

First Human Chronic Experience with Cardiac Contractility Modulation by Nonexcitatory Electrical Currents for Treating Systolic Heart Failure: Mid-Term Safety and Efficacy Results from a Multicenter Study

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Electrical Modulation of the Failing Contractility. *Introduction:* Conventional electrical therapies for heart failure (HF) encompass defibrillation and ventricular resynchronization for patients at high risk for lethal arrhythmias and/or with inhomogeneous ventricular contraction. Cardiac contractility modulation (CCM) by means of nonexcitatory electrical currents delivered during the action potential plateau has been shown to acutely enhance systolic function in humans with HF. The aim of this multicenter study was to assess the chronic safety and preliminary efficacy of an implantable device delivering this novel form of electrical therapy.

Methods and Results: Thirteen patients with drug-resistant HF (New York Heart Association [NYHA] class III) were consecutively implanted with a device (OPTIMIZER™ II) delivering CCM biphasic square-wave pulses (20 ms, 5.8–7.7 V, 30 ms after detection of local activation) through two right ventricular leads screwed into the right aspect of the interventricular septum. CCM signals were delivered 3 hours daily over 8 weeks (3-hour phase) and 7 hours daily over the next 24 weeks (7-hour phase). Safety and feasibility of this novel therapy were regarded as primary endpoints. Preliminary clinical efficacy, -as expressed by changes in ejection fraction (EF), NYHA class, 6-minute walking test (6-MWT), peak O₂ uptake (peak VO₂), and Minnesota Living with HF Questionnaire (MLWHFQ), was assessed at baseline and at the end of each phase. At the end of follow-up (8.8 ± 0.2 months), all patients were alive, without heart transplantation or need for left ventricular assist device. Serial 24-hour Holter analysis revealed no proarrhythmic effect. No devices malfunctioned or failed for any reason other than end-of-battery life. Throughout the two study phases, EF improved from 22.7 ± 7% to 28.7 ± 7% and 37 ± 13% (P = 0.004), 6-MWT from 418 ± 99 m to 477 ± 96 m and 510 ± 107 m (P = 0.002), MLWHFQ from 36 ± 21 to 18 ± 12 and 7 ± 6 (P = 0.002), peak VO₂ from 13.7 ± 1.1 to 14.9 ± 1.9 to 16.2 ± 2.4 (P = 0.037), and NYHA class from 3 to 1.8 ± 0.4 to 1.5 ± 0.7 (P < 0.001).

Conclusion: CCM therapy appears to be safe and feasible. Proarrhythmic effects of this novel therapy seem unlikely. Preliminary data indicate that CCM gradually and significantly improves systolic performance, symptoms, and functional status. CCM therapy for 7 hours per day is associated with greater dispersion near the mean, emphasizing the need to individually tailor CCM delivery duration. The technique appears to be attractive as an additive treatment for severe HF. Controlled randomized studies are needed to validate this novel concept. (*J Cardiovasc Electrophysiol*, Vol. 15, pp. 418-427, April 2004)

cardiac contractility modulation, heart failure

Introduction

Weakened contractility of failing cardiac myocytes is believed to result, in large part, from an abnormally low amount of Ca²⁺ delivered to the myofilaments during each beat, independent of disease etiology.¹ Initial attempts to electrically modulate contractility of the failing heart date back to the 1980s,² when continuous paired pacing to enhance heart propelling function by continuous post-extrasystolic potentiation was explored. However, this approach had significant drawbacks, including ventricular proarrhythmias.^{3,4}

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Greater understanding of Ca^{2+} handling in the normal and failing heart, which shows depressed Ca^{2+} transients with a shift from intracellular to extracellular ionic fluxes,⁵ led to the hypothesis of modulating these fluxes, and consequently cardiac contractility, by means of nonexcitatory electrical currents applied during the absolute refractory period.⁶

It has been long established that intracellular current injections into ventricular muscle can enhance the magnitude of contraction, but this approach is not applicable to the intact heart.^{6,7} The possibility of altering contractility using extracellular electric fields has been demonstrated.⁸ Such currents, referred to as cardiac contractility modulation (CCM) signals, prolong the action potential; hence, they allow for enhanced sarcolemmal Ca^{2+} transient and increased SR Ca^{2+} loading and cycling, thereby affecting the excitation-contraction coupling process.⁹

Experimental in vitro and in vivo studies indicate that nonexcitatory electrical stimuli delivered during the absolute refractory period may modulate cardiac contractility.⁹⁻¹¹ Thus, after extensive preclinical testing⁹⁻¹¹ and assessment of acute hemodynamic efficacy in humans,¹² we prospectively conducted a multicenter treatment-only clinical pilot study to assess mid-term safety and preliminary efficacy of chronically implanted generators of CCM signals in patients with severe drug-refractory chronic systolic heart failure (HF).

Methods

Inclusion and Exclusion Criteria

Eligible patients were recruited at two centers, the San Raffaele University Hospital, Milan, Italy, and the University of Vienna, Vienna, Austria, between October 2001 and February 2002.

All patients had to be in normal sinus rhythm and have subjective and objective evidence of HF, as demonstrated by exertional symptoms (New York Heart Association [NYHA] functional class III), in association with left ventricular (LV) ejection fraction (EF) $\leq 35\%$ and LV end-diastolic diameter ≥ 55 mm, despite treatment for at least 3 months with three of the following medications at the maximal tolerable dose: digoxin, diuretics, beta-blockers, and an angiotensin-converting enzyme inhibitor (ACEI). All patients had to have a baseline $\text{VO}_2\text{max} > 11$ mL $\text{O}_2/\text{min}/\text{kg}$ by cardiopulmonary exercise testing.

Patients could not participate in the study if they had any of the following conditions: QRS duration ≥ 140 ms, recent (within 3 months) acute coronary syndromes, recent or scheduled coronary revascularization, exercise intolerance due to noncardiac conditions, or standard but otherwise untreated indication for an implantable cardioverter defibrillator (ICD).

