# Effects of Neuromuscular Electrical Stimulation on Physiologic and Functional Measurements in Patients With Heart Failure

## A SYSTEMATIC REVIEW WITH META-ANALYSIS

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■ **BACKGROUND:** Neuromuscular electrical stimulation (NMES) is potentially attractive as a method of training in heart failure (HF) and could be performed in patients unable to participate in standard exercise training.

■ **PURPOSE:** To examine the effects of NMES on physiologic and functional measurements in patients with HF.

■ **METHODS:** MEDLINE, Cochrane, EMBASE, Scielo, and PEDro were searched from the earliest date available to July 2014. Two independent reviewers screened the titles and abstracts and selected randomized controlled trials, examining the effects of NMES versus exercise and/or of NMES versus control on physiologic and functional measurements in patients with HF. Two independent reviewers screened the randomized controlled trials. The PEDro score was used to evaluate methodological quality. Weighted mean differences and 95% CI were calculated.

■ **RESULTS:** Thirteen studies met the study criteria. Neuromuscular electrical stimulation resulted in improvement in peak oxygen uptake ($\dot{V}O_2$) (4.86 $mL \cdot kg^{-1} \cdot min^{-1}$; 95% CI, 2.81-6.91), 6-minute walk test (6MWT) distance (63.54 m; 95% CI, 35.81-91.27), muscle strength (30.74 N; 95% CI, 3.67-57.81), flow-mediated dilatation (2.67%; 95% CI, 0.86-4.49), depressive symptoms (−3.86; 95% CI, −6.46 to −1.25), and global quality of life (0.89; 95% CI, 0.55-1.24). Nonsignificant differences in ($\dot{V}O_2$) peak, 6MWT, and quality of life were found for participants in the exercise group compared with NMES.

■ **CONCLUSIONS:** Neuromuscular electrical stimulation improved peak $\dot{V}O_2$, 6MWT distance, quality of life, muscle strength, endothelial function, and depressive symptoms in patients with HF and could be considered for inclusion in cardiac rehabilitation for selected patients.

K E Y W O R D S

heart failure

quality of life

rehabilitation

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Heart failure (HF) is a syndrome considered to be the final common pathway for many patients with cardiac disease and is associated with a low level of exercise capacity, poor quality of life, and depressive symptoms.[1] Moreover, HF is characterized by overactivity of the neurohormonal system and endothelial dysfunction.

Despite the well-known positive effects of exercise training in patients with HF, the best mode of exercise is still under discussion. These discussions are focused on low adherence, improvements in exercise capacity, and quality of life.[2] However, patients with very limited exercise capacity (New York Heart Association functional class III/IV) may be, in general, dependent in their everyday activities. Also, the adherence to a standard rehabilitation program can be impaired.[3] New modalities of exercise training are increasing in the scientific literature in an attempt to complement the preferences and requirements of the patient in the rehabilitation program.[4,5]

Neuromuscular electrical stimulation (NMES) has become a promising new modality of exercise training in cardiovascular rehabilitation. It is well known that NMES is largely used as an adjuvant tool of rehabilitation to treat muscle dysfunction secondary to disuse in healthy people and in patients with neuromuscular disorders.[6] However, a growing number of studies with patients with HF have been published with good results. Neuromuscular electrical stimulation has some advantages over standard exercises, such as less patient motivation and the possibility that it can be performed by patients unable to undertake conventional training. Moreover, it can be performed in a rehabilitation center, a hospital, or even at home.

The effects of NMES in patients with HF have been documented in previous reviews.[7,8] Despite these previous results, to date, there are no systematic reviews that have examined the different modalities and parameters for applying the stimulation in this population. Such evidence is crucial for optimizing patient care and planning future interventions.

Since the previous reviews were published,[7,8] randomized controlled trials (RCTs) have been completed and the Cochrane Collaboration recommends that systematic reviews are updated biannually.[9] The aim of this systematic review was to analyze the published RCTs that investigated the effects of NMES in exercise capacity and quality of life of patients with HF. The secondary aim was to analyze the effects of NMES on endothelial function and depressive symptoms.

# METHODS

## Data Sources

We searched the RCTs in EMBASE, LILACS, MEDLINE, Scielo, the PEDro data base, and the Cochrane Library to May 2014 without language restrictions. Key words and their synonymous were used to sensitize the search.

For the identification of RCTs in PUBMED, a optimally sensitive strategy was developed and used.[9] To identify the RCTs in EMBASE, a search strategy using similar terms was adopted. In the search strategy, there were 4 groups of keywords: study design, participants, interventions, and outcome measures.

All eligible articles for this systematic review had their reference lists analyzed in order to detect other potentially eligible studies. For ongoing studies or when the confirmation of any data or additional information was needed, the authors were contacted by e-mail.

