

Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure

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Aims

We performed a randomized, double blind, crossover study of cardiac contractility modulation (CCM) signals in heart failure patients.

Methods and results

One hundred and sixty-four subjects with ejection fraction (EF) < 35% and NYHA Class II (24%) or III (76%) symptoms received a CCM pulse generator. Patients were randomly assigned to Group 1 ($n = 80$, CCM treatment 3 months, sham treatment second 3 months) or Group 2 ($n = 84$, sham treatment 3 months, CCM treatment second 3 months). The co-primary endpoints were changes in peak oxygen consumption ($VO_{2,peak}$) and Minnesota Living with Heart Failure Questionnaire (MLWHFQ). Baseline EF ($29.3 \pm 6.7\%$ vs. $29.8 \pm 7.8\%$), $VO_{2,peak}$ (14.1 ± 3.0 vs. 13.6 ± 2.7 mL/kg/min), and MLWHFQ (38.9 ± 27.4 vs. 36.5 ± 27.1) were similar between the groups. $VO_{2,peak}$ increased similarly in both groups during the first 3 months (0.40 ± 3.0 vs. 0.37 ± 3.3 mL/kg/min, placebo effect). During the next 3 months, $VO_{2,peak}$ decreased in the group switched to sham (-0.86 ± 3.06 mL/kg/min) and increased in patients switched to active treatment (0.16 ± 2.50 mL/kg/min). MLWHFQ trended better with treatment (-12.06 ± 15.33 vs. -9.70 ± 16.71) during the first 3 months, increased during the second 3 months in the group switched to sham ($+4.70 \pm 16.57$), and decreased further in patients switched to active treatment (-0.70 ± 15.13). A comparison of values at the end of active treatment periods vs. end of sham treatment periods indicates statistically significantly improved $VO_{2,peak}$ and MLWHFQ ($P = 0.03$ for each parameter).

Conclusion

In patients with heart failure and left ventricular dysfunction, CCM signals appear safe; exercise tolerance and quality of life (MLWHFQ) were significantly better while patients were receiving active treatment with CCM for a 3-month period.

Keywords

Heart failure • Cardiopulmonary stress test • Minnesota Living with Heart Failure Questionnaire • Event-free survival

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Introduction

Medical and device-based therapies have favourably impacted on outcomes in patients with chronic heart failure (CHF). Cardiac resynchronization therapy (CRT) has become the standard of care for patients with symptomatic heart failure and delayed myocardial activation, indexed by a prolonged QRS duration.¹ CRT improves ventricular contractile strength, quality of life, exercise tolerance, and reduces mortality and hospitalizations. However, it is estimated that less than half of heart failure patients have dyssynchrony² and as many as 30% of implanted patients are considered non-responders.³

A new form of electrical therapy, called *cardiac contractility modulation* (CCM), was proposed for enhancing ventricular contractile strength independent of the synchrony of myocardial contraction.^{4,5} Preclinical studies indicate that CCM signals can enhance contractile performance acutely^{4,6} and that normalization of myocardial gene programmes, protein phosphorylation, and reverse remodelling are implicated during long-term CCM signal delivery in animal models of heart failure.⁷

CCM signals are delivered 30–40 ms after detection of local myocardial activation during the absolute refractory period. Thus, although ~100 times the amount of energy is delivered during a CCM pulse than during a standard pacemaker impulse, these signals do not initiate a contraction, recruit additional contractile elements, or modify the activation sequence and there is no additional action potential (as would be observed with paired pacing or post-extra systolic potentiation).

Initial non-randomized clinical studies with short-term application of these CCM signals in patients with heart failure have demonstrated acute haemodynamic effects and suggested improved quality of life and ventricular function.⁵ More recently, a small double blind feasibility study in 49 patients provided preliminary evidence of safety and trends to improve exercise tolerance and quality of life.⁸ Here, we describe the results of a prospective, randomized, double blind multicentre study of the safety and efficacy of CCM signals.

Methods

Patients

Patients were eligible for participation if they were older than 18 years, had symptomatic heart failure (New York Heart Association functional class \geq II), ischaemic or idiopathic cardiomyopathy, left ventricular ejection fraction (EF) \leq 35%, and peak oxygen uptake ($VO_{2,peak}$) between 10 and 20 mL O_2 /min/kg. Patients were required to be on appropriate, stable medical treatments for heart failure, including (unless shown to be intolerant) a diuretic, an angiotensin-converting enzyme inhibitor and/or angiotensin-receptor blocker and a beta-blocker. Patients could have a pre-existing implanted pacemaker or ICD or, if clinically indicated, could have one implanted at the same time as the experimental CCM device. Patients were excluded if they were eligible for CRT, if they had atrial fibrillation, recent myocardial infarction (within 3 months), clinically significant angina, were hospitalized for heart failure requiring intravenous treatments within 30 days, or \geq 8900 PVCs/24 h on a baseline Holter monitor recording. The Ethics Committee of each centre approved the study protocol and all patients provided written informed consent.

Study design

Patients meeting basic study entry criteria underwent baseline evaluations that included the following tests: New York Heart Association (NYHA) class, 6 min hall walk test (6MW), maximal cardiopulmonary exercise treadmill exercise test (customized slow ramp protocol), quality of life assessment using the Minnesota Living with Heart Failure Questionnaire (MLWHFQ), a two-dimensional echocardiogram, and a 48 h Holter monitor test. Patients fulfilling entry criteria underwent implantation of an OPTIMIZER™ System (IMPULSE Dynamics, Orangeburg, NY, USA) which consisted of an implanted pulse generator and three pacing leads (a standard right atrial lead and two active fixation leads inserted into the right ventricular septum).⁵ Haemodynamic responses to acute CCM signal application were measured with a micromanometer catheter (Millar Instruments, Houston, TX, USA) placed in the LV. It was required that the maximum rate of left ventricular pressure rise (dp/dt_{max} , an index of systolic function) increases at least 5% in response to CCM. If such changes could not be achieved, even after repositioning the electrodes, the device was not implanted and the patient was withdrawn from the study.