Prior to providing written informed consent, patients were informed about the expected battery life (4–10 months, depending on the amount of administered therapy), the need for generator replacements, and their participation in the first chronic human study. The study was approved by local institutional ethics committees and was performed in compliance with the Declaration of Helsinki.

Study Protocol

The OPTIMIZER™ II device for chronic CCM delivery was implanted upon evidence of $\Delta\text{dP}/\text{dtmax} \geq 5\%$ upon hemodynamic acute testing. Before hospital discharge, lead

and device performance were assessed and CCM signal duration, amplitude, and delay optimized. Follow-up consisted of an 8-week period (FIX HF-3 substudy) during which CCM therapy was administered 3 hours per day between 7 P.M. and 10 P.M. and a 24-week phase (FIX HF-3 Extension substudy) during which CCM was applied 7 hours per day during seven equally spaced 1-hour periods, with the rationale of dose ranging to determine the effects of CCM therapy in terms of safety and efficacy.

Echocardiographic, maximal exercise testing, and 24-hour Holter data were analyzed by an independent core laboratory that reviewed all the data, blinded as to the study time point.

CCM Signal Generator and Delivery Techniques

The investigational product is a triple-output implantable system, developed and manufactured under the name of OPTIMIZER™ II (Impulse Dynamics, Inc., Mount Laurel, NJ, USA), which is capable of monitoring cardiac electrical activity in both the right atrium and the interventricular septum, recognizing local activation, and then automatically delivering nonexcitatory CCM signals at preset times and for predetermined periods of time.

The CCM signal resembles a pacing signal in that it is characterized by a delay, a duration, and an amplitude (Fig. 1). Compared to a pacing signal, the CCM signal is multiphasic, with a wider pulse duration (two biphasic square-wave pulses of 10-ms duration) and a higher amplitude (between 5.8 and 7.7 V). By design, it is nonexcitatory and must be delivered within a precise time window of local refractoriness (30–60 ms after detection of local electric myocardial activation). Current delivery was coupled to sensed events by adaptive CCM timing and safety algorithms, which inhibit signal generation when irregular activation is detected so that CCM stimulation is suppressed on ectopic beats and resumes only after three consecutive normal beats. The amplitude of the signal initially was set at 7.7 V and reduced in steps of 1 V if stimulation caused chest discomfort.

An external programmer that interfaces with the OPTIMIZER II device via a standard programming wand provides means to set parameters and assess device diagnostics.

Implantation Procedure

All leads were implanted transvenously. A commercially available right atrial lead was placed high in the right atrium. Two commercially available right ventricular bipolar 8-French leads (Tendril DX 1388T, Pacesetter Inc., Sylmar, CA, USA) were screwed into the right aspect of the interventricular septum, and CCM currents were delivered from the lead tip to the ring electrode (Fig. 2). Target locations were mid-anterior and mid-posterior septum (minimal interlead distance 20 mm), but other sites also were acceptable. Intracardiac electrograms, specifically His and right bundle potentials, were simultaneously monitored in order to avoid current delivery in the region of the AV node or right bundle branch.

A 5-French dual-sensor micromanometer catheter (Millar Instruments, Houston, TX, USA) also was placed to measure the acute hemodynamic effectiveness of CCM therapy as changes in the maximal rate of pressure rise (dP/dtmax). Eligible patients ultimately were enrolled in the study and proceeded with device implantation if $\Delta\text{dP}/\text{dtmax}$ was $\geq 5\%$

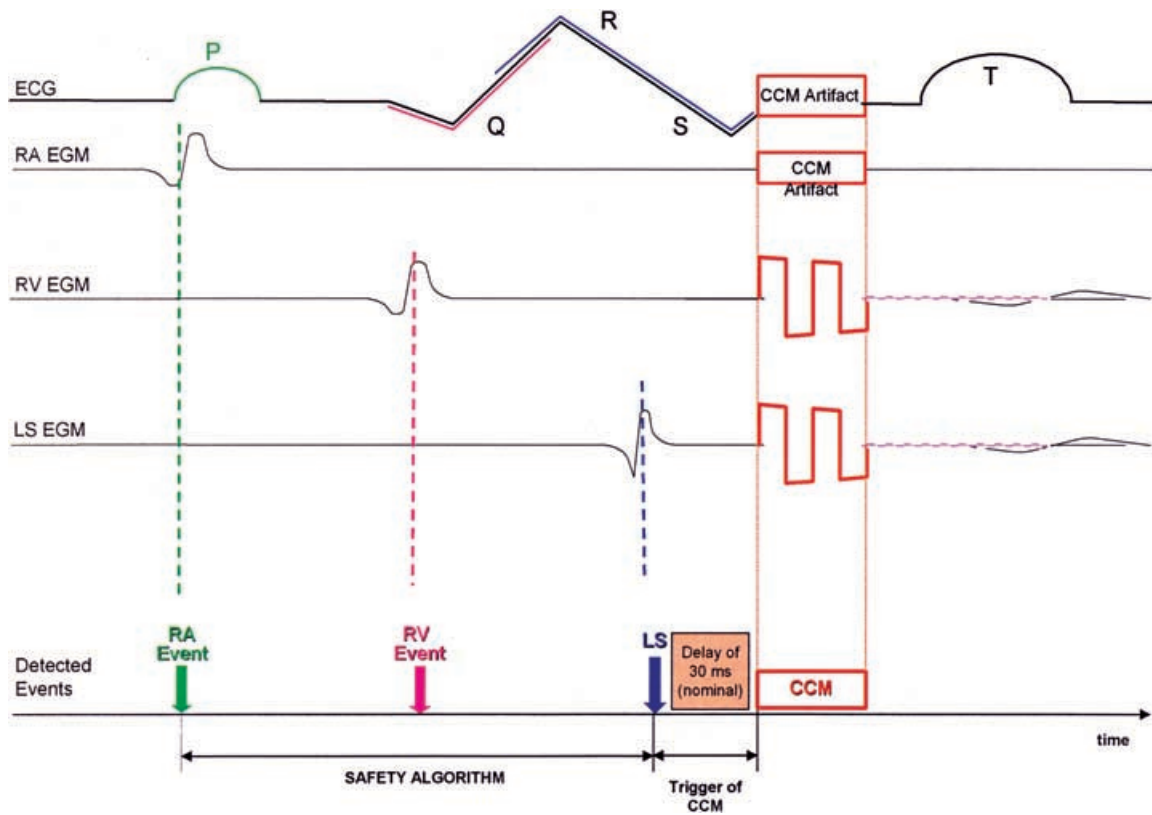


Figure 1. Timing of the OPTIMIZER II System. Surface ECG with intracardiac recordings showing the safety algorithm with cardiac contractility modulation (CCM) signal delivery. CCM delivery is triggered by the local electrogram (EGM) sensed by the proximal right ventricular lead, labeled LS EGM (local sense electrogram), and delivered 30 to 60 ms from the LS EGM. RA EGM = right atrial electrogram; RV EGM = distal right ventricular electrogram.