The search strategy was used to obtain titles and abstracts of studies that might be relevant for this review. Each abstract identified in the research was independently evaluated by 2 authors. If at least 1 of the authors considered a study to possibly be appropriate for inclusion, the full text was obtained for a complete assessment. A standardized data extraction form with inclusion and exclusion criteria was used. In the case of any disagreement, the authors discussed the reasons for their decisions and a final decision was made by consensus.

## Study Selection

This systematic review included all RCTs that reported the effects of any type of NMES in patients with HF. We considered the articles for inclusion independently of their language or sample size.

Trials enrolling patients with HF were included in this systematic review and should have randomized patients with HF to, at least, 1 group of NMES for a minimum of 2 weeks and compared that group to either conventional exercise training or a control group (sham or placebo). The studies that enrolled patients with respiratory diseases were excluded from this systematic review.

Main outcome measures of interest were peak oxygen uptake (peak $\dot{V}O_2$, mL·kg$^{-1}$·min$^{-1}$), distance walked in a 6-minute walk test (6MWT), muscle strength, and/or any measure of health-related quality of life (HRQOL).

## Data Extraction

Two authors independently extracted data from the published reports using a standard data extraction form adapted from the Cochrane Collaboration's[9] model for data extraction. Extracted data included (1) aspects of the study population (eg, average age and sex); (2) aspects of the intervention (sample size, type of NMES used, presence of supervision, frequency, and duration of each session); (3) followup; (4) loss to followup; (5) outcome measures; and (6) results. Any further information required from the original author was requested by e-mail.

The risk of bias for included studies was assessed independently by 2 authors using the Cochrane Collaboration's Risk of Bias tool.[9] The criteria assessed were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, intention-to-treat analysis, and completeness of followup. The quality of evidence was independently assessed by 2 researchers using the PEDro scale consisting of 11 items on the basis of a Delphi list.[10,11] One item on the PEDro scale (eligibility criteria) is related to external validity and is generally not used to calculate the method score, which results in a range of score from 0 to 10.[12]

### Statistical Analysis

Using a random-effects model, pooled-effect estimates were calculated and expressed as the weighted mean differences between groups. Two comparisons were made: (1) NMES versus control (nonexercise) group and (2) NMES versus exercise group. An $\alpha$ value of 0.05 was considered significant. Statistical heterogeneity of the treatment effect among studies was assessed using Cochran's Q-test and the inconsistency $I^2$ test, in which values above 50% were considered indicative of high heterogeneity.[13] Meta-analyses were performed by Review Manager version 5.0 (Cochrane Collaboration, London, UK).[14]

## RESULTS

The initial search resulted in the identification of 1680 abstracts, from which 14 studies were considered as potentially relevant and were considered for detailed analysis. Fourteen publications[15-28] met the eligibility criteria.

These 14 articles were fully analyzed and approved for data extraction by both reviewers. However, 13 articles[15-27] were included in the meta-analysis (Figure 1) and assessed using the PEDro scale by both reviewers. The results are presented in Table 1.

The sample sizes were from 10 to 46 participants and the mean age of participants ranged from 50 to 65 years. One study[20] included only men and the other studies included patients of both sexes, but there was a predominance of males. All studies analyzed in this review included outpatients with documented HF New York Heart Association classes II to IV, and all patients were on optimal medical therapy for HF before enrollment.

The protocols used in the application of NMES were reported in the studies. The duration of NMES programs ranged from 2 to 12 weeks, and the length of the sessions was from 30 to 120 minutes. The frequency of sessions ranged from 5 to 7 times per week. The intensity of NMES was adjusted for 25% to 30% of a preceding maximal voluntary contraction in 2 studies[26,27] and in the other studies was adjusted to obtain visible muscle contraction. Table 2 provides details of the characteristics of the NMES intervention programs in studies comparing NMES with aerobic exercise, and the characteristics of the NMES intervention in studies of NMES compared with controls are summarized in Table 3.

### NMES Versus Conventional Aerobic Exercise

Six studies (n = 217) assessed peak $\dot{V}O_2$ as an outcome. A significant improvement in peak $\dot{V}O_2$ of 0.44 mL·kg$^{-1}$·min$^{-1}$ (95% CI, 0.68-0.20) was found for participants in the aerobic exercise group compared

