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Effect of chronic neuromuscular electrical stimulation on primary cardiopulmonary exercise test variables in heart failure patients: A systematic review and meta-analysis☆,☆☆

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ABSTRACT

Background: Cardiopulmonary exercise testing (CPX) is an important clinical assessment in patients with heart failure (HF). Neuromuscular electrical stimulation (NMES) has shown promise as an approach to improving cardiopulmonary performance during exercise and thus could improve key CPX measures. The primary aim of the proposed study is to perform a systematic review and meta-analysis on the effects of NMES on key CPX measures in HF patients.
Methods: Data sources: A systematic search without date or language restriction was conducted using Medline, Embase.com, Cochrane Central Register of Controlled Trials and CINAHL, Amedeo and PEDro. *Study eligibility criteria*: Randomized controlled trials, with or without crossover strategy, of NMES-based interventions and a comparison group submitted to usual medical care or exercise. *Participants and interventions*: Systolic HF patients; NMES-based interventions using skin electrodes to produce a muscle contraction. *Study appraisal and synthesis methods*: Studies were independently rated for quality (The Jadad Scale, PEDro Scale and The Quality of Research Score Sheet). Net changes were compared by weighted mean difference and 95% confidence interval. Heterogeneity among included studies was explored qualitatively and quantitatively. Begg's funnel plots and the Egger's regression assessed publication bias.
Results: Findings suggest that NMES provides similar gains in CPX performance compared to traditional exercise or usual treatment.
Conclusions: CPX performance has substantial prognostic and functional importance in the HF population. Our results suggest that NMES improves CPX performance and thus may be a valuable therapeutic intervention, positively altering the clinical trajectory of patients with HF.

1. Introduction

Prognosis in heart failure (HF) is commonly determined using cardiopulmonary exercise test (CPX) results with a greater peak oxygen consumption, oxygen consumption at the anaerobic threshold, peak workload, and peak heart rate (VO_{2peak}, VO_{2AT}, PW, HR_{peak}, respectively) being associated with greater survival. Among other things, the combined HF disease process and a sedentary lifestyle lead to skeletal muscle weakness/atrophy and poorer CPX performance. Thus, skeletal muscle dysfunction appears to have the capacity to worsen key CPX measures, with prognostic importance, in patients with HF [1–9].

In fact, the Muscle Hypothesis of Chronic Heart Failure proposed by Coats et al. highlights the viscous cycle of HF in which skeletal muscle weakness and myopathy contribute from a proximal position to the dyspnea and fatigue as well as ventilatory, neurohumoral, and cardiovascular abnormalities associated with this condition [10,11]. Thus, improving skeletal muscle strength and endurance certainly improves functional performance and may have the potential to improve prognosis in HF. However, for a variety of reasons, not all patients with HF are able to participate in traditional exercise approaches needed to sufficiently increase skeletal muscle strength and endurance.

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Neuromuscular electrical stimulation (NMES) has been consistently shown to elicit positive skeletal muscle adaptations in patients unable to participate in traditional aerobic and/or resistance training programs at an appropriate stimulus [12]. Generally, NMES consists of repeated, rhythmic stimulation of skeletal muscle in a static state, using skin electrodes, at an intensity that evokes visible muscle contractions. A growing body of literature has emerged examining the effects of NMES in patients with HF, demonstrating beneficial effects in several different domains, including improvements in muscle strength, exercise capacity, endothelial and autonomic function [13–23]. Moreover, several systematic reviews have suggested that NMES may be an important adjunct in the rehabilitation of patients with HF [24,25]. However, to our knowledge, no previous systematic review has examined the effects of NMES on both maximal and sub-maximal CPX prognostic markers, which can impact on survival, functional status and quality of life [9–11]. Specifically, this systemic review reports on the effects of NMES compared to the standard treatment (moderate aerobic exercise or no-exercise control) on key CPX variables (VO_{2peak}, VO_{2AT}, PW, HR_{peak}) in HF patients.

2. Methods

This meta-analysis was conducted in accordance with the recommendations and criteria as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [26] and registered at PROSPERO (CRD42014009329).

Criteria for considering studies for this review:

2.1. Types of studies

Randomized controlled trials, with or without crossover strategy, of NMES-based interventions, according to Cochrane Review concept [12], with a comparison group submitted to usual medical care or exercise training.

2.2. Types of participants

The study population comprised adults aged between 50 and 65. Only those studies with a diagnosis of systolic HF [based on clinical findings and objective indices such as assessment of ejection fraction, LVEF < 45%, and NYHA (I–IV)] [27].

2.3. Types of interventions

An ambulatory or home-based NMES interventions, with application of any therapeutic electrical stimulation using surface electrodes to produce a muscle contraction in both quadriceps muscles, were included. The comparison group was an ambulatory or home-based moderate aerobic exercise group or a no-exercise control group as defined by the study. The exercise group interventions included an aerobic exercise program with the following parameters: 1) At least 30 min, 3 times per week of moderate aerobic exercise training (60–80% of HR_{peak}, HR at VO_{2AT} or RPE 13–15). Patients with pacemaker and musculoskeletal disorders that could limit exercise tolerance were excluded. Studies that included resistance exercise alone or combined with aerobic exercise were also excluded. Lastly, studies providing NMES and exercise simultaneously were also excluded.

2.4. Types of outcome measures

Outcome measures assessed included one or more of the following: 1) VO_{2peak} (mL kg^{-1} min^{-1}), 2) VO_{2AT} (mL.kg^{-1}.min^{-1}), 3) Peak Heart Rate (bpm), and/or 4) Peak Workload (watts).

