

Cardiac contractility modulation therapy: Are there superresponders?



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Introduction

Heart failure (HF) is a common cardiovascular disease, and it is associated with high morbidity and mortality despite advances in medical and device-related management.

Patients with HF with low left ventricular ejection fraction (LVEF) and narrow QRS complexes represent a special challenge, as they are not candidates for cardiac resynchronization therapy (CRT). These patients may benefit from cardiac contractility modulation (CCM) as shown by several studies.^{1,2} Patients with HF New York Heart Association (NYHA) functional class III and an LVEF of $\geq 25\%$ respond exceptionally well to CCM therapy as suggested by subgroup analysis.³

We are presenting a case of dilated cardiomyopathy with significant improvement in HF symptoms and LVEF after initiating CCM therapy.

Case report

We are reporting the case of a 35-year-old male patient with a history of dilated cardiomyopathy and an LVEF of 25% for >2 years. He has an 11-year history of smoking but has no other risk factors for coronary artery disease. His cardiac workup for coronary artery disease was found to be negative using the nuclear stress test.

An implantable cardioverter-defibrillator (ICD) was implanted for primary prevention of sudden cardiac death 8 months previously with no complications. Despite being on guideline-directed medical therapy (GDMT), he was still complaining of shortness of breath on exertion (NYHA functional class III). There was no history of orthopnea or paroxysmal nocturnal dyspnea. His 12-lead electrocardiogram revealed a sinus rhythm at 70 beats/min with a narrow QRS complex. Echocardiogram at baseline and 12 months on GDMT showed severely reduced left ventricular systolic

function with an LVEF of 25%. There were no regional wall motion abnormalities. The right ventricular systolic function was moderately reduced, but no significant valvular lesion was noted, and pulmonary artery pressure was normal.

The option of CCM therapy was discussed with the patient, and he accepted the procedure. The device was implanted into the right pectoral region. Three pacemaker leads were inserted via the right subclavian vein; 1 lead was placed in the right atrium (at right atrial appendage), and 2 leads were placed at the right ventricular septum about 2 cm apart. During the procedure, a crosstalk test with ICD was performed while the CCM device was active and no significant interaction between the 2 devices was identified. The procedure was uneventful, and the postprocedure chest radiograph is shown in **Figure 1**. At 3-month follow-up, he reported feeling better with improvement of his shortness of breath on exertion (NYHA functional class I). A 6-minute walk test showed improvement in walking distance from 363 to 528 m.

On cardiopulmonary exercise testing, his maximal oxygen consumption/maximal oxygen uptake ($\dot{V}O_{2\max}$) improved from 15.9 to 19.7 mL/(kg·min).

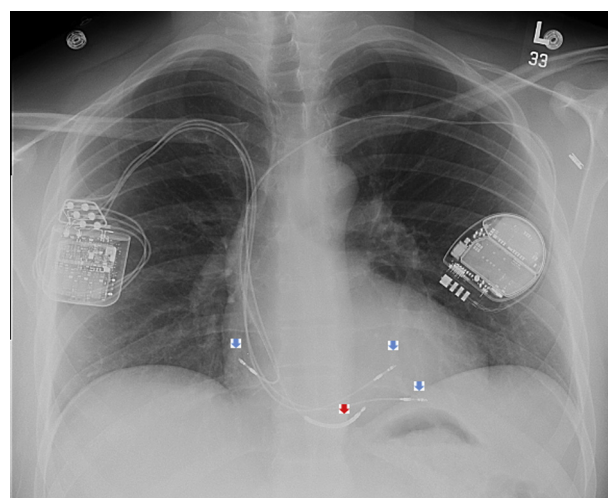


Figure 1 Posteroanterior chest radiograph showing the implantable cardioverter-defibrillator (ICD) on the left upper chest with an ICD lead (red arrow) and the cardiac contractility modulation device on the right upper chest with its leads (blue arrows).

