Nonexcitatory, cardiac contractility modulation electrical impulses: Feasibility study for advanced heart failure in patients with normal QRS duration

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BACKGROUND Cardiac contractility modulation signals are associated with acutely improved hemodynamics, but chronic clinical impact is not defined.

OBJECTIVES The purpose of this randomized, double-blind, pilot study was to determine the feasibility of safely and effectively delivering cardiac contractility modulation signals in patients with heart failure.

METHODS Forty-nine subjects with ejection fraction <35%, normal QRS duration (105 ± 15 ms), and New York Heart Association (NYHA) class III or IV heart failure despite medical therapy received a cardiac contractility modulation pulse generator. Patients were randomized to have their devices programmed to deliver cardiac contractility modulation signals (n = 25, treatment group) or to remain off (n = 24, control group) for 6 months. Evaluations included NYHA class, 6-minute walk, cardiopulmonary stress test, Minnesota Living with Heart Failure Questionnaire, and Holter monitoring.

RESULTS Although most baseline features were balanced between groups, ejection fraction (31.4% ± 7.4% vs 24.9% ± 6.5%, $P = .003$), end-diastolic dimension (52.1 ± 21.4 mm vs 62.5 ± 6.2 mm, $P = .01$), peak VO_2 (16.0 ± 2.9 mL O_2/kg/min vs 14.3 ± 2.8 mL O_2/kg/min, $P = .02$), and anaerobic threshold (12.3 ± 2.5 mL O_2/kg/min vs 10.6 ± 2.4 mL O_2/kg/min, $P = .01$) were worse in the treatment group than in the control group. Nevertheless, one death occurred in the control group, and more patients in the treatment group were free of hospitalization for any cause at 6 months (84% vs 62%). No change in ectopy was observed. Compared with baseline, 6-minute walk (13.4 m), peak VO_2 (0.2 mL O_2/kg/min), and anaerobic threshold (0.8 mL O_2/kg/min) increased more in the treatment group than in control. None of these differences were statistically significant (small sample size). NYHA and Minnesota Living with Heart Failure Questionnaire changed similarly in the two groups.

CONCLUSION Despite a sicker population in the treatment group, no specific safety concerns emerged with chronic cardiac contractility modulation signal administration. Further study is required to definitively define the safety and efficacy of cardiac contractility modulation signals.

KEYWORDS Cardiopulmonary stress test; Six-minute hall walk test; Minnesota Living with Heart Failure Questionnaire

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Introduction

Results of several studies performed over the past decade have led to widespread adoption of cardiac resynchronization therapy for treatment of patients with advanced heart failure with dyssynchronous myocardial contraction indexed by a prolonged QRS duration.[1–5] However, it is estimated that less than half of patients with advanced heart failure have a prolonged QRS duration and therefore currently are indicated for treatment with cardiac resynchronization therapy.[6,7]

A new form of electrical therapy, called *cardiac contractility modulation,* has been proposed as a device-based means of enhancing ventricular contractile strength that is independent of QRS duration.[8–15] The original concept derives from early studies of isolated cardiac muscle showing that voltage clamp techniques, which modify the amplitude and duration of membrane depolarization, modulate calcium entry and thus influence contractility.[16–19] Although voltage clamp techniques *per se* are not applicable to the

This study was supported by a research grant from IMPULSE Dynamics, Orangeburg, New York, USA, the manufacturer of the OPTIMIZER system. Dr. Burkhoff is an employee of IMPULSE Dynamics. **Address reprint requests and correspondence:** Dr. Koonlawee Nademanee, Pacific Rim Electrophysiology Research Institute, 575 E. Hardy Street, Suite 201, Inglewood, California 90301. E-mail address: Koonlawee@pacificrimep.com. (Received April 27, 2006; accepted June 26, 2006.)

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intact heart, early experiments demonstrated in isolated superfused muscle strips that similar effects could be achieved when extracellular fields with relatively high current densities were applied during the absolute refractory period.[8,13,14] Cardiac contractility modulation signals are delivered 30 to 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 cardiac contractility modulation pulse than during a standard pacemaker impulse, these signals do not initiate a contraction; they do not recruit additional contractile elements; they do not modify activation sequence; and there is no additional action potential (as would be observed with paired pacing or post-extrasystolic potentiation[20]). Therefore, cardiac contractility modulation signals are referred to as *nonexcitatory*.

