Journal of Cardiology 69 (2017) 326–332

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Cardiac contractility modulation in heart failure patients: Randomized comparison of signal delivery through one vs. two ventricular leads

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ARTICLE INFO

Article history:
Received 3 May 2016
Received in revised form 11 June 2016
Accepted 16 June 2016
Available online 30 August 2016

Keywords:
Cardiac contractility modulation
Heart failure
Leads

ABSTRACT

Background: Cardiac contractility modulation (CCM) is an electrical stimulation treatment for symptomatic heart failure (HF) patients. The procedure involves implantation of two ventricular leads for delivery of CCM impulses. The purpose of this study is to compare the efficacy and safety of CCM when the signal is delivered through one vs. two ventricular leads.

Methods: This prospective blinded randomized trial enrolled 48 patients. Eligible subjects had symptoms despite optimal HF medications, left ventricular ejection fraction <40% and peak$VO_2 \geq 9$ ml O_2/kg/min. All patients received a CCM system with two ventricular leads, and were randomized to CCM active through both or just one ventricular lead; 25 patients were randomized to receive signal delivery through two leads (Group A) and 23 patients to signal delivery through one lead (Group B). The study compared the mean changes from baseline to 6 months follow-up in peakVO_2, New York Heart Association (NYHA) classification, and quality of life (by MLWHFQ).

Results: Following 6 months, similar and significant ($p < 0.05$) improvements from baseline in NYHA (-0.7 ± 0.5 vs. -0.9 ± 0.7) and MLWHFQ (-14 ± 20 vs. -16 ± 22) were observed in Group A and in Group B. PeakVO_2 showed improvement trends in both groups (0.34 ± 1.52 vs. 0.10 ± 2.21 ml/kg/min; p = ns). No patient died. Serious adverse event rates (20 events in 10 subjects) were not different between groups. No statistically significant difference was found in any of the study endpoints.

Conclusions: The efficacy and safety of CCM in this study were similar when the signal was delivered through either one or two ventricular leads. These results support the potential use of a single ventricular lead for delivery of CCM.

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Introduction

Heart failure (HF) is a chronic and progressive disease that courses a span of years to decades. Despite the advances in pharmacological and medical device therapies, heart failure remains one of the leading causes of morbidity and mortality in the world. There has been a relative drought in new pharmacological therapies over the past two decades but this has allowed for a revolution in the development of medical devices to treat heart failure, including cardiac resynchronization therapy (CRT) [1,2]. Even if some methods were developed that have been shown to predict response to CRT [3,4] in order to improve outcome, yet still about 30% of the CRT cases are non-responders.

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http://dx.doi.org/10.1016/j.jjcc.2016.06.015
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Table 1
List of exclusion criteria.

1. Baseline peakVO_2 less than 9 ml O_2/kg/min.
2. Subjects with potentially correctable cause of heart failure, such as valvular or congenital heart disease.
3. Subjects with evidence of active ischemia.
4. Subjects hospitalized within 2 weeks prior to enrollment for heart failure requiring the use of intravenous diuretics or inotropic support.
5. Subjects with clinically significant amount of ambient ectopy, defined as more than total of 8900 premature ventricular contractions per 24 h on baseline Holter monitoring.
6. Persistent or permanent atrial fibrillation/flutter.
7. Exercise tolerance limited by a condition other than heart failure.
8. Subjects unable to participate in a cardiopulmonary stress test.
9. Subjects scheduled for coronary artery bypass graft or a percutaneous transluminal coronary angioplasty procedure, or who have undergone such procedure within 3 months or 1 month, respectively.
10. Subjects with history of myocardial infarction within 3 months of enrollment.
11. Mechanical tricuspid or aortic valves.
12. Prior heart transplant.
13. Subjects participating in another experimental protocol.
14. Subjects in vulnerable populations unable to provide informed consent.

However, the majority of patients with HF are not candidates for CRT because they lack a prolonged QRS. For such patients, cardiac contractility modulation (CCM) has become a potential therapeutic option.

