Other Devices for Heart Failure—Cardiac Contractility Modulation (CCM)

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Abstract
Substantial advances in the medical treatment of HFrEF have improved survival and cardiac function in these patients. However, despite the use of optimal medical therapy (OMT) and the use of recommended devices in those in whom they are indicated, persistent symptoms limit activity and adversely affect lifestyle in a substantial number of patients. For these patients newer devices other than ICD and CRT may offer an improvement in symptoms and/or survival. This paper reviews the evidence for the use of CCM and discusses in which patients it may be considered as recommended in the recent guidelines. CCM is an established treatment in the management of moderate to severely symptomatic heart failure with reduced EF and normal QRS duration. CCM impulse delivery is associated with acute improvements in cardiac contractility. Chronic changes include reversion from fetal to adult gene expression profiles in the heart, improved calcium handling, restorative ventricular remodeling, and improved cardiac function. The recent 2016 ESC/HFA guidelines for the management of heart failure considered that most of these newer devices had insufficient clinical trial data for a formal recommendation, but in the case of one, cardiac contractility modulation (CCM) the guidelines describe CCM as being something to be considered in selected patients with HF. This is based on a demonstrated improvement in exercise tolerance (peak VO2) and quality of life (by Minnesota LWHF questionnaire, MLWHFQ) produced by CCM in an individual patient data meta-analysis of all the randomised controlled trials of CCM.

Keywords: Heart failure, Cardiac Contractility Modulation; Guidelines

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Introduction
Substantial advances in the medical treatment of HFrEF have improved survival and cardiac function in these patients. However, despite the use of optimal medical therapy (OMT) and the use of recommended devices in those in whom they are indicated, persistent symptoms limit activity and adversely affect lifestyle in a substantial number of patients. For these patients newer devices other than ICD and CRT may offer an improvement in symptoms and/or survival. The recent 2016 ESC/HFA guidelines for the management of heart failure[1] considered that most of these newer devices had insufficient clinical trial data for a formal recommendation, but in the case of one, cardiac contractility modulation (CCM) the guidelines describe CCM as being something to be considered in selected patients with HF. This is based on a demonstrated improvement in exercise tolerance (peak VO2) and quality of life (by Minnesota LWHF questionnaire, MLWHFQ) produced by CCM in an individual patient data meta-analysis of all the randomised controlled trials of CCM.[2] We review in this chapter the evidence for the use of CCM and discuss in which patients it may be considered as recommended in the recent guidelines.

Symptomatic Heart Failure despite appropriate medication

- EF < 35%
- LBBB & QRS ≥130 or QRS ≥150 ms

Yes

No

CRT / CRT-D

May Consider CCM

Figure 1 Patients for whom CRT is indicated and those in whom CCM may be considered
Is there a need for novel devices?
Approximately half of heart failure patients receiving OMT with persistent and restrictive symptoms (NYHA II-IV) have EF<35% and are candidates for ICD (Figure 1). Of these, approximately one third have LBBB or wide QRS>150 ms and are candidates for CRT.[1] However for the remaining 2/3 of subjects with heart failure and EF<35%, CRT is not indicated or even contraindicated (normal QRS duration).[1,3] In these patients, cardiac contractility modulation (CCM) may be considered as a means to offer symptomatic and functional benefit.

CCM device characteristics
CCM is a novel cardiac stimulation device that delivers two large amplitude (±7V) biphasic electrical pulses to the ventricular septum (Figure 2) for between 5 and 12 hours/day. Because the impulses are delivered 30 ms after the onset of the QRS and are of 20 ms duration, they are initiated and completed within the absolute refractory period of heart. Therefore these signals do not evoke depolarizations or alter the underlying cardiac activation sequence. They are not associated with initiation of ventricular arrhythmias. CCM elicits both acute and sustained improvements in contraction with favorable cardiac remodeling and improvement in symptoms and exercise tolerance. They are not associated with initiation of ventricular arrhythmias. CCM elicits both acute and sustained improvements in contraction with favorable cardiac remodeling and improvement in symptoms and exercise tolerance. The CCM delivery system (OPTIMIZER IV) consists of three implantable commercial leads, one in the right atrium for detecting and timing atrial activation, and two bipolar electrodes in the right ventricular septum approximately 2 cm apart for sensing ventricular depolarization and delivering the CCM impulse. Leads are connected to a subcutaneously inserted pulse generator box over the pectoral muscle on the opposite side of the chest from other implanted devices (e.g. ICD). The insertion process is similar to that of a pacemaker. Because of the large current delivered, the pulse generator battery is typically charged weekly with a specialized external conductive magnet.