Initial nonrandomized clinical studies with short-term application of cardiac contractility modulation signals in failing hearts demonstrated acute hemodynamic effects and suggested improved quality of life and ventricular function. As a next step in the evaluation of this treatment modality, we conducted a prospective, randomized, double-blind, pilot study of the safety and efficacy of cardiac contractility modulation signals applied for 6 months.

Methods

Patients

Patients were eligible for the study if they had moderate or severe chronic heart failure (New York Heart Association functional [NYHA] class III or IV) due to either ischemic or nonischemic cardiomyopathy with left ventricular ejection fraction (EF) ≤35%. Patients were required to be receiving appropriate, stable medical treatment for heart failure, including a diuretic, an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, and a beta-blocker. The doses of these medications were required to have been stable for at least 1 month prior to enrollment (defined as no more than 50% reduction or 100% increase in daily dose), and beta-blocker treatment was required to have been administered for at least 3 months unless the patient was intolerant. Patients were required to have an implantable cardioverter-defibrillator (ICD) unless there were extenuating circumstances; these devices could have been implanted previously or implanted at the same setting as the experimental cardiac contractility modulation device. Patients were excluded if a cardiac resynchronization therapy device was implanted or if eligibility for cardiac resynchronization therapy was demonstrated. Other major exclusion criteria included peak VO_2 at baseline <11 mL/kg/mg, atrial fibrillation, recent myocardial infarction (within 3 months), clinically significant angina (i.e., including angina on baseline treadmill test), hospitalization for heart failure requiring intravenous treatment within 30 days, or ≥8,900 premature ventricular complexes within 24 hours on baseline Holter recording (which would limit the amount of cardiac contractility modulation treatment delivered). The study protocol was approved by the institutional review board of each center, and all patients provided written informed consent.

Study design

Patients who met the criteria for study entry underwent the following evaluations at baseline: determination of NYHA class, 6-minute hall walk test, maximal treadmill exercise test (using a customized slow ramp protocol[21]), quality-of-life assessment using the Minnesota Living with Heart Failure Questionnaire,[22] and two-dimensional echocardiogram. After the initial evaluation, patients underwent implantation of an OPTIMIZER system (IMPULSE Dynamics, Orangeburg, NY, USA) along with three pacing leads: a standard right atrial lead and two active fixation leads inserted into the right ventricular septum.[15] Hemodynamic responses to acute application of cardiac contractility modulation signals were measured using a Millar micromanometer catheter (Millar Instruments, Houston, TX, USA), placed in the left ventricle, that was connected to a specialized online analysis system (MONITA, IMPULSE Dynamics). As a requirement, the maximal rate of rise of left ventricular pressure (dP/dt_{max}, an index of contractility) had to increase by a minimum of 5%. If such changes were not observed even after the electrodes were repositioned, the device was not implanted and the patient withdrawn from the study. When an ICD was present, interaction testing between the OPTIMIZER and the ICD was performed to ensure that the devices did not interfere with each other. The chest x-ray appearance after a typical implant procedure in a patient who also had an ICD is shown in Figure 1.

The stabilization period was 2 weeks for patients who underwent implantation of the OPTIMIZER system alone and 4 weeks for patients who underwent implantation of both an ICD and the OPTIMIZER system at the same setting. The intention of the stabilization period was to allow the electrical characteristics of the OPTIMIZER leads to stabilize before the device was programed. Thus, during the stabilization period, the OPTIMIZER system was programmed to sense and record native heart electrical signals,