CCM is a device-based therapy for HF that includes an implantable pulse generator, the Optimizer™ system (Impulse Dynamics Inc., Orangeburg, New York, USA). The present Optimizer IVs (and the previous Optimizer III) device model utilizes three commercially available leads (one atrial and two ventricular). The pulse generator delivers highly specialized non-excitatory electric signals to the myocardium in the right ventricular septum during the absolute refractory period. The resulting enhancement in contractility involves changes in cardiomyocyte Ca^{2+} handling and normalizing mRNA expression of HF-related genes [5,6].

Currently, CCM is intended for the treatment of moderate to severe chronic HF with reduced ejection fraction despite optimal medical therapy. Clinical trials have demonstrated improvement in reverse remodeling and contractility in patients with New York Heart Association (NYHA) Classes II–IV heart failure and normal QRS duration [7–10]. CCM has been shown to improve peak oxygen consumption and quality of life [10–13]. Another study has also shown the clinical benefit with CCM in patients with wide QRS complexes who did not respond to CRT [14]. Recently, CCM therapy was reviewed in the European Society of Cardiology's guidelines on acute and chronic heart failure (2016) where it was stated that CCM may be considered in selected patients with HF [15].

Traditionally CCM is delivered through two leads placed in the right ventricular septum. Historically, this configuration was hypothesized to provide acute impact on larger portion of the muscle. However, the benefit of CCM delivery through two vs. one ventricular lead has never been prospectively studied in human subjects. Experience in patients with only one lead due to technical or symptom-related reasons suggests that activation via one lead does not attenuate the beneficial effect of CCM. Potentially, implantation of the CCM device would be easier, faster, and with reduced potential risk if only one ventricular lead were required. The objective of this study was to compare in a prospective, blinded, and randomized manner the impact of CCM therapy delivered through two ventricular leads versus one ventricular lead on symptoms, quality of life, and exercise tolerance in patients with medically refractory symptomatic heart failure due to reduced left ventricular function. We hypothesized that CCM delivery through one ventricular lead would not be inferior (efficacy and adverse effects) to delivery through two ventricular leads. This study does not include a comparator control group with no device implanted.

Materials and methods

Patient population

Fifty consecutive patients with symptomatic heart failure (NYHA Classes II–III) and reduced left ventricular ejection fraction (LVEF $\leq$ 40%) were implanted with a CCM Optimizer™ device between 2009 and 2014 in four medical centers after providing written informed consent. Approval for the study was obtained from the Ethics Committee of each participating institution and the study was conducted in compliance with the Declaration of Helsinki and applicable regulations. Enrolled subjects were over 18 years of age and receiving optimal medical therapy for HF based on standard of care for the participating institution, including implantable cardioverter-defibrillator (ICD) if indicated. Specifically, it was required that the subjects be clinically euvolemic and on a stable dose of a diuretic, angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker, and beta-blocker for a minimum of 2 weeks. If the subject was not already taking a beta-blocker, the subject and referring physician agreed that a beta-blocker would not be started until completion of scheduled follow-up visits for the study. Patients were excluded if they had a mechanical tricuspid or aortic valve, which would preclude CCM catheter placement and LV Millar catheter placement for dP/dt, respectively. Other exclusion criteria are listed in Table 1.

Investigational device

The Optimizer™ III and Optimizer™ IVs device models were utilized during the course of this study; each has a CE Mark. The Optimizer device consists of an implantable pulse generator (IPG), two right ventricular septal pacing leads, and an atrial sensing lead. The atrial lead is a regular IS-1 bipolar pacemaker lead. The ventricular leads that were qualified for use with CCM are commercially available leads and currently include some models of the Tendril® leads (e.g. 1888T/2088T/LPA1200M by St. Jude Medical, Saint Paul, MN, USA) or Setrox S/Siello S/Solia S (by Biotronik SE & Co. KG, Berlin, Germany) and Dextrus leads (by Boston Scientific, Marlborough, MA, USA). The Optimizer system delivers non-excitatory CCM signals to the heart and has no pacemaker or ICD functions.

The CCM stimulus consists of non-excitatory high amplitude (7.5 V) biphasic impulses of 20 ms duration applied to the RV septum during the absolute refractory period of the heart [7,8]. CCM signals were delivered for 7 h per day. Participants were randomized to receive CCM either through one of the

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