Effects of CCM on cardiac function and remodeling
Onset of the CCM signal is associated with a rapid increase in isolated myocyte muscle force occurring with the next beat (Figure 3A).[4] Offset of the force generation is equally swift. This parallels with the observed rapid increases (within 3–5 minutes) in LV ejection fraction, dP/dt, and stroke volume that are observed in vivo.[5–8] These hemodynamic improvements result in long term structural adaptive remodeling of the failing ventricle (Figure 11.3b).[8,9]

Chronic improvements in cardiac contractility and structure with CCM therapy are accompanied by reversal of the foetal gene programming that occurs with heart failure and by improvement in cardiomyocyte calcium handling. ANP and BNP levels which are elevated in heart failure, are reduced with CCM treatment. Conversely expression of the primary contractile protein, alpha myosin heavy chain, which is typically depressed in chronic heart failure, is increased following chronic treatment with CCM.[10,11] Heart failure is also associated with abnormal cardiomyocyte calcium handling. In humans and animals with heart failure, SERCA2a is downregulated, with reductions in phospholamban phosphorylation, reduced ryanodine receptor expression, and an elevation in the sodium-calcium exchanger content.[10] These changes reduce depolarization-induced calcium release thereby attenuating contractility. Chronic application of CCM in heart
failure restores these biochemical abnormalities towards normal, thus improving contractile efficiency of the failing myocardium. Interestingly these biochemical changes are first observed in the region where impulse delivery occurs but after a few months of treatment, the beneficial adaptation extends to remote regions of the myocardium as well.[10] Each of these benefits associated with CCM treatment (structural remodeling, reversion away from the foetal gene programming, and biochemical restoration of cardiomyocyte calcium handling drives an improvement in cardiac function. Collectively they are likely responsible for the observed improvement in contractile efficiency described with CCM treatment. In humans and in animal models, CCM is associated with an increase in contractile function without an increase in myocardial oxygen consumption, thus an improvement in cardiac contractile efficiency.[12,13]

Clinical evaluation of CCM therapy in heart failure with reduced ejection fraction

CCM has been evaluated in more than 10 clinical trials and registries, with clinical experience in nearly 3000 patients. Enrollment has focused on patients with symptomatic (NYHA II-IV) heart failure with reduced ejection fraction (typically 35% or less) and without prolonged QRS duration. Results from the three major randomized controlled clinical trials (FIX-HF-4, FIX-HF-5, and FIX-HF-5-pilot) [7,14,15] have been compiled into a meta-analysis based on collective analysis of individual data (Figure 4).[2] Exercise tolerance (peak VO₂), walking distance (6 min walk test), and quality of life (Minnesota living with heart failure questionnaire; MLWHFQ) were assessed across 641 individual subjects from the three trials. Compared to controls, those patients with CCM treatment had significantly higher pVO₂ (p=0.006) with a better quality of life (MLWHFQ; p=0.0001), and a borderline significant improvement in 6MW (p=0.05). The magnitude of the overall benefit is only slightly less than what has been published with CRT. [16,17] Safety was also examined and adverse events were not significantly increased in the CCM group. In the largest randomized controlled clinical trial to date there were no differences in serious adverse event rates between OMT and OMT+CCM groups.[7]