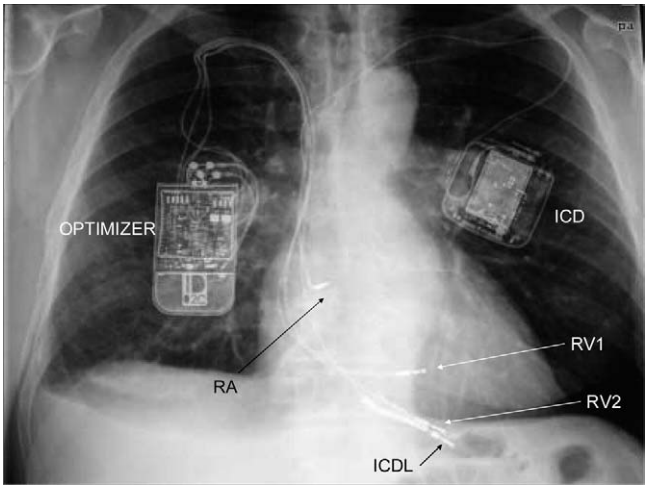

Figure 1 Chest x-ray film of a patient implanted with an OPTIMIZER system in the right subclavian region and an implantable cardioverter-defibrillator (ICD) in the left subclavian region. The associated two right ventricular leads (RV1 and RV2), right atrial lead (RA), and ICD lead (ICDL) are also seen.

but no cardiac contractility modulation signals were delivered. A longer period was allowed for patients who underwent simultaneous ICD and OPTIMIZER implantation to ensure that the ICD was operating properly and to allow more time for recovery from the two implants. Following the stabilization period and confirmation of proper device functioning, patients were randomly assigned to active cardiac contractility modulation treatment (5 hours of treatment per day, divided into five 1-hour treatment periods spaced equally over the day) or to a control group in which the device remained inactive for 6 months. In both groups, heart failure medications were kept constant unless clinical circumstances mandated otherwise. Randomization occurred in permuted blocks at each center and was stratified by etiology (ischemic vs nonischemic) to ensure balance between groups within centers. After the stabilization period following OPTIMIZER system implantation (2–4 weeks), an electrophysiologist otherwise not involved with the clinical care of the subject opened a sealed envelope containing the randomization assignment and programmed the device accordingly. The same electrophysiologist performed follow-up device interrogations regardless of group assignment so as to maintain blinding for the patient and other health care professionals. Baseline assessments were re-evaluated 3 and 6 months after randomization. Prior to performance of follow-up tests, devices were turned off to ensure that blinding could be maintained. Twenty-four-hour Holter recordings were obtained at 1, 3, and 6 months with device programmed according to randomization group and analyzed only at the core laboratory. Thus, neither the patients nor the physicians performing study follow-up evaluations were aware of the treatment assignment. Crossover from control to active cardiac contractility modulation treatment was not allowed. After completion of the 6-month follow-up, patients entered an additional 6-month study period of open-label cardiac contractility modulation treatment. This report deals exclusively with the initial 6-month blinded study period.

Core laboratories blinded to assignment group were used to assess ejection fraction from echocardiography and peak oxygen consumption ($VO_{2,peak}$) and oxygen consumption at anaerobic threshold. A core laboratory was also used to analyze Holter recordings.

Statistical analysis

This pilot study was not powered for definitive assessment of safety or efficacy. Nevertheless, several efficacy outcomes were considered, including peak VO_2, anaerobic threshold, Minnesota Living with Heart failure Questionnaire, and 6-minute hall walk test. Comparison of baseline values between randomization groups was based on t-tests for continuous variables and Chi-square tests (with a con-

Table 1 Baseline patient characteristics

	Control (n = 24)	Treatment (n = 25)	*P* value*
Age	59.6 ± 12.0	52.0 ± 15.0	
Gender (% male)	17 (71%)	17 (68%)	
Ethnicity (% white)	18 (75%)	15 (60%)	
Etiology (% ischemic)	16 (67%)	16 (64%)	
Implanted cardioverter-defibrillator (%)	20 (83%)	22 (88%)	
Already in place (%)	16 (67)	18 (72)	
Placed simultaneously (%)	4 (17)	4 (16)	
QRS duration (ms)	101.3 ± 14.2	109.2 ± 15.8	
NYHA class (% class III)	23 (96%)	25 (100%)	
Left ventricular ejection fraction (%)	31.4 ± 7.4	24.9 ± 6.5	.003
Left ventricular end-diastolic dimension (mm)	57.0 ± 7.8	62.5 ± 6.2	.01
Six-minute hall walk (m)	352.2 ± 95.4	321.2 ± .□□	
Minnesota Living with Heart Failure Questionnaire	52.1 ± 21.4	56.4 ± 24.8	
Peak oxygen consumption (mL O_2/kg/min)	16.0 ± 2.9	14.3 ± 2.8	.02
Anaerobic threshold (mL O_2/kg/min)	12.3 ± 2.5	10.6 ± 2.4	.01
Heart rate (bpm)	71.8 ± 12.5	74.0 ± 11.9	
Systolic blood pressure (mmHg)	115.0 ± 20.6	118.6 ± 19.7	
Medications (% receiving)			
Diuretic	21 (88%)	23 (96%)	
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	20 (83%)	23 (92%)	
Beta-blocker	23 (96%)	21 (84%)	
Digitalis	9 (38%)	9 (36%)	
Aldosterone inhibitor	12 (50%)	11 (44%)	
Statin	19 (79%)	15 (60%)	
Maximum rate of rise of left ventricular pressure (mmHg/s)	1005 ± 264.9	964.8 ± 279.3	
Change in dP/dt_{max} during acute cardiac contractility modulation testing (%)	8.0 ± 4.0	7.7 ± 3.2	

