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Case Series

Improved Physical Function After Cardiac Contractility Modulation Therapy in 10 Patients With Chronic Heart Failure

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Background: *A new generation of therapeutic devices has expanded the options for managing advanced heart failure. We examined the outcomes of cardiac contractility therapy in a series of 10 patients with chronic heart failure.* ***Methods:*** *Ten patients with chronic heart failure were nonrandomly selected to receive cardiac contractility modulation therapy. Hemodynamics, left ventricular ejection fraction, functional capacity, and clinical outcomes were evaluated at baseline and after 6 months of therapy.* ***Results:*** *Eight male and 2 female patients (mean [SD] age, 63.4 [9.4] years) received cardiac contractility modulation therapy. Between baseline and 6-month follow-up, mean (SD) left ventricular ejection fraction improved from 27.1% (4.18%) to 35.1% (9.89%), New York Heart Association class declined from 3.9 (0.32) to 2.44 (0.52), and 6-minute walk test distance increased from 159.2 (93.79) m to 212.4 (87.24) m. Furthermore, the mean (SD) number of hospital admissions within the 6 months before cardiac contractility modulation therapy was 2.4 (2.27) compared with 1 (1.52) during the 6 months after therapy.* ***Conclusion:*** *Cardiac contractility modulation therapy improved physical functioning and reduced hospital admissions in these patients.* ***(Tex Heart Inst J. 2022;49(6):e227905)***

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More than 6 million Americans are currently living with congestive heart failure (HF), with approximately 650,000 new cases diagnosed in the United States each year.[1] Despite optimal standard pharmacologic therapy, chronic HF remains difficult to treat.

Cardiac contractility modulation (CCM) is a novel treatment option in which high-voltage current is delivered during the absolute refractory period of the cardiac cycle. The CCM signals are produced by a pacemaker-like pulse generator: the Optimizer Smart system (IMPULSE Dynamics), which was first used clinically in 2001 in Milan, Italy.[2] The generator is connected to the heart with 2 standard active-fixation leads placed endocardially on the right ventricular septum.[3,4] Although a CCM pulse delivers nearly 100 times more voltage than a standard pacemaker pulse, CCM signals do not initiate a contraction or modify the myocardial activation sequence. Thus, CCM signals are referred to as "nonexcitatory."[5]

Patients and Methods

Ten patients with chronic HF were treated with CCM delivered by the Optimizer Smart system between March 2020 and February 2022. Pharmacologic treatment had been optimized in all patients. All patients underwent a clinical evaluation at baseline, including assessment of heart rate, blood pressure, symptom severity as reflected by New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) by 2-dimensional transthoracic echocardiography, and performance on a 6-minute walk test (6MWT). In addition, the number of hospital

admissions 6 months before and 6 months after CCM was assessed based on review of hospital charts and personal interviews. Resting hemodynamic parameters were evaluated noninvasively: heart rate, as measured by radial pulse, and blood pressure, as measured using an automated device. Baseline characteristics are summarized in Table I.

A total of 20 patients with HF of nonischemic or ischemic etiology were evaluated for CCM. The decision to implant the Optimizer Smart system was based on each patient's clinical presentation after optimization of medical therapy. Ten patients were deemed to be candidates for CCM, with 8 men and 2 women (mean [SD] age, 63.4 [9.4] years) (Table II). The remaining 10 patients were not enrolled in the study for the following reasons: 2 patients had chronic atrial fibrillation (AF; which at that time was a contraindication for CCM), 4 patients had received cardiac resynchronization defibrillator devices to manage end-stage HF with low EF. Cardiac contractility modulation is not a viable treatment option for patients with very low EF in end-stage HF with poor prognosis. Four patients decided to wait before considering CCM.

All patients underwent Optimizer Smart system implantation, with pulse generator pocket formation in the right upper chest by a transcutaneous approach. The system's 2 standard active-fixation leads were placed endocardially on the right ventricular septum, and the device was programmed for optimal daily pacing. The follow-up protocol included clinic visits at 1 week, 3 months, and 6 months after implantation.

