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Original article

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

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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.

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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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

ventricular leads or through both of the ventricular leads, and they were programmed as such prior to discharge.

The Optimizer system includes a programmer and a wireless battery charger.

Implant procedure

In each case, the CCM device was implanted, and in most cases local anesthesia and conscious sedation were used. Briefly, two ventricular bipolar screw-in leads were placed transvenously in the right ventricular septum. Septal position was confirmed fluoroscopically. Then a third lead was placed transvenously into the right atrium for sensing purposes. In some patients ventricular pressure including dP/dt_{max} was measured with a Millar catheter placed into the left ventricle via the femoral artery. This catheter was used to confirm an acute increase in dP/dt_{max} compared to baseline during application of CCM signals. The decision to evaluate left ventricular dP/dt_{max} was left to the discretion of the implanter. Finally, a cross-talk test was performed in every patient, where the ICD/pacemaker is interrogated while CCM is delivered in order to observe if any artifact of CCM is detected by the ICD/pacemaker as a sensed event. In the unlikely case that interference might be observed, the CCM impulse delivery may be reconfigured to exclude any identified interference. Prior to hospital discharge, subjects underwent chest X-ray according to hospital policy to rule out pneumothorax and to evaluate lead placement. Subjects also underwent a physical examination and documentation of medications.

Study design

This investigation was a randomized, blinded multicenter, study, over a 6-month period that was carried out from 2009 to 2014. The hypothesis is that the delivery of CCM through one ventricular lead is not inferior to delivery through two ventricular leads. Fifty (50) patients were implanted with the CCM device, however 2 of them were determined to be ineligible due to baseline $peakVO_2$ determined after enrollment to be too low. Baseline and eligibility evaluation included medical history, medication reconciliation, echocardiography, cardiopulmonary stress test, Minnesota Living With Heart Failure Questionnaire (MLWHFQ), electrocardiogram, and a 24-h Holter monitor. The first 26 patients were randomized according to a 1:1 randomization scheme between Group A (CCM active through two leads) vs. Group B (CCM active through one lead), in blocks of 4 per center. Due to a higher number of patients in Group A that were actually receiving CCM therapy through one lead only per the physician decision (e.g. if experiencing discomfort or sensation), for the remaining 24 patients the randomization was 2:1 between Group A vs. Group B in blocks of 6 per center. Since all patients received the same device implant with two ventricular leads, blinding was feasible. All subjects were invited to follow-up between weeks 2 and 4, and again 12 and 24 weeks after implantation. At each visit, the device was interrogated to assess proper functioning, and interim clinical assessment was made including NYHA classification, MLWHFQ, and measurement of $peakVO_2$.

Endpoints

The study co-primary endpoints were non-inferiority in each of the mean change in quality of life measured by the MLWHFQ score and mean change in exercise tolerance as assessed by peak oxygen consumption determined during cardiopulmonary exercise stress testing.

The secondary efficacy endpoint was mean change in NYHA symptom classification. The changes in the efficacy parameters were evaluated at 24 weeks vs. baseline. Safety endpoints included the incidence of mortality and the occurrence of severe adverse events.

Statistics

The assumptions underlying the power analysis for non-inferiority were that the baseline $peakVO_2$ would be about 14.5 ml/kg/min, the benefit in $peakVO_2$ in response to treatment will be similar to previous studies, namely about 1 ± 3.5 ml/kg/min, compared with an historic non treated population. Using a two sample Student's *t*-test with 80% power to determine non-inferiority with a margin set to be smaller than the standard deviation, 22 subjects per group were required for a one-sided alpha = 0.025. Assuming up to 15% loss to follow up a total sample size of 50 patients (25 per group) was determined.

Differences between the groups in changes in efficacy parameters from baseline to last follow up were evaluated, and a two sample Student's *t*-test was used to determine non-inferiority in each efficacy parameter. The overall level of significance used for determining a difference or non-inferiority in this study is 0.05.