dP/dt_{max}, maximal rate of rise of left ventricular pressure; NYHA, New York Heart Association Classification.
*P = NS unless otherwise specified.

Table 2 Summary of all serious adverse events

Event	Baseline	Implant-to-randomization	Treatment phase	
			Control	Treatment
Worsening heart failure	1	1	3 (2)	2 (2)
Ventricular fibrillation			2 (2)	
Supraventricular tachycardia				1
Chest pain	1		4 (3)	
Pericardial effusion				1
Optimizer lead dislodgment		1		
ICD failure†				1
General medical		3 (3)*	6 (4)	2 (2)
Upper respiratory infection				1
Totals	2 (2)	5 (4)	15 (8)	8 (7)

Values are given as number of events (number of patients).

*One event (metastatic brain cancer) was reported after implantation in a subject who was never randomized.

†Implantable cardioverter-defibrillator (ICD) failed to deliver therapy during defibrillation threshold testing at an implantation; the ICD was subject to a recall and was exchanged for a new device.

tinuity correction) for categorical outcomes. Analysis of covariance (ANCOVA) was used to estimate the mean change from baseline to 3 and 6 months for each randomization group.

The primary safety outcome was any hospitalization (>24 hours in duration or a hospital admission with a calendar date change). All analyses adhered to the intention-to-treat principle. Survival curves, estimated by the Kaplan-Meier method, were used to describe the time to first hospitalization. The log rank test was used to assess the difference of the curves between randomization groups. All statistical tests were two-sided and used a 0.05 significance level.

Results

One hundred seven potential study subjects signed informed consent to undergo baseline testing and 52 passed baseline screening and underwent the OPTIMIZER system implantation procedure. Left ventricular dP/dt_{max} increased by more than 5% in all patients except two (a 52-year-old man with ischemic cardiomyopathy with ejection fraction 15% and a 67 year old man with ischemic cardiomyopathy with ejection fraction 30%) in whom a device was not implanted. For the remaining patients, the rise in dP/dt_{max} in response to acute cardiac contractility modulation testing was 7.8% ± 3.6% (mean ± SD).

A metastatic brain tumor (unknown primary) was found in one patient following OPTIMIZER system implantation. This patient, who eventually died, was never randomized. Of the remaining 49 study subjects, 25 were randomized to the active group and 24 to the control group. One patient died during the initial 6-month study period. This was an 80-year-old man with ischemic cardiomyopathy randomized to the control group who died approximately 5 months after randomization of a perforated bowel. All the remaining patients (n = 23 control, n = 25 active) completed the 6-month primary follow-up.

Baseline characteristics

A summary of baseline characteristics reveals statistically and clinically significant imbalances between the groups with regard to several key parameters (Table 1). Compared with the control group, the treatment group had a lower ejection fraction (by 6.5 percentage points), increased left ventricular end-diastolic dimension (by 5.5 mm), lower peak VO_2 (by 1.7 mL O_2/kg/min), and lower VO_2 at anaerobic threshold (by 1.7 mL O_2/kg/min). All of these differences are indicative of a significantly more impaired population in the treatment group. Use of beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was appropriately high in both groups. ICD, digitalis, and aldosterone inhibitor use was balanced between groups.