Patients who underwent successful implantation were randomly assigned either to an active CCM treatment (Group 1: device programmed to deliver CCM signals for seven 1 h periods spaced equally over the day) or to a sham treatment group (Group 2: device programmed to OFF) for 12 weeks (study Phase I). During the subsequent 12-week period (study Phase II), all subjects crossed over to the opposite treatment. Randomization occurred 2–4 weeks following the OPTIMIZER System implant. An unblinded site clinical investigator opened a sealed envelope containing the randomization assignment and a technician programmed the device accordingly. Randomization codes were prepared and distributed by the data coordinating centre (Analytica International GmbH, Loerrach, Germany).

Following the 24-week blinded period, subjects were offered open label access to CCM treatment. This report will deal with the 24-week blinded study period.

The major follow-up visits occurred 12 and 24 weeks following randomization, at the end of Phase I and Phase II, respectively. Cardiopulmonary stress testing, MLWFQ, 6MW, and NYHA were repeated at these visits. Substantial efforts were made to maintain blinding of both patients and investigators. Specifically, devices were programmed to OFF by a technician not involved with the clinical follow-up or evaluation of the patients preventing detection of patient assignment by the testing physician. Devices were reprogrammed at the end of each visit to ON or OFF according to group assignment by the same technician.

A core lab blinded to assignment group was used to assess peak oxygen consumption ($VO_{2,peak}$) from the cardiopulmonary stress test.

Statistics

The prospectively defined co-primary efficacy endpoints of this study were the difference between end of phase measurements of $VO_{2,peak}$ and MLWHFQ. The statistical analysis compared each endpoint between randomization groups using the classical methods described by Fleiss⁹ and Armitage and Hills¹⁰ for the analysis of data from a two-period crossover study. The analysis is based on a *t*-test comparing the mean within-patient differences measured between the end of study Phase I and the end of study Phase II. Our strategy was to first assess whether there was evidence of a carryover effect as we believe the use of data from both periods would only be reasonable in the absence of such an effect. If no evidence of a carryover effect could be found, we would test for treatment differences using

the aforementioned *t*-test. The *t*-test is based on the contrast formed by the end of period measures.

Sample size calculations were performed assuming that the standard deviation of the difference in $VO_{2,peak}$ between periods of active and sham therapy is 2.75 $O_2/kg/min$. On the basis of a two-side 0.05 level *t*-test, a total sample size of 160 provides 80% power to detect a within-patient difference of 0.90 $ml O_2/kg/min$ or more in $VO_{2,peak}$ between periods of active and sham treatment.

Assessment of the primary null hypotheses was based on the intent-to-treat principle. We accounted for missing data using multiple imputation (MI) using a Markov chain Monte Carlo approach to simulate period differences (15 simulated data sets were created). Those data sets were analysed by the standard method for crossover studies (i.e. as described in Fleiss and discussed above), and the results were combined to produce estimates and confidence intervals as described by Rubin.¹¹ The variables used for the imputation were gender, QRS duration, heart failure aetiology (ischaemic or non-ischaemic), the baseline value of the respective endpoint ($VO_{2,peak}$ and MLWHFQ) and end of period values for $VO_{2,peak}$ for imputations of MLWHFQ, and end of period values of MLWHFQ for imputations of $VO_{2,peak}$. The imputations were performed using PROC MI and PROC MIANALYZE in SAS version 9.1. With regard to completeness of data, 66 Group 1 and 69 Group 2 had $VO_{2,peak}$ data at the end of

both study phases; 72 Group 1 and 73 Group 2 patients had MLWHFQ data at the end of both study phases.

Secondary efficacy endpoints included comparisons of changes in NYHA and 6MW. Summary values in tables and figures are expressed as mean \pm SD except as otherwise noted.

A data safety and monitoring board (DSMB) reviewed serious adverse events on three separate occasions during the course of the study to advise the sponsor of any imbalances in events between the groups that might be suggestive of safety concerns. No such concerns were ever raised.

Results

The overall flow of study subjects is summarized in Figure 1. Between May 2002 and May 2005, 181 potential study subjects signed informed consent to undergo baseline testing. Of these, 178 passed baseline screening and underwent the OPTIMIZER System implantation procedure. In response to acute CCM signal application, left ventricular dP/dt_{max} increased by $<5\%$ in 12 (6.7%) subjects; the device was not implanted in these subjects and they were withdrawn from the study.