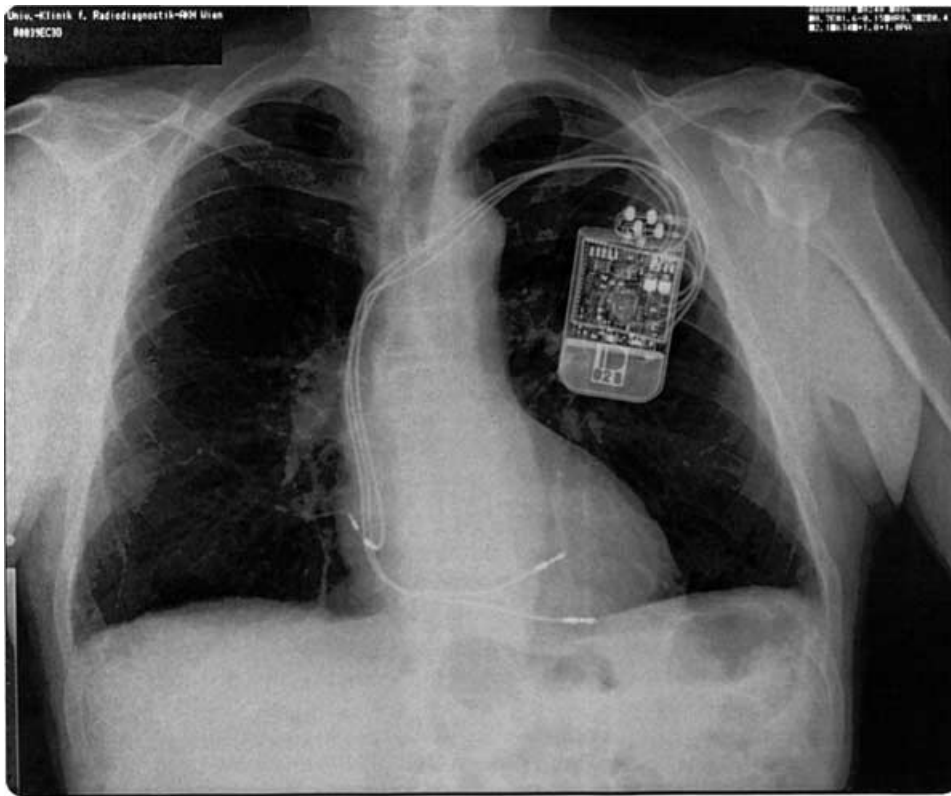


Figure 2. Chest radiograph in the anteroposterior view showing the positions of the three transvenous leads.

after the CCM system electrode had been in place and therapy delivered for 5 to 10 minutes. Means to achieve the minimum acceptable CCM effect ($dP/dt_{max} \geq 5\%$) encompassed ventricular lead repositioning and signal parameter adjustment, including signal amplitude, delay, and duration, and number of pulses (to a maximum of three) delivered within the set duration.

After proper insertion of leads into the receptacle of the pulse generator, the unit was placed in a subcutaneous thoracic pocket. Results of the implantations were assessed based on the positions of the leads on chest X-ray films. The devices were promptly replaced when batteries reached end-of-life.

Study Endpoints

We evaluated the safety and feasibility of chronic CCM signal delivery by the implantable OPTIMIZER II device as primary endpoints. Specifically, the safety endpoint was evaluation of the proarrhythmic potential (in terms of an increase over baseline in the amount of ventricular and supraventricular ectopy and/or sustained and nonsustained ventricular tachycardia) of CCM signal- and device-related adverse events. The feasibility endpoint was to evaluate, by interrogation of device statistics and manual revision of Holter data, whether the device delivered CCM signals on $>70\%$ of normal sinus beats during periods when the device was programmed to deliver CCM signals; whether the CCM signal was delivered during the QRS complexes; and whether the CCM signal was prevented from delivery in circumstances when it should not have been delivered.

As a preliminary evaluation of clinical efficacy, we ascertained changes in LV EF, peak O_2 uptake, and distance walked in 6 minutes. Other secondary clinical endpoints were NYHA functional class, quality of life, and hospital admissions because of worsening HF.

Evaluation of Patients

At baseline, at the time of implant, and at the end of each study phase, patients were evaluated according to NYHA classification, need for medication and hospitalization, quality of life as assessed using the Minnesota Living with Heart Failure Questionnaire (MLWHFQ),^{13,14} echocardiographic systolic and diastolic cardiac function and size, functional capacity as assessed by cardiopulmonary exercise testing (modified Bruce's protocol),¹⁷ and distance walked in 6 minutes (according to the recommendations of Guyatt et al.¹⁵ and Lipkin et al.¹⁶). Forty-eight-hour ECG Holter recordings were performed at baseline and every 4 to 8 weeks to exclude any instances of ventricular or supraventricular proarrhythmia and to document appropriate CCM delivery during QRS complexes. The device was tested and interrogated at each follow-up visit to retrieve device data, including the percentage of targeted normal sinus beats on which CCM signals were delivered.

