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Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: An individual patient's data meta-analysis of randomized controlled trials

Francesco Giallauria [a,b,*], Carlo Vigorito [a], Massimo F. Piepoli [c], Andrew J. Stewart Coats [d,e]

[a] Department of Translational Medical Sciences, University of Naples "Federico II", Naples (NA), Italy
[b] School of Science and Technology, University of New England, Armidale, NSW 2351, Australia
[c] Heart Failure Unit, Department of Cardiology, G. da Saliceto Hospital, Piacenza, Italy
[d] Monash University, Australia
[e] University of Warwick, United Kingdom

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ABSTRACT

Background: Although cardiac contractility modulation (CCM) has emerged as a promising device treatment for heart failure (HF), the effect of CCM on functional capacity and quality of life has not been the subject of an individual patient data meta-analysis to determine its effect on measures of functional capacity and life quality. This meta-analysis is aimed at systematically reviewing the latest available randomized evidence on the effectiveness of CCM on functional capacity and quality of life indexes in patients with HF.

Methods: The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE were searched in May 2013 to identify eligible randomized controlled trials comparing CCM with sham treatment or usual care. Primary outcomes of interest were peak oxygen consumption, 6-minute walk test distance and quality of life measured by Minnesota Living With Heart Failure Questionnaire. There was no sufficient information to address safety. Mean difference and 95% confidence intervals (C.I.s) were calculated for continuous data using a fixed-effects model.

Results: Three studies enrolling 641 participants were identified and included. Pooled analysis showed that, compared to control, CCM significantly improved peak oxygen consumption (mean difference +0.71, 95% C.I. 0.20 to 1.21 mL/kg/min, $p = 0.006$), 6-minute walk test distance (mean difference +13.92, 95% C.I. −0.08 to 27.91 m, $p = 0.05$) and quality of life measured by Minnesota Living With Heart Failure Questionnaire (mean difference −7.17, 95% C.I. −10.38 to −3.96, $p < 0.0001$).

Conclusions: Meta-analysis of individual patient data from randomized trials suggests that CCM has significant if somewhat modest benefits in improving measures of functional capacity and quality of life.

1. Introduction

In patients with advanced heart failure (HF), optimal standard medical therapy often fails to provide adequate symptom relief or hemodynamic compensation, and few treatments have been shown to objectively increase exercise functional capacity. Pharmacological therapeutic advances in chronic HF treatment have slowed dramatically in the last decade. This has given rise to the development and testing of a host of new device-based therapies, such as cardiac resynchronization therapy (CRT), which has shown to improve clinical status and quality of life [1] along with left ventricular function [2] and survival [3]. CRT is indicated for symptomatic HF patients with left ventricular ejection fraction (LVEF) of ≤35% and QRS duration of ≥120 ms, although more recent evidence and the latest guidelines restrict the strength of the evidence to those with QRS greater than 150 ms with a left bundle branch block pattern. Because of this, only a small proportion of HF patients are suitable candidates for CRT. Moreover, since 60% of patients with HF have a normal QRS duration and at least 30% of patients receiving CRT are non-responders [4], the development of new device-based treatments for patients with persistent symptoms despite optimal medical therapy (OMT) remains an important challenge.

Abbreviations: 6MWT, 6-minute walking test; CCM, cardiac contractility modulation; CRT, cardiac resynchronization therapy; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; NYHA, New York Heart Association; OMT, optimal medical therapy; Peak VO_2, peak oxygen consumption; RCTs, randomized controlled trials; VAT, ventilatory anaerobic threshold.

* Corresponding author at: Department of Translational Medical Sciences, University of Naples "Federico II", Via S. Pansini 5, 80131 Naples (NA), Italy. Tel./fax: +390817462639.
E-mail addresses: giallauriafrancesco@gmail.com, fgiallau@une.edu.au (F. Giallauria), vigorito@unina.it (C. Vigorito), m.piepoli@imperial.ac.uk (M.F. Piepoli), andrew.coats@monash.edu (A.J. Stewart Coats).

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Cardiac contractility modulation (CCM) signals are non-excitatory signals applied during the absolute refractory period that have been shown to enhance the strength of left ventricular (LV) contraction [5]. CCM signals are unique and differ from pacing pulses because they do not initiate a new contraction of the heart, but rather increase the heart's force of contraction by improving the function of the cardiac muscle cells. Currently, CCM therapy is delivered via a small implantable device which is inserted like a pacemaker in a minimally invasive procedure. Its mechanisms of action [6] and clinical effects [7] have been recently reviewed.

A recent meta-analysis attempted to review the evidence on the efficacy and safety of CCM in the treatment of HF: it performed a literature search, screened 151 potentially relevant records but identified only 3 randomized controlled trials (RCTs) for summary analysis. No clear benefits in clinical outcomes, including all-cause mortality, or all-cause hospitalizations, and no significant effect on quality of life (Minnesota Living With Heart Failure Questionnaire, MLWHFQ) were detected but without evidence of adverse effects with CCM [8]. However, despite these Authors analyzed data from the same trials, they did not explore the effects of CCM on indices of functional capacity nor did they have access to individual patient data [8].

Since in advanced severe chronic conditions, including HF, the role of any intervention on exercise intolerance is becoming increasingly important [9,10], we aimed at performing a new individual patient meta-analysis systematically to review the efficacy of CCM on functional capacity (as objectively evaluated by peak VO_2 and 6MWT) and quality of life in HF (as evaluated by the MLWHFQ); and we critically review the effect of CCM on objective endpoints (peak VO_2 and 6MWT) in comparison with other approved therapies (e.g. cardiac resynchronization therapy, CRT).