2.5. Search methods for identification of studies

Potential studies were identified by a systematic review librarian. A systematic search was conducted of Medline (Ovid) (1950 — March 2014), Embase.com (1974 — March 2014), Cochrane Central Register of Controlled Trials and CINAHL (1981 — March 2014) Amedeo (1997 — March 2014) and PEDro (1929 — March 2014), all of these without date restriction. The search strategy included a mix of keywords selected according to the Medical Subject Headings (Mesh) of the United States National Library of Medicine (NLM) and free text terms for the key concepts (Intervention + Population) described above with filters to limit to Clinical Trial's (Phases I–IV), RCT's and RS's search. No language or other limitations were imposed. Reference lists of papers found were scrutinized for new references. All identified papers and its methodological quality were assessed independently by two reviewers (LMTN and LC). Searches of published papers were conducted up until March 2014 and 2013.

2.6. Search terms strategy for interventions

"Electric Stimulation Therapy"[Mesh] OR "Neuromuscular Electrical Stimulation" OR "Neuromuscular Stimulation" OR "Functional Electrical" OR "Functional Electrical Stimulation" OR "Neuromuscular Electrical Stimulation" OR "Electrical Muscle Stimulation" OR "Electrical stimulation Muscle".

2.7. Search terms strategy for population

"*Heart Failure*"[Mesh] OR "Left-Sided Heart Failure" OR "Left Sided Heart Failure" OR "Right-Sided Heart Failure" OR "Right Sided Heart Failure" OR "Congestive Heart Failure" OR "Heart Failure, Congestive" OR "Heart Decompensation" OR *Cardiomegaly* [Mesh] OR *Cardiomyopathies* [Mesh] OR "Heart Enlargement" OR "Enlarged Heart" OR "Cardiac Hypertrophy" OR "Heart Hypertrophy" OR Cardiomyopathy OR "Myocardial Diseases" OR "Myocardial Disease" OR Myocardiopathies OR Myocardiopathy OR "Secondary Cardiomyopathies" OR "Secondary Cardiomyopathy" OR "Secondary Myocardial Diseases" OR "Secondary Myocardial Disease" OR "Primary Cardiomyopathies" OR "Primary Cardiomyopathy" OR "Primary Myocardial Diseases" OR "Primary Myocardial Disease".

3. Data collection and analyses

3.1. Study selection

The references identified by the search strategy were screened by title and abstract, and clearly, irrelevant studies were discarded. For selection, abstracts had to clearly identify the study design, an appropriate population, and relevant components of the intervention as described above. The main outcomes extracted were VO_{2peak} (mL kg^{-1} min^{-1}), VO_{2AT} (mL kg^{-1} min^{-1}), Peak Workload (watts), and Peak Heart Rate (bpm). The full-text reports of all potentially relevant trials were obtained and assessed independently by two review authors (LMTN and LC) for eligibility based on the defined inclusion criteria. Any disagreements were resolved by discussion (Fig. 1).

3.2. Data extraction

The data from the papers included in the review were extracted and input directly into a single data collection form consisting of the primary source of information (journal article) and included relevant data regarding inclusion criteria (study design; participants; interventions including type of NMES/exercise, frequency, duration, intensity, and modality; comparisons; and outcomes), risk of bias (randomization, blinding, attrition, and control), and results. The data extraction process was conducted independently by two persons from the same discipline