A subgroup analysis of FIX-HF-5, planned prior to the start of the trial, suggested a greater benefit of CCM in patients with less severely reduced ejection fractions. When evaluating the 205 subjects from this trial with EF>25%, the primary endpoint (ventilatory aerobic threshold) was significantly improved by CCM, even though no effect was observed in the total cohort. Improvements in NYHA classification and MLWHFQ were observed in these patients with less severe reductions in ejection fraction (Figure 5). When limiting the analysis to those patients with EF>35%, even greater improvements in peak VO₂ and MLWHFQ were observed in these patients with less severe reductions in ejection fraction (Figure 6).[18] A more recent study has also demonstrated a greater benefit of CCM in patients with moderate vs. severe reductions in EF in terms of all-cause mortality and heart failure hospitalizations.[19] These finding support an ongoing controlled randomized clinical trial of CCM+OMT vs. OMT alone in patients with moderately reduced EF (25–45%).[20] They have also prompted the Task Force that developed the 2016 ESC Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure to comment on CCM. Although a specific guideline recommendation was not made, the guideline document indicates that in contrast to other novel devices being considered for heart failure, "CCM may be considered in selected patients with HF [heart failure］.[1]"
Schau et al. were first to examine mortality in 54 consecutive patients with NYHA class III-IV heart failure and average EF of 23±6%. Long term mortality was assessed and compared with that predicted by SHFM. Follow up at 1, 2 and 5 years demonstrated a survival with CCM better than predicted by SHFM at each time point. In a recent study with the longest follow-up, Liu et al.[19] examined mortality in 41 consecutively implanted (CCM) patients from a single practice. They compared mortality, hospitalization, and the composite outcome with a contemporaneous control group from a registry of patients in the same practice. Controls were matched for age, gender, EF, and etiology of heart failure. Baseline EF was 27±7% and similar between groups. Outcomes were measured over 5 years (Figure 7) and revealed a significant reduction in mortality, hospitalization, and the composite outcome at all time points measured. When patients were stratified according to ejection fraction, the improvement in survival and heart failure hospitalizations was augmented in patients with EF between 25–45% compared to matched controls, but no longer was a difference seen between CCM vs. controls for EF<25%. In a recently presented study that has not yet been published, Abraham and colleagues determined 3.4 year mortality rates among patients who were implanted with a CCM device as part of their participation in FIX-HF-5. Survival curves were compared to the most contemporary comparator group; namely, patients participating in the PARADIGM-HF study comparing the combination drug Entresto with Lisinopril. Although statistical comparison was not possible between Entresto and CCM, in each group, age, gender, BMI, blood pressure, etiology of HF, and LVEF were similar. The PARADIGM-HF Enalapril group had the highest mortality rate at the 3.5 year study follow up time point, and the FIX-HF-5 subgroup (EFs25%) had the lowest. Mortality in the PARADIGM-HF entresto cohort was similar to that in the FIX-HF-5 total group.[26] Collectively (see Figure 8), these survival studies provide strong support for conducting a prospective randomized controlled survival outcome study of CCM in patients without QRS widening and with moderate reductions in EF.

**Conclusion**

In summary, CCM is an established treatment in the management of moderate to severely symptomatic heart failure with reduced EF and normal QRS duration. CCM impulse delivery is associated with acute improvements in cardiac contractility. Chronic changes include reversion from fetal to adult gene expression profiles in the heart, improved calcium handling, restorative ventricular remodeling, and improved cardiac function. These changes are responsible for an improvement in efficiency whereby contractility increases without a corresponding increase in oxygen consumption. Randomized controlled clinical trials and their meta-analysis demonstrate improvements in quality of life, exercise capacity, and symptoms of CHF. Multiple provocative retrospective analyses suggest that CCM is associated with a reduction in mortality (especially in those with EF>25%) vs. comparable subjects with heart failure treated by OMT. CCM appears to be most efficacious in that relatively large segment of the heart failure population who have moderate to severe symptoms despite optimal medical therapy, but who do not have prolonged QRS duration or LBBB.

**Declaration of Interest**

The author declares no conflicts of interest.
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