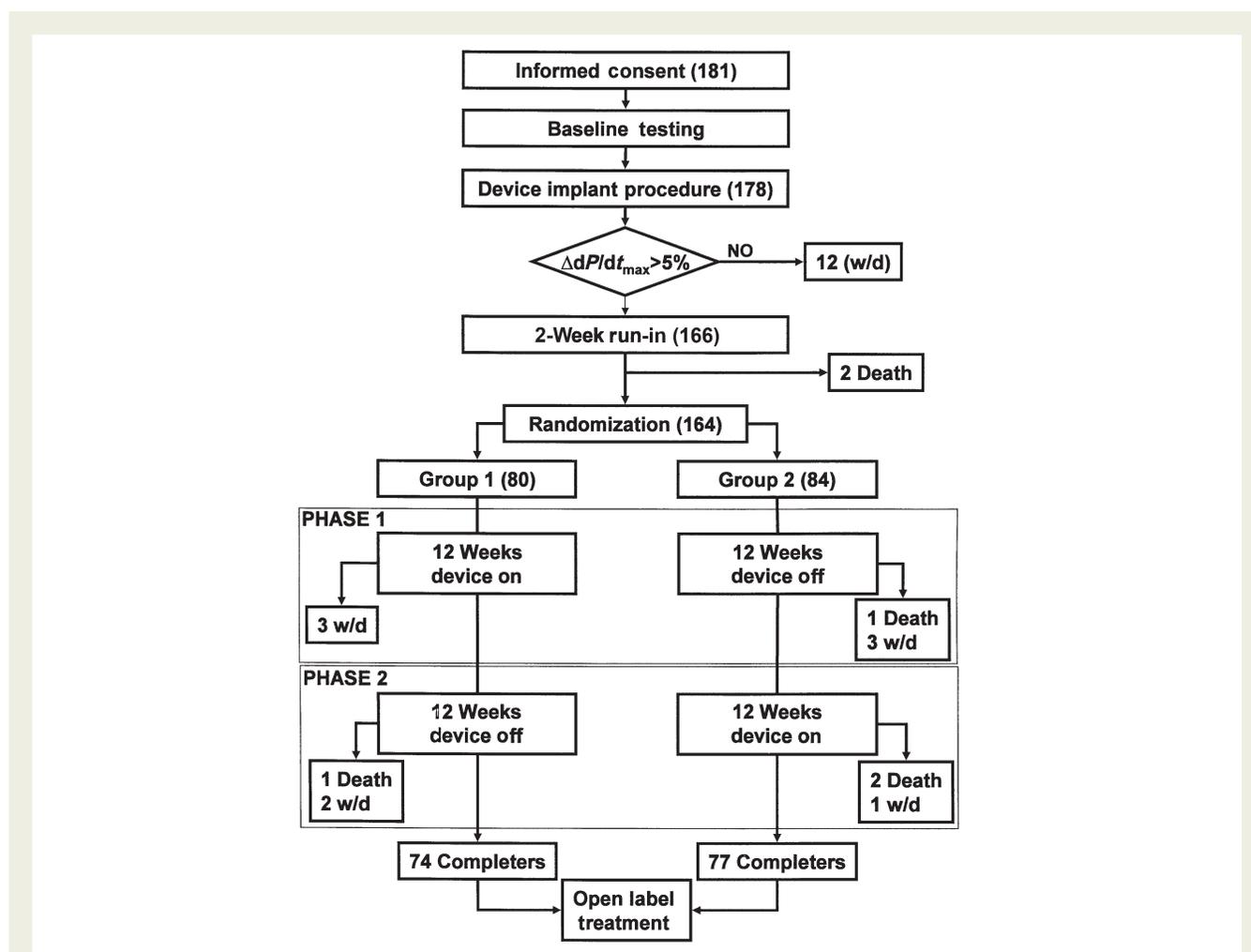


Figure 1 Summary of the study design and flow of patients. See text for details. w/d indicates subjects who are withdrawn from the study. dP/dt_{max} is maximal rate of rise of left ventricular pressure measured during the implant procedure.

For the remaining subjects, the mean (\pm SD) acute rise in dP/dt_{\max} was $10.7 \pm 0.8\%$. The duration of the procedure to implant the OPTIMIZER device was 172 ± 74 min (range 60–330 min); the average implant duration did not vary significantly if the patient had a prior ICD or not. With regard to placement of the two RV leads, the goal was to achieve a separation of 2 cm or more. On the basis of fluoroscopic assessments at the time of implantation, the distribution of placement of the first RV lead was: outflow track (52%), inferior septal wall (16%), apical region of the septum (17%), or mid-septal wall (15%). For the second RV lead, the distribution of placement was: outflow track (13%), inferior septal wall (38%), apical region of the septum (33%), and mid-septal wall (16%). Sensing thresholds (13 ± 6 mV), pacing thresholds (0.8 ± 0.7 mA), and impedances (573 ± 118 ohms) were similar for both leads.

Two of the patients who underwent device implantation died before randomization (one \sim 1 week after implantation due to ventricular fibrillation and the other 2 days after implantation due to worsening heart failure and renal dysfunction). CCM was never activated in these patients. Of the remaining 164 study subjects, 80 were randomized to Group 1 (CCM ON for first 12

weeks) and 84 were randomized to Group 2 (CCM OFF for first 12 weeks). Four subjects died during the randomized portion of the study. Nine additional patients withdrew from the study (two for continuous pocket infection, three who underwent heart transplant, one who developed an indication for CRT, and three for continued worsening of heart failure). The remaining subjects ($n = 74$ in Group 1, $n = 77$ in Group 2) completed the 6-month primary follow-up period.

Baseline characteristics

Demographics and baseline characteristics of all patients who underwent device implantation procedure are summarized in Table 1. The groups were reasonably well balanced for all characteristics, except that there was a greater proportion of patients with ischaemic cardiomyopathy in Group 1. Baseline features of note included average EF 29%, $VO_{2,\text{peak}}$ 13.9 mL/kg/min, and QRS duration 118 ms; 62% of subjects had an ICD. Pharmacological treatment for heart failure was comparable between the groups. There were no distinguishing features of the 17 subjects who were not randomized compared with the other study subjects.

