

Normalization of ventricular function after cardiac contractility modulation in noncompaction cardiomyopathy heterozygous positive for a pathologic TTN gene variant



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Introduction

Cardiac contractility modulation (CCM) may be used as an adjunct for the treatment of medically refractory class III chronic systolic congestive heart failure (CHF) with ejection fraction (EF) 25%–45% not indicated for biventricular pacing.^{1–3} CCM treats CHF through effecting improvement in myocardial cellular calcium handling and with reversal of adverse gene dysregulations.^{4,5} Enhanced phosphorylation of the giant myocardial protein titin also occurs with CCM, which can improve myocardial relaxation. This effect has been proposed as an additional mechanism explaining the potential benefit of CCM in heart failure.⁵ We present a case of left ventricular noncompaction (LVNC) cardiomyopathy (EF 25%), heterozygous positive for a pathologic gene defect encoding titin, TTN, c.95264G>A (p.Trp31755*), implanted with CCM technology after failing to improve with guideline-directed medical therapy (GDMT).

Case report

A 52-year-old man presented to an outside cardiologist owing to shortness of breath and chest discomfort with minimal exertion of approximately 9 months' duration. A transthoracic echocardiogram was abnormal for a left ventricular (LV) EF of 25%–30% (Supplemental Video 1) and findings concerning for LVNC. Carvedilol was titrated up to 12.5 mg twice daily along with spironolactone 25 mg daily and sacubitril-losartan 24–26 mg twice daily, with dosing limited due to positional dizziness. Nuclear stress testing was positive for ischemia. Cardiac catheterization

KEYWORDS Titin; Noncompaction; Cardiac contractility modulation; Cardiomyopathy; Heart failure
(Heart Rhythm Case Reports 2022;8:449–452)

Funding: None. Disclosures: Dr A. Hesselson is an unpaid consultant for Impulse Dynamics and Biotronik, Inc. **Address reprint requests and correspondence:** Dr Aaron B. Hesselson, 900 S. Limestone St, CDW 305D, Lexington, KY 40535. E-mail address: Aaron.hesselson@uky.edu.

KEY TEACHING POINTS

- Cardiac contractility modulation may be used as an adjunct for class III systolic heart failure, ejection fraction 25%–45%, not indicated for biventricular pacing.
- The giant myocardial protein titin plays a significant role in cardiac performance.
- Cardiomyopathy accompanied by specific titin genetic mutation may respond more favorably to cardiac contractility modulation therapy.

revealed no significant coronary artery defects. Cardiac magnetic resonance imaging (MRI) after 3 months of target GDMT was significant for a normal ventricular size (left ventricular end diastolic volume index 91 mL/m²), severely reduced global systolic function with LV EF of 29%, no late gadolinium enhancement (LGE), LV hypertrabeculation primarily in a basal-lateral location, noncompacted (NC)/compacted ratio >2.3:1, and NC/compacted mass >20% (Figure 1; Supplemental Video 2). Apixaban 5 mg twice daily was initiated for LV clot prevention. The patient was referred to the advanced heart failure service at the University of Kentucky owing to LVNC.

Dapagliflozin 5 mg daily was initiated, a 2-week ambulatory electrocardiogram monitor placed, a cardiac genomics panel ordered, and genetics consultation requested by the advanced heart failure service. Three heterozygous gene defects, ACTN c.2154+5G>A (intronic), ACTN c.899C>T (p.Thr300Met), and TTN c.95264G>A (p.Trp31755*), were found. The TTN defect was considered pathologic. Family history was remarkable for heart disease and sudden death in at least 2 maternal family members.

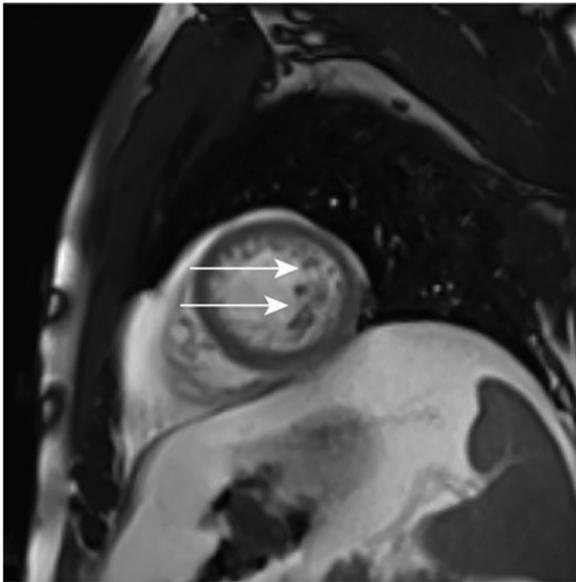


Figure 1 Cardiac magnetic resonance imaging. Hypertrabeculation is highlighted by white arrows.