KEYWORDS Heart failure; Cardiac contractility modulation; Left ventricular ejection fraction; $\dot{V}O_{2\max}$; Quality of life (Heart Rhythm Case Reports 2017;3:229–232)

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KEY TEACHING POINTS

- Heart failure is a common health care problem.
- Patients with heart failure and narrow QRS complexes who are refractory to medical therapy represent a management challenge, as they are not candidates for cardiac resynchronization therapy.
- Cardiac contractility modulation (CCM) therapy represents a promising therapeutic modality for these patients.
- CCM is associated with increased maximal oxygen consumption and improved quality of life in patients with heart failure.
- CCM may lead to left ventricular reverse remodeling, and it is expected to increase left ventricular ejection fraction (LVEF) by $\sim 5\%$.
- Patients with heart failure New York Heart Association functional class III and an LVEF of $\geq 25\%$ respond exceptionally well to CCM therapy as suggested by subgroup analysis of large studies in this field.

His echocardiogram showed improvement in LVEF from 20%–25% to 40%–45%. The right ventricle was normal in size and function, and the left ventricular internal diameter at end-diastole and end-systole improved from 7.2 and 6.6 to 6.5 and 5.3 cm, respectively (Figure 2).

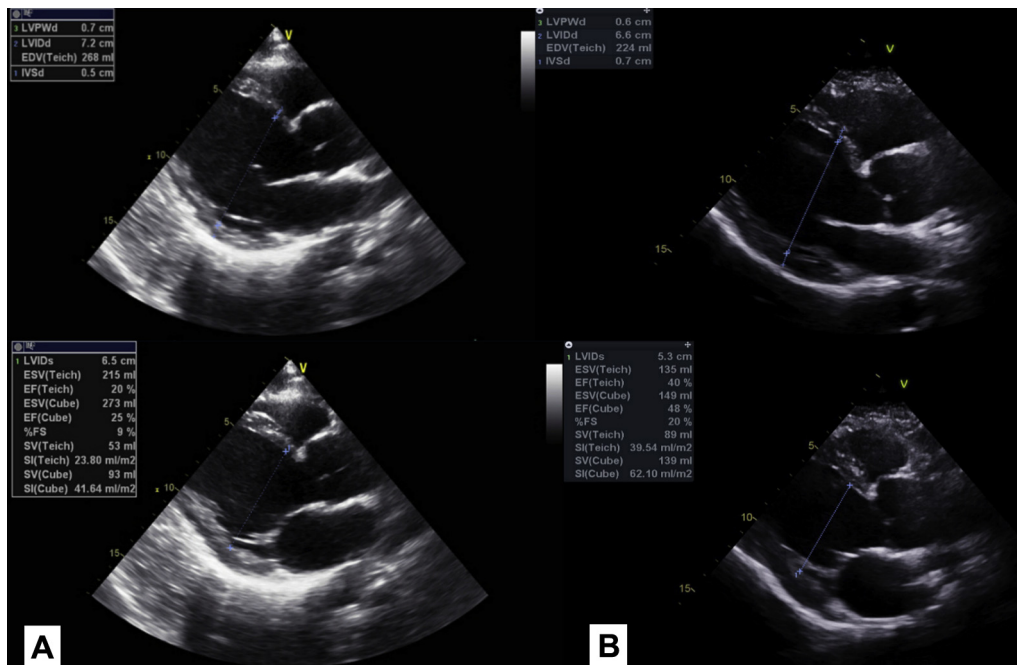


Figure 2 Echocardiogram parasternal long-axis views with left ventricular internal diameter end-diastole (LVIDd) and end-systole (LVIDs), pre (A) and post (B) cardiac contractility modulation implantation.

Discussion

In patients with symptomatic HF despite GDMT, CRT has proven to be an effective treatment with improvement in 6-minute walk distance, NYHA functional class, quality of life, $\dot{V}O_{2max}$, reduced left ventricular volumes and mitral regurgitation, and reduced all-cause mortality or hospitalization.⁴ However, CRT is generally recommended for patients in sinus rhythm and prolonged QRS complex (≥ 120 ms) with left bundle branch block or a QRS complex width of ≥ 150 ms in the absence of left bundle branch block. In patients with symptomatic HF with narrow QRS complex despite GDMT, CCM may represent an attractive alternative therapy.

