BRIEF REPORT

Genetic cardiomyopathy and significant systolic heart failure treated with cardiac contractility modulation therapy

Aaron B. Hesselson, MD, BSEE, FACC, FHRS, CCDS, Gaurang Vaidya, MD, Andrew Kolodziej, MD

From the Gill Heart and Vascular Institute, University of Kentucky, Lexington, Kentucky.

Introduction

Cardiac contractility modulation (CCM) can be a therapeutic aid in class III chronic systolic congestive heart failure, not indicated for biventricular pacing, and with left ventricular ejection fraction (LVEF) 25% to 45%.[1] Recent observational data by Fastner and colleagues[2] suggest a greater LVEF response to CCM in patients with nonischemic as compared with ischemic cardiomyopathy, for reasons that are not entirely clear. Two recent case reports have highlighted a potential role of genetic cardiomyopathy (GCM) for significant response to CCM in patients with laminopathy (LMNA) and truncated titin (TTN) dilated cardiomyopathy.[3,4] We sought to expand on this limited experience to determine if enhanced CCM response may exist within GCM.

KEY FINDINGS

- Cardiac contractility modulation may significantly improve left ventricular ejection fraction and New York Heart Association functional class in selected cases of genetic cardiomyopathy with significant systolic heart failure.
- Genetic cardiomyopathy is a heterogeneous group for which there are multiple mechanisms of action implicated with the application of cardiac contractility modulation therapy.
- Individualized decision making regarding primary prevention implantable cardioverter-defibrillator is still required in conjunction with cardiac contractility modulation therapy.

Methods

Participants were in compliance with human studies committees and animal welfare regulations of the University of Kentucky and Food and Drug Association guidelines, including patient consent where appropriate. All patients with nonischemic cardiomyopathy (NICM) meeting appropriate CCM indications[1] and presenting to the electrophysiology clinic (A.B.H.) at the University of Kentucky over a 3-year period were offered prospective genetic testing (n = 30) and CCM insertion vs implantable cardioverter-defibrillator (ICD) first. Ten patients were GCM positive and 8 successfully implanted with CCM therapy (Figure 1). One TTN+ patient refused, and the other, myosin heavy chain positive, decompensated requiring a left ventricular assist device before CCM implantation could occur.

Potential benefits evaluated 3 to 4 months from implantation for the patients included change in LVEF, New York Heart Association (NYHA) functional class, and freedom from arrhythmia or subsequent ICD insertion. Average age in the implanted cohort was 48 years with 6 (75%) of 8 patients being male. Preimplantation LVEF range was 25% to 34% (mean 29%), and left ventricular end diastolic volume index range was 91 to 238 mL/m^2 (mean 143 mL/m^2; normal 57–105 mL/m^2). Pathologic genotypes were 5 TTN (63.1%), and 1 each troponin T (TNNT2; 12.3%), LAMA4 (12.3%), and CSRP3 (12.3%).

Results

All patients were confirmed receiving appropriate CCM therapy[1] at follow-up by the implanting electrophysiologist (A.B.H.). Seven (88%) of 8 patients improved NYHA functional class and/or LVEF post-CCM (Table 1; see example in Figure 2). Change in LVEF was, on average,

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Address reprint requests and correspondence: Dr Aaron B. Hesselson, Gill Heart and Vascular Institute, University of Kentucky, 900 S. Limestone, CDW Suite 305D, Lexington, KY 40536. E-mail address: aaron.hesselson@uky.edu.