An adverse event (including death, myocardial perforation, arrhythmias, palpitations, cerebrovascular events, respiratory failure, and bleeding) was considered to be serious if it was fatal or life threatening, or required hospitalization. The event was considered to be device related when there was a logical connection between the device and the occurrence of the event. Benchmark values for the MLWHFQ were obtained from the SOLVD Prevention Trial.¹⁸ No modification

of medications other than adjustment of the dose of diuretic was permitted between the time of enrollment and the end of the study. Compliance was monitored by follow-up interviews and prescription checks.

Statistical Analysis

Continuous data were previously examined by normality test. Differences were tested for significance using the paired-sample Student's *t*-test or the Wilcoxon rank signed test for continuous variables, as appropriate. For discrete variables, the Chi-square test was performed, unless the Fisher exact test was required for frequency tables when $>20\%$ of the expected values were less than 5. Generalized linear models for repeated measures were used to model changes over time,¹⁹ with Bonferroni correction for multiple pairwise comparisons. Cumulative survival curves without an HF-related hospital admission were plotted as time-to-first-event according to the Kaplan-Meier survivorship method,²⁰ and curve differences before and after entering the study were tested for statistical significance by log rank statistics.²¹ Data are presented as mean \pm SD. Analyses were performed by S-PLUS for Windows and SPSS for Windows (release 10). The threshold of significance was set at 0.05.

Results

Study Patients

Four patients did not reach the qualifying $\Delta dP/dt_{max} \geq 5\%$ for enrollment. Thirteen patients (all male) entered and completed the whole trial (Table 1). Age averaged 63 ± 9 years. HF was of ischemic origin in 8 patients and idiopathic in 5. Four patients previously had a total of 6 myocardial infarctions, 3 had undergone coronary artery bypass grafting, and 2 had undergone percutaneous transluminal coronary angioplasty with stenting. More than a half of subjects (7/13

TABLE 1
Baseline Clinical Characteristics of the Study Population

Characteristic	
No.	13
Sex (M/F)	13/0
Age (years)	63 ± 9
Weight (kg)	76 ± 13
Distance walked in 6 minutes (m)	408 ± 110
Peak O_2 uptake (ml/kg of body weight/min)	13.8 ± 1.1
Quality-of-life score*	36 ± 21
Heart rate (beats/min)	73 ± 15
QRS interval (ms)	107 ± 22
Systolic blood pressure (mmHg)	119 ± 15
Diastolic blood pressure (mmHg)	73 ± 9
S3 gallop	1/13
Dependent edema	1/13
Respiratory frequency (breaths/min)	13 ± 4
Effort angina	1/13
PR interval (ms)	188 ± 18
LV ejection fraction (%)	23 ± 7
LV end-diastolic diameter (mm)	68 ± 4
Angiotensin-converting enzyme inhibitor	13/13
Beta-blockers	12/13
Spironolactone	6/13
Digoxin	7/13
Diuretics	11/13

*Higher score indicates poorer quality of life (range 0–105).

LV = left ventricular.

study patients) had diabetes. Mean LV EF was $23 \pm 7.6\%$ at a mean heart rate of 73 ± 15 beats/min.

All but 2 patients were taking diuretic agents for fluid retention control. ACEI and beta-blockers were co-prescribed in all but 1 patient. An additional 6 and 7 subjects also were taking spironolactone and a digitalis glycoside. During follow-up, the dosage of diuretic therapy was lowered in 4 patients, but the daily dose of furosemide was doubled in 1 patient.

Three patients with a remote myocardial infarction who were identified to be at high risk for sudden cardiac death underwent placement of an ICD. As of this writing, all patients are alive.

Implantation

Overall implant procedure duration averaged 80 ± 34 minutes. Implantation of the atrial lead and of the two right ventricular leads was attempted in all patients, with a 100% success rate and no serious complications. No reoperations for ventricular lead dislodgment were performed.

In all patients, acute testing included CCM delivery with a maximum output of 7.73 V. In 4 patients, the initial target position for CCM delivery induced the qualifying $dP/dt_{max} \geq 5\%$. In the remaining 9 patients, repositioning the leads in mid-septal positions allowed the threshold for a successful acute CCM device implant to be reached. As a result, 1.9 ± 1.4 lead positions were tested. Upon acute testing, the main increase in dP/dt_{max} averaged $7 \pm 2\%$.

Safety

By serial Holter ECG recordings, we analyzed the impact of CCM therapy on the amount of ventricular and supraventricular arrhythmias. By generalized linear model for repeated measures analysis, we found no significant trend over time toward an increase in the mean number of premature ventricular or supraventricular complexes per day (Table 2). As a post hoc observation, when comparing results of second study phases to baseline, a trend toward a reduction ($P = 0.05$) was observed. A similar decrease was observed in the number of nonsustained ventricular tachycardias per day across the study phases ($P = 0.01$). No significant changes in the duration of the QRS interval or QT interval were observed across the entire study.

TABLE 2

Impact of CCM Therapy on Amount of Ventricular and Supraventricular Tachycardias

Parameters*	Baseline	FIX HF-3 Phase	P Value†	FIX HF-3 Extension Phase	P Value†
PAC	395 ± 660	292 ± 612	1.00	103 ± 175	0.25
PVC	920 ± 612	632 ± 602	0.42	408 ± 582	0.05
NSVT	1.5 ± 0.9	0.4 ± 0.5	0.005	0.6 ± 0.6	0.08
VT	0 ± 0	0 ± 0	—	0 ± 0	—

*Mean number of episodes per day.

†P values by pairwise comparisons with Bonferroni correction, for changes from baseline to the end of each study phase.

CCM = Cardiac contractility modulation; PAC = premature atrial complex; PVC = premature ventricular complex; NSVT = nonsustained ventricular tachycardia; VT = ventricular tachycardia.

The device was replaced in all patients after a mean of 7 ± 3 months. Only one patient experienced a pocket infection after the device was replaced that was successfully treated with local measures and antibiotics. Thus, by the end of the study, the probability of CCM system generator infection was 4%. A second patient who was prophylactically implanted with an ICD had a surgical revision of the ICD pocket due to infection.

The output was lowered by approximately 2 V because of symptoms due to pocket stimulation in one patient, and phrenic stimulation prompted right ventricular lead repositioning in another patient.