Safety assessments

An overview of the serious adverse events (i.e., any untoward medical occurrences that resulted in death, were life-threatening, required inpatient hospitalization, prolonged an existing hospitalization, or resulted in persistent or significant disability/incapacity) as classified by the investigators is given in Table 2, according to the phase of the study. Two events occurred during baseline testing and five occurred during or following device implantation but prior to randomization. During the 6-month double-blind study period, eight events occurred in seven subjects in the active treatment group compared with 15 events in eight subjects in the control group. Among these events was one occurrence of an OPTIMIZER lead dislodgment (prior to randomization) and one event of chest sensation during cardiac contractility modulation signal application in the treatment group (resolved through adjustment of cardiac contractility modulation parameters). These were the only serious adverse events that were related to the device in the treatment group. Other serious events also thought to be possibly device related, including worsening heart failure, ventricular fibrillation, and chest pain, upon unblinding, all occurred in the control group.

In addition to the serious adverse events, other events occurred that were considered by the investigators to be nonserious but possibly or definitely related to the device. These included 2 episodes of lead dislodgment, 2 Optimizer

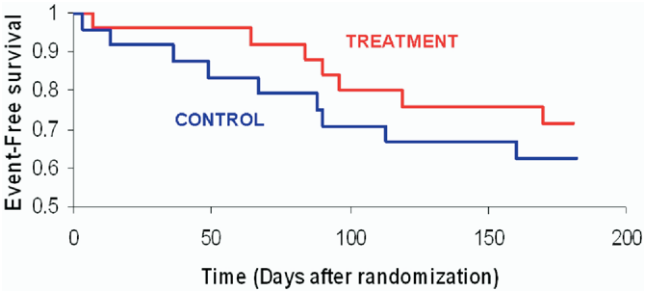

Figure 2 Kaplan-Meier curves depicting survival free of any hospitalization. Comparison between active treatment and sham groups.

pocket infections, 1 pericardial effusion, and 1 episode of inappropriate ICD firing. The ICD firing occurred the morning after implantation upon initial cardiac contractility modulation signal activation and was due to a blanking period that was set inappropriately short, which was readily rectified by device reprogramming.

There were a total of 31 hospitalizations in 15 patients: 3 during baseline, 4 after implantation and before randomization, and 24 after randomization. Of these 24, there were 18 hospitalizations in 9 control patients, compared with 6 hospitalizations in 4 treatment patients. In the treatment group, the reasons for hospitalizations included 2 for worsened heart failure, 1 for pericardial effusion, 1 for supraventricular tachycardia, 1 for upper respiratory infection, and 1 for gastric ulcer. In the control group, reasons for hospitalizations included 1 for ventricular fibrillation, 4 (in 3 patients) for chest pain, 4 (in 1 patient) for pancreatitis, 3 (in 2 patients) for worsened heart failure, and 6 (in 5 patients) for general medical problems (abdominal pain, anxiety, left arm swelling, perforated bowel, subarachnoid hemorrhage).

The curves depicting overall survival free of any hospitalization following randomization (i.e., hospitalizations occurring during baseline or stabilization period do not contribute) are summarized in Figure 2. As shown, the point estimates of event-free survival at 6-month follow-up was ~62% in the control group compared with ~84% in the treatment group. The hazard ratio (treatment/control) is 0.47 (95% confidence interval 0.16–1.40) so that the risk reduction for subjects receiving treatment is 53% compared with controls ($P = .17$).

Safety data were reviewed on three regularly scheduled occasions by an independent data safety monitoring committee. No safety concerns necessitating any changes to the original study plan emerged from these evaluations.

Holter monitoring

24-hour Holter monitor recordings were performed at baseline and at 12 and 24 weeks. A brief summary of the findings (Table 3) reveals no significant change in average heart rate, number of premature ventricular contractions (including single, double, triplets, and runs of tachycardia), and number of supraventricular premature contractions (also including single, double, triplets, and runs of tachycardia) over the course of the study.

Efficacy assessments

Although the sample size is small and this study is underpowered to detect what could be clinically significant changes in patient status, measurements of quality of life, exercise tolerance, and ventricular function were repeated at the 12- and 24-week follow-up visits. In most cases, changes in parameter values at 24 weeks were statistically significant within each group when compared with their respective baseline values. However, although some trends emerged (detailed later), no statistically significant differences between groups were observed.

