeks 4 and 8, in healthy participants [51]. In other studies, the subject is acquired after NMES sessions to be compared with their baseline naïve condition [28] or after sham acquisition [15, 18, 21] or using two different frequencies of stimulation [22], or after resistance training [19] with a washout period included between the two conditions. Of note, the washout period should be carefully selected to avoid any baseline bias. The unpaired experimental designs may include two or more groups of different participants. In unpaired groups, the control group can receive a sham stimulation by using the same setup (electrodes, stimulator and connection system) as for the treated group. Participants in the sham group may not receive active electrical stimulation during the visits [14, 20, 27], or they may receive very low frequency (*i.e.* 5 Hz [24, 29]) or amplitude (*i.e.* 0–20 mA [21, 32]) to provide a stimulus detectable by the participant, but insufficient to elicit a tetanic muscular contraction. The rationale is that patients are not supposed to know what, if any, sensations to expect during the stimulation. Since patients are not in contact with each other they remain blinded to the randomisation. When the frequency of stimulation is the main question, the two groups differ only in terms of the frequency, typically high *versus* low [25, 26, 37]. There can also be the possibility of a crossover study, with the sham group receiving NMES after the control period and *vice versa*. These patients are therefore assessed three times: before and after the control period and after the further period of NMES, acquired after a proper washout period [15, 18]. NMES can also be studied compared to or in association with other treatments. In these cases, the control group would receive only the standard intervention [16, 17, 19, 33–35, 47], while the intervention group would receive NMES alone [19, 30, 34, 35, 47] or NMES plus the conventional exercise and/or care [16, 17, 26, 29, 33, 34, 36, 48], respectively. Finally, the control group does not necessarily need to be composed of COPD patients. One study included only healthy elderly male adults in the control group [31].

Outcome measures

The possible benefits of NMES in COPD patients can affect muscle function, exercise capacity, health-related quality of life and respiratory response. According to the variety of clinical benefits of this training approach, there are many possible outcome measures to be considered. Muscle performance can be measured in terms of geometry, strength and endurance. Geometry was assessed through corrected thigh circumference [27], through quadriceps skin fold thickness, *i.e.* (anterior thigh skin fold thickness+posterior thigh skin fold thickness)/2 [17], and through cross-sectional area assessed by ultrasonography [32]. The total muscle mass was determined according to the criteria of Lee *et al.* [17, 52] or by dual-energy X-ray absorptiometry [18].

Muscle biopsy can be obtained, the median fibre cross-sectional areas measured, and the capillaries around fibres counted [18, 24]. Muscle oxidation can be assessed by measuring total protein, myosin heavy chain carbonylation, and the level of 4-hydroxy-2-nonenal protein adducts by immunoblotting and lipid peroxidation (by measuring hiobarbituric acid reactive substances). Muscle structure can also be identified on frozen sections from the muscle biopsies in terms of fibre typology, fibre number and fibre size [20, 24]. Muscle strength can be assessed using scores commonly adopted in physical medicine [23, 26, 27] or a chair-up test [29]. Alternatively, muscle strength can be quantified using an isokinetic dynamometer during leg movements (typically extension and flexion) with adequate resting periods between efforts and the best peak torque value recorded (in Nm units) [14, 15, 18, 21, 23, 26, 31, 37, 47]. Strength can also be measured with a strain gauge tensiometer (in kg units) during maximal voluntary contraction against a resistance [17, 28] or not [20, 24, 25, 32].

An endurance test for peripheral muscle requires subjects to perform the maximum possible number of contractions at a certain angular velocity during a time frame [26]. The total work (in J), the mean power (in W) and a fatigue index (the % ratio between the work performed in the last and initial contractions) can be calculated [15]. Alternatively, quadriceps endurance can be evaluated using a squat and 2-min step test [29]. Exercise capacity can be assessed through the shuttle walk test [14, 24, 25, 28–30] and/or the 6MWD test [17, 18, 20, 26, 27, 32, 33, 37, 47]. Exercise endurance can be estimated by the time to reach the limit of tolerance of a constant work rate exercise, with constant work rate being a percentage of the peak work rate obtained in a previous maximal incremental test [15, 21, 26, 27, 37], during the shuttle walk test [24, 30] and/or during the sit-to-stand test [36, 47]. The health-related quality of life is usually evaluated through

