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Established and Emerging Device Therapy in Heart Failure: Cardiac Contractility Modulation

Justin Haloot, DO, MS[1]; Mihail G. Chelu, MD, PhD[1,2]

[1]Division of Cardiology, Baylor College of Medicine, Houston, Texas
[2]Department of Cardiology, The Texas Heart Institute, Houston, Texas

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Introduction

Cardiac contractility modulation (CCM) is a device-based treatment for heart failure with reduced ejection fraction (HFrEF). Cardiac contractility modulation provides a nonexcitatory electrical stimulation applied during the absolute refractory period. This device-based therapy was shown to improve exercise tolerance and quality of life[1] and to reduce a composite of all-cause mortality and HF hospitalizations driven mostly by hospitalizations.[2,3]

Current Limitations

Cardiac resynchronization therapy has been established for medically refractory HF and has an American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines class I recommendation for patients with left ventricular ejection fraction (LVEF) of 35% or less and QRS duration greater than 150 ms.[4] It has a class IIa indication for patients with LVEF less than 35% and QRS duration greater than 120 ms.[4] Cardiac resynchronization therapy was shown to be detrimental, however, in patients with a normal QRS duration of less than 120 ms, which includes a significant proportion of patients with HFrEF.[1-3,5] Hence, there is a need for effective therapies for patients with HFrEF and QRS duration less than 120 ms. Cardiac contractility modulation has been developed to address the needs of this patient population.

Recent Developments

Because of its benefit in treating this underserved HF population, the US Food and Drug Administration has approved CCM as a novel device-based therapy that applies a relatively high-voltage (approximately 7.5 V), long-duration (approximately 20 ms) electrical signal during the absolute refractory period (approximately 30 ms delay) (Fig. 1). The Optimizer device (Impulse Dynamics) is composed of an implantable pulse generator with a rechargeable battery, an optional atrial lead for sensing, and 2 ventricular leads that are placed along the right ventricular septum for sensing and signal delivery. In the standard configuration, the device delivers electrical signals for five 1-hour sessions in a 24-hour therapy clock, with 3.8-hour rest periods between sessions. The device can be recharged weekly with (a 1-hour charging period) and has a longevity of more than 15 years. Recent studies have demonstrated that CCM may have rapid, intermediate, and long-term effects in patients with HF.

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Corresponding author: Mihail G. Chelu, MD, PhD, Division of Cardiology, Baylor College of Medicine, 7200 Cambridge, Ste A6.137, MS: BCM621, Houston, TX 77030 (mihail.chelu@bcm.edu)

Rapid effects of CCM are related to calcium cycling and contractile force. In isolated rabbit papillary myocytes, CCM signals induced sarcoplasmic reticulum calcium loading and affected action potential duration, myocyte contractility, and relaxation.[6] In human ventricular trabecular myocytes, CCM signal amplitude was associated with increased contractility and peak isometric force without significant changes in resting tone.[6] In canine hearts, it was found that CCM increased global contractility and left ventricular pressure owing to increased sarcoplasmic reticulum and increased calcium release to myofilaments.[7]

An improved expression of genes related to HF has been seen within 3 months of CCM use.[8] Eleven patients in the FIX-HF-4 study underwent endomyocardial biopsy, which showed that CCM therapy led to an improvement in downregulated genes *SERCA 2A, alpha-MCH, PLB,* and *RyR2* as well as improvement in upregulated genes *ANP, BNP, NCX, p38 MAPK,* and *p21 RAS*.[8] Therefore, intermediate CCM effects are related to a shift of gene expression to a normalized state.

Long-term benefits of CCM have been studied with both clinical and imaging outcomes. In the FIX-HF-4 study of 164 patients with HFrEF, CCM was found to be safe and efficacious. It led to improved exercise tolerance (mean [SD] peak oxygen consumption, 14.1 [3.0] vs 13.6 [2.7] mL/kg/min) and quality of life (mean [SD] Minnesota Living With Heart Failure Questionnaire score of 38.9 [27.4] vs 36.5 [27.1] points) compared with sham treatment.[2] In the FIX-HF-5C study of 160 patients, CCM was found to improve peak oxygen consumption (0.65 mL/kg/min; $P = .024$) and Minnesota Living With Heart Failure Questionnaire score (9.7 points; $P < .0001$) compared with optimal medical therapy.[3] In the FIX-HF-5C study of 160 patients with New York Heart Association Functional Classification class III or IV disease, QRS duration less than 130 ms, and LVEF of 25% to 45%, CCM improved exercise tolerance and quality of life as well as the combined end point of HF hospitalization and mortality ($P = .042$).[1] Specifically, patients with an LVEF greater than 35% had better outcomes than those with LVEF less than 35%.[1] This outcome may be related to the long-lasting reverse modeling seen with 3-dimensional echocardiography, demonstrating improved global and regional LV contractility with CCM.[9]

Abbreviations and Acronyms

CCM	cardiac contractility modulation
HFrEF	heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction

Future Directions

Currently, the Optimizer smart CCM system is in a long-term postapproval study of 620 patients to examine safety, morbidity, and mortality at 3 years (ClinicalTrials.gov ID NCT03970343). Because of limited EF in the current study populations, the AIM HIGHer Trial is evaluating the safety and efficacy of CCM in 1500 patients with EF between 40% and 60% (ClinicalTrials.gov ID NCT05064709). The INTEGRA-D study will assess devices that combine CCM and an

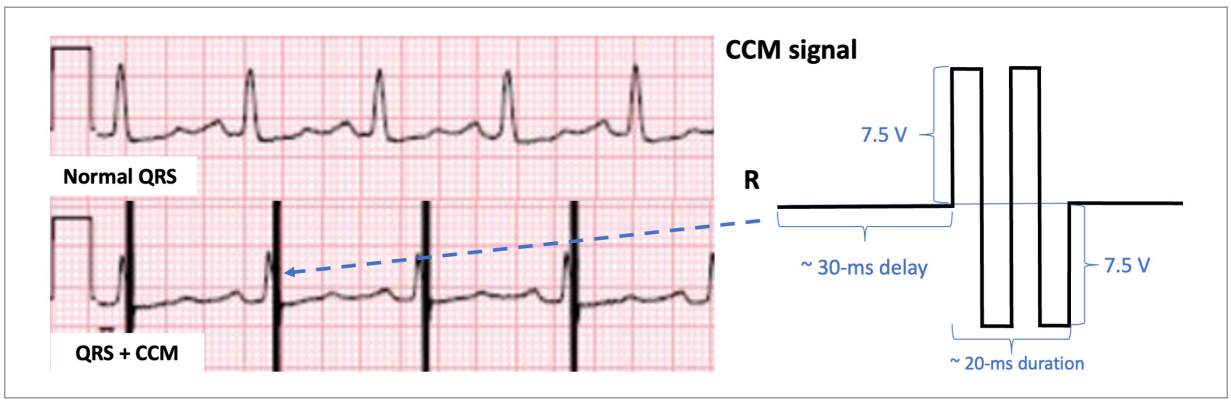

Fig. 1 Cardiac contractility modulation (CCM) signaling is a nonexcitatory signal applied during the absolute refractory period with an approximately 30-ms delay, a duration of approximately 20 ms, and an amplitude of 7.5 V. "R" is during the R component of the QRS complex.

implantable cardioverter-defibrillator into a single device in 300 patients and determine 2-year outcomes.

In conclusion, CCM can be beneficial in selected patients with LVEF of 25% to 45%, normal sinus rhythm or atrial fibrillation with QRS duration less than 120 ms, and New York Heart Association Functional Classification class III or ambulatory class IV disease.

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