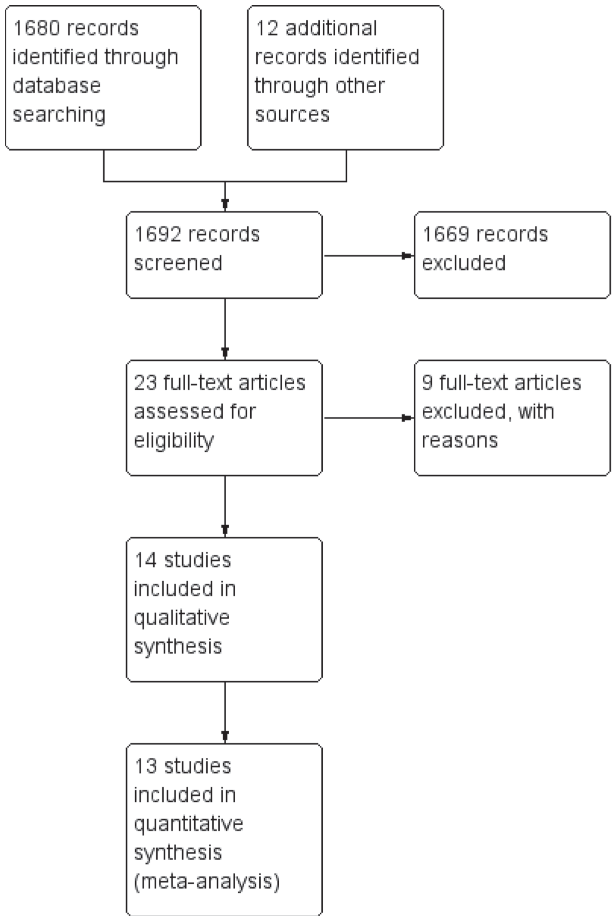


**Figure 1.** Search and selection of studies for systematic review according to PRISMA criteria.

**Table 1 • Study Quality Assessment Using the PEDro Scale[a]**

| | 1[b] | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dobšák et al[15] | | ✓ | | ✓ | | | | | | ✓ | ✓ | 4 |
| Deley et al[16] | | ✓ | | ✓ | | | | ✓ | | ✓ | ✓ | 5 |
| Dobšák et al[17] | | ✓ | | ✓ | | | | | | ✓ | ✓ | 4 |
| Deley et al[18] | | ✓ | | ✓ | | | | | | ✓ | ✓ | 4 |
| Eicher et al[19] | | ✓ | | | | | | | | | ✓ | 2 |
| Harris et al[20] | ✓ | ✓ | | ✓ | | | | ✓ | | ✓ | ✓ | 5 |
| Karavidas et al[21] | ✓ | ✓ | | ✓ | | | ✓ | ✓ | | ✓ | ✓ | 6 |
| de Araújo et al[22] | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | | ✓ | ✓ | 7 |
| Banerjee et al[23] | ✓ | ✓ | | | | | | | | ✓ | ✓ | 3 |
| Karavidas et al[24] | | ✓ | | ✓ | | | ✓ | | | ✓ | ✓ | 5 |
| Karavidas et al[25] | | ✓ | | ✓ | | | ✓ | ✓ | | ✓ | ✓ | 6 |
| Nuhr et al[26] | | ✓ | ✓ | ✓ | | | | ✓ | | ✓ | ✓ | 6 |
| Quittan et al[27] | ✓ | ✓ | | ✓ | | | ✓ | | | ✓ | ✓ | 5 |

[a]PEDro scale criteria: 1, eligibility criteria and source of participants; 2, random allocation; 3, concealed allocation; 4, baseline comparability; 5, blinded participants; 6, blinded therapists; 7, blind assessors; 8, adequate followup; 9, intention-to-treat analysis; 10, between-group comparisons; 11, point estimates and variability.
[b]Not included in calculation of the total score.

with NMES group (Figure 2A). The meta-analysis of the 5 studies (n = 168) showed a nonsignificant improvement in 6MWT distance of 0.72 m (95% CI, −23.74 to 25.18) for participants in the aerobic exercise group compared with NMES (Figure 2B). For HRQOL, we observed that the exercise intervention resulted in a nonsignificant improvement of 2.21 (95% CI, −4.58 to 8.99; n = 76) in the Minnesota Living With Heart Failure Questionnaire total score (Figure 2C).

In secondary analyzes, considering the total time of stimulation (categories of ≤30 hours or >30 hours), the results were similar for peak $\dot{V}O_2$ and 6MWT. The cut-off point of 30 hours set in this secondary analysis was based on studies that observed significant differences between sessions of 50 and 60 minutes, 3 and 5 times per week and duration of 8 and 12 weeks.[29] The total average duration of exercise in these studies ranged from 20 to 40 hours, so we considered an average time of 30 hours as the cut-point.