Trends in subjective measures of health status

NYHA classification improved similarly in both groups. For the treatment group, the proportion of patients in class I, II, and III at 24 weeks were 19, 45 and 36, respectively. This compared to 18, 52, and 30, respectively, in the control group. Minnesota Living with Heart Failure Questionnaire also improved significantly and similarly in both groups. At the 6-month follow-up, the Minnesota Living with Heart Failure Questionnaire decreased from baseline values by 16.2 ± 5.9 and 18.3 ± 4.8 in the control and treatment groups, respectively. The significant and sustained improvements in NYHA and Minnesota Living with Heart Failure Questionnaire observed in both groups speaks to the presence of a significant placebo effect.

Trends in measures of function and exercise tolerance

Six-minute hall walk (Figure 3) showed similar improvements in both groups at 12 weeks, with the curves diverging by 6 months with an approximately 15-m greater increase in the treatment group. Peak VO_2 decreased over time in both groups but remained higher in the treatment group than in

Table 3 Summary of results of Holter analysis

	Baseline	12 Weeks	24 Weeks
Average heart rate (bpm)			
Control	78 ± 11	80 ± 14	79 ± 13
Treatment	78 ± 11	76 ± 12	77 ± 11
Premature ventricular contractions (counts/24 hr)			
Control	2,727 ± 5,847	1615 ± 2,827	1274 ± 2,901
Treatment	1,612 ± 2,684	2708 ± 6,522	1822 ± 5,149
Supraventricular premature contractions (counts/24 hr)			
Control	124 ± 421	420 ± 1,302	1521 ± 5,511
Treatment	482 ± 1,169	698 ± 1,523	604 ± 1,487

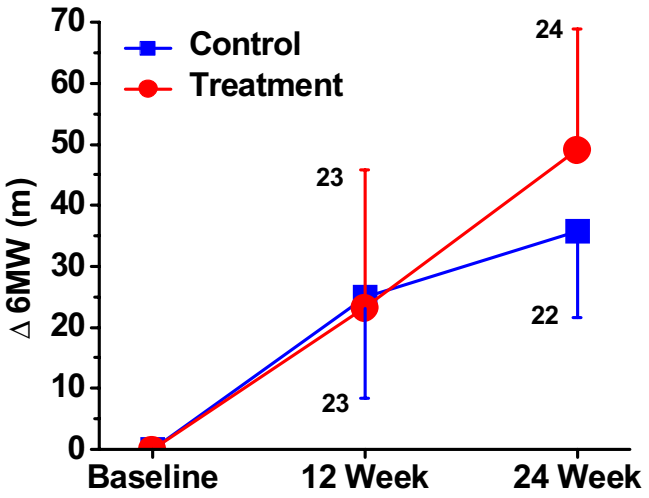

Figure 3 Changes in 6-minute hall walk test (6MW) between groups compared with their respective baseline values. Number of observations is indicated next to each symbol.

controls, by ~0.2 mL O_2/kg/min (Figure 4). In contrast, anaerobic threshold, which decreased in the control group, decreased initially but then returned to baseline values at 6 months in the treatment group. At the final follow-up, the difference between the two groups averaged 0.82 mL O_2/kg/min. Ejection fraction increased minimally in both groups at 6 months (1.8 ± 0.8 in the treatment group vs 1.3 ± 1.6 in the control group).

Discussion

Initial clinical study of cardiac contractility modulation involved short-term (10–30 minutes) signal application using temporarily placed electrodes in patients with heart failure.[9,10,23] The results of those studies showed the feasibility of delivering cardiac contractility modulation treatment in humans and demonstrated that left ventricular contractile performance could be acutely enhanced with this approach, as shown in earlier preclinical studies.[8,13–15,24–27] Results of another study also showed these acute enhancements of contractile state did not have associated changes in myocardial oxygen consumption.[15,28] Chronic cardiac contractility modulation signal applications initially was used in patients with NYHA class III symptoms and QRS duration ≤120 ms.[11,12] These were unblinded, uncontrolled, treatment only, feasibility studies designed mainly to test the functionality of the OPTIMIZER system. Nevertheless, in addition to showing that the device operated as intended, that study provided important early safety data by showing no change in ambient ectopy after 8 weeks of treatment and no overt safety issues; it also provided suggestions of improved NYHA class, Minnesota Living with Heart Failure Questionnaire, and ejection fraction.