Feasibility

By interrogation of the device statistics, all 13 patients reached the threshold of $>70\%$ of normal sinus beats during which CCM therapy was applied. By serial Holter analyses, we found no instance of CCM signal delivery outside the QRS interval or in circumstances when it should not be delivered as premature ventricular complex and the two subsequent normal sinus beats. By the end of the study, no system had failed for any reason other than end-of-battery life.

Preliminary Efficacy

Echocardiographic LV function and dimension

LV EF increased and end-diastolic and end-systolic dimensions decreased at the end of each study phase compared with preimplant ($P = 0.004$ for all comparisons, Table 3 and Figs. 3 and 4). LV EF increased from $22.7 \pm 7\%$ to $28 \pm 7\%$ at the end of the FIX HF-3 phase ($P = 0.036$ for comparison with baseline), with a further significant increase at the end of the FIX HF-3 extension phase ($P = 0.006$ compared with baseline and $P = 0.021$ compared with the previous FIX HF-3 phase, after Bonferroni adjustment for multiple pairwise comparisons).

TABLE 3

Echocardiographic Left Ventricular Systolic and Diastolic Function During Follow-Up

Parameters	Baseline	FIX HF-3 Phase	P Value*	FIX HF-3	P Value*
				Extension Phase	
LVESV (mL)	136 ± 15	116 ± 16	<0.01	96 ± 21	<0.01
LVEDV (mL)	176 ± 13	163 ± 11	0.08	149 ± 15	<0.01
SV (mL)	40 ± 13	46 ± 11	0.21	55 ± 21	0.08
LVEDD (mm)	68 ± 4	66 ± 5	0.27	62 ± 6	<0.01
LVEF (%)	22.7 ± 7	28.7 ± 7	0.03	36.9 ± 12.5	<0.01
Mitral early velocity (cm/s)	85 ± 5	86 ± 5	0.82	85 ± 5	0.99
Mitral atrial velocity (cm/s)	91 ± 4	90 ± 5	0.67	91 ± 5	0.88
Early/atrial ratio	1.1 ± 0.1	1.05 ± 0.1	0.61	1.1 ± 0.1	0.99
Early deceleration time (ms)	179 ± 10	178 ± 9	0.89	178 ± 19	0.92
IVRT (ms)	106 ± 5	105 ± 5	0.99	105 ± 6	1.00

*P values by pairwise comparisons with Bonferroni correction, for changes from baseline to the end of each study phase.

LVESV = LV end-systolic volume; LVEDV = LV end-diastolic volume; SV = stroke volume; LVEDD = LV end-diastolic diameter; LVEF = left ventricular ejection fraction; IVRT = isovolumic relaxation time.