surveys, namely the St George's Respiratory Questionnaire [15, 26, 27, 29, 30, 32, 47], the 28-item Maugeri Respiratory Failure questionnaire [17], the Canadian Occupational Performance Measure to assess problematic activities of daily life [26], the Chronic Respiratory Disease Questionnaire [32] and the EQ-5D [36]. Different parameters were used to assess respiratory response, comprising lower ventilatory reserve (*i.e.* the ratio of peak minute volume over maximum minute ventilation) [14], maximal voluntary ventilation [19, 22], peak minute ventilation [19, 22, 24, 26, 28], reduced dyspnoea (measured through the Borg scale of perceived exertion [14, 19, 21, 22, 24, 27, 28, 47] or the Medical Research Council (MRC) scale [20, 22, 25, 26, 29, 30, 47] or London Chest Activity of Daily Living Scale [36]), improvement in oxygen consumption at peak exercise [14, 15, 19, 21, 26–28] and respiratory rate [16, 34]. Pulmonary function tests can be evaluated before and after stimulation to verify whether NMES has affected lung volumes, capacities, flows and respiratory muscle strength [14, 17, 18, 21, 24, 25, 27, 29, 31, 33, 36, 37, 47]. Cardiac function can be assessed by monitoring oxygen saturation and heart rate [16, 17, 21, 22, 24, 26, 34, 47]. The number of days needed to transfer from bed to chair is an important clinical outcome in bedbound, severely ill COPD patients [16]. The authors used these outcome measures to investigate the effect of NMES on lung and breathing function and exercise capacity. Only a few authors noted significant differences in spirometry values. Vieira *et al*. [27] and Lopez-Lopez *et al*. [36] showed NMES to increase forced expiratory volume in 1 s (FEV_1). Only the former also found an increase in FEV_1/forced vital capacity [27]. One study noted a small but statistically significant reduction in dead space at peak exercise in the NMES group [14]. NMES improved respiratory rate in bedridden patients [16]. Exercise capacity (in terms of 6MWD and time, shuttle walk distance, cycle endurance time and number of repetitions in the 1-min sit-to-stand test) and tolerance were largely found to increase in patients treated with NMES alone or in association with other treatments [14, 15, 17, 20, 21, 25–27, 30, 32, 33, 37, 47]. Finally, NMES decreased the days needed to transfer from bed to chair [16]. Although this is not an exercise, it is the main goal for a bedridden patient. Notably, breathing-perceived exertion was one of the parameters that mainly improved secondary to the use of NMES in terms of reduced Borg dyspnoea score and MRC score [14, 15, 17, 20, 26, 27, 30, 36, 47].

Frequency of stimulation

The stimulation frequencies of NMES used for humans range from 1 to 120 Hz. High-frequency NMES is defined when the muscle is stimulated with frequencies >50 Hz. This induces tetanic fusion of the muscle fibres and, over a short period, corresponds to resistance training. Low-frequency NMES is defined when the stimulation frequencies are <50 Hz, corresponding to *in vivo* endurance over a long period. The effect of modifying the stimulation frequency on the NMES training outcomes is still debatable, as the effects of high or low frequency are not necessarily confined to a specific muscle fibre type. Only stimulation frequencies >50 Hz seem to allow muscle strength to improve to a significant extent [11]. In addition, ⩾12 training sessions are required to induce an increase in muscle strength in healthy participants [53]. Four authors have investigated the effect of stimulating with low *versus* high frequencies [22, 25, 26, 37]. Both Sillen *et al*. [22] and Chaplin *et al*. [25] showed that one frequency was not superior to the other. However, the former tested the acute effect of a single session of NMES on oxygen uptake, ventilation and symptoms of dyspnoea and fatigue [22]. The latter applied NMES daily for the length of the hospital stay of the patients [22] (table 1).