Results

A total of 50 patients received an Optimizer device. All implant procedures were performed without complications. All but 3 cases had ICD prior to the study, one of them had a pacemaker. In all cases with prior implanted devices, cross-talk testing was conducted and in no case a reprogramming of the CCM signal delivery was required due to interference. Two subjects were excluded for low $peakVO_2$ (<9 ml/kg/min). Thus 48 were included for analysis. Three patients voluntarily withdrew (Fig. 1). Baseline characteristics of the 48 subjects included in the final analysis are presented in Table 2. There were no significant differences in baseline characteristics between groups, nor were there any differences when stratified by analysis [intention to treat (ITT) or per treatment protocol (PP) groups]. The mean increase in acute dP/dt during implant was 14.8% with both leads functional.

Some patients randomized to dual lead CCM delivery were converted to delivery through one lead per the physician decision, usually due to sensation or discomfort. Therefore, results are provided by analysis per the randomization in an intention to treat (ITT) manner, as well as by analysis per treatment protocol (PP) based on the actual configuration.

In seven cases the last follow up cardiopulmonary stress testing (CPX) is not available for final analysis (Fig. 1): 3 cases voluntarily withdrew, and in 4 cases a CPX system malfunction prevented data analysis. Instances of incomplete data were handled by last observation carried forward.

In the ITT analysis (Fig. 2), mean MLWHFQ score at 24 weeks of CCM was significantly improved in both groups (−13.8 in Group A vs. −16.3 in Group B; *p*-values 0.002, 0.003, respectively vs. baseline). Changes in $peakVO_2$ from baseline were also similar in Group A (+0.34 ml/kg/min) and Group B (+0.10 ml/kg/min), both with no statistical significance. Both groups showed significant and similar improvement in NYHA class (−0.72 Group A vs. −0.85 in Group B, *p*-values for both groups are <0.001). Non-inferiority was confirmed since there were no statistically or clinically significant differences between groups in any of the measured parameters, and no consistent trend among any parameters favoring either the 1- or the 2-lead groups.

In the PP group comparison (Fig. 3), MLWHFQ score improved significantly and similarly in both groups (−15.6 vs. −14.5; *p*-values 0.003, 0.002, respectively) after 24 weeks of CCM therapy. $PeakVO_2$ trended toward similar improvement in both groups