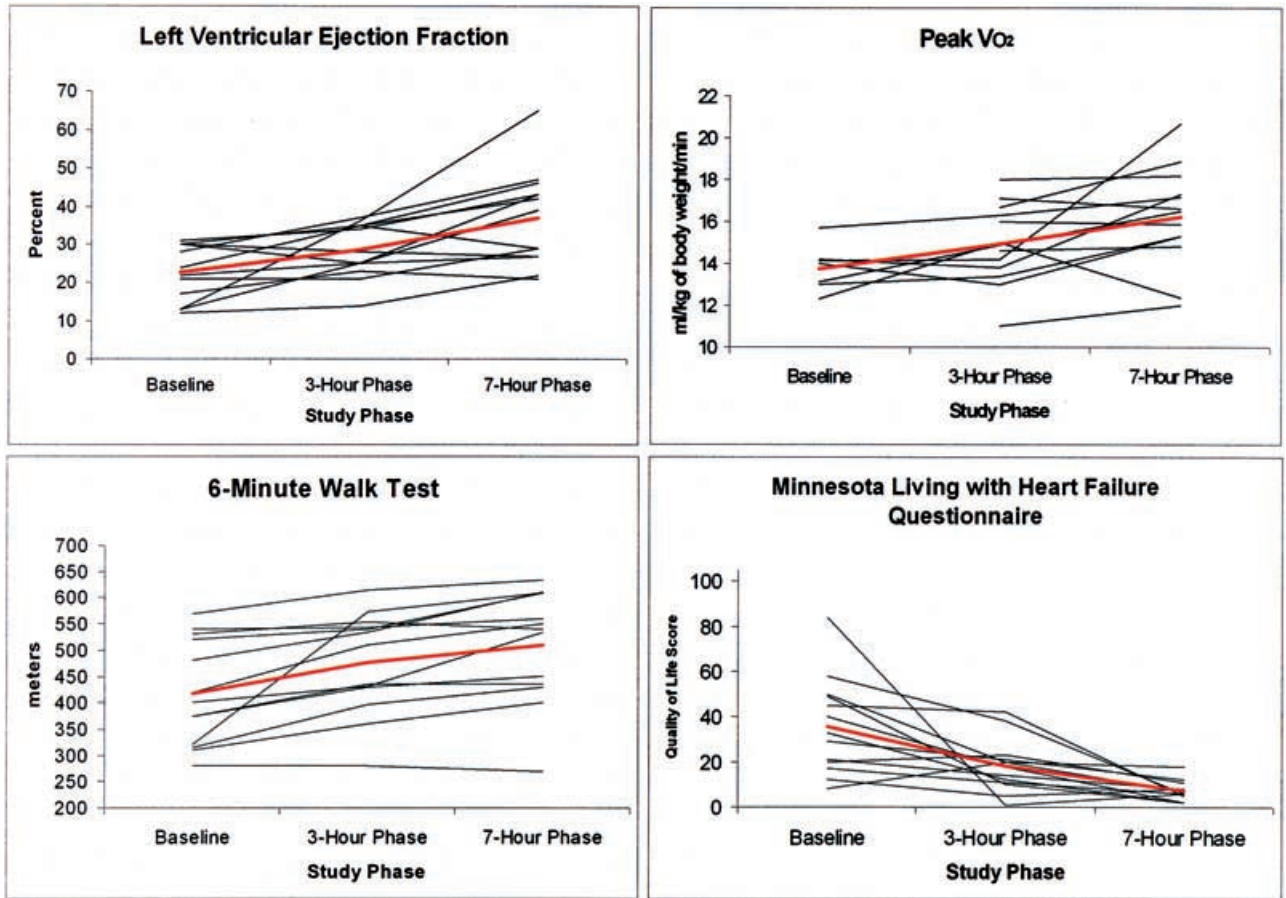


Figure 3. Changes in echocardiographic left ventricular systolic and diastolic function, maximal and submaximal exercise function, and clinical course during follow-up. A: Time course of left ventricular ejection fraction in the study phases compared with baseline in single patients (black lines) and in the overall study population (red line). B, C: Time course of the peak $\dot{V}O_2$ (in mL/kg of body weight/min) and the distance walked in 6 minutes (in meters) in the study phases compared with baseline in single patients (black lines) and in the overall study population (red line), respectively. D: Patients' perception of the effects of heart failure on their daily lives (scores of the Minnesota Living with Heart Failure Questionnaire) in the study phases compared with baseline in single patients (black lines) and in the overall study population (red line). Subjects had mean scores that were substantially above the benchmark of 10 (e.g., reduced quality of life).

No significant changes in parameters of diastolic function were found, considering either isovolumic relaxation time or the pattern of mitral inflow, including Doppler early diastolic filling velocity and atrial velocity filling, their ratio, and early deceleration time (Table 3).

Exercise performance

Peak $\dot{V}O_2$, a parameter of maximal exercising, gradually and significantly improved when comparing baseline, 3-hour phase, and 7-hour phase, from 13.7 ± 1.1 to 14.9 ± 1.9 mL/kg of body weight/min at the end of week 8 of the 3-hour phase to 16.2 ± 2.4 at the end of the 7-hour phase (overall, $P = 0.037$, Fig. 3).

During the FIX HF-3 phase, the mean distance walked in 6 minutes was 14% longer compared with baseline, with an additional 19% increase at the end of the FIX HF-3 extension phase ($P = 0.004$). The mean distance walked in 6 minutes (418 ± 99 m at baseline) increased by 59 m (477 ± 96 m, $P = 0.02$) and 80 m (510 ± 97 m, $P = 0.003$) at the end of each phase compared with baseline (Fig. 3).

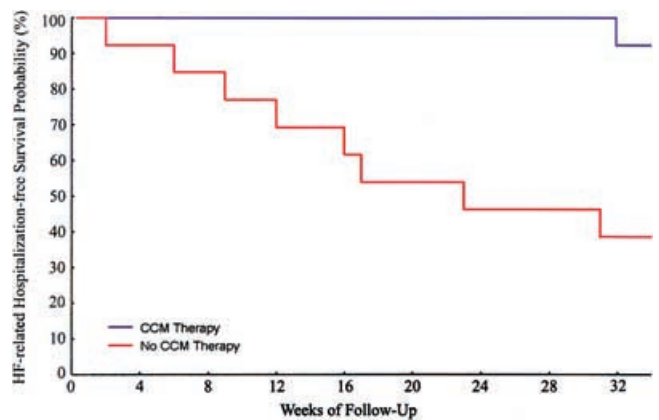


Figure 5. Kaplan-Meier estimates of the percentages of patients remaining free from hospitalization for worsening heart failure (HF). Percentages of patients remaining free from HF-related hospitalization were 100% and 92% at 6 and 32 weeks after entering the study and 61% and 38% for a correspondent period before entering the study, respectively ($P = 0.002$), showing an absolute risk reduction that approached 54% by the end of the entire study. CCM = cardiac contractility modulation.

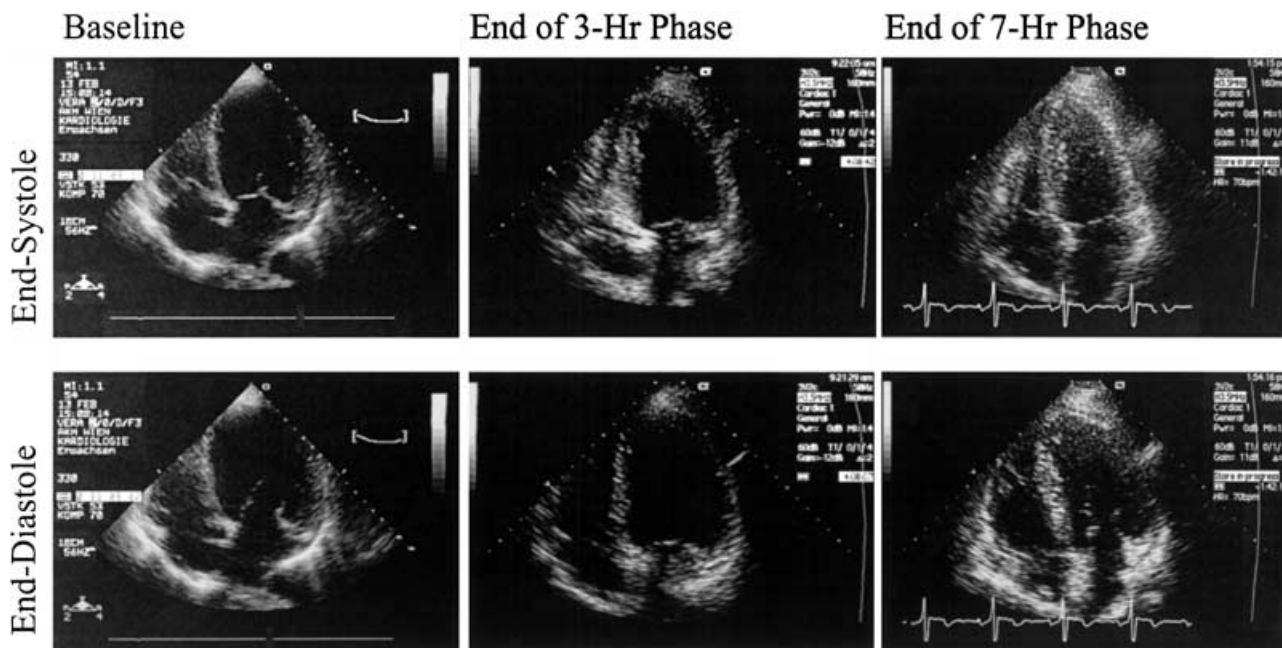


Figure 4. Illustrative apical four-chamber end-systolic (top) and end-diastolic (bottom) frames for a patient at baseline (left panel), after 8 weeks of cardiac contractility modulation therapy 3 hours per day, and at the end of the entire study. Note the stepwise decrease in both end-systolic and end-diastolic dimensions.