Rehabilitation protocol

Studies on the benefits of NMES rehabilitation in COPD patients considered either NMES alone [14, 15, 18, 19, 21–25, 27, 28, 30, 32, 37] or together with other formal pulmonary rehabilitation programmes and/or conventional exercise training and/or respiratory physical therapy (bronchial hygiene techniques) [17, 27, 29, 33, 37]. Other standard treatments/physical rehabilitation protocols associated with NMES may comprise active limb mobilisation [16, 17, 20, 34], slow walking on a treadmill and arm-lifting [17], resistance training of the quadriceps femoris muscles [19, 29, 35], strength training [26], lower limb exercise [36], segmental exercise [17], self-management programme [36], cycle ergometer training [47], endurance training [29] or low-level resistance training for the shoulder girdle and elbow muscles [29].

Trial designs: noninferiority versus *superiority* versus *equivalence*

Meta-analysis studies were conducted to assess the strength of evidence on COPD and NMES. One aim is to determine whether an effect exists; another is to determine whether the effect is positive or negative; ideally, a single summary estimate is obtained. Indeed, when the effect of one treatment is compared to another, there are three possible hypotheses: noninferiority, superiority or equivalence. Noninferiority means that the treatment of interest is as good as the other treatment, but it can also be better: it provides at least the same benefit to the patient. Superiority is usually against placebo, with the effect in the treatment group being superior to any placebo group effects. Finally, in case of equivalence, the new treatment cannot be worse or better than the traditional ones. This is another crucial aspect to consider while

critically evaluating the results of an NMES study. This could also be an important achievement if NMES was shown to be "not unacceptably worse" than (*i.e.* noninferiority) or equivalent to current standard therapy. For example, when the effect of NMES was similar to exercise, this might be an outstanding outcome for those COPD patients who are expected to be nonadherent to exercise, due to poor exercise tolerance or self-reported exercise limitation despite pharmacological treatment and/or for bedridden patients. Of course, exercise has a broader range of benefits on many systems (*i.e.* cardiovascular, respiratory, skeletal, immune, digestive and nervous) of the body. Still, NMES can be the starting point to break the vicious circle of dyspnoea–inactivity frequently experienced by COPD patients. In this process, also known as the "disease spiral" or "vicious cycle" theory of dyspnoea–inactivity, airflow limitation, hyperinflation, dyspnoea, physical activity, exercise capacity and COPD exacerbations are linked (figure 1). COPD is characterised by chronic airflow limitation and persistent respiratory symptoms (*i.e.* dyspnoea) that limit patients' activities, often leading to dynamic hyperinflation during exercise. The reduced physical activity leads to physical deconditioning and further impairment of respiratory symptoms (*i.e.* exacerbations) [54, 55]. In this scenario, NMES might be an early implementation of muscle reconditioning to start breaking the vicious cycle to improve the ability to do everyday activities.

Assessment of the quality of the evidence

A quality score for each study is usually included in the meta-analysis to ensure that better studies receive more weight. There are different types of quality measurement tools and the results can vary accordingly. A sensitivity analysis may be needed to determine the impact of the quality score on the results. The I^2 statistic [56, 57] is used to quantify inconsistency across trial conditions, therefore assessing the clinical heterogeneity. Another important issue to consider is the risk of bias in included studies. Risks of bias are the likelihood that features of the study design or conduct will give misleading results or systematic errors or a deviation from reporting the truth or an appropriate evidence finding in the meta-analysis. The most important risks of bias are selection bias (*i.e.* random sequence generation and allocation concealments), performance bias (*i.e.* blinding of participants and/or personnel), detection bias (*i.e.* blinding of outcome measurements), attrition bias (*i.e.* incomplete outcome data) and reporting bias (*i.e.* selective reporting) [40, 41]. The methodological quality of the included studies can be assessed using the PEDro scores [39, 58], the Jadad scale [42, 59] and the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach [60–63]. For each outcome, the GRADE system considers five items (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence. The main reasons for downgrading the quality of the evidence were 1) inconsistency of results across studies (wide variance of point estimates and inconsistent direction of the effect or whether or not there is an effect); 2) imprecision regarding estimates of the effect (the lower 95% confidence interval for the effect estimate was less than the established minimally important difference); 3) risk of bias (in particular lack of blindness of group allocation and the absence of sham stimulation); 4) high degree of heterogeneity (I^2 values >0.5); and 5) small population size [41, 44]. Interestingly, the authors of the meta-analyses never critically discussed the types of interventions. Only Hill *et al.* [44] considered the rehabilitation protocol. They considered NMES applied in isolation or concurrently with conventional exercise training to determine the effects of NMES in isolation from other exercise rehabilitation strategies or as an adjunct to conventional exercise training. However, we have previously listed the variety of the conventional exercise training associated with NMES: active limb mobilisation [16, 17, 20, 34], slow walking [17] or cycle ergometer training [47], resistance [19, 29, 35], strength [26] or endurance training [29], lower-limb exercise [36], segmental exercise [17], self-management programme [36], upper-limb lifting [17] or resistance training [29]. We believe that the rehabilitation protocol *per se* is an important factor contributing to the inconsistency of results across studies.

