

*Ali Massumi Cardiac Arrhythmia Symposium*

# Recent Developments in Cardiac Contractility Modulation for Heart Failure

Joshua R. Hirsch, MD<sup>1</sup>; Hamid Afshar, MD<sup>1,2</sup>

<sup>1</sup>Section of Cardiology, Baylor College of Medicine, Houston, Texas

<sup>2</sup>Department of Cardiology, Michael E. DeBakey Department of Veterans Affairs Medical Center, Houston, Texas



**Keywords:** Heart failure; action potentials; cardiac resynchronization therapy; myocardial contraction

## Background

Cardiac contractility modulation delivers an electrical current during the absolute refractory period, 30 milliseconds to 40 milliseconds after detection of local myocardial activation and without generating an action potential or cellular contraction (ie, “nonexcitatory”). Studies have demonstrated that these signals modulate action potential duration, contractility, and cardiac relaxation through cellular mechanisms involving sarcoplasmic reticulum calcium entry.<sup>1</sup> In addition, improvements in global and regional contractility suggestive of reverse remodeling have been demonstrated in small-cohort studies.<sup>2,3</sup> Cardiac contractility modulation may provide a benefit to patients with heart failure (HF) for whom implantable cardioverter-defibrillator implantation and cardiac resynchronization therapy (CRT) are not recommended as well as to specific patients with New York Heart Association (NYHA) class III symptoms and a left ventricular ejection fraction (LVEF) of 25% to 45%.<sup>4</sup>

## Current Opportunities for Improvement

For patients with American College of Cardiology/American Heart Association stage C HF, CRT has demonstrated benefits in reducing symptoms, hospitalizations, and mortality rates and. In the absence of a pacing requirement, CRT is recommended for patients who meet specific criteria: either (1) NYHA class I symptoms, with an LVEF of no more than 30%, ischemic cardiomyopathy, and a left bundle-branch block (LBBB) of at least 150 milliseconds (class of recommendation [COR] 2b) or (2) NYHA class II to ambulatory class IV symptoms, with LBBB of at least 150 milliseconds (COR 1) or between 120 milliseconds and 149 milliseconds (COR 2a) or non-LBBB of at least 150 milliseconds (COR 2a) or between 120 milliseconds and 149 milliseconds (COR 2b). Cardiac resynchronization therapy is not recommended (COR 3: no benefit) for patients with a QRS duration less than 120 milliseconds or with NYHA class I or II symptoms and a non-LBBB pattern less than 150 milliseconds.<sup>4</sup> Device-based therapies for patients with HF but for whom CRT is contraindicated remain an area of interest and clinical development.

## Recent Developments

The current generation of cardiac contractility modulation device, Optimizer Smart (Impulse Dynamics), was approved by the US Food and Drug Administration in October 2019 and includes an implantable pulse generator and 2 leads, each of which is implanted in the right ventricular septum. Previous generations of cardiac contractility

---

**Citation:** Hirsch JR, Afshar H. Recent developments in cardiac contractility modulation for heart failure. *Tex Heart Inst J*.

2024;(51)2:e248464. doi:10.14503/THIJ-24-8464

**Corresponding author:** Hamid Afshar, MD, Department of Cardiology, Michael E. DeBakey Department of Veterans Affairs Medical Center, 2002 Holcombe Blvd, Houston, TX 77030 ([hamida@bcm.edu](mailto:hamida@bcm.edu))

modulation devices included a third lead that was implanted in the right atrium. The 2 ventricular leads perform sensing and cardiac contractility modulation signal delivery, applying a biphasic electrical signal of  $\pm 7.5$  V and a 20-millisecond duration during the absolute refractory period. The pulse generator delivers five 1-hour therapies across a 24-hour period, each separated by 3.8 hours, and is wirelessly rechargeable, with expected battery longevity exceeding 15 years.

Randomized clinical evidence in support of cardiac contractility modulation in patients with HF was predominantly performed with the previous generation's 3-lead cardiac contractility modulation device. Borggreffe et al<sup>5</sup> randomly assigned 164 patients with an LVEF less than 35% and NYHA class II or III symptoms and who had received cardiac contractility modulation device implantation to 3 months of cardiac contractility modulation therapy followed by sham or vice versa and demonstrated improved exercise tolerance and quality of life (QOL). Kadish et al<sup>6</sup> randomly assigned 428 patients with NYHA class III or IV symptoms and an LVEF no more than 35% but who did not meet CRT criteria to optimal medical therapy with or without cardiac contractility modulation; their study did not demonstrate improvement in the primary outcome of ventilatory anaerobic threshold but did find improved secondary outcomes of peak maximal oxygen consumption and quality-of-life measures without a significant difference in safety. Post hoc subgroup analyses suggested a possible benefit for patients with an LVEF at least 25% and NYHA class III symptoms.<sup>7</sup> The Evaluate Safety and Efficacy of the OPTIMIZER® System in Subjects With Moderate-to-Severe Heart Failure (FIX-HF-5C; ClinicalTrials.gov identifier NCT01381172) study examined this cohort further, randomly assigning 160 patients with NYHA class III or IV symptoms, an LVEF between 25% and 45%, and a QRS duration less than 130 milliseconds, finding improvement in peak maximal oxygen consumption, QOL, and 6-minute walk distance with cardiac contractility modulation compared with optimal medical therapy.<sup>8</sup> Notably, the composite of cardiovascular death and HF hospitalizations was reduced from 10.8% to 2.9%, driven by a significant reduction in events for patients with an LVEF between 25% and 35% and narrowly meeting significance by Kaplan-Meier estimates at exactly 24 weeks, though not by log-rank testing.<sup>8</sup> A prospective registry study compared 140 patients with an LVEF between 25% and 45% who received cardiac contractility modulation therapy with mortality estimates by