## NMES Versus No Exercise Controls

Three studies assessed peak $\dot{V}O_2$ as an outcome.[23,25,26] Significant improvements were found among individual trials of NMES when compared with the no exercise controls. The meta-analysis showed a significant improvement in peak $\dot{V}O_2$ of 1.85 mL·kg$^{-1}$·min$^{-1}$ (95% CI, 0.46-3.23) for participants in the NMES group compared with

**Table 2 • Characteristics of the NMES Intervention (NMES vs AE Groups) in the Studies Included in the Review**

| | Intensity | Current | Frequency | Muscles | Pulse Width | Time, min/d | Frequency, d/wk | Duration, wks |
|---|---|---|---|---|---|---|---|---|
| Dobšák et al[15] | ↑ to maximum of 60 mA | Biphasic | 10 Hz | QDC/CM | 200 ms | 2 × 60 | 7 | 12 |
| Deley et al[16] | Maximum tolerated | Biphasic | 10 Hz | QDC/CM | 0.2 ms | 60 | 5 | 5 |
| Dobšák et al[17] | ↑ to maximum of 60 mA | Biphasic | 10 Hz | QDC/CM | 200 ms | 60 | 7 | 8 |
| Deley et al[18] | Maximum tolerated | Biphasic | 10 Hz | QDC/CM | 0.2 ms | 60 | 5 | 5 |
| Eicher et al[19] | NA | NA | 10 Hz | QDC/CM | 200 ms | 60 | 7 | 3.5 |
| Harris et al[20] | Visible muscle contraction | NA | 25 Hz | QDC/GM | NA | 30 | 6 | 6 |

Abbreviations: AE, aerobic exercise training; NA, not available; NMES, neuromuscular electrical stimulation, QDC/CM, quadriceps and calf muscles; QDC/GM, quadriceps and gastrocnemius muscles.

**Table 3 • Characteristics of the NMES Intervention (NEMS vs Control Groups) in the Studies Included in the Review**

| | Intensity | Current | Frequency | Muscles | Pulse Width | Time, min/d | Frequency, d/wk | Duration, wks |
|---|---|---|---|---|---|---|---|---|
| Karavidas et al[21] | Visible muscle contraction | NA | 25 Hz | QDC/GM | NA | 30 | 5 | 6 |
| de Araújo et al[22] | NA | Biphasic | 20 Hz | RM | 200 μs | 120 | 7 | 2 |
| Banerjee et al[23] | Maximum 300 mA | NA | 4 Hz | QDC/HAM/GLUT/CM | NA | 60 | 5 | 8 |
| Karavidas et al[24] | Visible muscle contraction | NA | 25 Hz | QDC/GM | NA | 30 | 5 | 6 |
| Karavidas et al[25] | Visible muscle contraction | NA | 25 Hz | QDC/GM | NA | 30 | 5 | 6 |
| Nuhr et al[26] | 25%-30% of maximum voluntary contraction | Biphasic symmetric | 15 Hz | QDC/HM | 0.5 ms | 240 | 7 | 10 |
| Quittan et al[27] | 25%-30% of maximum voluntary contraction | Biphasic symmetric | 50 Hz | QDC/HM | 0.7 ms | 2wk: 30; then 6 wk: 60 | 5 | 8 |

Abbreviations: NA, not available; NMES, neuromuscular electrical stimulation; QDC/GM, quadriceps and gastrocnemius muscles; QDC/HAM/GLUT/CM, quadriceps, hamstrings, gluteal, and calf muscles; QDC/HM, quadriceps and hamstrings muscles; RM, rectus femoris.

the no exercise group (Figure 3A). With regard to 6MWT distance, a significant improvement of 63.54 m (95% CI: 35.81-91.27) occurred in the NMES group compared with the no exercise control group (Figure 3B)

Five studies measured HRQOL.[21,24-27] Significant improvements were found among individual trials of NMES compared with no exercise controls. Because of the different instruments used in the measurement