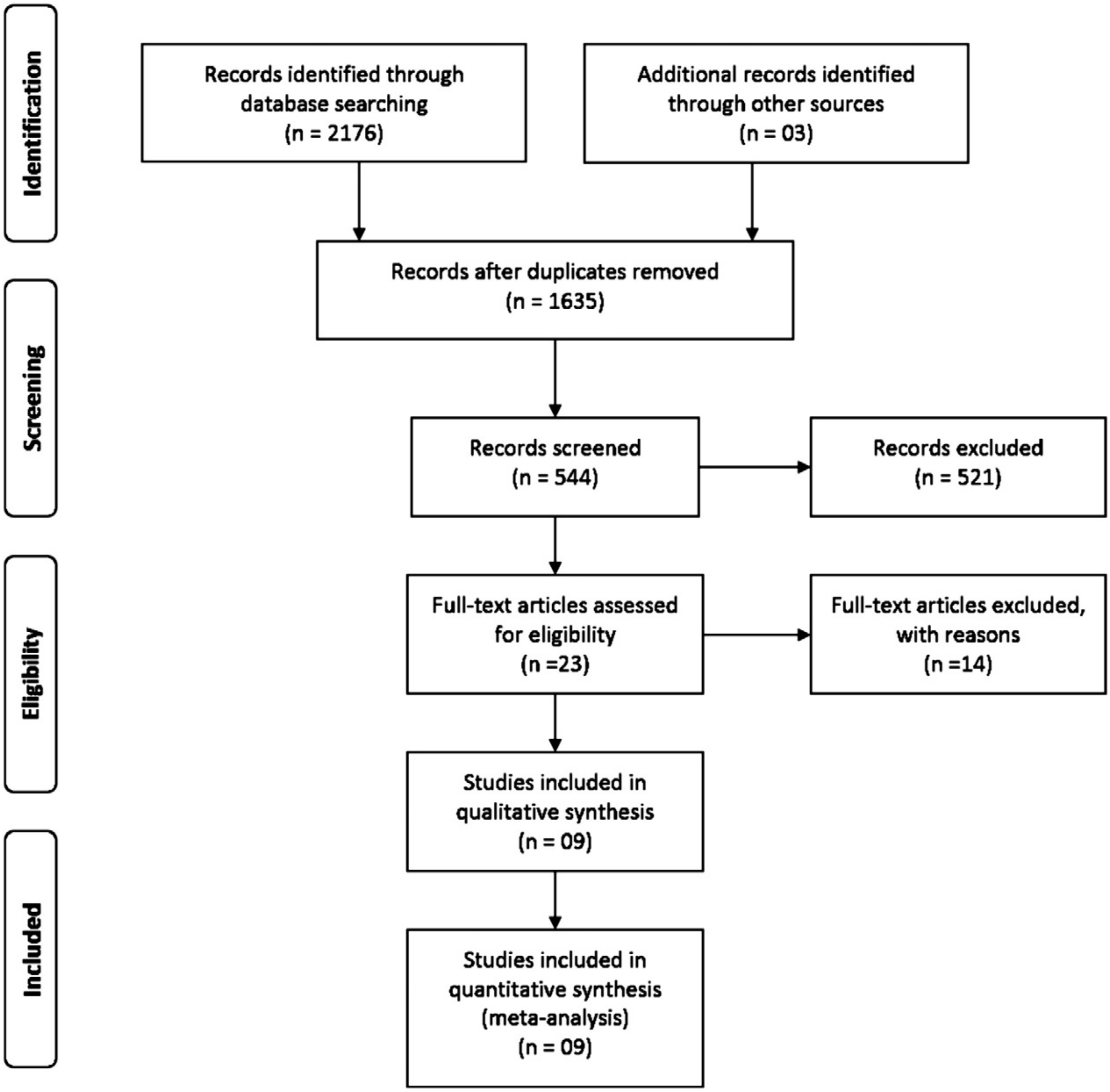

Fig. 1. Flowchart summary of study selection process.

area (LMTN and MLS). Inter-reviewer disagreements were resolved by consensus. The agreement ratio prior to amending any discrepancies was assessed using the kappa statistic and was found to be greater than 0.90. Study authors were contacted to seek clarification on the issues of reporting or to obtain further outcome details.

3.3. Quality assessment

The risk of bias and study quality of eligible trials was assessed independently by 2 reviewers (LMTN and LC). Study quality was performed using three different scales [28]: The Jadad Scale, PEDro Scale [6,7] and The Quality of Research Score Sheet (QRSS) [8]. The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding, and the flow of patients considering 7 items. Items were marked as either present (yes/1) or absent (no/0). The last 2 items are assigned a negative score, achieving the range of possible scores from 0 (bad) to 5 (good) [29]. The PEDro Scale is a checklist used to measure the quality of reports based on the Delphi list, developed by Verhagen et al. [30]. The PEDro Scale included eligibility criteria (not used to calculate score), random allocation, concealment of allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, adequacy of follow-up, intention-to-treat analysis, between-group statistical analysis, and reports of both point estimates and measures of variability. Items were marked as either present (yes/1) or absent (no/0), and a score out of 10 was obtained [31]. The QRSS was first used by Smith et al. [32] and included 16 items: concealed allocation, random sequence generation, patients were matched according to relevant patient characteristics, blinding of observer(s), blinding of those performing statistical, blinding of patients, drop-out number description, intercurrent drop-out description, intention-to-treat analysis, intra/inter-observer reliability, the relevant measurement instruments were compared statistically with other instruments measuring, other co-interventions leading to systematic differences between groups were avoided, adjunctive (medical) interventions were reported, comparability of patients, predetermined rehabilitation time and/or number and/or dosage of exercises, actual rehabilitation time and/or number and/or dosage of exercises. Items were marked as either present (yes/1) or absent (no/0), and a score out of 16

