Circulation

PERSPECTIVE

Cardiac Contractility Modulation in 2018

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Cardiac contractility modulation (CCM) is a device-based therapy for heart failure (HF) that involves applying relatively high-voltage (≈7.5 V), long-duration (≈20 milliseconds), biphasic electric signals to the right ventricular septal wall during the absolute myocardial refractory period. Accordingly, CCM signals do not elicit a new contraction; rather, they influence the biology of the failing myocardium. CCM signals have been shown to induce an acute, mild augmentation of left ventricular (LV) contractile strength without an increase in myocardial oxygen consumption in both animal HF models[1] and patients with reduced ejection fraction (EF). Three-dimensional echocardiographic studies showed that CCM induces reverse LV remodeling and improves LVEF over time. The myocardial effects of CCM are multifactorial: Studies show effects on molecular, cellular, and extracellular properties that express themselves over different time frames. Acute effects appear to involve alterations of myocardial calcium handling, whereas over intermediate and longer time frames, CCM exerts a multitude of biochemical and molecular effects locally and remotely from the site of stimulation, including shifts of a large number of abnormally expressed genes toward normal, many of which involve pathways that regulate calcium cycling and myocardial contraction. Although the major clinical trials (reviewed below) have focused on patients with normal conduction, CCM effects appear to be additive to those of cardiac resynchronization therapy (CRT) when applied to patients with prolonged QRS duration.

Three randomized prospective studies have compared patients treated with guideline-directed optimal medical therapy (including an implanted cardiac defibrillator, when indicated) with those treated with optimal medical therapy plus CCM. The earliest of these, the FIX-HF-4 study, which was conducted in European Union, showed that 3 months of CCM treatment improved exercise tolerance and quality of life.[2] Although the FIX-HF-5 study, which randomized 428 patients who were followed up for 1 year, missed its US Food and Drug Administration–mandated primary end point (an analysis of anaerobic threshold measured on cardiopulmonary stress test), it showed significant improvements in the secondary end points of peak V_{O_2} and Minnesota Living With Heart Failure Questionnaire score with treatment effects of 1.4 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ and 11.8 points, respectively.[3] This study was also the first to show that patients with an LVEF between 35% and 45% benefited the most, whereas those with EF <25% derived inadequate benefit. Most recently, the FIX-HF-5C study (n=160), conducted in sites in the United States and European Union, was designed to confirm findings that CCM improves peak V_{O_2} and Minnesota Living With Heart Failure Questionnaire score in patients with LVEF between 25% and 45% and, secondarily, to confirm even larger effects in patients with LVEF of 35% to 45%.[4] The study used a bayesian statistical design, meaning that there was statistically appropriate pooling of data from the prior FIX-HF-5 study conducted in the United States.[3] Data from

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the combined study showed an ≈50% reduction in the composite end point of cardiovascular death and HF hospitalizations. FIX-HF-5C met its primary and secondary end points, showing treatment effects in the entire cohort (LVEF, 25%–45%) amounting to 0.84–mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ improvements in peak Vo_2 (P=0.011) and 11.7-point incremental improvement over the control group in Minnesota Living With Heart Failure Questionnaire score (P<0.001), as well as a 24.6-m improvement in the 6-minute walk test (P=0.006). For patients with LVEF of 35% to 45%, the incremental improvements were 1.8 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ for peak Vo_2 (P=0.009), 14.9 points for the Minnesota Living With Heart Failure Questionnaire score (P=0.003), and 57.1 m for the 6-minute walk test (P=0.003). This study also showed an ≈50% reduction in the composite end point of death and HF hospitalizations.

In addition to these randomized studies, a number of real-world registry studies have shown that CCM-mediated improvements in symptoms, exercise tolerance, and quality of life are sustained through 2 years of follow-up.[5] They have also shown that patients with EF between 35% and 45% have even greater clinical improvements than those with LVEF <35% and that for all patients CCM reduces the rate of HF hospitalizations compared with the year before treatment.