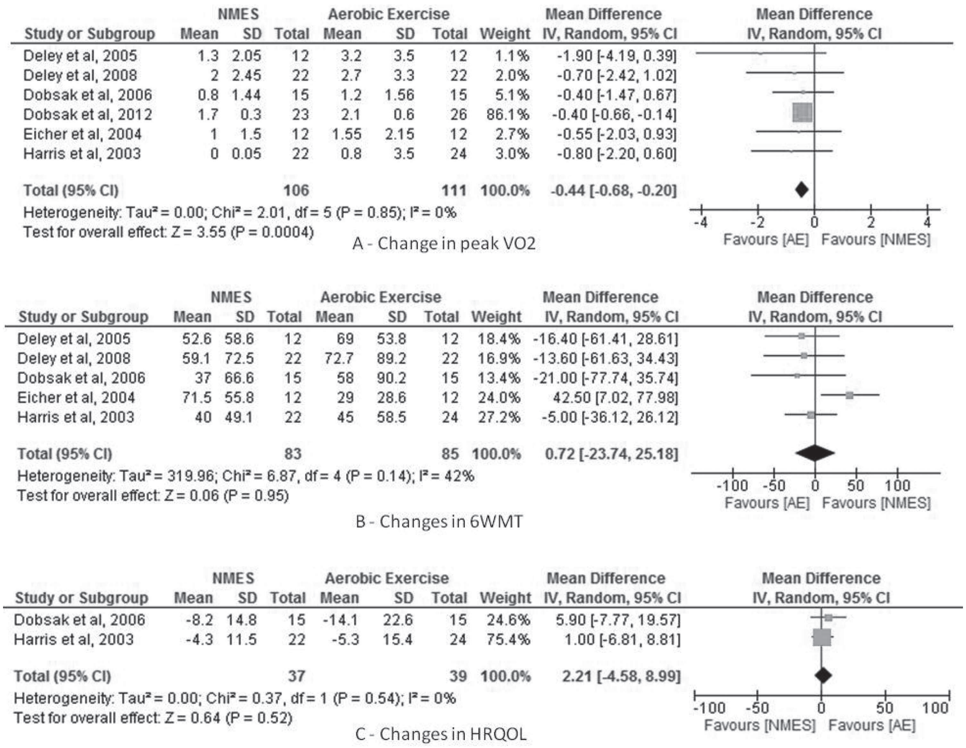


**Figure 2.** (A) WMD and 95% CI for peak $\dot{V}O_2$. (B) WMD and 95% CI for 6MWT. (C) WMD and 95% CI in HRQOL for treatment with the NMES versus AE. AE, aerobic exercise; HRQOL, health-related quality of life; 6MWT, 6-minute walk test; NMES, neuromuscular electrical stimulation; $\dot{V}O_2$, oxygen uptake; WMD, weighted mean difference.

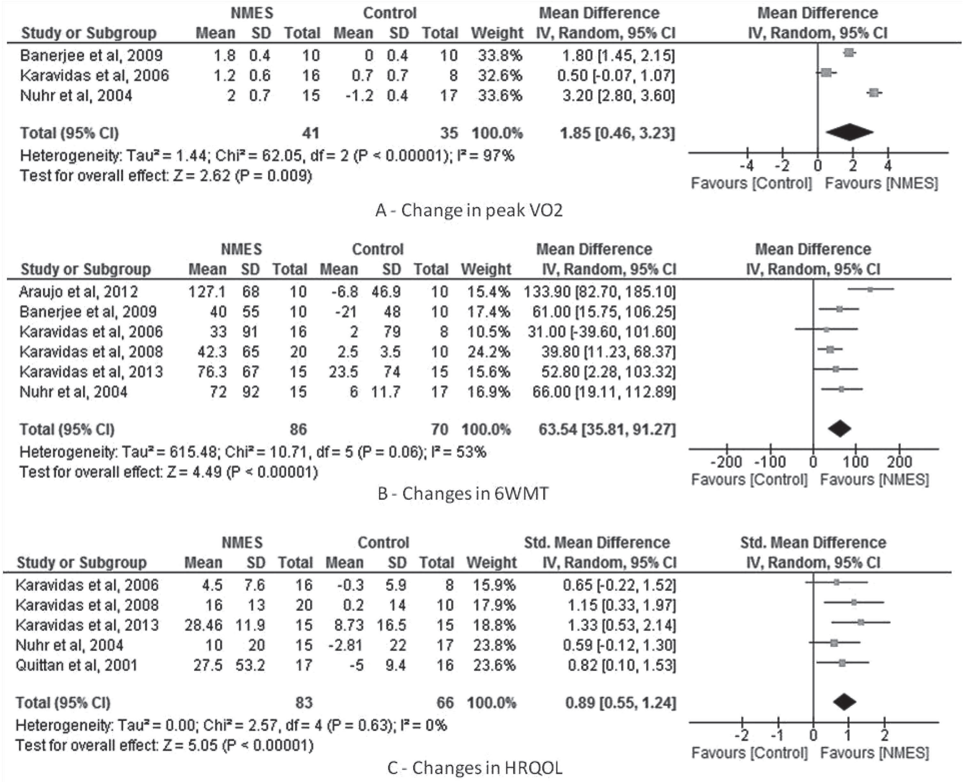


**Figure 3.** (A) WMD and 95% CI for peak $\dot{V}O_2$. (B) WMD and 95% CI for 6MWT. (C) WMD and 95% CI for HRQOL for treatment with the NMES versus no exercise (control). HRQOL, health-related quality of life; 6MWT, 6-minute walk test; NMES, neuromuscular electrical stimulation; $\dot{V}O_2$, oxygen uptake; WMD, weighted mean difference.

of quality of life, a meta-analysis with standardized mean difference was used. The meta-analysis showed that there was a significant improvement in HRQOL of 0.89 (95% CI, 0.55-1.24) for participants in the NMES group compared with the no exercise control group (Figure 3C).

