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Improvement of long-term survival by cardiac contractility modulation in heart failure patients: A case–control study

Ming Liu, Fang Fang, Xiu Xia Luo, Ben-Haim Shlomo [1], Daniel Burkhoff [1], Joseph Y.S. Chan, Chin-Pang Chan, Lili Cheung, Benny Rousso [1], David Gutterman [1], Cheuk-Man Yu *

Division of Cardiology and HEART Centre, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong
Institute of Vascular Medicine, The Chinese University of Hong Kong, Hong Kong
LCW Institute of Innovative Medicine, The Chinese University of Hong Kong, Hong Kong
Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong

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ABSTRACT

Introduction: Cardiac contractility modulation (CCM) has been shown to be effective in improving symptoms and cardiac function in heart failure (HF). However, there is limited data on the role of CCM on long-term survival, which was explored in the present study.
Methodology: Forty-one consecutive HF patients with left ventricular ejection fraction (EF) <40% received CCM and were followed for approximately 6 years. They were compared with another 41 HF patients who were enrolled into the HF registry in the same period, and had similar age, gender, EF and etiology of HF. The primary end-point was all cause-mortality. This was stratified by EF. Secondary end-points included HF hospitalization, cardiovascular death, and the composite outcome of death or heart failure hospitalization.
Results: The CCM and control groups were well balanced for demographic data, medications and baseline left ventricular EF (27 ± 6 vs 27 ± 7%, p = NS). The mean follow-up duration was 75 ± 19 months in the CCM group and 69 ± 17 months in the control group. All-cause mortality was lower in the CCM group than the control group (39% vs. 71%, respectively; Log-rank $\chi^2 = 11.23$, p = 0.001). Of note, the improvement of all-cause mortality is more dramatic in patients with EF ≥ 25–40% (36% vs. 80%, Log-rank $\chi^2 = 15.8$, p < 0.001) than those with EF < 25% (50% vs. 56%, p = NS), CCM vs. control respectively. Similar results were shown for the benefit of CCM in the secondary endpoints of cardiovascular death, and the composite outcome of death or heart failure hospitalization. The occurrence of HF hospitalization showed no significant difference between CCM and control groups in the whole cohort (41% vs. 49%, p = NS), but was significantly lower with CCM in subjects with EF ≥ 25–40% at baseline (36% vs. 64%, Log-rank $\chi^2 = 7.79$, p = 0.005).
Conclusion: CCM resulted in significant improvement of long-term survival, in particular in those with EF ≥ 25–40%. A reduction in heart failure hospitalizations was also seen in this group of patients with less severely reduced EF.

1. Introduction

The incidence of heart failure is increasing in part due to more aggressive treatment of acute coronary syndromes, leaving more survivors who have had significant loss of cardiac function. The growing incidence of heart failure is expected to continue, especially in China where Westernization has propelled the prevalence of cardiovascular disease over 230 million and rank it as the commonest cause of death [1]. As a result the number of patients in China with heart failure is expected to increase rapidly from its current prevalence of 4.2 million.

Even though therapies for chronic heart failure have advanced significantly in the past two decades, an enlarging number of patients with ejection fractions (EF) < 45% on optimal medical therapy experience life-style limiting symptoms. For these subjects, several types of device-linked therapies are potentially available including implantable cardiac defibrillators (ICD), cardiac resynchronization therapy (CRT), and cardiac contractility modulation (CCM). Although many of these patients are candidates for the life-prolonging effects of ICDs, in the subset of patients with EF < 35%, this therapy does not improve symptoms or functional status. Use of ICDs has regional variability across the globe. About one fourth of this group of patients with heart failure has left bundle branch block or otherwise prolonged QRS duration and benefits from CRT [2,3]. However for the remaining majority, who do not have

* Corresponding author at: Division of Cardiology and HEART Centre, Department of Medicine and Therapeutics, Prince of Wales Hospital, Institute of Vascular Medicine, LCW Institute of Innovative Medicine, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong.
E-mail address: professorcmyu@gmail.com (C.-M. Yu).
[1] Impulse Dynamics.

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QRS widening, CRT does not help or may be detrimental [4]. In this group, CCM (Optimizer device, Impulse Dynamics) has proven to be safe and effective, improving peak VO_2, New York Heart Association (NYHA) classification, symptoms and well-being (Minnesota Living with Heart Failure questionnaire), 6-Minute Hall Walk test and EF [5–7].

CCM delivers a biphasic high voltage signal to the right ventricular septum during the absolute refractory period, triggered by detecting the tissue depolarization within the QRS complex with a timed delay. CCM acutely increases EF by about 5% and over time improves other parameters of cardiac function and symptoms. The mechanism of action involves improvement of cardiac calcium handling through upregulation of phospholamban, sarcoendoplasmic reticulum calcium transport ATPase, and L-type calcium channels both locally near the CCM signal delivery site and remotely throughout the heart [6]. CCM use also elicits left ventricular reverse remodeling of the fetal gene program towards that seen in normal hearts with elevation of myosin heavy chain-α and reduction in B-type Natriuretic Peptide levels [8]. While the acute and short term benefits (months) are well-established, much less data exist regarding longer term benefits including effects on mortality and hospitalization. This report provides long-term follow-up on 41 consecutive symptomatic subjects with EF < 40% in whom an Optimizer device was implanted and compared to a matched control group from a local heart failure registry of selected patients who did not receive CCM.