Table 1 Baseline demographics (numbers are either mean \pm SD or percentages)

	Group I (n = 80)	Group II (n = 84)	NR (n = 17)
Age (years)	58.9 \pm 9.8	59.9 \pm 10	57.4 \pm 11.4
Gender	71 (88.8%) M 9 (11.2%) F	68 (81%) M 16 (19%) F	15 (88.2%) M 2 (11.8%) F
CHF aetiology			
Ischaemic	51 (63.8%)	47 (56%)	13 (76.5%)
Idiopathic	28 (35%)	32 (38%)	4 (23.5%)
Other	1 (1.2%)	5 (6%)	
Resting HR (b.p.m.)	71 \pm 11.3	72.6 \pm 12.7	74.2 \pm 12.2
Systolic BP (mmHg)	114.7 \pm 17	117.1 \pm 17.9	120 \pm 19.6
QRS Duration (ms)	119.9 \pm 28.3	116.3 \pm 26.6	121.5 \pm 33.5
NYHA			
II	22 (27.5%)	17 (20%)	4 (23.5%)
III	58 (72.5%)	67 (80%)	13 (76.5%)
MLWHFQ	38.9 \pm 27.4	36.5 \pm 27.1	40.8 \pm 26
6 min walk (M)	386 \pm 103	394 \pm 102	406 \pm 88
Peak VO_2 (ml O_2 /min/kg)	14.1 \pm 3	13.6 \pm 2.7	13.2 \pm 2
EF (%)	29.3 \pm 6.6	29.8 \pm 7.8	25.3 \pm 11.7
LV EDD (mm)	69.3 \pm 9.1	68.3 \pm 7.7	69.8 \pm 10.2
Treatments			
Patients with ICD	54 (67%)	48 (57%)	9 (53%)
Patients with PM	1 (1.3%)	2 (2.4%)	1 (5.9%)
Medications			
Diuretics	61 (76%)	68 (81%)	16 (94.1%)
ACE-I	58 (72.5%)	61 (73%)	12 (71%)
ARB	13 (16%)	19 (23%)	1 (6%)
β -blocker	62 (77.5%)	65 (77%)	14 (82%)
Aldosterone inhibitor	33 (41%)	41 (49%)	10 (59%)
Digoxin	31 (39%)	35 (42%)	12 (71%)

NR, not randomized due to inability to increase dP/dt_{\max} by $\geq 5\%$ in response to acute CCM signal application during implant and other.

In order to assess the degree of unblinding, blinded physicians and patients were polled at the last study visit to determine if they became aware of their group assignment. In only two patients, both in Group 1, was it apparent that unblinding had occurred.

Primary efficacy assessments

During Phase I, $VO_{2,peak}$ increased similarly in both groups by ~ 0.4 mL/kg/min, independent of whether the device was turned on or off (Figure 2). In the second phase of the study, however, $VO_{2,peak}$ remained increased in subjects who crossed over from sham to active treatment, whereas $VO_{2,peak}$ decreased by ~ 0.8 mL/min/kg in subjects who crossed from active treatment to sham. A formal test of carryover effect was performed and none was noted ($t = 0.055$, $P = 0.96$). Likewise no significant period effect was noted ($t = 1.43$, $P = 0.15$). Mean (\pm SD) $VO_{2,peak}$ improved significantly while on active therapy compared with sham therapy by 0.52 ± 1.39 O₂/kg/min ($t = 2.16$, $P = 0.032$, 95% confidence interval, 0.04–0.99).

MLWHFQ (Figure 3) improved in both groups during Phase I, but the improvement tended to be better in subjects receiving active treatment (Group 1). As with $VO_{2,peak}$, MLWHFQ trends back towards baseline when Group 1 subjects crossed from active to sham treatment and there was continued improvement in Group 2 subjects who crossed from sham to active treatment.

As for $VO_{2,peak}$, no carryover effect ($t = 1.54$, $P = 0.13$) or period effects ($t = 1.67$, $P = 0.096$) were noted. Mean (\pm SD) values of MLWHFQ score improved significantly while on active therapy compared with sham therapy by 2.93 ± 8.01 ($t = 2.20$, $P = 0.030$, 95% confidence interval 0.29–5.56).

Significant differences ($P < 0.05$) were also noted for both $VO_{2,peak}$ and MLWHFQ when using both a last observation carried forward (LOCF) approach and the MI approach to account for missing data. The estimated treatment effect was very similar for all analyses. Quantitative summary of data shown in these figures is provided in Table 2.

Secondary efficacy assessments

Changes in 6-min hall walk test (Figure 4 and Table 2) paralleled changes in $VO_{2,peak}$, increasing similarly in both groups during the first phase, increasing further in Group 2 upon crossing over to active treatment, and decreasing in Group 1 upon crossing over to sham treatment.

New York Heart Association classification improved significantly but similarly in both groups in both phases of the study. For Group 1 subjects, the percent of patients in Classes I, II, III, and IV at the final follow-up (when the device was turned off) was 8, 46, 24, and 2%, respectively. This was compared with 9, 50, 23, and 2%, respectively, in Group 2 subjects.

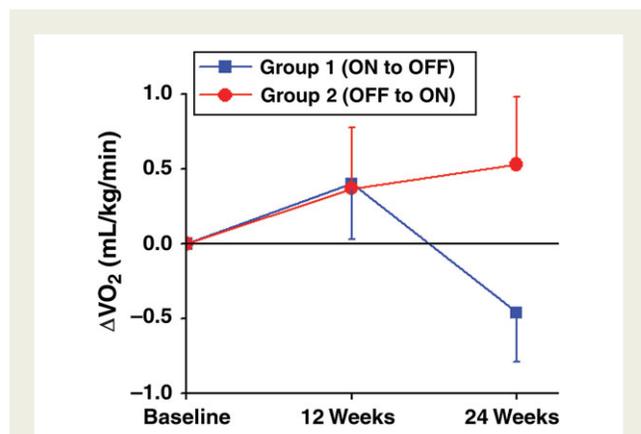


Figure 2 Changes in $VO_{2,peak}$ in each group compared with their respective baseline values. Results presented for the cases with complete data; these results agree substantively with those based on multiple imputation. Values are means \pm SEE.

