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Editorial Commentary

Cardiac Contractility Modulation Therapy: Should We Be Aiming Higher for Patients With Moderately Severe Heart Failure?

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In this issue of the *Texas Heart Institute Journal*, von Schwarz et al[1] present a case series of 10 patients with chronic heart failure with reduced ejection fraction (HFrEF) treated with cardiac contractility modulation (CCM) therapy. Patients were evaluated at baseline and after 6 months, during which time their mean left ventricular ejection fraction (LVEF) improved from 27% to 35%, New York Heart Association class improved from 3.9 to 2.4, 6-minute walk test distance increased from 159 m to 212 m, and hospital admissions fell by half. Although only a case series, this article adds clinically relevant information about this underused therapy, including the fact that 50% of screened patients were not considered ideal candidates for it. This paper highlights the role of CCM in patients with symptomatic HFrEF who previously had only 2 options—medical therapy or mechanical circulatory support—to improve their symptoms.

Although goal-directed medical therapy has improved LVEF and survival in many patients, implantable cardiac electrical device therapy is also commonly used. Implantable cardioverter-defibrillators used for primary prevention improve survival in patients with HFrEF but do not improve their left ventricular function or symptoms of HF. Cardiac resynchronization therapy is limited to patients with HFrEF and wide QRS complex durations (mainly left bundle branch block), who account for approximately 30% of individuals with HFrEF. In addition, approximately 30% of patients with HFrEF do not respond to cardiac resynchronization therapy. Cardiac contractility modulation therapy can improve symptomatic HFrEF with narrow QRS complex durations, and recent US Food and Drug Administration (FDA) labeling of this therapy specifically removed the requirement for "normal sinus rhythm"; now, CCM can be offered to patients with HFrEF who are in atrial fibrillation (AF). This requirement had limited patient enrollment in the von Schwarz et al series. In the initial trials of CCM, the device used had a 3-lead design, with an atrial lead that necessitated the exclusion of patients with AF.[2] Subsequent trials of a 2-lead CCM system without the atrial lead have shown similar pulse delivery and outcomes in patients with sinus rhythm and in those with rate-controlled AF.[3]

The concept of CCM therapy has been around for decades. The Optimizer Smart device (IMPULSE Dynamics) delivers high-output biphasic (±7.5 V), long-duration (20-ms) electrical pulses during the absolute refractory period of the cardiac cycle.[4] Although the pulses are 300 times the typical pacing capture threshold for ventricular tissue, the timing of the pulses makes the therapy nonexcitatory. The mechanism of benefit may be secondary to improvement in calcium handling and, over time, the normalization of pathologic HF gene expression.[4,5]

Several clinical trials have studied the safety and efficacy of CCM. The FIX-HF-5 study was a prospective, unblinded, randomized, parallel-group, controlled trial in which 428 patients were randomly assigned to receive optimal medical therapy (OMT) plus CCM therapy (n = 215) vs OMT alone (n = 213). Enrolled patients had site investigator–determined LVEF of 35% or less and New York Heart Associa-

tion class III or ambulatory class IV symptoms despite goal-directed medical therapy.[6] The results showed that OMT plus CCM was as safe as OMT alone but was no more effective in improving patients' ventilatory anaerobic threshold, the study's primary efficacy end point, although CCM did improve peak oxygen consumption. Furthermore, the results suggested that patients with more preserved LVEFs (25%-45%) benefit most from CCM. This finding has initiated further investigation of this therapy in individuals with higher LVEF.

The Assessment of CCM in HF With Higher Ejection Fraction (AIM HIGHer; ClinicalTrials.gov identifier NCT05064709) trial,[7] which is in progress, is assessing the safety and efficacy of CCM therapy in patients with HFrEF and also in patients with HF with higher LVEFs (40%-60%). These symptomatic patients currently have few options beyond OMT to treat persistent symptoms and reduce hospitalizations. All enrolled patients had an Optimizer Smart device implanted, but patients were randomly assigned in a 2:1 ratio to CCM-on to CCM-off (sham treatment) groups. This study is intended to establish the safety and efficacy of CCM in this patient population. Specifically, this trial will assess functional capacity as change in 6-minute walk distance and in scores on a health status questionnaire. The trial will also assess procedure-related complications and a composite 18-month end point of cardiovascular mortality, HF hospitalizations, and urgent HF-related visits requiring intravenous diuretics.

After the AIM HIGHer trial began, the FDA approved the use of CCM for patients with HFrEF who are not candidates for cardiac resynchronization therapy, including those with AF. This population has few other options for therapy. We look forward to the results of AIM HIGHer because patients with symptomatic HF and higher LVEF currently have even fewer options to improve quality of life and outcomes.

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