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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