In a secondary analysis considering the total time of stimulation (<30 hours or ≥30 hours), the results were different for peak $\dot{V}O_2$ and 6MWT. With regard to peak $\dot{V}O_2$, the meta-analysis showed a significant improvement in peak $\dot{V}O_2$ of 4.98 mL·kg$^{-1}$·min$^{-1}$ (95% CI, 3.75-6.21; n = 52) versus a nonsignificant improvement of

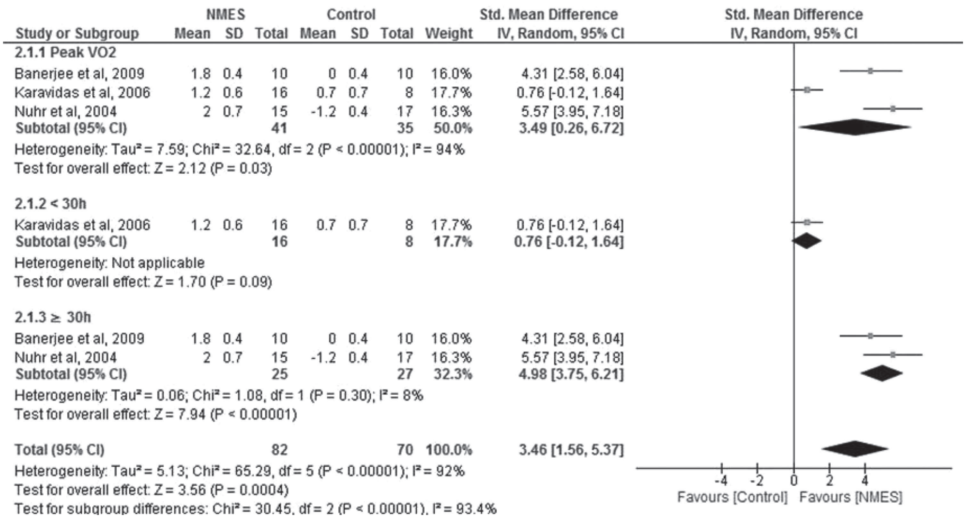


**Figure 4.** WMD and 95% CI for peak $\dot{V}O_2$ for treatment with the NMES (stimulation ≥30 total hours) compared for studies with NMES (stimulation <30 total hours) versus no exercise (control). NMES, neuromuscular electrical stimulation; $\dot{V}O_2$, oxygen uptake; WMD, weighted mean difference.

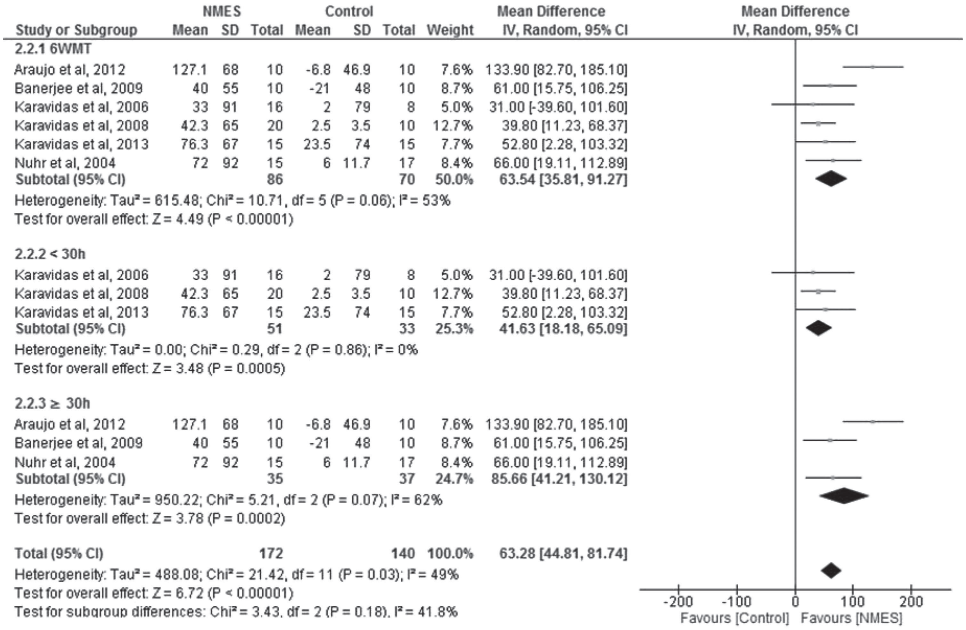


**Figure 5.** WMD and 95% CI for the 6MWT for treatment with the NMES (stimulation ≥30 total hours) compared with studies with NMES (stimulation <30 total hours) versus no exercise (control). NMES, neuromuscular electrical stimulation; 6MWT, 6-minute walk test; WMD, weighted mean difference.

0.76 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI, −0.12 to 1.64; n = 24) for studies with NMES stimulation ≥30 hours compared for studies with NMES stimulation <30 hours in relation to the nonexercising control group (Figure 4).