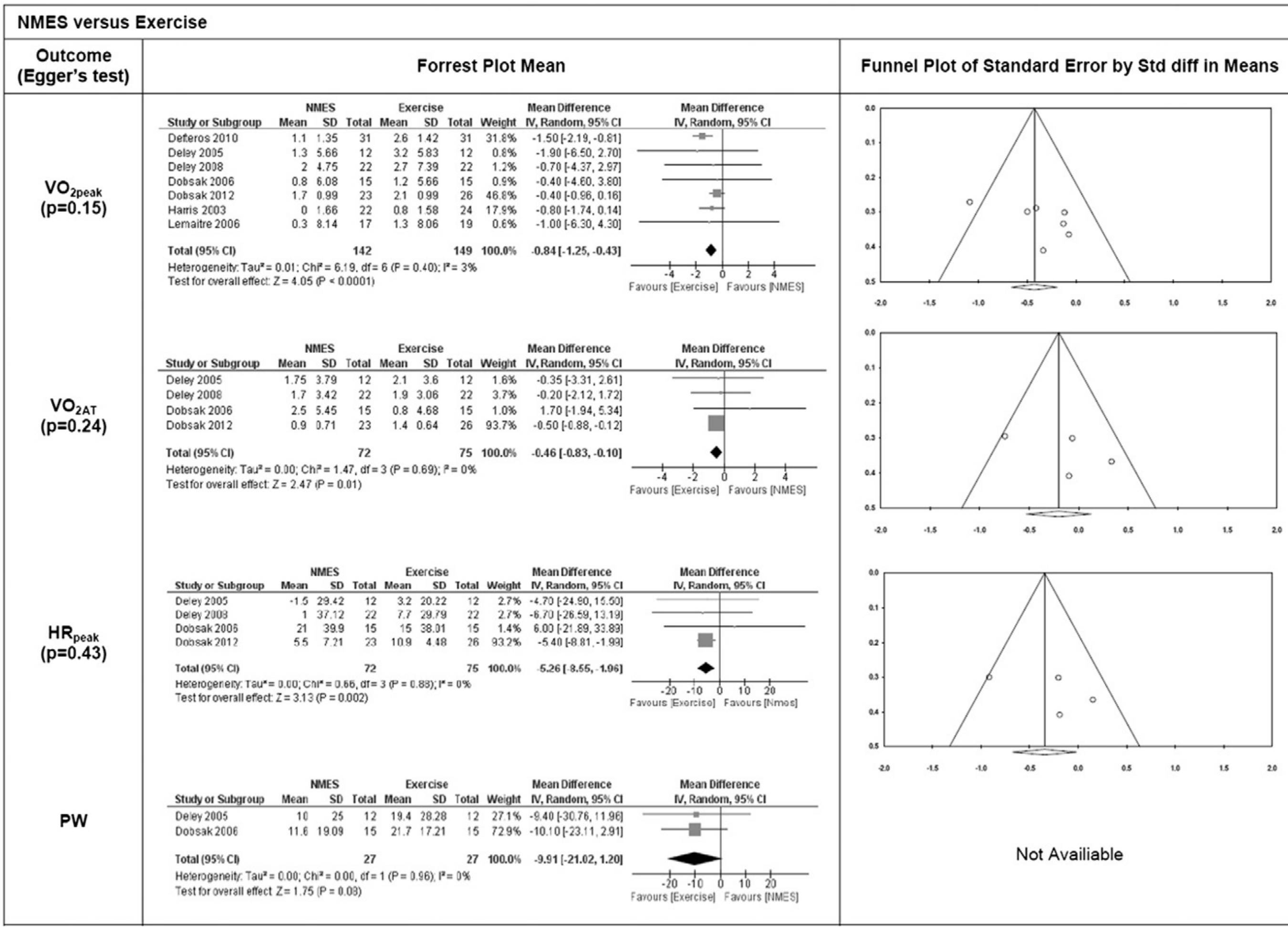

Fig. 2. Forest plot mean, funnel plot of standard error by standard differences in means for the comparison of neuromuscular electrical stimulation (NMES) versus exercise for peak oxygen consumption (VO_{2peak}), oxygen consumption at anaerobic threshold (VO_{2AT}), peak hear rate (HR_{peak}) and power workload (PW).

was obtained. Also, to assess for evidence of publication bias, Begg's funnel plots and Egger's regression test were examined [29] and were considered adequate when $p > 0.05$ (Figs. 2 and 3).

3.4. Data analysis

Data were processed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [30]. The outcomes are presented as continuous data using the data extracted from eligible studies and included the mean value of the outcome measurements in each intervention and control group (M_E and M_C), the standard deviation of the outcome measurements in each intervention and control group (SD_E and SD_C) and the number of participants on whom the outcome was measured in each intervention and control group (N_E and N_C). Net changes were compared (that is NMES group minus exercise/control group to give differences) by weighted mean difference (WMD) and 95% confidence interval (CI). The standard deviation was calculated for each study based on the change score method. Heterogeneity among included studies was explored qualitatively (by comparing the characteristics of included studies) and quantitatively (using the chi-square test of heterogeneity and the I^2 statistic). The funnel plot of standard difference of means was used as the qualitative method to examine heterogeneity when more than two studies were analyzed. Where appropriate, the results from included studies were combined for each outcome to give an overall estimate of treatment effect. For all variables NMES intervention was compared exclusively to moderate aerobic exercise intervention or usual treatment (moderate aerobic and no-exercise control). For VO_{2peak}, NMES intervention was compared exclusively to no-exercise control. A fixed-effect model meta-analysis was used based on qualitative evaluation of the heterogeneity and the low risk of bias. All analyses were conducted using Review Manager Version 5.2 and comprehensive meta-analysis (Biostat Inc., Englewood, USA, 2013).

4. Results

The initial search led to the identification of 2176 studies for NMES and HF patients from which 23 were considered as potentially relevant and were retrieved for detailed analysis. Only 9 [14–18,20–23] were included for all outcomes and comparison. The comparison of NMES versus moderate aerobic exercise comparison included 7 [14–18,20,22] studies for VO_{2peak}, 4 studies [15–18] for VO_{2AT}, 2 studies [16,17] for PW and 4 studies [15–18] for HR_{peak}. The comparison of NMES versus no-exercise control comparison included 2 studies [21,23] for VO_{2peak} and NMES versus usual treatment included 9 studies [14–18,20–23] for VO_{2peak}, 5 studies [15–18,23] for VO_{2AT}, 3 studies [16,17,23] for PW and 5 studies [15–18,23] for HR_{peak}. Fig. 1 shows the flow diagram of studies in this review. The level of concordance between the two reviewers examined by Kappa statistic was 0.95 [IC 95% (0.88; 1.0)].