TABLE I. Characteristics of the Study Cohort at Baseline and 6-Month Follow-Up

Variable	Baseline, mean (SD)	6 mo after CCM, mean (SD)	Improvement (baseline vs follow-up), %
Resting heart rate, x/min	74.1 (13.2)	72.5 (14.3)	–
BP, mm Hg			
Systolic	124.7 (15.5)	122.6 (13.6)	–
Diastolic	82.3 (14.8)	82.7 (14.4)	–
NYHA class	3.9 (0.3)	2.44 (0.52)	37.4
LVEF, %	27.1 (4.2)	35.1 (9.9)	29.5
6MWT, m	159.2 (93.8)	212.4 (87.2)	33.4
Hospital admissions (within 6 mo before CCM vs 6 mo after CCM), No.	2.4 (2.3)	1.00 (1.52)	58.3

6MWT, 6-minute walk test; BP, blood pressure; CCM, cardiac contractility modulation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association

Table II. Baseline Demographics, LVEF, and Medical History of the Study Population

Age, y	Sex	Medical history	LVEF at baseline, %
79	Female	NICM, cardiac amyloidosis, chronic HF—NYHA class IV	25
62	Male	ICM, CAD, status after MI, chronic HF—NYHA class IV	26
66	Male	ICM, chronic HF—NYHA class IV; type 2 diabetes	35
65	Male	ICM, chronic HF, CAD, status after CABG—NYHA class IV	25
66	Male	ICM, chronic HF, CAD, status after MI—NYHA class IV; type 2 diabetes	30
66	Male	ICM, chronic HF, CAD, status after CABG—NYHA class IV; type 2 diabetes	25
65	Male	ICM, chronic HF, status after AF ablation—NYHA class IV	30
65	Male	ICM, chronic HF—NYHA class IV	25
39	Female	NICM, chronic HF—NYHA class IV; type 2 diabetes	20
61	Male	ICM, chronic HF—NYHA class III	30

AF, atrial fibrillation; CABG, coronary artery bypass graft; CAD, coronary artery disease; HF, heart failure; ICM, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NICM, nonischemic cardiomyopathy NYHA, New York Heart Association

Results

All measures showed improvement from baseline to 6-month follow-up: the mean (SD) LVEF increased from 27.1% (4.18%) to 35.1% (9.89%) (Fig. 1A), 6MWT distance increased from 159.2 (93.79) m to 212.4 (87.24) m (Fig. 1B), and NYHA class decreased from 3.9 (0.32) to 2.44 (0.52) (Fig. 1C). During 6-month follow-up after CCM, patients underwent no relevant changes in medical treatment: dosages of diuretics and HF medications remained the same.

Discussion

In this series, 10 patients with ischemic or nonischemic HF received CCM therapy provided by the Optimizer Smart system in addition to standard medical therapy. All patients improved clinically and had significant reductions in shortness of breath and fatigue, as evidenced by changes in NYHA class and improvement in functional capacity.

Despite medical therapy, patients with chronic HF have recurrent hospital admissions and require intensification of pharmacologic therapy in case of volume overload and worsening of functional capacity. Cardiac contractility modulation provided by a pacemaker-like pulse generator has emerged as a promising therapy for HF and was approved by the US Food and Drug Administration in March 2019.

The results of this case series are in line with most published data. According to a study conducted by Fastner et al,[6] after 3 years of CCM therapy in 174 patients, the mean (SD) LVEF was significantly higher in patients with nonischemic cardiomyopathy (NICM; n = 67) than in patients with ICM (n = 107) (35% [9%] vs 30% [9%], respectively; *P* = .0211). After 5 years, patients with non-ICM had significantly greater mean (SD) tricuspid annular plane systolic excursion than did patients with ICM (21% [5%] vs 18% [5%], respectively; *P* = .0437). There were no differences in other effectiveness parameters. Over the entire follow-up period,