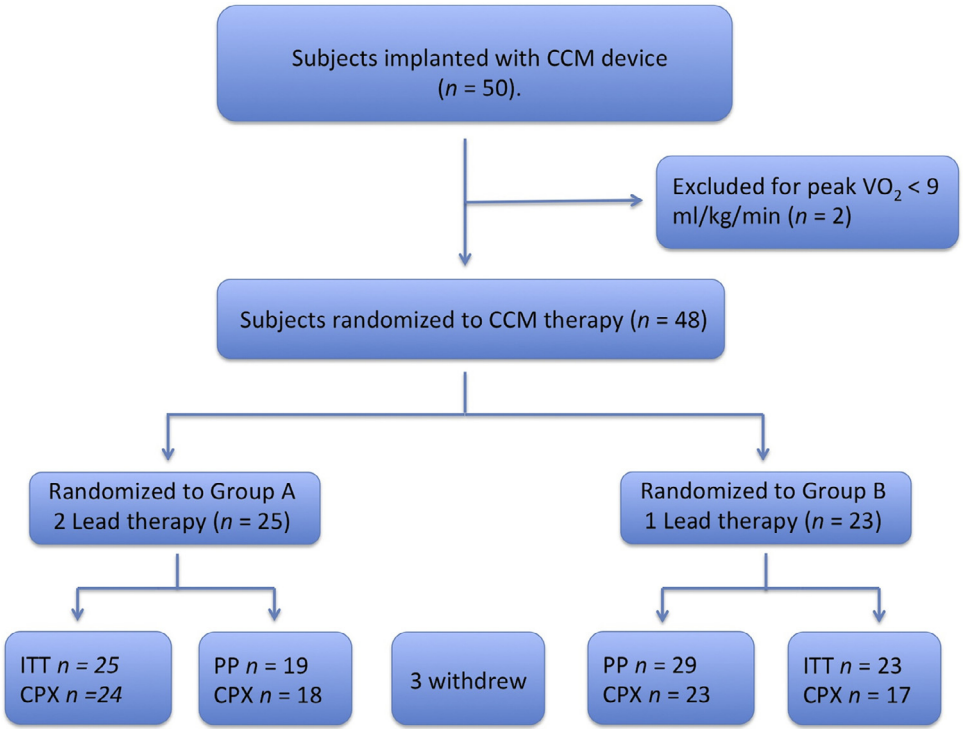

Fig. 1. Study enrollment, randomization, and follow-up. CCM, cardiac contractility modulation; CPX, cardiopulmonary exercise test; ITT, intention to treat; PP, per treatment protocol

(+0.15 ml/kg/min in Group A and +0.32 ml/kg/min in Group B). There were similar and significant improvements in NYHA class in both groups (−0.74, −0.81, respectively, *p*-values for treatment vs. baseline in both groups are <0.001).

Table 2
Demographics.

Demographics	2 leads	1 lead	All
N	25	23	48
Age	60 ± 14	60 ± 8.8	60 ± 11.4
Gender			
Male	24 (96%)	21 (91%)	45 (94%)
Female	1 (4%)	2 (9%)	3 (6%)
Cardiomyopathy			
Ischemic	13 (52%)	14 (61%)	27 (56%)
Dilated + other	12 (48%)	9 (39%)	21 (44%)
NYHA			
Class II	4 (16%)	2 (9%)	6 (13%)
Class III	21 (84%)	21 (91%)	42 (88%)
MLWHFQ	42.2 ± 21.8	48.2 ± 19.9	45.0 ±20.9
PeakVO$_2$ (ml/kg/min)	13.9 ± 3.3	14 ±2.9	13.9 ±3.1
LVEF	25.7 ±7.3	24.9 ± 7.1	25.3 ± 7.1
LVEDD	65.5 ± 10.4	67.3 ± 9.8	66.4 ± 10.0
Medications			
Beta blockers	25 (100%)	22 (96%)	47 (98%)
ACE-I/ARB	23 (92%)	21 (91%)	44 (92%)
Diuretics	22 (88%)	23 (100%)	45 (94%)
MRA	15 (60%)	13 (57%)	28 (58%)
Digitalis	4 (16%)	2 (9%)	6 (13%)
Amiodarone	2 (8%)	1 (4%)	3 (6%)
QRS duration (ms)	104.0 ± 24.8	111.0 ± 18.7	107.5 ± 22.0
ICD	23 (92%)	22 (96%)	45 (94%)
Pacemaker	1 (4%)	0 (0%)	1 (2%)

No *p*-values given as no statistical difference between the groups was shown. NYHA, New York Heart Association; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardioverter-defibrillator.

A total of 26 adverse events were reported in 15 subjects over the 6-month study period. Twenty were serious adverse events (SAEs), reported in 10 subjects. Table 3 summarizes the SAEs per ITT group.

Of the 4 lead-related SAEs, 2 were classified by the investigator as related to the device and procedure (lead dislodgement and muscle contraction due to lead fracture), 1 was classified as related to the device and possibly related to the procedure (muscle contraction at implant site), and 1 was classified as possibly related to the device and not related to the procedure (insulation defects of ventricular leads). No other adverse events were classified by the investigators as related to either the device or the procedure. Overall, the frequency of reported adverse events is typical of patients suffering from heart failure.

Comparing by ITT or PP, both groups experienced similar numbers of SAEs recorded. There were no statistically significant differences between the groups in the percentage of patients experiencing at least one SAE by either ITT comparison or PP comparison. Similarly, no statistically significant difference was observed between the groups with regard to the percentage of patients experiencing at least one SAE in any of the cardiac-related

Table 3
ITT safety.

ITT safety	Group A – 2 leads (#=25) # events/# patients	Group B – 1 lead (#=23) # events/# patients
Atrial fibrillation/flutter	–	4/2
Worsening heart failure	–	2/1
Irregular heartbeats/shock	–	2/1
Lead related	2/1	2/2
Dyspnea	–	2/2
Other/general medical	6/4	–
Total	8/4	12/6

ITT, intention to treat; #, number.