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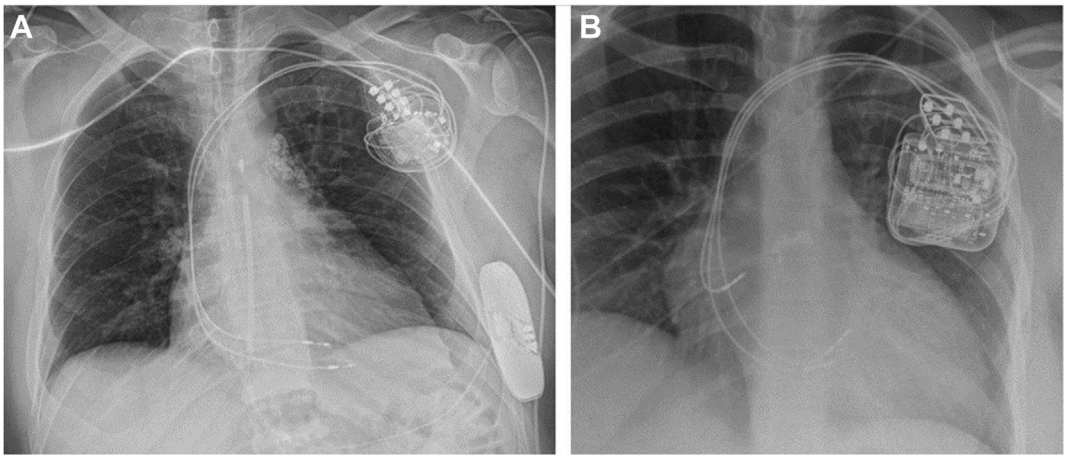

Figure 1 Implanted hardware examples. A: Patient 6 with both implantable cardioverter-defibrillator and cardiac contractility modulation. B: Patient 2 with a 3-lead stand-alone cardiac contractility modulation.

+16% for the group. One (12%) patient did not improve NYHA functional class. Patient 4 (TTN) was emergently admitted for atrial fibrillation with rapid response refractory to conversion, acute-on-chronic renal failure, and cardiogenic shock with decreased LVEF to 20%, and had insertion of an intravascular heart pump as a bridge to combined heart/kidney transplantation. The LVEF for patient 3 (TTN) did not change post-CCM; however, continuous intravenous ambulatory milrinone was stopped, they were removed from the cardiac transplant list, NYHA functional class improved to II, and syncope with hypotension resolved.

There were 5 patients (63%; patients 1, 2, 5, 7, and 8) without ICD pre-CCM. A shared decision-making discussion offered ICD vs CCM first. All elected CCM first and had LVEF improve above 35% afterward. There were no postimplantation clinical events attributable to atrial or possible sustained ventricular arrhythmia based on monitor or history. A repeat shared decision-making discussion resulted in all choosing not to have an ICD for primary prevention post-CCM implantation. Of the patients with pre-CCM ICD, there were no ventricular arrhythmia events postimplantation, and only patient 4 had atrial fibrillation post-CCM.

Discussion

Improved intracellular myocardial calcium handling, reversal of gene dysregulation, and reverse remodeling of collagen deposition have been demonstrated with the application of CCM therapy.[5,6] Our institution has previously proposed post-translational phosphorylation of the giant myocardial protein titin as an additional means for response to CCM and may be more particularly relevant in TTN-related GCM.[4] Increased mitogen-activated protein kinase (MAPK) expression occurs in LMNA and is known to increase myocardial stress. D'Onofrio and colleagues[3] suggested that inhibition of MAPK signaling in LMNA played an important additional role for CCM response in their case presentation. This is also supported by the findings of Butter and colleagues, in which MAPK expression was reduced in their crossover study of all patients implanted with CCM therapy.[6] Post-translational modification of troponin T[7] and increased actin availability through inhibition of protein kinase C[8] would be additional means for explaining the possible positive effects of CCM for our patients with TNNT2 and CSRP3 genetic defects. Effects of CCM on troponin phosphorylation and protein kinase C expression, however, have not been studied to date.[6] There are also currently no available data specific to LAMA4 GCM to explain any additional mechanistic means for response to CCM therapy.