Considering the 6MWT, the meta-analysis showed a significant improvement of 85.66 m (95% CI, 41.21-130.12; n = 72) for studies with NMES stimulation ≥30 hours compared with a significant improvement of 41.63 m (95% CI, 18.18-65.09; n = 84) compared with studies with NMES stimulation <30 hours. Both of these analyses compared NMES to the no exercise control groups (Figure 5).

For the other outcomes (muscle strength, endothelial function expressed as flow mediated dilatation) and depressive symptoms (Beck Depression Inventory) analyzed in this systematic review, the meta-analyses (Figure 6) showed a significant improvement of 30.74 N (95% CI, 3.67-57.81), 2.67% flow-mediated dilatation (95% CI, 0.86-4.49), −3.86 (95% CI, −6.46 to −1.25) and in Beck Depression Inventory score, respectively, for participants in the NMES groups compared with the no exercise control groups.

The studies analyzed failed to give enough detail to assess the potential risk of bias. Details of the generation and concealment of the random allocation sequence were particularly poorly reported. Only 3 studies presented objective evidence of the random allocation characteristics.[15,22,26] The studies presented objective evidence of balance in baseline characteristics. Only 1 study stated that the authors blinded those involved in the assessments.[22]

## DISCUSSION

In the present systematic review, the meta-analysis showed that conventional exercise training was more effective than NMES for improving peak $\dot{V}O_2$ in patients with HF. Despite this, no differences were found when the distance walked in the 6MWT and HRQOL were analyzed. Moreover, NMES was efficient in improving peak $\dot{V}O_2$, distance walked in the 6MWT, HRQOL, muscle strength, and endothelial function in patients with HF when compared with nonexercising control.

The association of HF with muscle impairment and low exercise capacity is well known in cardiovascular rehabilitation. Classically, NMES is largely indicated to treat muscle atrophy secondary to disuse in both healthy people and in patients with neuromuscular disorders.[30] In this context, NMES has been proposed as a promising adjuvant therapy to potentiate the effects of exercise training in patients engaged in cardiovascular rehabilitation programs. This systematic review with meta-analysis is important because it analyzed the NMES as a potential coadjuvant modality in cardiovascular rehabilitation. Moreover, the eligibility of peak $\dot{V}O_2$, distance walked in the 6MWT, and HRQOL as outcomes in this systematic review are relevant because they are related to prognosis in patients with HF.[31]

Considering the improvement in peak $\dot{V}O_2$ in the NMES group compared with control, it is known that an increase in peak $\dot{V}O_2$ >10% after a cardiovascular