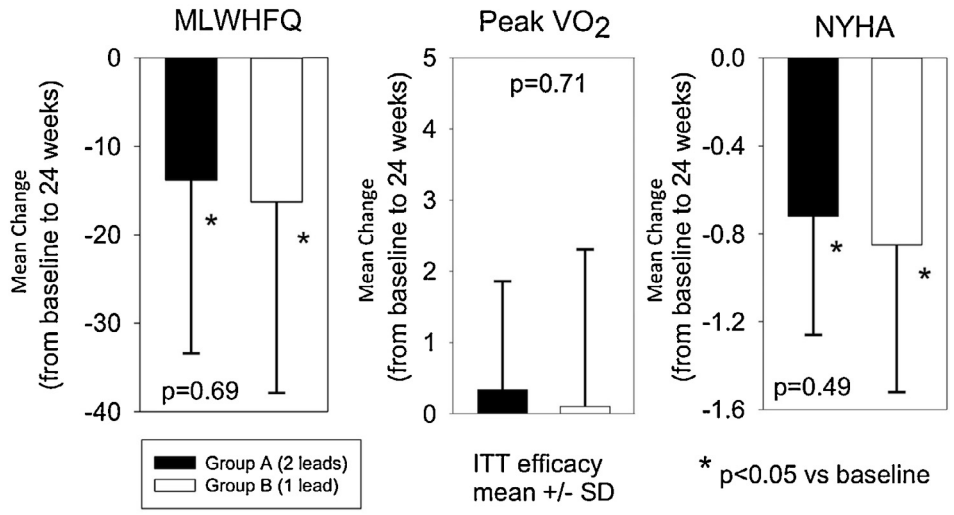

Fig. 2. Efficacy results. Analysis of outcomes by intention to treat (ITT) analysis. No differences in MLWHFQ, peakVO_2, or NYHA were observed between Group A (dual lead) and Group B (single lead) subjects after 24 weeks. MLWHFQ, Minnesota Living With Heart Failure Questionnaire; NYHA, New York Heart Association.

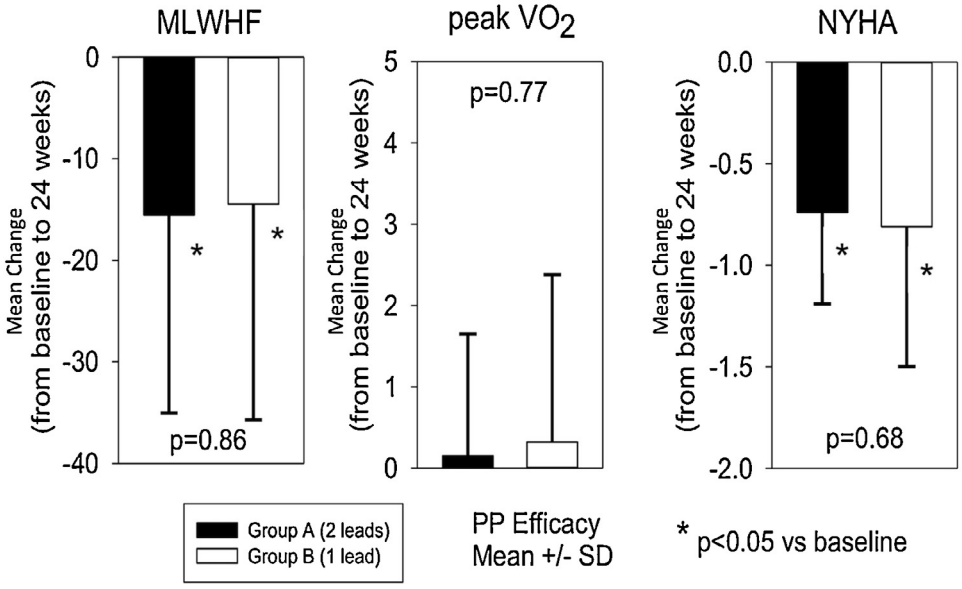

Fig. 3. Per treatment protocol (PP) analysis – efficacy results. Analysis of outcomes by PP analysis. No differences in MLWHFQ, peakVO_2, or NYHA were observed between Group A (dual lead) and Group B (single lead) subjects after 24 weeks. In both groups there was an improvement in symptoms. Both intention to treat and PP analyses yielded similar outcomes. MLWHFQ, Minnesota Living With Heart Failure Questionnaire; NYHA, New York Heart Association.