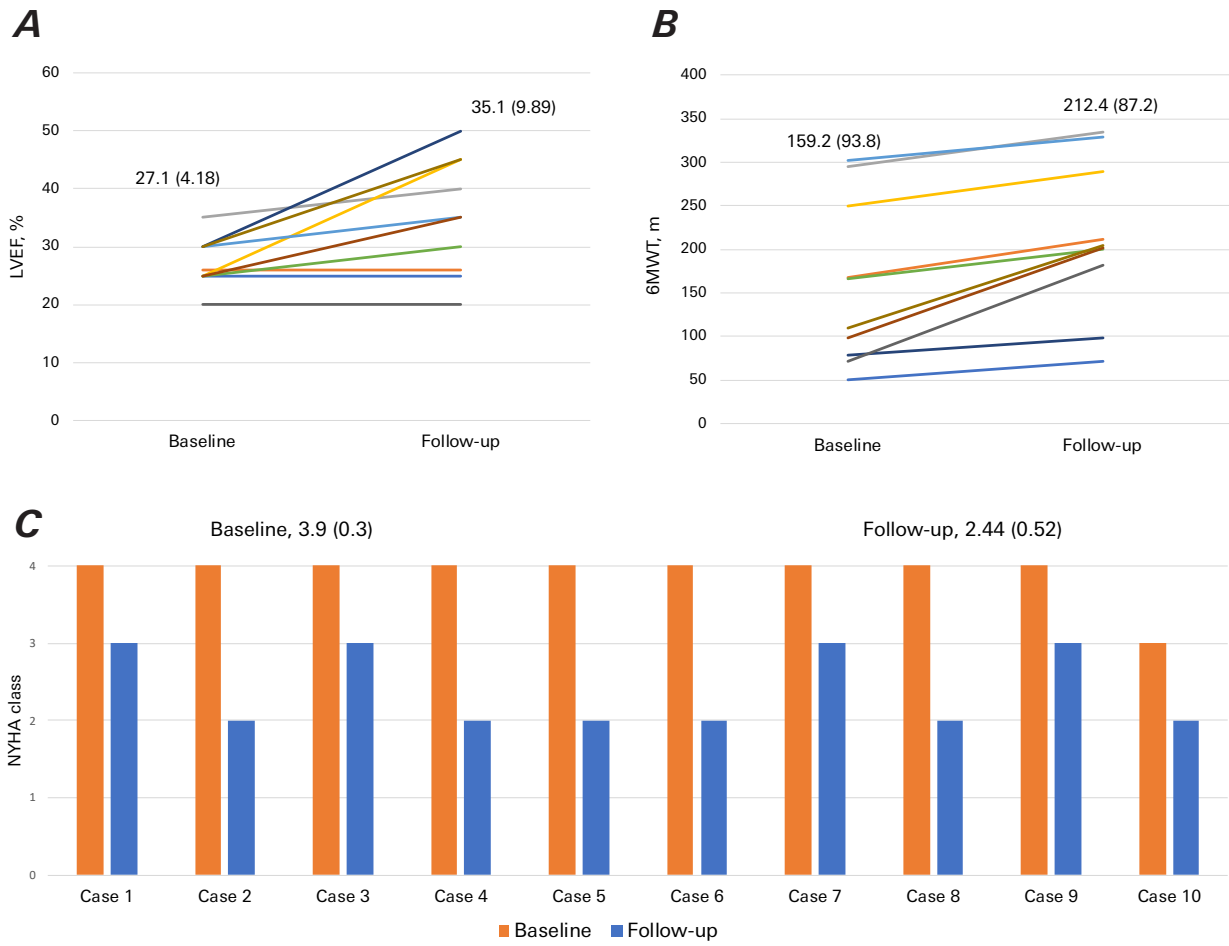

Fig. 1 *Graphs compare baseline and 6-month follow-up results for* ***A****) LVEF,* ***B****) 6MWT, and* ***C****) NYHA class in 10 patients who underwent contractility modulation therapy. Data are presented as mean (SD).*

6MWT, 6-minute walk test; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

35% of all patients died; for the patients with ICM, mortality was lower than predicted at 3 years (35% vs 43%, $P = .0395$).

Cardiac resynchronization therapy has been the mainstay of device therapy for patients with advanced HF since its advent nearly 2 decades ago. Until recently, no new device therapy had proven to be effective for this population. Kuschyk et al[7] noted that cardiac resynchronization therapy is effective in approximately 30% of cases. In a multicenter, open-label, treatment-only feasibility study, these researchers evaluated the efficacy of CCM in 17 patients with reduced LVEF who, despite cardiac resynchronization therapy, remained moderately to severely symptomatic. After 6 months of CCM, changes in NYHA class, ejection fraction, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score, exercise tolerance (6MWT), and mixed venous oxygen tension (pVO_2) as well as mortality and hospitalization rates indicated that CCM therapy improved these patients' quality of life (QOL) and exercise tolerance.

The impact of CCM on a variety of genes and proteins was explored in studies of animals with experimentally induced chronic HF. One of the most rapid effects of CCM is that near the site of signal delivery, there is, within minutes, an increase in phosphorylation of phospholamban,[8] a key protein that modulates the activity of sarcoplasmic reticulum calcium adenosine triphosphatase type 2a, which in turn modulates calcium handling by the sarcoplasmic reticulum. Shortly thereafter, changes in gene expression can be observed.[9] These changes contribute to the clinical effects of CCM.

All Optimizer devices use safety algorithms, incorporating regional stored electrocardiograms from the atrial and ventricular leads, to precisely apply CCM signals during the absolute refractory period of sinus beats and to abolish CCM signals during ectopic beats or arrhythmias, thereby avoiding signal application during the relative refractory period (when electrical stimulation could provoke ventricular arrhythmias).[8] In patients with advanced HF, expression and activity of gap junction proteins[10] are reduced, which slows signal conduction and contributes to arrhythmia generation. Therefore, some individuals may also require an ICD or already have one implanted. The Optimizer Smart system is designed to work in parallel with any ICD device[11] and does not interrupt ICD function.