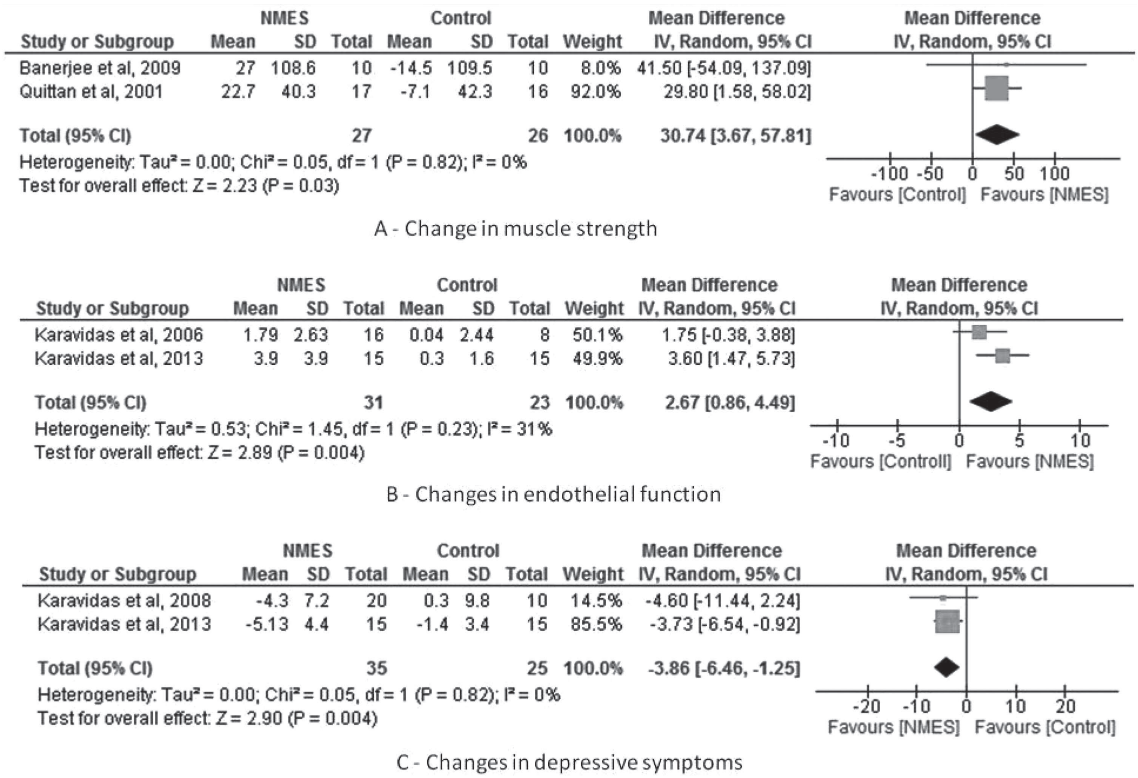


**Figure 6.** (A) WMD and 95% CI in muscle strength. (B) WMD and 95% CI in FMD. (C) WMD and 95% CI in BDI for treatment with the NMES versus no exercise (control). BDI, Beck Depression Inventory; FMD, flow-mediated dilatation; NMES, neuromuscular electrical stimulation; WMD, weighted mean difference.

rehabilitation program is satisfactory and represents a good prognosis in patients with HF.[32] Our meta-analysis showed a 10.1% improvement in peak $\dot{V}O_2$ in the NMES compared with control. Paterson et al[3] demonstrated that a minimum $\dot{V}O_2$ peak of 15 mL·kg$^{-1}$·min$^{-1}$ in women and 18 mL·kg$^{-1}$·min$^{-1}$ in men aged 85 years was necessary for full and independent living (eg, gardening activities and walking up stairs). The mean peak $\dot{V}O_2$ in studies analyzing NMES versus no exercise was 16.2 mL·kg$^{-1}$·min$^{-1}$ at baseline and 17.8 mL·kg$^{-1}$·min$^{-1}$ at the end of the intervention. Thus, the improvement of 10.1% generated by NMES can contribute to patients with HF having an increased ability to carry out their everyday activities.

Shoemaker et al estimated the minimum detectable difference and minimum clinically important difference of the 6MWT in patients with HF. The 95% CI for the minimum detectable difference for the 6MWT was 32.4 m and the minimum clinically important difference was 30.1 m (95% CI, 20.8-39.4). Our meta-analysis found an improvement of 63.54 m in 6MWT distance in the NMES group compared with the no exercise controls. Studies have reported that the 6MWT distance might best be described as a measure of functional exercise tolerance that is closely associated with the ability to perform activities of daily living.[33,34]

It has been demonstrated that muscle strength is inversely associated with cardiovascular and all-cause mortality. It is also known that patients with HF are expected to increase muscle strength after a cardiac rehabilitation program. Our search strategy did not find any RCT that aimed to compare conventional strength training with NMES. Despite this, our meta-analysis has shown that NMES seems to be relevant in patients who are not able to perform a conventional strength training program.[35]

The methodology for using NMES can vary greatly and depends on the muscle being stimulated, parameters used, and overall goal of the intervention.[36] None of the RCTs compared different methods of application. When we analyzed studies with different methodologies, our meta-analysis showed a significant improvement in peak $\dot{V}O_2$ and 6MWT for studies with $\geq$30 hours of stimulation compared with $<$30 hours.

The assessment of the HRQOL is an essential issue in HF. Quality of life is well known to be related to exercise capacity and improves significantly when the patient is engaged in a cardiac rehabilitation program.[37] Our meta-analysis showed that NMES is not superior to conventional exercise training, but it seems that NMES can contribute to improvements in

HRQOL when the patient is not able to perform conventional rehabilitation exercises.

This is potentially relevant for those patients who are not motivated to exercise or cannot perform conventional rehabilitation exercise or those with low adherence. Moreover, no specific risks were reported in the NMES trials, which is important in clinical practice. On the other hand, negative aspects are related to the cost and the dependence of the device.

On the basis of the results of our meta-analysis, we recommend that NMES should be considered for those patients with HF who cannot perform conventional rehabilitation exercises.

Caution is warranted when interpreting the results of this review and meta-analysis given the small amount of available studies and the significant heterogeneity evident in the primary analysis. In the present review, included studies did not report concealment allocation or randomization in an appropriate way, which may have affected the results.

Further research is required to investigate how to sustain the positive effects of NMES over time and to determine the characteristics of NMES (mode, stimulation intensity, frequency, duration, and dosing of stimulation) for optimal effects on HRQOL and its domains.

## CONCLUSIONS

Considering the available data, our meta-analysis showed that NMES should be considered as an alternative method in the rehabilitation of patients with HF, especially for those who cannot perform the conventional exercises. Well-controlled RCTs are needed to further the understanding of the effects of NMES in patients with HF in cardiac rehabilitation programs.

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