We are presenting a case with an exceptionally good response to CCM therapy in a patient with dilated cardiomyopathy and narrow QRS complex who had been on GDMT for at least 1 year with no significant improvement in his symptoms and LVEF.

The CCM device is a cardiac implantable electronic device that enhances ventricular contractile strength by delivering high-voltage, nonexcitatory, biphasic waveform, electrical impulses during the absolute refractory period of the cardiac muscle cells.⁵ These signals do not affect cardiac activation sequence or initiate a new contraction.⁵

To date, the only clinically available system for CCM delivery is the Optimizer IVs system (Impulse Dynamics Inc., Orangeburg, NJ). The device is similar to a pacemaker and consists of 4 components: implantable pulse generator, leads (1 atrial and 2 ventricular leads), battery charger, and a programming unit (Figure 3). The CCM device is implanted into the pectoral region, and 3 bipolar pacemaker leads are introduced into the right side of the heart (commonly Tendril ST, St. Jude Medical, Inc., St. Paul, MN). Two leads are



Figure 3 Cardiac contractility modulation device components: (A) Optimizer IVs active implantable pulse generator, (B) external charger used to recharge the battery of the generator on a weekly basis, and (C) device programmer (leads not shown).

positioned ~ 2 cm apart at the ventricular septum for delivery of impulses, and 1 lead is placed into the right atrium to detect the atrial electrical activity.⁶

Based on the approval of CCM devices, CCM is a treatment option for patients who are at least 18 years old and suffer from HF symptoms due to left ventricular systolic dysfunction despite adequate medical treatment.⁶

Studies of the mechanisms underlying the acute and prolonged effects of CCM signals have focused on the impact on action potentials, peak intracellular calcium level, calcium loading of the sarcoplasmic reticulum, and gene expression.^{7–9} Most clinical studies on CCM therapy have involved patients with HF who were classified initially as NYHA functional class II, III, or IV and had a normal QRS duration (QRS duration ≤ 120 ms). Subgroup analysis has suggested a particular patient group who responds exceptionally well to CCM therapy. Patients were characterized by a disease severity of NYHA functional class III and an LVEF of $\geq 25\%$.³ It has been shown in meta-analyses that CCM significantly improved $\dot{V}O_{2\max}$ and 6-minute walk distance.^{9,10} There was a significant improvement in quality of life in participating patients, measured by the Minnesota Living with Heart Failure Questionnaire.^{10,11}

In some cases, reverse remodeling of the heart by CCM pulses with partial reversal of the disease-related changes in the ventricular heart structure has been noted. The LVEF is expected to improve by $\sim 5\%$.¹²

In a recent case-control study, it was found that CCM resulted in significant improvement in long-term survival, in particular in those with EF $\geq 25\%$ – 40% .¹³ A reduction in HF hospitalizations was also seen in this group of patients with less severely reduced EF.¹³

As the CCM produces a nonexcitatory impulse, there is no interaction with pacemaker in patients with pacemaker or ICD with ventricular pacing. As a matter of fact, there have been reports that show feasibility of combining CCM and CRT in CRT nonresponders. The initial results show that CCM applied in the acute setting to patients with HF receiving CRT results in additive effects on left ventricular contractility.^{14,15} However, prospective studies are needed to confirm these findings.

Although CCM is currently indicated only in patients with sinus rhythm, experience with CCM in patients with HF and atrial fibrillation has been described.¹⁶

CCM devices are approved and available for clinical use in all European Union countries, countries that recognize CE marking for medical devices and in some other countries. It is not yet approved for clinical use in the United States. However, there is an ongoing study underway seeking to obtain Food and Drug Administration approval.

CCM therapy may follow in the same footsteps as CRT, where with time optimal patients for therapy are identified. Further clinical research is required to identify which patient group within the scope of the device approval benefits most from CCM treatment.

Conclusion

CCM therapy could be associated with a significant improvement in LVEF in selected patients. More studies are needed to identify those patients who would benefit most from a CCM device.

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