Clinical status

Compared with baseline, patients had an improvement in NYHA functional class at the end of both phases (from 3 to 1.8 ± 0.4 and to 1.5 ± 0.7 , respectively, $P < 0.001$ for both pairwise comparison with baseline, Fig. 3), with no difference when directly comparing results of the two study phases ($P = 0.82$).

As expected, at baseline, self-perceived quality of life was severely impaired and lower than the benchmark of 10 for a general population sample aged 65 to 74 years (Fig. 3 and Table 4).¹⁸ After 8 weeks of CCM delivery for 3 hours per day, patients tended to rate their quality of life as improved: scores for the Minnesota questionnaire decreased by a mean of 49% ($P = 0.06$), from 36 ± 21 to 18 ± 12 . Further improvement was detectable at the end of the FIX HF-3 extension phase, at the end of which we observed an absolute reduction in the Minnesota score of 29 and 11 points compared with baseline and the previous study phase, respectively (final score 7 ± 6 , $P = 0.02$ for both comparisons, Fig. 3). Improvement in the general score was paralleled by both emotional and physical dimension measures (Table 4).

Of note, all patients enjoyed a better quality of life when CCM therapy was delivered 3 hours per day, whereas two patients reported a slightly worsened quality of life when directly comparing the first and the second study phases.

Hospitalization

The crude overall frequency of hospitalization for worsening HF was 4% for the overall study period, corresponding to hospitalization of one patient during follow-up.

Specifically, the patient was admitted to the hospital for symptoms of worsening HF, including marked rest dyspnea and signs of fluid retention. The patient reported CCM generator pocket swelling that was medically managed at an-

other institution by a prolonged (8-week) course of gentamicin (320 mg daily) and amoxicillin (3 g daily). Biochemistry was suggestive of acute renal failure. Acute HF resolved a few days after antibiotic therapy cessation and diuretic dosage increase. The patient recovered well, and there were no additional hospital admissions.

Thus, after a mean follow-up of 8.8 ± 0.2 months, 92% of patients were free from HF-related hospitalizations, showing an absolute risk reduction that approached 54% by the end of the entire study ($P = 0.002$ by two-sample log rank test, Fig. 5).

Discussion

This pilot study reports the first data on mid-term safety and feasibility of a novel form of permanent electrical therapy, the CCM therapy, in patients with drug-refractory HF

TABLE 4
Quality of Life*

Parameters	Baseline	FIX HF-3 Phase	P Value†	FIX HF-3 Ext Phase	P Value†
Total	35.9 ± 21.4	18.1 ± 11.7	0.06	7.1 ± 6.1	0.002
Physical	13.7 ± 8.1	6.9 ± 4.4	0.06	2.8 ± 1.7	0.002
Emotional	8.7 ± 5.1	4.3 ± 2.9	0.05	1.5 ± 1.3	0.002

*Minnesota Living with Heart Failure Questionnaire (MLWHFQ) consists of 21 brief questions, each of which is answered on a scale from 0 to 5. Eight questions have a strong relationship to the symptoms of dyspnea and fatigue and are referred to as physical dimension measures. Five other questions are strongly related to emotional issues and are referred to as emotional dimension measures. The test is self-administered and takes only 5–10 minutes to complete. For each question, the patient selects a number from 0 to 5. Zero indicates that heart failure had no effect, and 5 indicates a very large effect. †P values by pairwise comparisons with Bonferroni correction, for changes from baseline to the end of each study phase.

secondary to LV systolic dysfunction. Unlike other types of electrical intervention for HF, such as cardiac resynchronization therapy (CRT), which is intended primarily to retune the failing heart by exciting critical regions of the left heart, the purpose of CCM stimulation is primarily to correct the weakened contractility that characterizes the failing heart, independent of disease etiology and QRS duration.

The data presented in this pilot study are consistent with a significant and persistent improvement in LV function, symptoms, and exercise tolerance of patients with advanced HF secondary to LV systolic dysfunction.

Feasibility and Safety

The procedure was well tolerated, with an overall implant procedure duration not different from that for standard dual-chamber pacemakers and less than that reported for biventricular pacemakers.^{22,23} Among the technical difficulties with biventricular pacing is effectively and reliably pacing the left ventricle.²²⁻²⁴ In contrast, in our first human chronic experience, implantation of the atrial lead and of the two right ventricular leads was 100% successful in all patients, with no ventricular lead dislodgments triggering reoperation during follow-up. The only case of reoperation was due to phrenic stimulation that was successfully treated by lead repositioning. We found that the device satisfies the endpoint of functionality as assessed by device statistics interrogation and serial 24-hour Holter ECG recordings in all patients. In no patient did the device deliver CCM signals on less than the threshold of 70% of normal sinus beats. By the end of the study, no system had failed for any reason other than end-of-battery life. Furthermore, the device proved safe, as we did not observe CCM signal delivery outside the QRS complex.

We saw no evidence of increased ventricular irritability due to CCM signal delivery during the QRS complex at follow-up. On the contrary, at the end of the 24 weeks of the second phase, the frequency of premature ventricular complexes declined below the baseline level, and although this was not prespecified, the changes across study phases reached statistical significance.

The increase in Ca^{2+} cycling due to CCM delivery did not impact diastolic function. It could be expected that increased Ca^{2+} delivery to myofilaments might also affect lusitropy.^{6,7} However, none of the parameters of diastolic function that we measured across the study varied, suggesting that increased Ca^{2+} delivery during CCM application may not reach the threshold to affect lusitropy.