The patient's mother had a history of EF 35%, along with "heart valve problems," "clots," and sudden death at 52 years of age. A maternal cousin died suddenly of an unknown history and cause. Two sons, aged 26 and 23 years, and a younger sister had no known significant health issues. The cardiac electrophysiology service was consulted in March 2021 for further management.

Electrophysiology management

Electrophysiology evaluation was additionally notable for continued class III New York Heart Association (NYHA) CHF symptoms, a 0.6% premature ventricular contraction burden with one 3-beat and one 7-beat run of nonsustained ventricular tachycardia on the ambulatory monitor, and an electrocardiogram with a QRS duration of 84 ms (Figure 2). There were no complaints of syncope or presyncope. Both implantation of a primary prevention single-chamber defibrillator and a 2-lead CCM system for management of the medically refractory heart failure symptoms were discussed. It was mutually agreed to

start with implantation of a CCM system. Septal pacemaker leads, confirmed via steep lateral oblique fluoroscopic viewing (Supplemental Video 3), were successfully inserted for CCM delivery without intraoperative chest wall stimulation identified, and the system programmed for 5 hours of daily therapy (Figure 3). Discharge occurred with no changes in heart failure regimen and no patient complaints.

Follow-up at 3 months was notable for a significant improvement in shortness of breath, a 99.3% delivery of CCM therapy for all eligible beats since implant, and no episodes of ventricular tachycardia on the device counters. However, there were intermittent complaints of chest wall pain on a daily basis. Focal intercostal chest wall contraction was noted on exam when CCM therapy was delivered. This was only relieved when the output on the local sense ventricular lead was turned off. Daily CCM therapy delivery was increased to 7 hours. Subsequent echocardiography demonstrated no wall motion abnormalities; LVEF >55%; LV end-systolic and end-diastolic dimensions of 3.7 cm and 4.8 cm, respectively; and normal right ventricular function (Supplemental Video 4). It was elected to not proceed with defibrillator implantation, given biventricular function normalization, no scar on cardiac MRI, and lack of ventricular arrhythmia. Heart failure service made no changes to the medical regimen.

Revisit to the electrophysiology service 9 months post-implant was significant for a class I–II NYHA status, freedom from chest wall contraction, 96.8% CCM delivery for all eligible beats since reset at prior visit, and no ventricular tachycardia on device counters. First-degree relatives have been contacted and cascade testing recommended, but has not been accepted.

Discussion

CCM has been studied in a general population of patients with medically refractory class III systolic CHF, EF 25%–45%, not indicated for biventricular pacing. Prospective randomized reports have demonstrated improvement in Minnesota Living with Heart Failure Questionnaire scoring, NYHA classification, 6-minute hall walk tests, peak oxygen consumption, and a significantly improved combined endpoint of cardiovascular death and heart failure

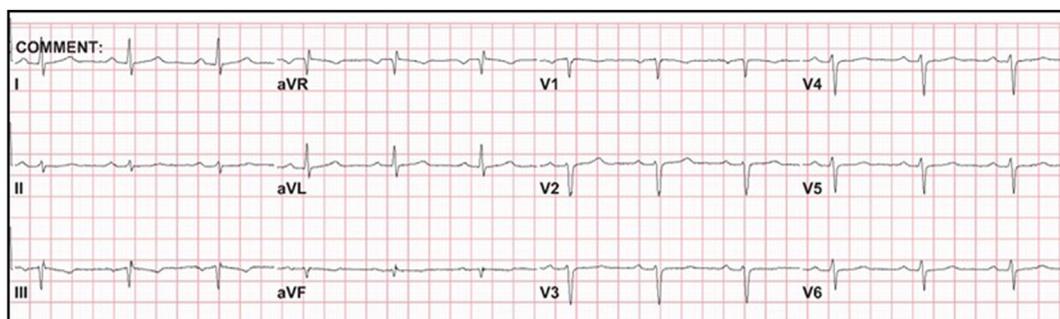


Figure 2 Baseline 12-lead electrocardiogram shows normal sinus rhythm 73 beats/min, left axis deviation, QRS width 84 ms, and poor precordial R-wave progression.

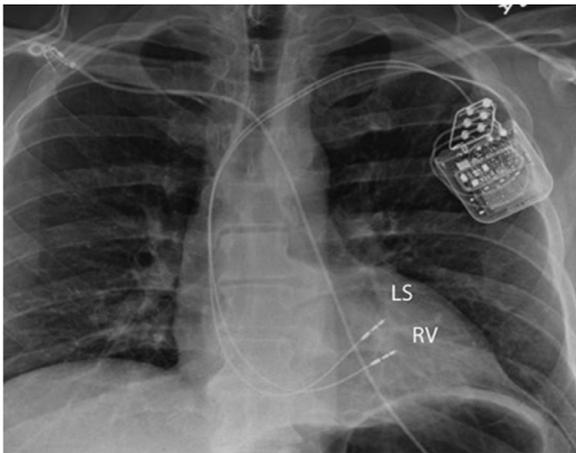


Figure 3 Post-cardiac contractility modulation implant chest radiograph. Two septal pacing leads, local sense (LS) and right ventricular (RV), are shown delivered to the high and mid septal RV regions.