2. Methods

2.1. Search strategy

The Cochrane Database, MEDLINE, and EMBASE were searched in May 2013 to identify eligible human studies using the keyword: "cardiac contractility modulation". No language restrictions were applied. Reference lists of retrieved records were screened for further relevant studies. All review articles with a subject of "cardiac contractility modulation" and their reference lists were also searched. Clinical trial registers (http://www.clinicaltrials.gov, http://www.controlled-trials.com) were searched for ongoing studies. The results of study selection are presented in a flow diagram as depicted by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Fig. 1) [11]. A total of 196 potentially relevant records were screened and 3 ongoing studies (1 active not recruiting, 2 recruiting) were identified (www.clinicaltrials.gov).

2.2. Study selection

Inclusion criteria were: (1) RCTs, (2) adult patients (≥18 years) with documented HF (NYHA functional classification ≥II), (3) intervention group allocated to CCM, and (4) control group allocated to sham treatment or optimal medical therapy. Concomitant medical therapy was given in both groups (intervention and control). Studies were selected independently by two authors (F.G. and M.F.P.) and disagreements were resolved by consensus.

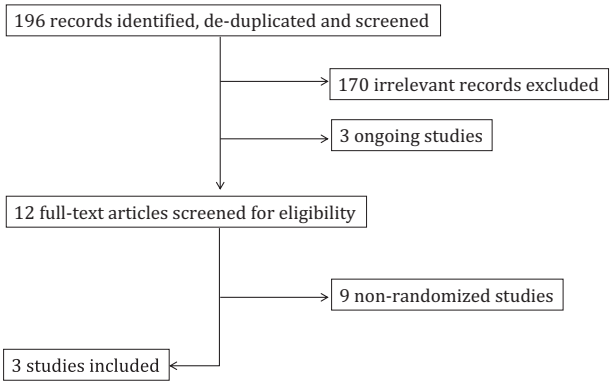

Fig. 1. Study selection presented in a flow diagram as depicted by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

2.3. Outcome measures

Primary outcomes were: (1) peak VO_2 (mL/Kg/min), (2) 6MWT distance (m), and (3) quality of life measured by MLWHFQ. Peak VO_2 as evaluated by cardiopulmonary exercise testing, has consistently demonstrated prognostic significance and is the most frequently analyzed cardiopulmonary exercise test parameter. In conjunction with other typically more invasive evaluation techniques, peak VO_2 is used to assess survival and the need for heart transplantation [12–14]. It is a measure of peak aerobic capacity, and measures maximal integrated cardiopulmonary capacity. Six-minute walk distance is the distance covered in meters over 6 min of maximal self-paced walking [15]. A lower score (reflecting less distance covered in 6 min) indicates worse function. The MLWHFQ was used to assess the patients' perception of the effects of HF on the physical, socioeconomic and psychological aspects of their life. Patients respond to 21 items using a six-point Likert scale (0–5); the higher the score the worse the quality of life [16].

2.4. Study quality assessment

The Cochrane Collaboration's tool for assessing risk of bias was used to assess quality of included trials on the following domains: (1) random sequence generation, (2) allocation concealment, (3) blinding, (4) incomplete outcome data, and (5) selective reporting [9] Categories of "low risk," "high risk," or "unclear risk" were used as judgments against the criteria stated by the assessment tool.

2.5. Statistical analysis

Revman 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to conduct meta-analyses for outcome measures. Data used were continuous and were reported as mean and standard deviation. The results were presented as weighted mean differences for continuous data, along with the 95% confidence intervals (C.I.s). A Mantel–Haenszel random-effects model was adopted taking into account potential heterogeneity across studies. The I [2] statistic was used to explore statistical heterogeneity. P values ≤0.05 for 2-sided tests were considered to be statistically significant. An Egger plot was produced to identify sources of publication bias [17]. Subgroup analyses (not prespecified in each of the parent trials) were conducted by subdividing the study population according to age (<60 vs. >60 years old), gender (male vs. female), left ventricular ejection fraction (LVEF, <25% vs. 25–45%); and heart failure etiology (ischemic vs. non-ischemic). These reflect common questions asked of effective heart failure therapies, in areas patient pre-treatment characteristics are thought to affect treatment response.

3. Results

3.1. Description of studies

The three randomized clinical trials included in this review had an aggregate of 641 subjects. Baseline characteristics of the included studies were similar: the most common etiology of HF was ischemic and the majority of the participants were of NYHA classification III (Table 1). All studies used the OPTIMIZER™ System as the intervention and control groups consisted of either sham treatment (FIX-HF-5 Pilot [18] and FIX-CHF-4 [19]) or optimal medical therapy (FIX-HF-5) [20]. One trial [18] was conducted in a single institution whereas the other two were multicenter studies. Withdrawals and associated reasons were described in all trials and no evidence of selective outcome reporting was observed.

3.2. Data analyses

3.2.1. Peak VO_2

Data showed a significant increase in peak VO_2 (from 14.5 to 14.7 mL/kg/min, +2.6%) in the CCM group (n = 283) (mean difference +0.71, 95% C.I. 0.20 to 1.21 mL/kg/min, p = 0.006) (Fig. 2, panel A).

In the FIX-HF-5 Pilot study [18], both groups showed a slight decline in peak VO_2 from baseline over the 24-week period, although more evident among the controls (−1.43 ± 3.01 mL/kg/min vs. −0.96 ± 2.6, p = 0.29).

In FIX-CHF-4 [19], during phase I, peak VO_2 increased similarly in both groups by ~0.4 mL/kg/min, independent of whether the device was turned on or off; however, in the phase II of the study, peak VO_2 remained increased in subjects who crossed over from sham to active