In addition, in patients with LVEF of 35% to 45%, 3-year mortality is less than predicted by both the Meta-Analysis Global Group in Chronic Heart Failure score and the Seattle Heart Failure Model score, whereas the effect for those patients with an LVEF of 25% to 35% does not reach statistical significance.

As a result of the earliest of the studies noted above, CCM has been made available to patients in countries that recognize the CE Mark and in China, India, Brazil, the Middle East, and Australia. CCM was already mentioned in the European Society of Cardiology guidelines for the management of patients with HF. CCM is currently under review for approval by the US Food and Drug Administration.

The algorithm in the Figure summarizes a suggested pathway for how CCM fits, compared with CRT, in the treatment of patients with HF in New York Heart Association functional class III or ambulatory class IV despite optimal medical therapy with an EF ≤45%. It is important to note that there are variations in clinical practice between the United States and the European Union and that CCM is not yet approved in the United States. Thus, the actual indications for use in the United States are not yet defined; therefore, the suggested algorithm needs to be considered accordingly. Nevertheless, in both regions, optimal medical therapy generally consists of a diuretic, a β-blocker, an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or valsartan combined with sacubitril and, when tolerated, a mineralocorticoid receptor inhibitor. If the QRS

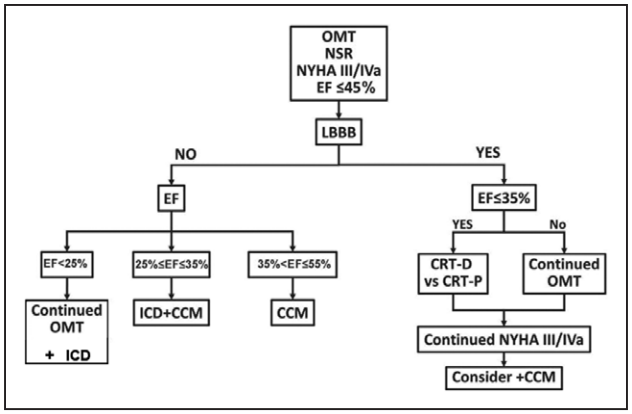

Figure. Suggested pathway for how cardiac contractility modulation (CCM) fits, compared with cardiac resynchronization therapy (CRT), in the treatment of patients with heart failure.
CRT-D indicates cardiac resynchronization therapy–defibrillator; CRT-P, cardiac resynchronization therapy–pacing; EF, ejection fraction; ICD, implanted cardiac defibrillator; LBBB, left bundle-branch block; NSR, normal sinus rhythm; NYHA, New York Heart Association; and OMT, optimal medical therapy.

complex shows a left bundle-branch block pattern (with QRS duration ≥150 milliseconds) and the LVEF is ≤35%, CRT-pacing is indicated, typically in combination with a CRT-defibrillator. However, CRT is not indicated for patients with normal QRS duration, and studies show that it may be harmful even for patients with a narrow QRS and echocardiographic evidence of contractile dyssynchrony. It is for such patients that clinical trials show that CCM provides benefit, particularly those with LVEF between 25% and 45%. For patients with an LVEF of 25% to 35%, CCM can be safely combined with an implanted cardiac defibrillator, and for patients with an LVEF of 35% to 45%, CCM is offered as the only device-based therapeutic option. In addition, particularly in the European Union, CCM may be considered an option for patients not responding to CRT and those without an indication for CRT who continue to have symptomatic HF.

CRT has proved to be an effective treatment for patients with left bundle-branch block, normal sinus rhythm, and LVEF ≤35%. However, a majority of HF patients are not indicated for CRT, and for these patients, CCM is an option. Further studies are underway to help define expanded roles for routine use of CCM in combination with CRT and in patients with HF and preserved LVEF.

ARTICLE INFORMATION

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