Fashioned after the MIRACLE (Multicenter Randomized Clinical Evaluation ([North America]) study of cardiac resynchronization therapy,[3] the present multicenter, randomized, double-blind pilot study represents the next important step in the clinical evaluation of the safety and efficacy of cardiac contractility modulation as a therapy for heart failure. Fifty of 51 patients (98%) with normal QRS duration who fulfilled entry and baseline testing criteria demonstrated an acute hemodynamic response to cardiac contractility modulation signals. All of these patients underwent implantation of the OPTIMIZER system and were randomly assigned to 6 months of active treatment with cardiac contractility modulation signals or to a control group that did not receive treatment. Unfortunately, significant imbalances in important baseline characteristics existed between randomization groups, indicative of a significantly sicker population in the treatment group. Despite this finding, the incidences of serious adverse events and hospitalizations were low, and the overall event-free survival tended to be better in the active treatment group. Both cardiac and noncardiac events contribute to event-free survival. However, even considering just serious cardiac events listed in Table 2 (heart failure, ventricular fibrillation, supraventricular tachycardia, chest pain, and pericardial effusion), they occurred more frequently in the control compared with the treatment group (9 vs 4 events). Furthermore, there was no change in ambient ectopy (ventricular and

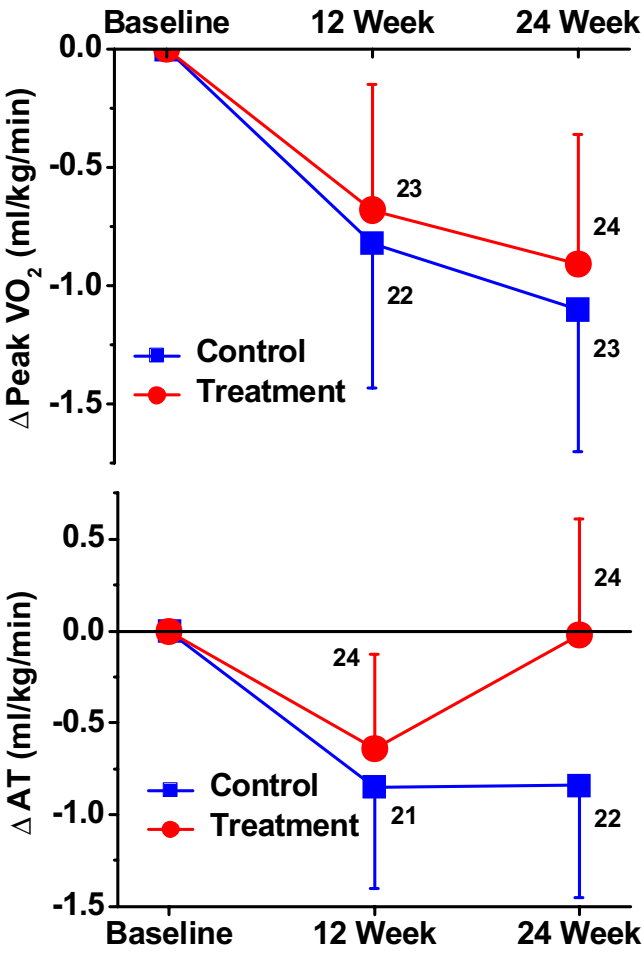

Figure 4 Changes in peak VO_2 (**A**) and VO_2 at anaerobic threshold (AT, **B**) between groups compared with their respective baseline values. Number of observations is indicated next to each symbol.

supraventricular) as assessed by repeated 24-hour Holter monitor recordings. Although there were trends for greater improvements in 6-minute walk and anaerobic threshold in the treatment group at the end of the 6-month study period, these changes were not statistically significant.