### Abbreviations and Acronyms

COR	class of recommendation
CRT	cardiac resynchronization therapy
HF	heart failure
LBBS	left bundle-branch block
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
QOL	quality of life

the Seattle Heart Failure Model and with pretherapy hospitalization rates, QOL, and symptom measures; researchers found a reduction in cardiovascular and HF-related hospitalizations and improvement in QOL and NYHA class for patients receiving cardiac contractility modulation and lower mortality compared with a Seattle Heart Failure Model prediction in patients with an LVEF between 35% and 45% in nonrandomized, nonblinded observational analysis.<sup>9</sup> Patients receiving therapy through the current-generation 2-lead cardiac contractility modulation device were compared with patients in the control group from the FIX-HF-5C trial in the nonrandomized, observational FIX-HF-5C2 cohort study; this comparison suggested similar cardiac contractility modulation signal delivery and similar safety profiles, with fewer device-related adverse events with the 2-lead system than with the 3-lead system.<sup>10</sup>

### Future Directions

Post Approval Study (PAS) of the OPTIMIZER Smart and CCM Therapy (PAS) (ClinicalTrials.gov identifier NCT03970343), a prospective, multicenter, nonrandomized, single-arm, open-label study, is currently enrolling 620 participants with NYHA class III symptoms and an LVEF of 25% to 45% to assess the long-term safety and efficacy of the current 2-lead cardiac contractility modulation device in a real-world cohort. Additional randomized controlled trials include Assessment of CCM in HF With Higher Ejection Fraction (AIM-HIGH; ClinicalTrials.gov identifier NCT05064709), a prospective, multicenter, randomized, quadruple-blind trial of 1500 participants with an LVEF of 40% to 60% undergoing cardiac contractility modulation therapy vs sham, and Assessment of Combined CCM and ICD Device in HF with EF (INTEGRA-D; ClinicalTrials.gov identifier NCT05855135), a single-arm, prospective, multicenter study to examine a combined cardiac contractility

modulation—implantable cardioverter-defibrillator device in 300 participants with an LVEF of no more than 40%; each study is expected to be completed by early 2026.

## Article Information

**Published:** 17 September 2024

**Open Access:** © 2024 The Authors. Published by The Texas Heart Institute®. This is an Open Access article under the terms of the Creative Commons Attribution-NonCommercial License (CC BY-NC, <https://creativecommons.org/licenses/by-nc/4.0/>), which permits use and distribution in any medium, provided the original work is properly cited, and the use is noncommercial.

**Author Contributions:** Drs Hirsch and Afshar contributed equally to the development and writing of this manuscript.

**Conflict of Interest Disclosure:** None.

**Funding/Support:** The authors have no conflict of interest or relevant funding to report.

**Section Editor:** Mohammad Saeed, MD.

**Meeting Presentation:** Presented at the Ali Massumi Cardiac Arrhythmia Symposium; February 24, 2024; Houston, TX.

## References

1. Brunckhorst CB, Shemer I, Mika Y, Ben-Haim SA, Burkhoff D. Cardiac contractility modulation by non-excitatory currents: studies in isolated cardiac muscle. *Eur J Heart Fail.* 2006;8(1):7-15. doi:10.1016/j.ejheart.2005.05.011
2. Butter C, Rastogi S, Minden HH, Meyhöfer J, Burkhoff D, Sabbah HN. Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. *J Am Coll Cardiol.* 2008;51(18):1784-1789. doi:10.1016/j.jacc.2008.01.036
3. Yu CM, Chan JYS, Zhang Q, et al. Impact of cardiac contractility modulation on left ventricular global and regional function and remodeling. *JACC Cardiovasc Imaging.* 2009;2(12):1341-1349. doi:10.1016/j.jcmg.2009.07.011
4. Writing Committee Members; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *J Card Fail.* 2022;28(5):e1-e167. doi:10.1016/j.cardfail.2022.02.010
5. Borggrefe M, Burkhoff D. Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure. *Eur J Heart Fail.* 2012;14(7):703-712. doi:10.1093/eurjhf/hfs078
6. Kadish A, Nademane K, Volosin K, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. *Am Heart J.* 2011;161(2):329-337.e1-e2. doi:10.1016/j.ahj.2010.10.025
7. Abraham WT, Nademane K, Volosin K, et al; FIX-HF-5 Investigators and Coordinators. Subgroup analysis of a randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. *J Card Fail.* 2011;17(9):710-717. doi:10.1016/j.cardfail.2011.05.006
8. Abraham WT, Kuck KH, Goldsmith RL, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. *JACC Heart Fail.* 2018;6(10):874-883. doi:10.1016/j.jchf.2018.04.010
9. Anker SD, Borggrefe M, Neuser H, et al. Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction. *Eur J Heart Fail.* 2019;21(9):1103-1113. doi:10.1002/ejhf.1374
10. Wiegand P, Chan R, Jost C, et al. Safety, performance, and efficacy of cardiac contractility modulation delivered by the 2-lead optimizer smart system: the FIX-HF-5C2 study. *Circ Heart Fail.* 2020;13(4):e006512. doi:10.1161/CIRCHEARTFAILURE.119.006512