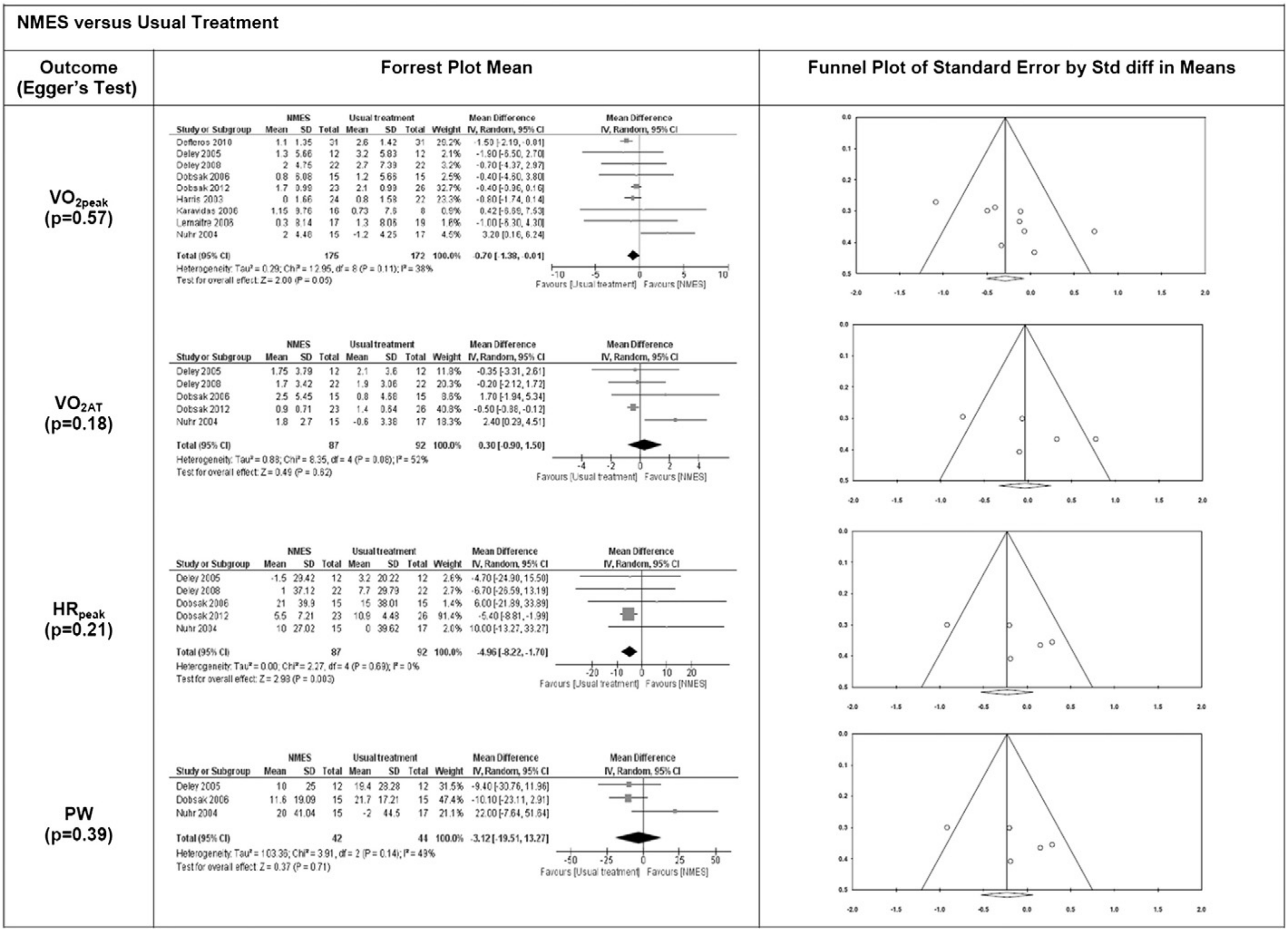

Fig. 3. Forest plot mean, funnel plot of standard error by standard differences in means for the comparison of neuromuscular electrical stimulation (NMES) versus usual treatment (exercise + control) for peak oxygen consumption (VO_{2peak}), oxygen consumption at anaerobic threshold (VO_{2AT}), peak hear rate (HR_{peak}) and power workload (PW).

Table 1
Characteristics of included studies;— clinical, demographics and intervention description.

Study	Quality assessment	Outcome	HF population	N	Age (years)	Intervention description			
						Type (frequency/pulse/ time on–off and modality/ intensity)	Frequency (days/week)	Duration (min/day)	Protocol (weeks)
Harris et al., 2003 [20]	J-2/P-5/Q-9	VO_{2peak}	NYHA I–III LVEF <40%	NMES (24)	63 ± 10	25 Hz/ND/5–5 s	5	30	6
				Exercise (22)	62 ± 10.8	Bicycle/70% HRmax	5	30	6
Nuhr et al., 2004 [23]	J-3/P-6/Q-10	All	NYHA II–IV LVEF <35%	NMES (15)	53 ± 7	15 Hz/500 μs/2–4 s	5	60	5
				Control (17)	53 ± 13	Control	ND	ND	ND
Deley et al., 2005 [16]	J-2/P-4/Q-11	All	NYHA II–III LVEF <40%	NMES (12)	56 ± 8	10 Hz/200 μs/12–8 s	5	60	5
				Exercise (12)	57 ± 6	Bicycle, treadmill or cycling/60–70% HRmax	5	60	5
Dobsak et al., 2006 [17]	J-1/P-4/Q-5	All	NYHA II–III LVEF <40%	NMES (15)	ND	10 Hz/200 μs/20–20 s	7	60	8
				Exercise (15)	ND	Bicycle/VO_{2AT}	3	60	8
Karavidas et al., 2006 [21]	J-2/P-6/Q-10	VO_{2peak}	NYHA II–III LVEF <40%	NMES (16)	57 ± 15.3	25 Hz/ND/5–5 s	5	30	6
				Control (8)	64 ± 8.1	Control	ND	ND	ND
Lemaitre et al., 2006 [22]	J-2/P-5/Q-7	Only VO_{2peak}	NYHA II–III LVEF <35%	NMES (17)	64 ± 4.7	25 Hz/ND/5–5 s	5	30	5
				Exercise (19)	61 ± 2.6	Bicycle/70% HRmax	5	30	6
Deley et al., 2008 [15]	J-2/P-5/Q-8	Not PW	NYHA II–IV LVEF <40%	NMES (22)	55 ± 10	10 Hz/200 μs/12–8 s	5	60	5
				Exercise (22)	56 ± 7	Bicycle or treadmill/ Borg 13–15	5	60	5
Defteros et al., 2010 [14]	J-2/P-4/Q-7	VO_{2peak}	NYHA II–III LVEF <35%	NMES (31)	61 ± 2.1	25 Hz/ND/5–5 s	5	30	5
				Exercise (31)	61 ± 2.1	Bicycle/70% HRmax	5	30	6
Dobsak et al., 2012 [18]	J-3/P-4/Q-11	Not PW	NYHA II–III LVEF <40%	NMES (23)	59 ± 1.4	10 Hz/200 μs/20–20 s	7	120	12
				Exercise (26)	59 ± 2.2	Bicycle/VO_{2AT}	3	60	12

Legend: P = PEDro Scale; J = Jadad scoring; Q = Quality of Research Score Sheet; VO_{2peak} = peak consumption of oxygen; VO_{2AT} = consumption of oxygen at anaerobic threshold; PW = peak workload; HR_{peak} = peak hear rate; NYHA = New York Heart Association; LVEF = Left-ventricular ejection fraction; NMES = neuromuscular electrical stimulation; and ND = not described.

Table 2
Characteristics of excluded studies.