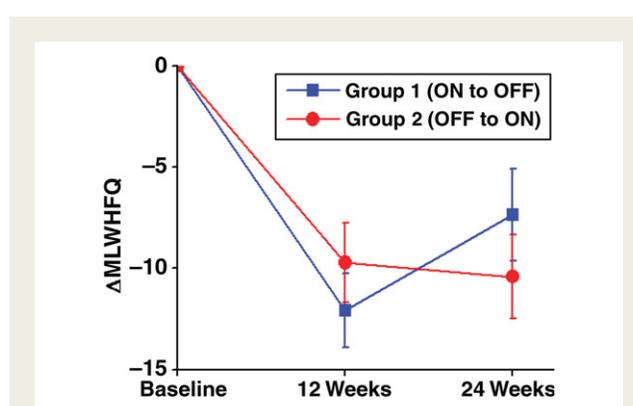


Figure 3 Changes in Minnesota Living with Heart Failure Questionnaire in each group compared with their respective baseline values. Results presented for the cases with complete data; these results agree substantively with those based on multiple imputation. Values are means \pm SEE.

Table 2 Numerical summary of results presented in Figures 2–4 (mean \pm SEE)

	Difference from baseline			
	Phase I		Phase II	
	Group 1	Group 2	Group 1	Group 2
Peak VO_2 (mL/kg/min)	0.40 ± 0.37	0.37 ± 0.41	-0.46 ± 0.33	0.53 ± 0.45
MLWHFQ	-12.1 ± 1.8	-9.7 ± 2.0	-7.4 ± 2.2	-10.4 ± 2.1
6MW (m)	16.9 ± 8.9	10.8 ± 8.8	-6.3 ± 10.4	19.6 ± 9.1

Echocardiograms were performed at baseline and at the end of study Phases I and II. Interpretable studies were obtained in approximately half of the patients. There were no significant changes in EF detected in any group at any time point in this small sampling of patients.

Safety assessments

There were six deaths during the study, two prior to randomization (ventricular fibrillation and worsening heart failure), one in Group 1 during the OFF period (undetermined cause), one in Group 2 during the OFF period, and two in Group 2 during the ON period (sudden cardiac death and renal failure).

In total, there were 48 serious adverse events in 40 patients during CCM OFF periods, compared with 45 serious adverse

events in 41 patients during CCM ON periods. There were 46 hospitalizations in 31 patients during CCM OFF periods, compared with 41 hospitalizations in 31 patients during CCM ON periods. The major reasons for hospitalizations were similar in the groups and included worsening heart failure and pneumonia.

An overview of serious cardiovascular adverse events is provided in Table 3. The most frequently reported events were episodes of decompensated heart failure, atrial fibrillation, bleeding at the OPTIMIZER System implant site, and pneumonia. There were no significant differences between ON and OFF phases in the number or types of adverse events. Adverse events specifically related to the device and/or the procedure as reported by the investigators included lead dislodgement, device pocket infections, bleeding at the insertion site, and pericardial effusion. Investigators listed several other events as being of 'unknown' relationship to the device and/or procedure, including atrial fibrillation, episodes of heart failure exacerbations, cardiogenic shock, angina, ventricular tachycardia, and ICD sensing defect.

Because of the crossover design, hospitalizations and mortality were analysed for the first period only. In all, there were 14 hospitalizations Group 1 patients (CCM ON phase) compared with 20 hospitalizations in Group 2 patients (CCM OFF phase). In addition, there was one death in a Group 2 patient vs. no deaths in Group 1 patients. With the relatively small sample size, the difference in overall event-free survival between groups did not reach statistical significance ($P = 0.31$).

Another safety endpoint in the study was an evaluation of whether the use of the OPTIMIZER™ Systems was associated with changes in the incidence and nature of arrhythmias assessed by Holter monitoring. At baseline, the total number of PVCs/hour was balanced between the groups with median (range) values of 21 (0–511) and 25 (0–712) in Groups 1 and 2,

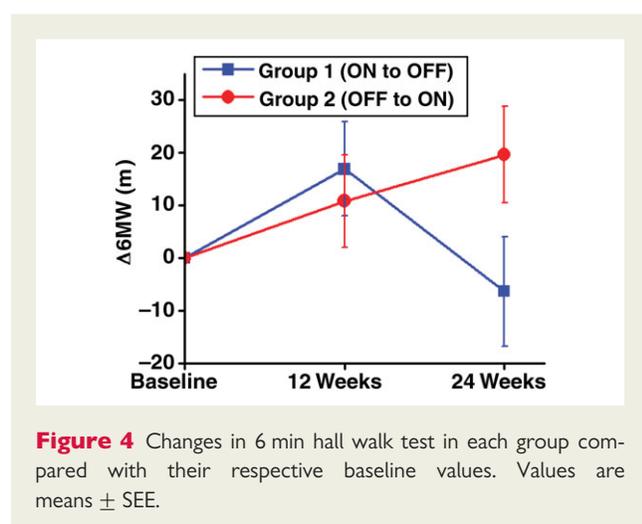


Figure 4 Changes in 6 min hall walk test in each group compared with their respective baseline values. Values are means \pm SEE.