In the European Union, patients not in normal sinus rhythm, including those with AF,[12] have been widely treated with CCM therapy with excellent outcomes since 2016. Since the introduction of the 2-lead configuration of the Optimizer Smart system[13] in 2019, the device's design has been able to support patients with heart rhythms other than normal sinus rhythm; however, CCM therapy for such patients in the United States was not approved until October 27, 2021. This approval vastly increased the number of patients who can be treated with CCM therapy.

Therapy with CCM has been tested in several randomized studies,[14] including a double-blind crossover study in Europe (the FIX-HF-4 study),[15] a blinded, randomized pilot study in the United States,[16] a prospective randomized study conducted in 428 patients in the United States (the FIX-HF-5 trial),[17,18] an exploratory subgroup analysis,[19] and a second prospective randomized study involving 160 patients in the United States and European Union (the FIX-HF-5C study).[20] Collectively, the results of these randomized studies indicated that CCM improves functional class, QOL, and exercise tolerance, particularly in patients with LVEF between 25% and 45%; NYHA class III symptoms, despite guideline-directed medical therapy (and an ICD, if indicated); normal QRS duration; and sinus rhythm.

Müller et al[21] studied 106 patients after CCM implantation. The mean (SD) LVEF at baseline was 28.3% (6.4%) compared with 30.5% (9.2%) at 6-month follow-up ($P = .03$).[21] In fact, LVEF increased further by 2.2%, 2.9%, 5.0%, and 4.9% at 6, 12, 18, and 24 months, respectively. Mean (SD) NYHA class and MLWHFQ in the entire cohort improved at each time point, as well: NYHA class was 2.9 (0.5) at baseline and 2.2 (0.8) at 6 months ($P = .05$), and MLWHFQ improved from 45.0 (19.2) at baseline to 31.4 (19.7) ($P = .05$) at 6-month follow-up. Eighteen deaths (including 7 with a cardiovascular cause) over 2 years were reported. Overall survival at 2 years was 86.4% (95% CI, 79.3%-91.2%). Although trends toward improvement were observed, the authors found no statistically significant improvement in the 6MWT performance or pVO_2 during follow-up, even though other prospective clinical trials did observe improvement in 6MWT at shorter follow-up times.

In 2018, Kuschyk et al[7] conducted a multicenter study involving 17 patients (82% male; mean [SD] age, 69.4 [9.6] years) with a mean (SD) baseline ejection fraction of 22.8% [6.5%]. At 6-month follow-up after CCM therapy, mean (SD) LVEF showed a trend toward improvement (25.7% [5.8%]; $P = .08$). Among the primary end points, mean (SD) 6MWT performance increased from 264 (102) m at baseline to 316 (60) m ($P = .01$) at follow-up, and MLWHFQ improved from 45 (18) to 29 (16) ($P < .01$). Mean (SD) baseline NYHA class declined from 2.9 (0.2) at baseline to 2.6 (0.5) ($P = .02$) at follow-up, and peak VO_2 increased from 11.5 (2.2) mL/kg/min to 12.6 (1.6) mL/kg/min ($P = .03$).

Kuschyk et al[12] assessed the long-term clinical effects of CCM on QOL, functional status, LVEF, hospitalizations, and mortality in a prospective, observational study of patients with different ranges of ejection fraction and in patients with AF. The results showed CCM-associated improvements in QOL and NYHA functional class over the 2-year postimplant follow-up

period as well as fewer hospitalizations than in the year before implantation. Improvements in LVEF were seen in all subgroups, with the largest in patients with the lowest baseline LVEF (≤25%). Patients with AF fared just as well with regard to these metrics as patients in normal sinus rhythm. Moreover, survival was significantly better for the total cohort than predicted by the Meta-Analysis Global Group in Chronic Heart Failure risk score.

Similarly, this case-series analysis revealed improvement in all evaluated parameters. Up to the 6-month follow-up, we observed the death of 1 patient (patient 1). After initial postimplantation improvement, the patient had progressive clinical deterioration resulting from cardiac amyloidosis. After 1 year, it was decided to terminate CCM therapy and to deactivate the patient's ICD. The patient died shortly thereafter. Another patient (patient 3) improved initially but developed septic shock, resulting in deterioration of cardiac function. This patient was then evaluated for a cardiac transplant, which was subsequently performed. All patients presented in this case series experienced clinical improvement. There were no major complications related to CCM therapy.

The introduction of CCM therapy bridged a gap for patients with few or no other therapeutic options for NYHA class III HF. This study presents descriptive data from 10 nonrandomized patients considered for CCM therapy. Several limitations should be acknowledged: a limited number of patients, the absence of a control group and randomization of treatment, and a relatively short follow-up period of 6 months. Consistent with previous clinical studies, however, this case series suggests that CCM therapy improves functional capacity in select patients with advanced heart failure.

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Conflict of Interest Disclosures: The authors declare no conflicts of interest.

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