Study	Reasons for exclusion
Malek and Mark (1989)	No application of any NMES
Crevenna et al. (2004)	Without control group
Dobsak et al. (2006b)	Without control group
Fritzsche et al. (2010)	Without control group
Maillefert et al. (1998)	Without control group
Quittan et al. (1999)	Without control group
Wiesinger et al. (2001)	Without control group
Karavidas et al. (2010)	Review study
Vaquero et al. (1998)	Non-HF population
Araújo et al. (2012)	None of selected outcome
Karavidas et al. (2008)	None of selected outcome
Quittan et al. (2001)	None of selected outcome
Bittencourt et al. (2001)	None of selected outcome
Eicher et al. (2004)	No measure of variability

Legend: NMES = neuromuscular electrical stimulations; HF = heart failure.

For the included studies (Table 1) the date of publications ranged from 2003 to 2012. The 9 studies included 316 patients, 259 (81.96%) male, with mean age ranged from 53 to 65 years. The NMES-intervention group number of hours of treatment ranged from 12.5 to 280 (5–7 times per week, for 6–12 weeks), with the stimulation frequency from 10 to 25 Hz, the pulse from 200 to 500 μs, the time on from 2 to 20 s, the time off from 4 to 20 s, the number of contraction from 90 to 2400 and the total energy delivered from 900 to 4800 J. Five of the moderate aerobic exercise-intervention studies used bicycle training, one study used bicycle or treadmill training, and one study used bicycle, treadmill or cycling training. The moderate aerobic exercise-intervention number of hours of treatment ranged from 15 to 36 (3–5 times per week, for 6 to 12 weeks).

The characteristics of studies excluded are presented in Table 2. Four studies had data in different units. The VO_{2AT} expressed in metabolic equivalents (METs) was converted to mL kg^{-1} min^{-1} (1 MET = 3.5 mL kg^{-1} min^{-1}) in one study [16]. The standard deviations were not given in two studies [16,19], but in one study the standard deviations were extracted by visual analyses while the second study was excluded because of the absence of information on variability. In another study [18] the data of peak workload were presented in W/kg and in another study [13] the data of VO_{2peak} were presented in L/min. Requests for the above data were made via e-mail to the authors of the above studies, but none of the authors responded which led the exclusion of the both studies. All of the included studies were classified as RCTs [14–18,20–23].

Heterogeneity of the included studies was low with non-significant chi-squared test ($p < 0.05$) and the I^2 value ≤52%. Comparing the use of NMES versus moderate aerobic exercise the results were favorable to exercise for VO_{2peak}, VO_{2AT} and HR_{peak}, but PW was similar for NMES and Exercise (Fig. 2). Comparing the use of NMES versus usual treatment, the results were favorable to usual treatment for only HR_{peak} (Fig. 3). Comparing the results of use of NMES versus no-exercise control for VO_{2peak}, the results were not favorable to any of interventions (Fig. 4).

5. Discussion

To our knowledge, this is the first systematic review with meta-analysis which has assessed key CPX variables, with both prognostic and functional significance. We found that for HF patients NMES apparently provides similar improvement in PW compared to moderate aerobic exercise or usual treatment, and produces beneficial effects on VO_{2peak}, VO_{2AT} and HR_{peak} but not greater than moderate aerobic exercise.

Two previous systematic reviews in HF patients examined the effect of functional electrical stimulation (FES) compared to exercise training or no-exercise control on the magnitude of change in VO_{2peak} in mL kg^{-1} min^{-1} [24,25]. Sbruzzi et al. [24] compared the effects of FES versus conventional aerobic exercise training for at least 5 weeks in NYHA I–IV HF patients and observed that FES produced a beneficial effect, but not greater than exercise (−0.74 mL kg^{-1} min^{-1} [95% C.I. −1.38 to −0.10 $p < 0.02$]). Similarly, Smart et al. [25] conducted a systematic review with meta-analysis in NYHA III–IV HF patients examined the effects of FES versus conventional aerobic cycle exercise training for at least 2 weeks on VO_{2peak} and also observed that FES produced beneficial effects, but not greater than exercise (−0.32 mL kg^{-1} min^{-1} [95% C.I. −0.63 to −0.02, $p = 0.04$]). The results of the present study are in agreement, but are slightly lower than our findings (−0.84 mL kg^{-1} min^{-1} [95% C.I. −1.25 to −0.43 $p < 0.0001$]).

Our findings for VO_{2AT} suggest that the NMES can produce effects equal to usual treatment [0.3 mL kg^{-1} min^{-1} (95% C.I. −0.90 to 1.5, $p = 0.62$)], but not greater than moderate aerobic exercise (−0.46 mL kg^{-1} min^{-1} [95% C.I. −0.83 to 0.10, $p = 0.01$]). NMES also appears to produce beneficial effects in HR_{peak}, but also not greater than with exercise [−5.26 bpm (95% C.I. −8.55 to −1.96, $p = 0.002$)] or usual treatment [−4.96 bpm (95% C.I. −8.22 to −1.7, $p = 0.003$)]. The favorable changes in VO_{2peak}, VO_{2AT} and HR_{peak} from both NMES and moderate aerobic exercise were expected since the improvement in these variables is secondary to peripheral adaptations. Over half of studies examining the effect of NMES and moderate aerobic exercise on VO_{2peak} were observed to have a clinical significant improvement (>1 L/kg min) [31]. Despite the fact that there does not appear to be a clinical significant value for increase in HR_{peak} and VO_{2AT} any increase in both is important for exercise capacity in patients with HF since lower values are related to poor outcomes [32]. The maintenance of the results for HR_{peak} even with usual treatment was unexpected and may be related to the small sample size of the no-exercise study [21,23].