hospitalization.^{1–3} More recent observations from the European registry in CCM described a possible mortality benefit for those implanted in the EF 35%–45% range. Patients also experienced an on average absolute increase in EF of approximately 5%.⁶ Caution regarding interpretation of these registry data are appropriate, given the retrospective manufacturer-sponsored nature of the analysis. As such, the 2021 European Society of Cardiology updated guidelines for the diagnosis and management of CHF considered the evidence to date insufficient to support specific recommendations for a reduction in mortality or hospitalization.⁷

Of the known genetic defects associated with LVNC, those encoding titin are most frequently found.⁸ This is the first case study describing the application of CCM in a patient with LVNC having such a known pathologic gene defect. Wong and Fung⁹ reported a case of hypertrabeculation regression and improved EF in an LVNC patient treated with CCM in 2012. However, it is unclear if an underlying titin defect was involved, as no genetic description was made in their presentation. Similarly in our case, biventricular function completely normalized, and despite CCM therapy delivery limited to a single lead within 4 months of implant in this patient. This benefit has persisted. Single-lead delivery of CCM therapy with successful clinical response has previously been shown, but is not generally recommended.¹⁰ The local sense ventricular lead caused the intercostal muscle stimulation despite a septal location. This phenomenon is suspected from a closer proximity to the anterior chest wall with a superior location, as compared to a lower septal position.

A direct CCM therapy effect enhancing phosphorylation of the giant myocardial protein titin seems a plausible mechanism for “super-response” in this case, since ventricular function did not improve on GDMT. This does not discount contributions of improved calcium handling from reversal of ryanodine, myosin heavy chain, and sarcoplasmic reticulum calcium-ATPase 2a gene dysregulations, as well as effects on calcium sequestration from phosphorylation of

phospholambin.^{4,5} However, a complete reversal of significant biventricular dysfunction is historically not expected from these CCM effects alone. Titin spans half the myocardial sarcomere distance, from Z-disk to M-band. Post-translational cardiomyocyte modifications, of which phosphorylation of titin is such an example, underlie a major determinant of cardiac function by influencing the “spring” force of titin.^{5,11}

The SGLT-2 inhibitor dapagliflozin can improve outcomes in CHF¹² and was instituted just proximal to the CCM implant. However, dapagliflozin has not been shown to improve EF in such patients to date.¹² Conversely, it cannot be discounted that the absence of LGE on MRI may have been a significant factor allowing EF recovery with CCM. Data for LGE on MRI prior to CCM is minimal. Our institution has a small case series experience for CCM use in patients treated with ambulatory milrinone and preprocedure cardiac MRI. No conclusions regarding LGE on MRI can be drawn from these data.¹³

This case raises the question of whether titin-specific gene defects in LVNC, and for that matter titin-related dilated cardiomyopathy, may predict enhanced response to CCM therapy. CCM more effectively increases EF in nonischemic vs ischemic cardiomyopathy, according to a recent European review.¹⁴ The upcoming “AimHigher” study of CCM in CHF with EF 40%–60% (NCT05064709) may also shed more light on the relation of titin to heart failure. Titin becomes more elastic with phosphorylation,¹¹ which can be improved with CCM therapy,⁵ and may be particularly relevant for CHF in this population.

There is a known risk for sudden cardiac death (SCD) in LVNC.¹⁵ In a 2021 observational review of the largest cohort in LVNC to date from the Mayo Clinic, Vaidya and colleagues¹⁵ also reported findings suggesting that location of the NC myocardium affects prognosis, regardless of EF being less than or greater than 50%. EF >50% and apical NC location had similar prognosis to the general population; otherwise, SCD was increased. MRI EF was 29% with a basal-lateral location of NC myocardium and no LGE in this instance. What to make of the SCD risk in this case with respect to normalization of EF following CCM with no LGE on MRI? A shared discussion with the patient regarding the clinical history and an understanding of the limitations of these observational data describing prognosis resulted in the mutual decision to not implant a defibrillator. It was also agreed to monitor for symptoms and the CCM generator counters for ventricular tachycardia. A defibrillator with CCM capabilities in patients without a pacing indication will be studied in the “Integra-D” trial starting later this year. An updated protocol is currently under review by the United States Food and Drug Administration.

Conclusion

CCM therapy may benefit selected populations of CHF patients with EF 25%–45%. Further study is needed to determine if genetic evaluation of patients with nonischemic forms

of cardiomyopathy may identify “super-responders” to the therapy. If so, this might imply a viable alternate strategy in even more advanced cases of heart failure being considered for a left ventricular assist device or cardiac transplantation.

Acknowledgments

The authors would like to thank Colleen McMullen for assistance in manuscript preparation.

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrcr.2022.03.016>.

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