Table 3 Serious cardiovascular adverse events by treatment period [number of events (number of patients)]

	Pre-implant	Implant to randomization	Active	Sham
Number of Subjects	178	166	164	164
Total*	1	20 (20)	22 (20)	26 (22)
CHF decompensation	—	1 (1)	7 (6)	8 (8)
Atrial fibrillation	—	—	2 (2)	3 (3)
Bleeding at OPTIMIZER Site	—	4 (4)	—	—
Pneumonia	—	2 (2)	—	3 (3)
VF	—	—	1 (1)	1 (1)
VT	1 (1)	2 (2)	3 (2)	—
Angina	—	—	1 (1)	3 (2)
Optimizer II pocket infection	—	1 (1)	1 (1)	3 (2)
ICD sensing defect**	—	4 (4)	1 (1)	—
Renal failure	—	—	1 (1)	3 (1)
Pulmonary oedema	—	—	1 (1)	1 (1)
Pericardial effusion	—	1 (1)	1 (1)	—
Cardiogenic shock	—	—	1 (1)	—
Optimizer II lead dislodgement	—	2 (2)	1 (1)	—

There were no statistically significant differences in the rate of events between active and sham periods (McNemar's statistic based on the exact binomial probability).

*Includes all serious events reported by investigators.

**All due to either T-wave over-sensing or the need for ICD lead repositioning.

respectively. During ON periods, there was a median of 20 (0–777) and 17 (0–459) PVCs/hour in Groups 1 and 2, respectively, compared with 16 (0–1007) and 15 (0–764) during the OFF periods. In addition, there were no significant differences in other Holter parameters between baseline and follow-up in either group.

Discussion

A large number of patients have symptomatic heart failure, despite all available treatments. Although CRT is a viable option for such patients also having dyssynchronous ventricular activation/contraction, <50% of heart failure patients meet criteria for implantation of a CRT device.² In addition, as many as 30% of patients receiving a CRT device are considered as ‘nonresponders’.¹² Thus, a treatment delivered by an implantable pulse generator through standard pacing leads that can provide similar clinical benefits in patients independent of the synchrony of ventricular contraction could significantly enhance the therapeutic armamentarium for heart failure.

Initial clinical study of CCM involved short-term (10–30 min) signal application using temporarily placed electrodes.⁵ The results of those studies showed the feasibility of delivering CCM treatment and demonstrated that left ventricular systolic performance could be acutely enhanced as was shown in earlier pre-clinical studies.⁴ Other studies showed these acute enhancements of contractile state were not associated with changes in myocardial oxygen consumption.^{13,14} Most recently, a multicentre, double blind feasibility study of 49 patients in the USA provided additional confirmations of safety and, despite the small number of patients, trends in efficacy with regard to exercise tolerance and quality of life.⁸ Fashioned after the MUSTIC (Multisite Stimulation in Cardiomyopathies) study of CRT,¹⁵ the present study represents the next important step in the clinical evaluation of CCM as a therapy for heart failure.

Patients who showed an acute response to CCM (93% of enrolled patients) were randomly assigned to immediate CCM treatment or sham treatment for 3 months, followed by crossover to the opposite group for an additional 3 months. A significant placebo effect (much more pronounced than reported in similar studies) was observed in the present study so that efficacy parameters improved significantly and similarly in both treatment and control groups during the first phase of the study. This can be attributed to the extreme measures taken to ensure blinding of both patients and investigators during the study period. During study Phase II, following crossover, patients switched to active treatment demonstrated maintained or even continued clinical improvement, whereas those crossing to sham treatment generally showed a return in clinical status back towards baseline such that there were statistically and clinically significant differences between the groups in the primary endpoints. Although our analysis showed no evidence of carryover effect from the first to second phase of the study, the study had relatively low power to detect such an effect. However, if a carryover were in fact present, it would be evident in the group switched from active to sham therapy (i.e. in Group 1), and not in the group switched from sham to active therapy. Therefore, if carryover did exist, it would likely have reduced the estimated treatment benefit, not

inflate it. Thus, in this regard, we believe that the estimates of the treatment effects are conservative.

With regard to safety, two patients died following implant, but prior to randomization or CCM signal delivery; although there was no specific link between these deaths and adverse events, it cannot be excluded that factors related to the implant were contributory. Overall, the incidences of death and adverse events were relatively low and were balanced between active and sham treatment during the randomized phases of the study. There was a trend for a reduction in hospitalizations in patients receiving active treatment. On the whole, this suggests that this form of treatment is safe in the target patient population with a trend for reduction in hospitalizations.

In order to put the present results into clinical perspective, it is relevant to compare and contrast our findings with CCM in CHF patients with narrow QRS duration to those obtained in CHF patients with prolonged QRS duration in response to CRT. As noted above, the present randomized, 3-month double blind, crossover study design was fashioned after the MUSTIC study of CRT.¹⁵ Thus, the results of that study are most pertinent. The MLWHFQ results of the two studies are compared in *Figure 5*. *Figure 5A* shows results from Group 1 patients (device ‘on’ first, then ‘off’) whereas *Figure 5B* shows results from Group 2 (device ‘off’ first, then ‘on’). As seen, results in Group 1 patients are nearly identical in both studies for both ‘on’ and ‘off’ phases. In Group 2 patients, the placebo effect is much more prominent in the present CCM study, i.e. patients with device ‘off’ first showed little improvement in the MUSTIC study. Thus, the main difference in findings between the studies is explained by the lack of a placebo effect in the MUSTIC study. These findings are similar to those obtained with the 6MW test as shown in *Figure 5C* and *D*. With regard to $VO_{2,peak}$, comparison of results from several studies of CRT in patients with prolonged QRS duration (all showing results with 6 months of treatment except for the MUSTIC study)^{12,15–17} to those of the present study are shown in *Figure 6*. Also included are the previously published results of a double blind placebo controlled feasibility study of CCM in patients followed for 6 months (Phase 1 of the FIX-HF-5 study).⁸ As seen, the overall impact of CCM on $VO_{2,peak}$ is slightly less than that reported in the studies of CRT. Thus, on the whole, the findings of the present study show CCM to be of comparable impact on quality of life and exercise tolerance as CRT, albeit in a different patient population.