What is next?

These considerations should not be confined to healthcare settings, but extend to in-home management of stable COPD patients. Prevention of out-of-hospital exacerbations and breaking the cycle of dyspnoea–inactivity are vital goals for COPD patients at risk. Several innovative technological NMES solutions are currently available for home settings. These devices allow the painless application of strong muscular contractions through a wide surface area of stimulating electrodes and through the exponential climbing electrical pulse resulting in intense muscle stimulation with very little pain and/or discomfort for the patient. In addition, modern technological devices allow a self-healthcare system based on smartphone technology. In this way, gathering information about the patient's health and providing a feedback system for the clinician to track the patient's compliance with the therapy is possible. The new devices are portable generators of NMES with batteries specially designed for daily use with independent outputs/channels that the user can adjust. These new electrode technologies are user-friendly, with a simple device user manual and the positioning of the "electrodes". They have an easy interface and provide different pre-set programmes of involuntary exercise training for everybody (*i.e.* resistance, resistant strength, basic

or fast or explosive strength, sequential tonic or phasic contraction, agonist/antagonist). They allow the patient to adjust the current intensity, with the device's screen showing the overall treatment time and the intensity set on each channel. Different wave characteristics can be provided for contraction and recovery, with the option to set a different current intensity for the two stimulations, or to set all the characteristics of the stimulation wave, according to the specific indications of the clinician. Finally, the newer-generation stimulators can also detect the connection of the electrodes for the patient's safety and the quality of the treatment. Figure 2 shows the main differences between the old and the modern technological devices, with the possibility to set and control the stimulation programmes and feedback from the patients and monitoring the patient's compliance being the most important features. Thanks to these characteristics, the new devices are user-friendly enough to be used by the patient at home. The in-home NMES could be a good surrogate for in-hospital NMES, particularly for COPD patients in stable conditions. There is potential for in-home NMES is to impact lifestyle-related COPD issues while being a valuable modality for rehabilitation. Indeed, the aim of in-home settings is not to perform a diagnostic test, but to maintain or even improve the patient's condition on a regular basis. Patients would benefit from enhancing exercise tolerance, particularly those with better-preserved fat-free mass (because they tolerated higher training stimulus levels) [21]. However, larger, well-designed trials are still needed to improve the understanding of NMES and to clarify how it can be optimally used in COPD in both inpatient and in-home settings.

Conclusions

In the past 20 years, meta-analyses of NMES in COPD patients have presented conflicting conclusions because of many factors that may influence the results. These comprise the inhomogeneity in the population (disease severity of the treated group and the group chosen as control), in the outcome measures (muscular, exercise capacity, questionnaires, *etc*.) and in the protocol of acquisition (frequency stimulation and the protocol chosen). Indeed, some protocols compared outcomes between NMES alone and usual care/rehabilitation, compared NMES plus conventional exercise training and conventional exercise training alone, or compared NMES with sham treatment. Knowing all the potential biases is