categories. There was a trend toward a higher number of total SAEs of any type, particularly cardiac-related in the single-lead activation group compared with the two-lead activation group which trended toward more general medical SAEs (p = ns). It is important to note that both the single-lead and dual-lead groups received the same implantation procedure with placement of two transvenously-placed ventricular leads, although only one lead was actively used for CCM delivery in the single-lead group. No deaths occurred during this study in any group.

Discussion

Currently, CCM device therapy is applied using the Optimizer IVs system with one atrial lead and two ventricular leads [16,17]. Many patients receiving CCM do also have a transvenous ICD. As known about implantable systems, complications associated with transvenous leads include systemic infections, lead displacement, venous-thrombosis, and insulation failure or lead fractures [18]. Cumulative data related to transvenous ICD leads suggest that there may be a 20% risk of lead failure at 8–10 years post-implant [19]. Complications are associated with the number of implanted electrodes [20]. At present, there is no device combining CCM with ICD functions, therefore many CCM patients have multiple leads.

Experience with regard to CCM therapy suggested similar clinical benefit when converting from two to one active leads. Nevertheless, this has not yet been confirmed in a prospective randomized trial. Non-inferiority of the benefit using single-lead activation would support the potential future implantation of a single ventricular lead, thus helping to reduce the number of potential complications associated with implanting a higher number of leads.

The principal finding of this study is that delivery of the CCM signal using one ventricular lead is not inferior to the typical

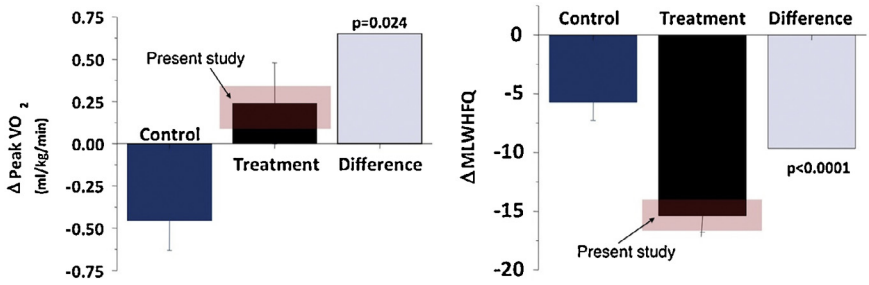

Fig. 4. Efficacy results in view of past data. Putting the efficacy results in the perspective of the FIX-HF-5 study, the improvements in peakVO_2 and in MLWHFQ of the present study are marked on the figure showing the results of the FIX-HF-5 results. The magnitude of improvements are similar. MLWHFQ, Minnesota Living With Heart Failure Questionnaire.

dual-lead stimulus. CCM signal, when delivered using one ventricular lead, is no less efficacious than when delivered through two ventricular leads simultaneously and the safety profile did not seem to differ between the groups, probably because all patients had two ventricular leads implanted.

Putting the results of the current study in perspective, the improvement from baseline in quality-of-life scores and NYHA symptoms was similar to that reported in previous clinical trials [10,11,13,17]. For example, both groups in the present study experienced an improvement in MLWHFQ by a range of −14 to −16 points, which is similar to the approximately −15 points improvement shown in the treatment group of the FIX-HF-5 study [13]. Similarly, both groups had mean changes of peakVO_2 in the range of 0.10–0.34 ml/kg/min, which is similar to the approximately 0.25 ml/kg/min change in the treatment group of the FIX-HF-5 study (Fig. 4).