Ongoing basic research focuses on newly recognized mechanisms by which myocardial properties appear to be influenced by CCM signals, particularly in the chronic setting. For example, results of recent studies suggest that within 6 h of CCM signal delivery, there are significant changes in myocardial gene expression (including a reversal of several aspects of the foetal gene programme expressed in heart failure), improved expression, and phosphorylation of the sodium–calcium exchanger, phospholamban, and connexin 43.⁷ Restoration of normal gene expression profiles have also been confirmed in a subset of the patients participating in the present study as summarized in a recent preliminary report.¹⁸

One potential concern associated with the concept of CCM treatment relates to its inotropic actions. Prior attempts at pharmacological inotropic therapy with β -agonists and phosphodiesterase inhibitors (i.e. milrinone), which act directly via cAMP

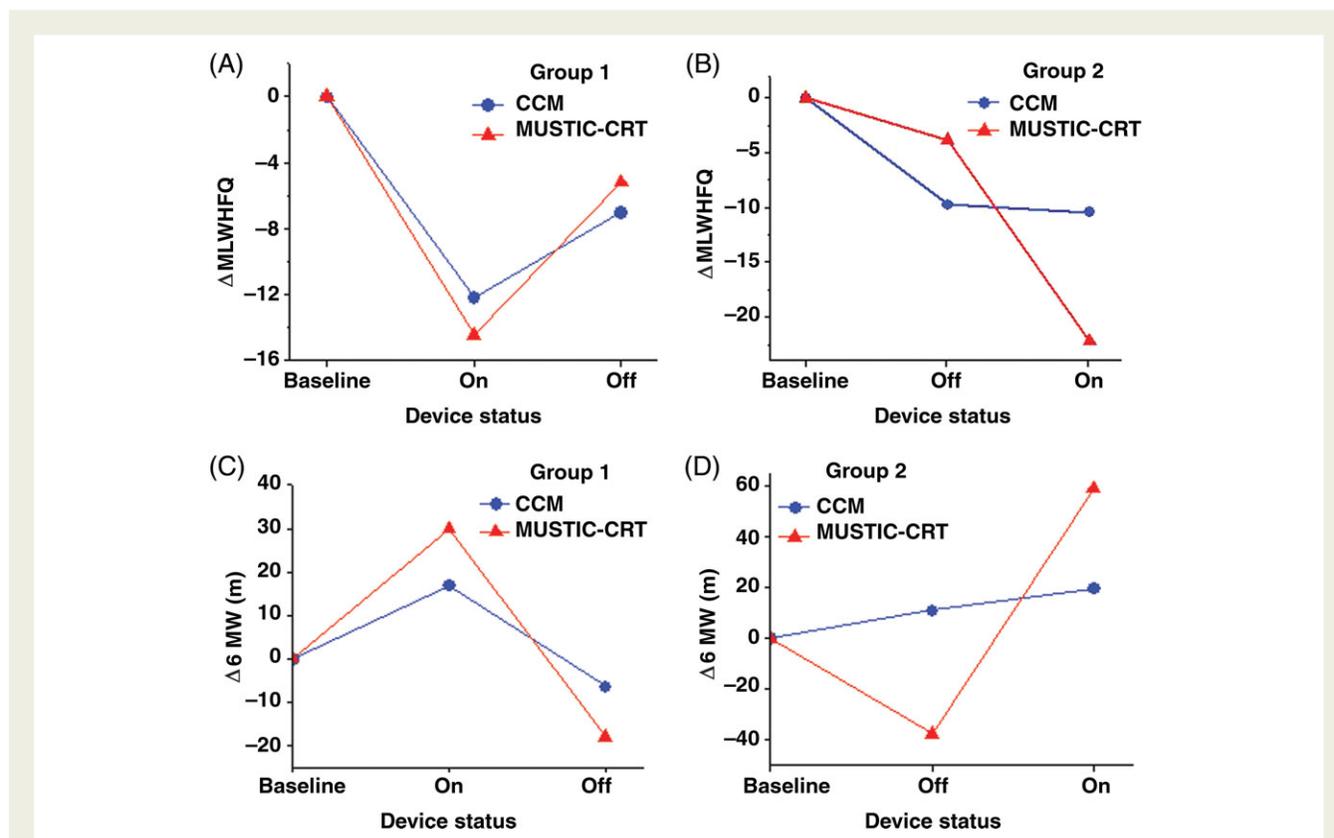


Figure 5 Results of the present study are compared with those of the MUSTIC study¹⁵ of cardiac resynchronization therapy. A and C show MLWHFQ and 6MW results from study subjects in which the respective device was 'ON' for the first 3 months and 'OFF' for the second three months. B and D show results for same parameters from study subjects in which the respective device was 'OFF' for the first 3 months and 'ON' for the second three months. The main difference in the results of the two studies for both parameters is in Study Group 2, first study phase; subjects in the present study show a placebo effect which is absent from the MUSTIC study. See text for further details.

mechanisms, resulted in worsened outcomes.¹⁹ However, we have seen more recently that the mechanism by which inotropy is achieved impacts on the safety profile of a particular treatment. For example, β -blockers and CRT, treatments which increase ventricular contractile strength via mechanisms not directly related to cAMP pathways, are associated with improved survival. In addition, the use of β -blockers and ICDs have been introduced since the early studies of inotropic agents; these treatments have the potential to impact on the safety profile of other forms of treatment.