In the case of NYHA class, 6-minute walk, and Minnesota Living with Heart Failure Questionnaire, relatively strong placebo effects were noted so that improvements were similar in both groups. In contrast, a placebo effect was not apparent in peak oxygen consumption or anaerobic threshold, parameters that are considered more objective measures of exercise tolerance and that were evaluated by a blinded core laboratory (and therefore not subject to potential investigator bias). Both anaerobic threshold and peak VO_2 actually decreased over time in the control group, suggestive of deteriorating status in the overall population, despite the improvements in NYHA class and Minnesota Living with Heart Failure Questionnaire in both groups. In the treatment group, however, anaerobic threshold returned to baseline values at 24 weeks compared with the continued deterioration seen in control subjects. With regard to these findings from metabolic stress testing, we also note that more noncardiac serious events and hospitalizations occurred in the control group compared with the treatment group, which could have influenced these findings.

The implantation procedure requires placement of two right ventricular leads inserted specifically into the right ventricular septum. The purpose of acute hemodynamic testing during the implantation procedure, along with fluoroscopic imaging, is intended to ensure proper placement. Because of this requirement, the procedures can be longer than that used for standard pacemakers and require more lead manipulations. It is possible that a learning process exists such that implantation times may decrease as the implanter becomes more experienced, although this was not evaluated in the present study. Nevertheless, it is possible that these factors may contribute to the relatively high combined rate of pocket infections, lead dislodgments, and pericardial effusions observed in this cohort.

The mechanisms by which cardiac contractility modulation signals enhance contractile performance are under investigation. Early studies suggest that these extracellular electrical signals can impact on action potential configuration in a manner that can enhance transsarcolemmal calcium influx, increase peak intracellular calcium (with no detectable impact on diastolic calcium), and increase myocardial contractility.[13,14,27,29] Such signals applied in one region of an intact heart impact on contractile performance locally but appear to secondarily impact on remote regions because of modification of the mechanical load on remote myocardium and because of the impact on overall global performance.[10,27] Ongoing basic research focuses on new mechanisms by which myocardial properties appear to be influenced by cardiac contractility modulation signals, particularly in the chronic setting. For example, results of preliminary studies in animals suggest that within 6 hours of cardiac contractility modulation signal delivery, there are significant changes in myocardial gene expression (including a reversal of several aspects of the fetal gene program expressed in heart failure[30,31]) and improved expression and/or phosphorylation of the sodium/calcium exchanger, phospholamban, and connexin43.[32–37] Therefore, it is possible that chronic effects may be independent of the acute effects discussed earlier in terms of their nature, their underlying mechanisms, and their potential impact on patient health status.

Study limitations

One limitation of the current study was the significant chance imbalance between control and treatment groups with regard to ejection fraction and exercise tolerance. Such imbalances can occur in randomized studies, especially with small sample sizes as in the present study. Furthermore, the small sample size and large inherent variability in all the efficacy parameters measured in this pilot study preclude meaningful statistical comparisons between groups so that definitive conclusions about safety or efficacy are not possible, nor was it anticipated that such conclusions would have been possible. Therefore, it was only possible to observe trends in changes in parameter values, and it is possible that such trends may not be reproduced in larger scale studies. It also is not clear that the cardiac contractility modulation effects have plateaued by 24 weeks and that differences between groups could continue to widen over longer periods of follow-up, so longer follow-up times may provide an opportunity to observe more robust differences between the groups. Finally, another potential limitation of the present study design is that baseline tests are performed at least 2 to 4 weeks prior to randomization (because of the stabilization period used following implantation). An alternate design would have also evaluated baseline parameters following implantation just prior to randomization, which was not performed in the present study. However, both control and treatment groups were exposed to the same stabilization period, so comparison of changes in parameter values between groups should account for any impact of this time period.

Conclusion

Results of this pilot study provide new safety data concerning the use of cardiac contractility modulation signals and thus represent an important next step in the evaluation of the OPTIMIZER system for treatment of heart failure. Currently, a randomized trial that is powered adequately to definitively test the safety and efficacy of cardiac contractility modulation as a treatment of advanced heart failure is under way (FIX-HF-5). If such a study proves cardiac contractility modulation treatment to be safe and effective, a new, easily deployable treatment will be made available for patients with otherwise untreatable symptoms. Future studies also could test whether cardiac contractility modulation is effective in patients with wide QRS who do not respond to cardiac resynchronization therapy or, if combining cardiac resynchronization therapy with cardiac contractility modulation, is more effective than cardiac resynchronization therapy alone.

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