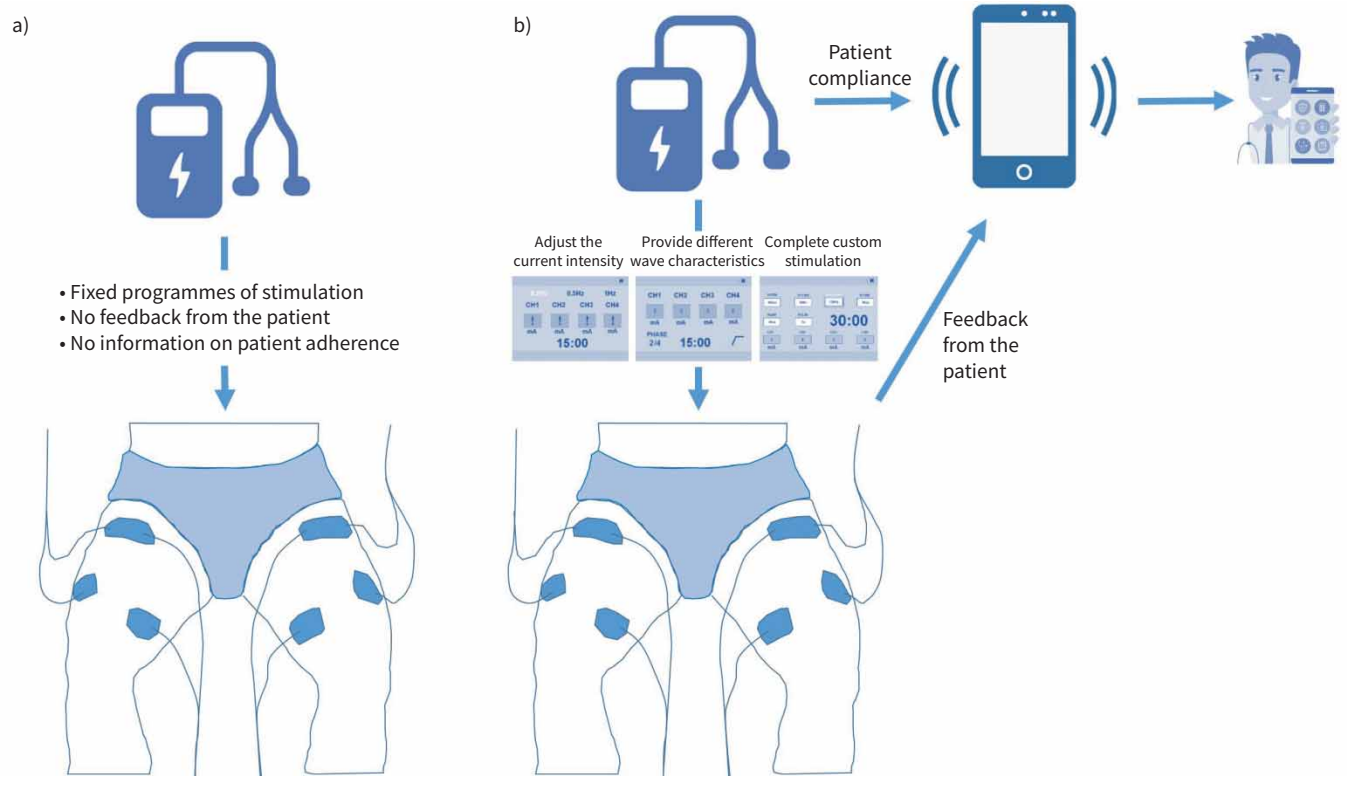

FIGURE 2 Main differences between a) an old and b) a modern technological device. The possibility to set and control the stimulation programmes (*i.e.* adjusting the current intensity, providing different wave characteristics or setting all the characteristics of the stimulation wave according to the specific indications of the clinician) and the feedback from the patient, as well as information about patient compliance are the most important features that make the new devices user-friendly for use by the patient at home.

essential before starting a new study on NMES in COPD patients. This does not mean researchers should design their study "for" the meta-analysis. Still, they should be aware of the various protocols and items in the literature (therefore approved by the scientific community). The researchers should identify the determinants of subpopulation analysis or covariates that may be appropriate to explore, include, or exclude. The main reason for this discrepancy is the lack of dedicated guidelines for the NMES programme. High-quality, multicentre studies are urged to determine the optimal parameters for an NMES programme, the patients likely to benefit, and the impact on morbidity. Despite this, NMES can potentially enhance the strength of the quadriceps and exercise capacity in COPD patients. The final goal of NMES should be to break the vicious circle induced by COPD.