The probability of adverse events directly and indirectly related to the device was quite low and acceptable. Only one patient experienced a pocket infection after the device had been replaced, although the device was replaced in all patients. Other than the patient with pocket stimulation, the output had to be lowered by approximately 2 V because of symptoms due to phrenic and/or diaphragmatic stimulation in only one patient. Thereafter, no undue discomfort was observed when the CCM currents were delivered.

Preliminary Efficacy Results

This early study shows that permanent CCM therapy improves several parameters of LV function and functional status. These beneficial effects become apparent at an early stage and persist throughout follow-up, as observed for other forms of electrical therapy for HF.²²⁻²⁴ It is worth noting that these

improvements were observed despite stringent criteria for entry into this pilot clinical study. The initial subjects had to be highly symptomatic despite full medical therapy encompassing diuretics, digoxin, ACEI, and in most cases beta-blockers. The morbidity figures for our series before entering the study are close to those reported in the literature.^{25,26} Nevertheless, to date all patients are alive, and only one patient required hospital admission due to worsening HF during a mean follow-up of 8.8 ± 0.2 months. Thus, the hospitalization rate was strikingly reduced after CCM implantation in a cohort of patients who already were receiving maximal pharmacologic therapy for HF with an ACEI and beta-blocker.

During follow-up, an echocardiographic pattern suggestive of progressive LV chamber reverse remodeling was observed. LV EF gradually increased during follow-up. The increase in LV EF rose from a decrease in both the end-systolic and the end-diastolic LV volume. These findings are compatible with the hypothesis that CCM signal application may affect cardiac contractility by a primary effect on the LV end-systolic pressure-volume relationship, as shown in animal models,^{9-11,27} with secondary effects on the reduction of end-diastolic volume. Of note, the graded increase in LV EF between the two study phases was paralleled by changes in the distance walked in 6 minutes and in several parameters of maximal exercise tolerance.

During the study, both physicians and patients were asked about any changes in the patients' overall condition. When the patients assessed their own overall progress, most of them reported that they felt moderately better or much better compared with preimplant, with their physical and psychological well-being scores reaching levels of the general population. The possibility of a persistent placebo effect of CCM therapy clearly exists; however, during the study, both physicians and patients were asked about any changes in the patients' overall condition, and when the patients' clinical course was assessed by investigators, improvement in NYHA functional class was reported in all patients.

Dose Ranging

In this study, we aimed at dose ranging to determine the effects of CCM therapy in terms of safety and efficacy. We investigated if administering a greater dose of therapy resulted in the potential for increased toxicity. We also investigated if a once-daily dose was as effective as seven doses administered daily at equally spaced intervals.

Although the sample size of this study is too small to permit a conclusion regarding dose efficacy, a general pattern can be recognized across the two study phases: most patients improved when CCM therapy was delivered for 3 hours per day, whereas some patients further improved and some did not when CCM signals were applied for 7 hours. Thus, in the overall study population, a slighter but still significant improvement was detected when the results of the two study phases were compared, with a greater dispersion near the mean values. Thus, although the duration of electrical therapy seems to have a role in determining efficacy, the need to individual tailor CCM dose must be emphasized.

Future Directions: CRT and CCM

Many device-based therapies are now being investigated for treatment of the growing number of HF patients because this condition has remained a progressive disorder despite

improved pharmacologic therapies. Effective therapies that can be deployed relatively noninvasively have the potential for relatively widespread application. One such therapy is CRT. A growing body of evidence suggests that CRT may be effective in the setting of conduction delays.²²⁻²⁴ The technology to deliver CCM therapy in a pacemaker-like device in principle could be applicable to a significantly larger group of patients because the inotropic effects are not restricted to patients with baseline conduction delays. Furthermore, these two forms of electrical therapy—CRT and CCM—may be synergistic, as has been shown in an acute hemodynamic setting and in animal models.^{12,28,29} We excluded from our study those patients who could benefit from CRT; however, future studies with devices capable of providing both forms of electrical therapies on a chronic basis will address the issue of their additive effects.

Lead selection was based on our prior acute hemodynamic experience showing that both LV and right ventricular CCM stimulation increased systolic performance to a similar degree.¹² Applying CCM therapy to the right aspect of the interventricular septum is technically easier although conceivably less effective, and it should be remembered that the primary endpoint of this study was to rule out therapy toxicity in terms of proarrhythmia. Thus, the possibility of delivering chronic CCM therapy to the left ventricle, as already assessed in our prior acute experience,¹² remains to be investigated.

Study Limitations

The main limitation of our study is that the study was not controlled or blinded; therefore, data analysis must be interpreted within the limits of the methodology used. First, the possibility of a persistent placebo effect as reported in CRT trials clearly exists; however, safety was regarded as a primary endpoint. Furthermore, larger studies are needed to confirm our preliminary results. Finally, although the results are encouraging because they demonstrate a significant improvement with CCM therapy, it must be recalled that the purpose of this study was to provide a rationale basis allowing for the design of prospective, randomized, controlled studies.

Conclusion

Although our preliminary experience supports the validity of the assumptions on which the device is based and confirms preclinical and acute human results, it is not our intention to suggest that most of the problems related to clinical implementation of this approach are solved. For example, the requirement for frequent generator replacement due to battery depletion represents a distinct but, we hope, temporary drawback. Increased ventricular irritability and/or proarrhythmia after implantation of the device, although not observed in our patients or in previous animal or human studies, is a theoretical possibility. It is important to remember, moreover, that the OPTIMIZER II, like other cardiac devices, could malfunction because of component failure, battery depletion, improper sensing or CCM delivery, or lead fracture.

Although considerable additional work is needed to perfect the therapeutic capability of this device, it is a potentially important contribution that allows improvement of symptomatic and functional status in HF patients in whom survival but not quality-of-life benefit is provided by HF medications.

Specifically, this technique appears promising as an adjuvant treatment of drug-refractory HF, particularly in NYHA class III-IV patients who are being treated with beta-blockers but cannot tolerate full doses.

Further controlled randomized studies could provide additional information to validate this novel concept and assess the actual impact in terms of quality of life, exercise tolerance, mortality rates, and cost-effectiveness ratio.

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