The change in peak VO_2 did not achieve statistical significance in either group of the current study, and there was no difference between the groups. A likely reason for the lack of significance of the change in peak VO_2 is the comparison to baseline rather than to a non-treated control group where peak VO_2 would tend to deteriorate. This is similar to findings in prior studies [10,13].

There were a larger than expected number of dropouts encountered. Some subjects crossed over from Group A to Group B due to clinically indicated reasons. To account for these crossover events, data were analyzed both by ITT and PP, which revealed that the crossover did not alter the interpretation of the results.

Analyzing by ITT, both groups experienced similar numbers of SAEs. There were no statistically significant differences between groups in the percentage of patients experiencing at least one SAE by either ITT or PP comparison. Similarly, no difference was observed between the groups in the percentage of patients experiencing at least one SAE in any of the cardiac-related categories. Overall, the frequency of reported adverse events are typical of patients suffering from HF.

Adverse events were sporadic and varied between the groups. For example incidents of atrial fibrillation, worsening HF, and irregular heart beats/shock tended to be prevalent in one group compared to other events in the other group, but even still the overall numbers in each group are within the range expected based on prior safety studies, and not statistically different between the groups. Since the implant procedure was identical between the groups and since the safety of this therapy has already been determined, one would not expect to observe differences between the groups in safety aspects. Therefore the study was designed to assess efficacy and was not powered to detect differences in safety. No deaths occurred during this study in any group. Studying more subjects over a longer period would be needed to determine if any differences in SAE rate might potentially exist between the groups, and would help to better refine the interpretation regarding SAEs, although one would intuitively expect fewer CCM-dependent adverse effects with a future device having a single vs. dual lead being implanted.

Our findings support the use of CCM therapy through one versus two ventricular leads in patients with chronic HF. These results support greater feasibility of using CCM in eligible patients, because of similar efficacy with two leads but with the opportunity for a more streamlined implantation procedure and the expectation of potentially reduced lead complications over time.

Limitations

Despite the design with power to demonstrate non-inferiority, this was a small study that did not have a control group. As a result, the changes in peak oxygen consumption were not significant as they were compared to baseline rather than to control. However, in larger published studies [10,11] CCM has been shown to change exercise performance including peakVO_2 vs. baseline, which was a clinically and statistically significant improvement compared with a non-treated control group.

The two endpoints that did demonstrate significant improvement from baseline after CCM therapy are subjective in nature and might be biased by a placebo effect (FIX-HF-4 study) [10]. However, it was seen in the FIX-HF-4 study that the placebo effect faded after 3 months and was no longer observed at 6 months – even though the benefit of active therapy persisted. Therefore, the duration of the present study extends beyond the time course of any suspected improvement due to placebo. Likewise, it was also seen in the FIX-HF-5 study and in other publications related to long-term benefit with CCM that these improvements are sustained over periods of a year and beyond [11–13].

In addition, some patients that were randomized to signal delivery through two leads (the intention to treat) eventually had the system configured to 1-lead signal delivery by physician decision (per treatment protocol). In order to handle these changeovers, the randomization was adjusted, and the analysis was done twice – per intention to treat and per actual setting (per treatment protocol). Confirmation of these findings in future studies with a broader cross-section of patients could help to define if there are subpopulations that benefit more or less from the single-lead configuration.

Conclusion

After 6 months of CCM therapy, efficacy in treatment of HF was similar whether one or two ventricular leads deliver the CCM signal. There were no significant differences between groups for any of the study endpoints. Adverse events were sporadic and varied between groups, but the incidence was not statistically different between groups and was in the range expected from this HF population. This study suggests that CCM delivered through one lead was not inferior to CCM delivered through two leads after

about 6 months of therapy. These findings may have positive implications in supporting future devices with fewer leads, that can potentially shorten the duration and complexity of the CCM implantation procedure, reduce typical risk associated with chronic implantable device therapy, and support combined implantation with other devices such as ICDs.

Conflict of interest

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

SR, AK, JK and MB have received modest speaker fees from Impulse Dynamics. DG is a consultant for Impulse Dynamics. BR is an employee of Impulse Dynamics. SS, TL, UE – none.

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