Points for clinical practice

- Limb muscle dysfunction is a key systemic consequence of COPD that impacts on patients' physical activity, exercise tolerance, quality of life, and even survival.
- NMES is an alternative training modality that does not give rise to dyspnoea, suitable for those COPD patients who may not be able to tolerate exercise training due to incapacitating breathlessness or unwillingness to undertake whole-body exercise.
- Unfortunately, the data from meta-analyses examining NMES for COPD brought conflicting conclusions because of many factors, due to the high heterogeneity of the protocols.
- Despite this, there is overall evidence of the benefits of NMES in enhancing quadriceps strength and exercise capacity in COPD patients.

Questions for future research

- Further research should determine the optimal parameters and protocols for a NMES programme, both for inpatient and in-home settings.
- Home management of stable COPD patients should also comprise NMES, with the potential to make a major impact on lifestyle-related COPD issues while being a useful modality for rehabilitation.

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References

1 World Health Organization (WHO). Chronic Obstructive Pulmonary Disease (COPD). 2023. www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd) Date last accessed: 13 September 2022. Date last updated: 16 March 2023.
2 Celli BR, MacNee W, Agusti A, *et al.* Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
3 Gross NJ. Extrapulmonary effects of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2001; 7: 84–92.
4 Chaouat A, Bugnet AS, Kadaoui N, *et al.* Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 189–194.
5 Graumam RQ, Pinheiro MM, Nery LE, *et al.* Increased rate of osteoporosis, low lean mass, and fragility fractures in COPD patients: association with disease severity. *Osteoporos Int* 2018; 29: 1457–1468.
6 O'Toole J, Woo H, Putcha N, *et al.* Comparative impact of depressive symptoms and FEV_1% on chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2022; 19: 171–178.

7 Casaburi R, Gosselink R, Decramer M, *et al.* Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med* 1999; 159: S1–S40.

8 Maltais F, Decramer M, Casaburi R, *et al.* An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014; 189: e15–e62.

9 Gosker HR, Wouters EFM, van der Vusse GJ, *et al.* Skeletal muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: underlying mechanisms and therapy perspectives. *Am J Clin Nutr* 2000; 71: 1033–1047.

10 Jaitovich A. Impaired regenerative capacity contributes to skeletal muscle dysfunction in chronic obstructive pulmonary disease (COPD). *Am J Physiol Cell Physiol* 2022; 323: C974–C989.

11 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: 79–91.

12 Hamada T, Kimura T, Moritani T. Selective fatigue of fast motor units after electrically elicited muscle contractions. *J Electromyogr Kinesiol* 2004; 14: 531–538.

13 Moritani T. Electrical muscle stimulation: application and potential role in aging society. *J Electromyogr Kinesiol* 2021; 61: 102598.

14 Bourjeily-Habr G, Rochester CL, Palermo F, *et al.* Randomised controlled trial of transcutaneous electrical muscle stimulation of the lower extremities in patients with chronic obstructive pulmonary disease. *Thorax* 2002; 57: 1045–1049.

15 Neder JA, Sword D, Ward SA, *et al.* Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax* 2002; 57: 333–337.

16 Zanotti E, Felicetti G, Maini M, *et al.* Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: effect of electrical stimulation. *Chest* 2003; 124: 292–296.

17 Vivodtzev I, Pépin JL, Vottero G, *et al.* Improvement in quadriceps strength and dyspnea in daily tasks after 1 month of electrical stimulation in severely deconditioned and malnourished COPD. *Chest* 2006; 129: 1540–1548.

18 Dal Corso S, Nápolis L, Malaguti C, *et al.* Skeletal muscle structure and function in response to electrical stimulation in moderately impaired COPD patients. *Respir Med* 2007; 101: 1236–1243.

19 Sillen MJH, Janssen PP, Akkermans MA, *et al.* The metabolic response during resistance training and neuromuscular electrical stimulation (NMES) in patients with COPD, a pilot study. *Respir Med* 2008; 102: 786–789.

20 Abdellaoui A, Préfaut C, Gouzi F, *et al.* Skeletal muscle effects of electrostimulation after COPD exacerbation: a pilot study. *Eur Respir J* 2011; 38: 781–788.