2. Methods

The study group consisted of forty-one consecutive patients with NYHA III symptomatic heart failure and EF < 40% who were on stable doses of heart failure medications and in whom an Optimizer III device was deployed. Patients were recruited from a University teaching hospital from 2005 to 2012. The protocol was approved by the local ethics board and all study subjects provided written informed consent. The comparator group consisted of 41 heart failure patients enrolled in the same hospital's heart failure registry over the same time period and who were also receiving optimal medical therapy (non-CCM control group). Control group subjects were matched 1:1 to the CCM group by age, gender, medications at baseline, left ventricular EF at baseline, follow-up duration, and etiology of heart failure (Table 1). Based on local standards of care, ICDs were not typically implanted in the patients. Two patients had an ICD at the time the study began and none were implanted during the course of the study.

Table 1
Baseline characteristics of the CCM and control groups.

Parameters	CCM (n = 41)	Control group (n = 41)	P value
Demographic data			
Age, years	61 ± 10	64 ± 11	0.15
Male, n (%)	35 (85)	35 (85)	1.00
Follow-up duration (months)	75 ± 19	69 ± 17	0.10
LVEF, %	27 ± 7	27 ± 6	0.95
NYHA class, n (%)	3.0 ± 0.0	3.29 ± 0.68	<0.001
I	0 (0)	1 (2)	
II	0 (0)	2 (5)	
III	41 (100)	22 (54)	
IV	0 (0)	16 (39)	
PAF[a] at baseline, n (%)	6 (15)	15 (37)	0.02
Ischemic causes of HF, n (%)	21 (51)	16 (39)	0.38
Medications at admission			
Diuretics, n (%)	29 (71)	25 (61)	0.35
Aldosterone antagonists, n (%)	6 (15)	1 (2)	0.11
ACEI/ARB, n (%)	31 (76)	26 (63)	0.34
Beta-blocker, n (%)	32 (78)	27 (66)	0.22
Digoxin, n (%)	5 (12)	6 (15)	0.75

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; HF, heart failure; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers.
[a] No patients had permanent AF or any AF at the time of implantation.

The primary end-point was all cause-mortality. Secondary endpoints included HF hospitalization, cardiovascular death, and the composite outcome of death or heart failure hospitalization. Endpoints were stratified by EF.

2.1. Device implantation and programming

CCM implantation was performed under local anesthesia. Three standard pacing leads were tunneled subcutaneously into the subclavian vein. One was advanced into the right atrium and the other two were secured into anterior and inferior aspects of the right ventricular endocardium. The generator was inserted into a subcutaneous pocket formed in the left subclavicular area. In some patients, acute LV + dP/dt(max) was measured with a Millar catheter before and during CCM activation and the physician could then decide whether to reposition the right ventricular leads based on the acute changes in + dP/dt(max).

After closing incisions, the Optimizer III was wirelessly programmed to deliver impulses only when atrial sensed signal is followed by ventricular signal occurring at a pre-specified interval. CCM is designed to be active only in heart beats when ventricular arrhythmias are absent. Treatment was delivered during several one hour periods spread throughout the day for 7 h/day.

2.2. Baseline measurements and follow-up

Patients who received CCM were followed up prospectively and were monitored as an outpatient approximately every 6 months with device interrogation performed with each visit. During the peri-implantation period subjects underwent history and physical examination, echocardiography, laboratory testing, and assessments of symptoms. Patients included in the study arm had 1) NYHA Class III or IV heart failure with left ventricular EF ≤ 40% and 2) were required to be on a stable medical regimen for heart failure (appropriate doses of a beta-adrenergic blocker, ACE-inhibitor or angiotensin receptor blocker, aldosterone antagonist, and/or diuretic) for at least 1 month. Other inclusion criteria were 3) age > 18, and 4) QRS < 130 ms (unless not appropriate for CRT). Patients were excluded for 1) permanent atrial fibrillation or atrial flutter (some had paroxysmal atrial fibrillation but were in sinus rhythm at the time of implantation), 2) severe symptomatic heart failure appropriate for transplantation, 3) treatment with intravenous inotropic medications within the past 3 weeks, 4) baseline peak VO_2 known to be <9 ml/min × kg, 5) clinically significant angina pectoris (Canadian Cardiovascular Society Angina score of II or more) or an episode of unstable angina or myocardial infarction within 30 days of enrollment, or resting ischemia by ECG or symptoms of angina, 6) potentially correctible cause of heart failure, 7) ICD firing within 1 month of enrollment, 8) >8900 premature ventricular contraction per 24 h by Holter, 9) inability to complete a 6 min walk test or non-cardiac condition that markedly reduces exercise capacity (e.g. chronic obstructive pulmonary disease, peripheral vascular disease, orthopedic disease, orthopedic disease), 10) scheduled or completed coronary artery bypass grafting or percutaneous coronary intervention within the past 3 months, 11) indication for CRT therapy, 12) prior cardiac transplant, mechanical tricuspid or aortic valves, 13) inability to provide informed consent, or 14) participation in another simultaneous experimental protocol. The analysis is based on data from 41 patients who were followed until the end of the study or until a primary endpoint was reached. Three of these subjects failed to complete the follow up. Among them, one failed to return for testing 3 months after implantation and two had explantation as explained below.

2.3. Statistical analysis

All data are presented as mean ± standard deviation. Statistical significance was defined as $p < 0.05$. Groups were assigned in the analysis per intention-to-treat, independent of CCM therapy being active for the