Our findings suggest that the NMES can produce effects equal to moderate aerobic exercise [−9.91 W (95% C.I. −21.02 to 1.2, $p = 0.08$)] or usual treatment [−3.12 W (95% C.I. −19.51 to 13.27, $p = 0.71$)]. Greater levels of PW have been associated with improved prognosis in patients with HF [2,4,9], thus making it a clinically relevant measurement. The production of repeated skeletal muscle contractions at a dose sufficient to evoke visible muscle contractions induces muscle hypertrophy [33]. Considering that the improvement in PW may be the primary mechanism driving the improvement in the other CPX variables, the benefits on muscle strength that NMES produces appear to positively impact global aerobic capacity. Thus, the findings of our

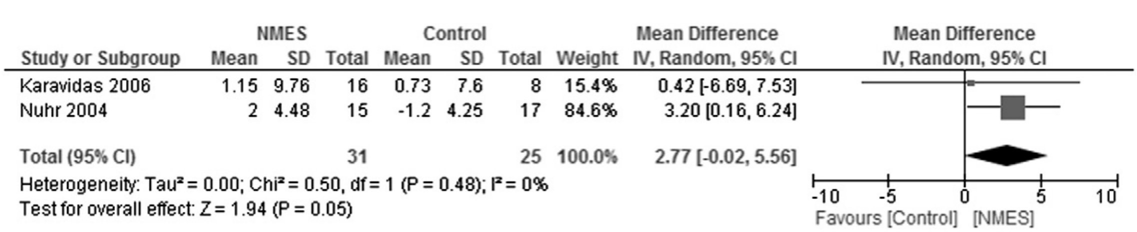

Fig. 4. Forest plot mean of standard error by standard differences in means for the comparison of neuromuscular electrical stimulation (NMES) versus no-exercise control for peak oxygen consumption (VO_{2peak}).

systematic review with meta-analysis are important since improved prognosis in all patients with HF, specially for who are unable to exercise, may benefit from NMES.

In fact, although the results of our study found traditional exercise led to a greater improvement in VO_{2peak}, VO_{2AT}, and HR_{peak}, NMES was still found to improve all of the above CPX variables, but not to the extent produced by exercise. Furthermore, our finding of similar effects of both NMES and exercise on PW is an important finding that has not been previously reported and thus provides a potentially greater rationale for either intervention to improve prognosis in HF.

6. Study limitations

The selection data of population was embracing including all severity class (NYHA I—IV) in consequence of the lack of studies that intent to compare individuals with different severities and the selection data of intervention was in accordance with the current guidelines for aerobic exercise prescription for HF patients [10]. Even the analysis presented a low heterogeneity, clinically the NMES protocols demonstrate a high variance of parameters inducing different muscle fiber type stimulation. Because of the lack of studies evaluating these prognostic variables comparing NMES with no-exercise control group, we also chose a combined analysis of both exercise and control which was defined as "usual treatment". Despite the fact that this methodology was previously used in a published meta-analysis [12], these results should be cautiously interpreted because of the heterogeneity of the interventions which can increase the occurrence of null results. The studies included in this meta-analysis were of a moderate to high quality, with principal weaknesses of small sample size, concealment of allocation and adequacy of follow-up.

The findings of this systematic review with meta-analysis suggest that NMES may be an important vehicle for all HF patients specially for who are unable to perform aerobic or strength training to improve skeletal muscle strength and endurance in order to avoid some of the adverse manifestations of HF as well as improve exercise capacity, prognosis and survival [10,11,34–37]. Systematic reviews and guidelines [27,38] strongly recommend traditional exercise-based interventions for patients with HF and also identify the importance of the improvement and long-term maintenance of functional capacity. Also, considering the fact that not all patients adhere to exercise or are able to perform aerobic exercise at a sufficient dose to elicit training adaptations, the addition of new technologies such as NMES to produce positive effects on exercise capacity and CPX results is highly important. We also believe that further details are necessary to clarify if the synergistic use of NMES and traditional exercise-based interventions is able to produce better clinical outcomes in comparison to either [39].

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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References

[1] Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, et al. The prognostic value of the heart rate response during exercise and recovery in patients with heart failure: influence of beta-blockade. Int J Cardiol 2010;138(2):166–73.

[2] Cahalin LP, Chase P, Arena R, Myers J, Bensimhon D, Peberdy MA, et al. A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. Heart Fail Rev 2013;18(1):79–94.

[3] Huelsmann M, Stefenelli T, Berger R, Frey B, Pacher R. Prognostic impact of workload in patients with congestive heart failure. Am Heart J 2002;143(2):308–12.

[4] Lang CC, Agostoni P, Mancini DM. Prognostic significance and measurement of exercise-derived hemodynamic variables in patients with heart failure. J Card Fail 2007; 13(8):672–9.

[5] Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996;93(8):1520–6.

[6] Leeper NJ, Dewey FE, Ashley EA, Sandri M, Tan SY, Hadley D, et al. Prognostic value of heart rate increase at onset of exercise testing. Circulation 2007;115(4):468–74.

[7] Manetos C, Dimopoulos S, Tzanis G, Vakrou S, Tasoulis A, Kapelios G, et al. Skeletal muscle microcirculatory abnormalities are associated with exercise intolerance, ventilatory inefficiency, and impaired autonomic control in heart failure. J Heart Lung Transplant 2011;30(12):1403–8.

[8] Myers J, Gullestad L, Vagelos R, Do D, Bellin D, Ross H, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. Ann Intern Med 1998;129(4):286–93.

[9] Pardaens S, Calders P, Derom E, De Sutter J. Exercise intolerance in heart failure: update on exercise parameters for diagnosis, prognosis and therapeutic interventions. Acta Cardiol 2013;68(5):495–504.

[10] Coats AJ. The "muscle hypothesis" of chronic heart failure. J Mol Cell Cardiol 1996; 28(11):2255–62.

[11] Coats AJ, Clark AL, Piepoli M, Volterrani M, Poole-Wilson PA. Symptoms and quality of life in heart failure: the muscle hypothesis. Br Heart J 1994;72(2 Suppl.):S36–9.