21 Nápolis LM, Corso SD, Neder JA, *et al.* Neuromuscular electrical stimulation improves exercise tolerance in chronic obstructive pulmonary disease patients with better preserved fat-free mass. *Clinics* 2011; 66: 401–406.

22 Sillen MJH, Wouters EFM, Franssen FME, *et al.* Oxygen uptake, ventilation, and symptoms during low-frequency *versus* high-frequency NMES in COPD: a pilot study. *Lung* 2011; 189: 21–26.

23 Giavedoni S, Deans A, McCaughey P, *et al.* Neuromuscular electrical stimulation prevents muscle function deterioration in exacerbated COPD: a pilot study. *Respir Med* 2012; 106: 1429–1434.

24 Vivodtzev I, Debigaré R, Gagnon P, *et al.* Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial. *Chest* 2012; 141: 716–725.

25 Chaplin EJL, Houchen L, Greening NJ, *et al.* Neuromuscular stimulation of quadriceps in patients hospitalized during an exacerbation of COPD: a comparison of low (35 Hz) and high (50 Hz) frequencies. *Physiother Res Int* 2013; 18: 148–156.

26 Sillen MJH, Franssen FME, Delbressine JML, *et al.* Efficacy of lower-limb muscle training modalities in severely dyspnoeic individuals with COPD and quadriceps muscle weakness: results from the DICES trial. *Thorax* 2014; 69: 525–531.

27 Vieira PJC, Chiappa AM, Cipriano G, *et al.* Neuromuscular electrical stimulation improves clinical and physiological function in COPD patients. *Respir Med* 2014; 108: 609–620.

28 Vivodtzev I, Rivard B, Gagnon P, *et al.* Tolerance and physiological correlates of neuromuscular electrical stimulation in COPD: a pilot study. *PLoS One* 2014; 9: e94850.

29 Tasdemir F, Inal-Ince D, Ergun P, *et al.* Neuromuscular electrical stimulation as an adjunct to endurance and resistance training during pulmonary rehabilitation in stable chronic obstructive pulmonary disease. *Expert Rev Respir Med* 2015; 9: 493–502.

30 Kaymaz D, Ergün P, Demirci E, *et al.* Comparison of the effects of neuromuscular electrical stimulation and endurance training in patients with severe chronic obstructive pulmonary disease. *Tuberk Toraks* 2015; 63: 1–7.

31 Azevedo DdeP, Medeiros WM, de Freitas FFM, *et al.* High oxygen extraction and slow recovery of muscle deoxygenation kinetics after neuromuscular electrical stimulation in COPD patients. *Eur J Appl Physiol* 2016; 116: 1899–1910.

32 Maddocks M, Nolan CM, Man WDC, *et al.* Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomized double-blind, placebo-controlled trial. *Lancet Respir Med* 2016; 4: 27–36.