Available evidence from animal models and patients indicate that CCM enhances contractile performance without increasing myocardial oxygen consumption. Furthermore, clinical studies available thus far have shown lack of increases in ambient ectopy.²⁰ The present study adds significantly to the body of evidence suggesting CCM treatment to be safe and devoid of deleterious effect on the myocardium with regard to both contractile performance and arrhythmias (specifically, no noted increased incidences of ICD firings or arrhythmic deaths).

Potential limitations

One limitation of this study is the relatively short duration to which subjects were exposed to CCM treatment (3 months). Many therapies, including β -blockers and CRT, require relatively long

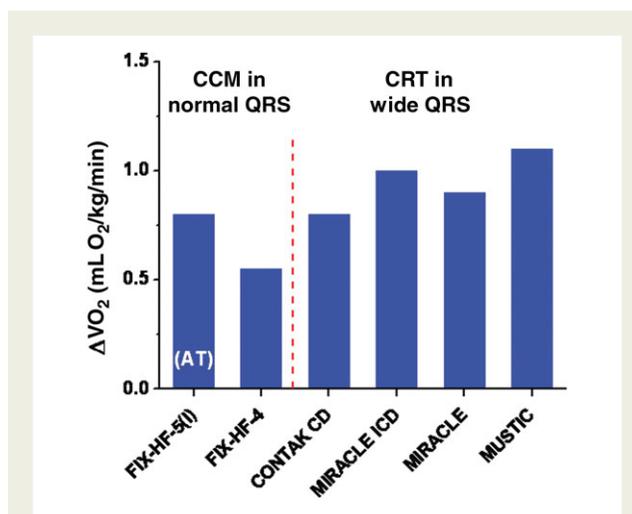


Figure 6 Comparison of the effect of CCM on Δ VO_{2,peak} to that observed in prior studies of CRT in patients with prolonged QRS duration. Studies for comparison include MUSTIC,¹⁵ MIRACLE,¹² Contak-CD,¹⁶ and MIRACLE ICD.¹⁷ In addition, results of one prior feasibility study of CCM, the FIX-HF-5 (Phase I), which measured anaerobic threshold as the primary endpoint is also included.⁸

time periods to reach their maximal effects. Thus, it is possible, if not likely, that the clinical impact of CCM treatment may continue to grow over longer periods of time. One aspect where this is most evident is the lack of detectable changes in the echocardiographically determined EF. This position is reinforced by experience with CRT; results of the MIRACLE study showed that after 3 months of treatment, there was only a 1.5% difference increase in EF in the treatment compared with the control group.²¹ With 6 months of follow-up, several studies of CRT show more significant increases in EF over sham treatment (e.g. a 2.3% increase in the CONTAK CD study¹⁶ and 4.8% increase in the MIRACLE study¹²), as well as an ~3 mm reduction in end-diastolic dimension.^{12,16} In contrast, however, no changes in EF or dimension were found in the MIRACLE-ICD study even after 6 months.¹⁷ Under the assumption that CCM has a similar impact on function, and given the relatively small number of patients who had follow-up echocardiograms (~45 per group) and inherent variability in echocardiography, it would not be possible to detect a change of this magnitude. Interestingly, changes in EF and LV size were not reported in the MUSTIC study,¹⁵ perhaps also because of the relatively short (3 month) duration of follow-up and relatively small number of patients.

Another aspect of this study is the relatively large placebo effect that was noted during study Phase I. Patients in this study received a significant amount of medical attention by treating physicians, nurses, and other study-related personnel. Patients in both groups returned for clinical and device evaluations very frequently; a total of six visits following implantation over a 6-month period, two within the first month in addition to the implant procedure. This could have contributed significantly to the placebo effect. This high level of medical attention may have also contributed to the relatively low observed rate of hospitalizations and mortality.

As in all studies, missing data are a potential limitation that needs to be considered. The missing data in this study are relatively balanced across study periods and between treatment groups. We imputed missing data and found results nearly identical to those obtained from the complete case analysis. The concordance of results from different analyses speaks to the robustness of the conclusions.

Patients with permanent atrial fibrillation were excluded from the study because the OPTIMIZER device, in its current configuration, requires detection of an appropriately timed P wave as part of a safety algorithm that ensures CCM signals are never delivered during the vulnerable period where they might insight an arrhythmia. New algorithms have been developed to overcome this technical limitation which will ultimately permit use and testing of CCM in patients with atrial fibrillation and also eliminate the need for the atrial lead.

The current study has explored application of CCM signals for 7 h per day. Prior studies have employed 3, 5, and 7 h per day.^{8,22} It is likely that further up-titration of the number of hours per day could result in larger clinical effects.

Finally, patients enrolled in the study averaged 59 years of age and were predominantly male. Although the average age is representative of patients enrolling in current heart failure studies, it should be noted that the general heart failure population includes older individuals and a greater proportion of females.

Summary and conclusions

The results of the present study contribute to the growing body of literature showing that exercise tolerance and quality of life are better during CCM treatment and the treatment is safe when applied over a 3-month period. These findings are a pivotal step in the evaluation of this new and novel treatment modality provided by the OPTIMIZER System as a therapy for heart failure. Larger scale studies of safety and effectiveness of CCM signals are underway. If those studies are confirmatory of the current findings, a new treatment will be made available to patients with otherwise untreatable symptoms.

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Clinical trial registration information: ISRCTN16213127 <http://www.controlled-trials.com/ISRCTN16213127>.

Conflict of interest: D.B. is an employee of IMPULSE Dynamics. M.P. is a consultant to IMPULSE Dynamics. M.M.B., T.L., C.B. and G.H. receive honoraria for their participation in a speakers bureau for IMPULSE Dynamics.

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