[12] Maddocks M, Gao W, Higginson IJ, Wilcock A. Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. Cochrane Database Syst Rev 2013;1.

[13] Banerjee P, Caulfield B, Crowe L, Clark AL, et al. Prolonged electrical muscle stimulation exercise improves strength, peak VO_2, and exercise capacity in patients with stable chronic heart failure. J Card Fail 2009;15(4):319–26.

[14] Deftereos S, Giannopoulos G, Raisakis K, Kossyvakis C, Kaoukis A, Driva M, et al. Comparison of muscle functional electrical stimulation to conventional bicycle exercise on endothelium and functional status indices in patients with heart failure. Am J Cardiol 2010;106(11):1621–5.

[15] Deley G, Kervio G, Verges B, Hannequin A, Petitdant MF, Grassi B, et al. Neuromuscular adaptations to low-frequency stimulation training in a patient with chronic heart failure. Am J Phys Med Rehabil 2008;87(6):502–9.

[16] Deley G, Kervio G, Verges B, Hannequin A, Petitdant MF, Salmi-Belmihoub S, et al. Comparison of low-frequency electrical myostimulation and conventional aerobic exercise training in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil 2005;12(3):226–33.

[17] Dobsak P, Nováková M, Fiser B, Siegelová J, Balcárková P, Spinarová L, et al. Electrical stimulation of skeletal muscles. An alternative to aerobic exercise training in patients with chronic heart failure? Int Heart J 2006;47(3):441–53.

[18] Dobsak P, Tomandl J, Spinarova L, Vitovec J, Dusek L, Novakova M, et al. Effects of neuromuscular electrical stimulation and aerobic exercise training on arterial stiffness and autonomic functions in patients with chronic heart failure. Artif Organs 2012;36(10):920–30.

[19] Eicher JC, Dobšák P, Berteau O, Walker P, Vergès B, Maillefert JF, et al. Rehabilitation in chronic congestive heart failure: comparison of bycilebicycle training and muscle electrical stimulation. Scr Med (BRNO) 2004;77(5–6):261–70.

[20] Harris S, LeMaitre JP, Mackenzie G, Fox KAA, Denvir MA. A randomised study of home-based electrical stimulation of the legs and conventional bicycle exercise training for patients with chronic heart failure. Eur Heart J 2003;24(9):871–8.

[21] Karavidas AI, Raisakis KG, Parissis JT, Tsekoura DK, Adamopoulos S, Korres DA, et al. Functional electrical stimulation improves endothelial function and reduces peripheral immune responses in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil 2006;13(4):592–7.

[22] LeMaitre JP, Harris S, Hannan J, Fox KA, Denvir MA. Maximum oxygen uptake corrected for skeletal muscle mass accurately predicts functional improvements following exercise training in chronic heart failure. Eur J Heart Fail 2006;8(3):243–8.

[23] Nuhr MJ, Pette D, Berger R, Quittan M, Crevenna R, Huelsman M, et al. Beneficial effects of chronic low-frequency stimulation of thigh muscles in patients with advanced chronic heart failure. Eur Heart J 2004;25(2):136–43.

[24] Sbruzzi G, Ribeiro RA, Schaan BD, Signori LU, Silva AM, Irigoyen MC, et al. Functional electrical stimulation in the treatment of patients with chronic heart failure: a meta-analysis of randomized controlled trials. Eur J Cardiovasc Prev Rehabil 2010;17(3): 254–60.

[25] Smart NA, Dieberg G, Giallauria F. Functional electrical stimulation for chronic heart failure: a meta-analysis. Int J Cardiol 2013;167(1):80–6.

[26] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62(10): 1006–12.

[27] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128(16):1810–52.

[28] Olivo SA, Macedo LG, Gadotti IC, Fuentes J, Stanton T, Magee DJ. Scales to assess the quality of randomized controlled trials: a systematic review. Phys Ther 2008;88(2): 156–75.

[29] Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997; 315(7121):1533–7.

[30] Lundh A, Gotzsche PC. Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies. BMC Med Res Methodol 2008;8:22.

[31] Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J 2008;156(2):292–300.

[32] Lauer MS, Snader CE. Using exercise testing to prognosticate patients with heart failure. Which parameter should we measure? Cardiol Clin 2001;19(4):573–81.

[33] Maffiuletti NA, Minetto MA, Farina D, Bottinelli R. Electrical stimulation for neuromuscular testing and training: state-of-the art and unresolved issues. Eur J Appl Physiol 2011;111(10):2391–7.
[34] Artero EG, Lee DC, Lavie CJ, España-Romero V, Sui X, Church TS, et al. Effects of muscular strength on cardiovascular risk factors and prognosis. J Cardiopulm Rehabil Prev 2012;32(6):351–8.
[35] Hulsmann M, Quittan M, Berger R, Crevenna R, Springer C, Nuhr M, et al. Muscle strength as a predictor of long-term survival in severe congestive heart failure. Eur J Heart Fail 2004;6(1):101–7.
[36] Clark A, Rafferty D, Arbuthnott K. Relationship between isokinetic muscle strength and exercise capacity in chronic heart failure. Int J Cardiol 1997;59(2):145–8.
[37] Fulster S, Tacke M, Sandek A, Ebner N, Tschöpe C, Doehner W, et al. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). Eur Heart J 2013;34(7):512–9.
[38] Rees K, Taylor RS, Singh S, Coats AJ, Ebrahim S. Exercise based rehabilitation for heart failure. Cochrane Database Syst Rev 2004;3:CD003331.
[39] Karavidas A, Parissis JT, Matzaraki V, Arapi S, Varounis C, Ikonomidis I, et al. Functional electrical stimulation is more effective in severe symptomatic heart failure patients and improves their adherence to rehabilitation programs. J Card Fail 2010; 16(3):244–9.