33 Kucio C, Niesporek J, Kucio E, *et al.* Evaluation of the effects of neuromuscular electrical stimulation of the lower limbs combined with pulmonary rehabilitation on exercise tolerance in patients with chronic obstructive pulmonary disease. *J Hum Kinet* 2016; 54: 75–82.
34 Akar O, Günay E, Sarinc Ulasli S, *et al.* Efficacy of neuromuscular electrical stimulation in patients with COPD followed in intensive care unit. *Clin Respir J* 2017; 11: 743–750.
35 Latimer LE, Constantin D, Greening NJ, *et al.* Impact of transcutaneous neuromuscular electrical stimulation or resistance exercise on skeletal muscle mRNA expression in COPD. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 1355–1364.
36 Lopez-Lopez L, Valenza MC, Rodriguez-Torres J, *et al.* Results on health-related quality of life and functionality of a patient-centered self-management program in hospitalized COPD: a randomized control trial. *Disabil Rehabil* 2020; 42: 3687–3695.
37 Meys R, Sillen MJ, Franssen FME, *et al.* Impact of mild-to-moderate exacerbations on outcomes of neuromuscular electrical stimulation (NMES) in patients with COPD. *Respir Med* 2020; 161: 105851.
38 Israel H, Richter RR. A guide to understanding meta-analysis. *J Orthop Sports Phys Ther* 2011; 41: 496–504.
39 Roig M, Reid WD. Electrical stimulation and peripheral muscle function in COPD: a systematic review. *Respir Med* 2009; 103: 485–495.
40 Maddocks M, Gao W, Higginson IJ, *et al.* Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. *Cochrane Database Syst Rev* 2013; 1: CD009419.
41 Jones S, Man WDC, Gao W, *et al.* Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. *Cochrane Database Syst Rev* 2016; 10: CD009419.
42 Pan L, Guo Y, Liu X, *et al.* Lack of efficacy of neuromuscular electrical stimulation of the lower limbs in chronic obstructive pulmonary disease patients: a meta-analysis. *Respirology* 2014; 19: 22–29.
43 Chen RC, Li XY, Guan LL, *et al.* Effectiveness of neuromuscular electrical stimulation for the rehabilitation of moderate-to-severe COPD: a meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 2965–2975.
44 Hill K, Cavalheri V, Mathur S, *et al.* Neuromuscular electrostimulation for adults with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2018; 5: CD010821.
45 Gutiérrez-Arias RE, Zapata-Quiroz CC, Prenafeta-Pedemonte BO, *et al.* Effect of neuromuscular electrical stimulation on the duration of mechanical ventilation. *Respir Care* 2021; 66: 679–685.
46 Kirby A, Gebski V, Keech AC. Determining the sample size in a clinical trial. *Med J Aust* 2002; 177: 256–257.
47 Péran L, Beaumont M, Le Ber C, *et al.* Effect of neuromuscular electrical stimulation on exercise capacity in patients with severe chronic obstructive pulmonary disease: a randomized controlled trial. *Clin Rehabil* 2022; 36: 1072–1082.
48 Alonso J, Vilagut G, Mortier P, *et al.* Mental health impact of the first wave of COVID-19 pandemic on Spanish healthcare workers: a large cross-sectional survey. *Rev Psiquiatr Salud Ment* 2021; 14: 90–105.
49 He J, Li H, Yao J, *et al.* Prevalence of sarcopenia in patients with COPD through different musculature measurements: an updated meta-analysis and meta-regression. *Front Nutr* 2023; 10: 1137371.
50 Krzywinski M, Altman N. Points of view: designing comparative experiments. *Nat Methods* 2014; 11: 597–598.
51 Gondin J, Guette M, Ballay Y, *et al.* Electromyostimulation training effects on neural drive and muscle architecture. *Med Sci Sports Exerc* 2005; 37: 1291–1299.
52 Lee R, Wang Z, Heo M, *et al.* Total-body skeletal muscle mass: development and cross-validation of anthropometric prediction models. *Am J Clin Nutr* 2000; 72: 796–803.
53 Parker MG, Bennett MJ, Hieb MA, *et al.* Strength response in human femoris muscle during 2 neuromuscular electrical stimulation programs. *J Orthop Sports Phys Ther* 2003; 33: 719–726.
54 Ramon MA, Ter Riet G, Carsin AE, *et al.* The dyspnoea-inactivity vicious circle in COPD: development and external validation of a conceptual model. *Eur Respir J* 2018; 52: 1800079.
55 Cooper CB. Exercise in chronic pulmonary disease: limitations and rehabilitation. *Med Sci Sports Exerc* 2001; 33: Suppl. 7, S643–S646.
56 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
57 Higgins JPT, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
58 PEDro Physiotherapy Evidence Database. Indexing Criteria and Codes. https://pedro.org.au/english/learn/indexing-criteria-and-codes/ Date last updated: 5 February 2024.
59 Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.
60 Guyatt GH, Oxman AD, Montori V, *et al.* GRADE guidelines: 5. Rating the quality of evidence – publication bias. *J Clin Epidemiol* 2011; 64: 1277–1282.
61 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines 6. Rating the quality of evidence – imprecision. *J Clin Epidemiol* 2011; 64: 1283–1293.
62 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines: 7. Rating the quality of evidence – inconsistency. *J Clin Epidemiol* 2011; 64: 1294–1302.
63 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines: 8. Rating the quality of evidence – indirectness. *J Clin Epidemiol* 2011; 64: 1303–1310.