Our data are consistent with the MAINTAINED observational study (MAnnheim cardIac coNtracTility modulAtIoN obsErvational stuDy) by Fastner and associates[2] regarding expected improvement of LVEF in NICM. Post-approval data for current CCM indications within the United States[1] are currently being generated (NCT03970343), and could potentially validate these findings. However, genetic data in the MAINTAINED study were not collected,[2] nor are they being collected in the United States postapproval study, so it is not presently possible to determine whether response to CCM in NICM may be driven by patients with GCM.

Limitations of this observational report also include a small sample size generated by a single center. Longer-term data in this cohort as well as a blinded crossover of CCM therapy would help clarify the durability and validity of therapy response, along with freedom from arrhythmia/ICD consideration.

Conclusions

It is tantalizing to consider that a cohort of patients within GCM may demonstrate significant response, even LVEF normalization, as seen in 3 (38%) of our patients. Larger registry data from multiple centers applying CCM to

Table 1 Baseline Patient Characteristics and Results

Patient	Age (Years)	Sex	Comorbidities	Phenotype	Genotype	LGE on MRI	LVEDVI (mL/m^2)	GDMT	Pre-CCM LVEF (%), Echocardiography	Pre-CCM NYHA	Post-CCM LVEF (%), Echocardiography	Post-CCM NYHA Functional Class
1	52	M	None	NICM, LVNC	Heterozygous TTN c.95264G.A (p.Trp31755*)	None	91	A, BB, MRA, SGLT2i	27	III	60	I
2	28	F	None	NICM	Heterozygous TTN c.89265G.A (p.Trp29755*)	None	136	A, BB, MRA, SGLT2i	25, moderate MR	III	45, mild MR	I
3	46	M	HoTN, ICD, syncope	NICM	Heterozygous TTN c.66985dup (p.Ala22329Glyfs*14)	None	238	A, BB, MRA, SGLT2	25, severe MR, RVEF mildly reduced	III†	25, severe MR, RVEF mildly reduced	II
4	66	M	AF, CRI, HoTN, HTN, ICD, VT	NICM	Heterozygous TTN c.7746_77662delinsAGA (p.lle25883Aspfs*3)	Minimal	186	A, BB	30, RVEF mildly reduced, severe BAE	III	20, RVEF moderately reduced, severe BAE	IV
5	43	M	DM, HTN	NICM	Heterozygous LAMA4 c.308G>A (p.Arg103Gln)	None	94	A, BB, MRA, SGLT2i	30, RVEF mildly reduced	III	50, RVEF normal	II
6	44	M	AF, ICD, VT	NICM, LVNC	Heterozygous TTN c.86821+2T>A (Splice donor)	None	107	A, BB, MRA, SGLT2i	25, RVEF mildly reduced	III	38, RVEF mildly reduced	II
7	48	M	HTN	NICM, LVNC	Heterozygous TNNT2 c.584_585del (p.Glu195Alafs*9)	Minimal	147	A, BB	34, RVEF 33	III	64, RVEF > 55	I
8	57	F	CRI, DM, HTN	NICM	Heterozygous CSRP3 c.377C>T (p.Ser126Leu)	NA	NA	A, BB, MRA, SGLT2i	33	III	55	I

A = angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor neprilysin inhibitor; AF = atrial fibrillation; BAE = biatrial enlargement; BB = beta blocker; CCM = cardiac contractility modulation; CRI = chronic renal insufficiency; DM = diabetes mellitus; F = female; GDMT = guideline-directed medical therapy; HoTN = hypotension; HTN = hypertension; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVNC = left ventricular noncompaction; M = male; MR = mitral regurgitation; MRA = mineralocorticoid antagonist; MRI = magnetic resonance imaging; NA = not applicable; NICM = nonischemic cardiomyopathy; NYHA = New York Heart Association; RVEF = right ventricular ejection fraction; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TNNT2 = cardiac troponin T; TTN = truncated titin; VT = ventricular tachycardia.

†After receiving continuous ambulatory milrinone for NYHA functional class IV status and heart transplant listing.

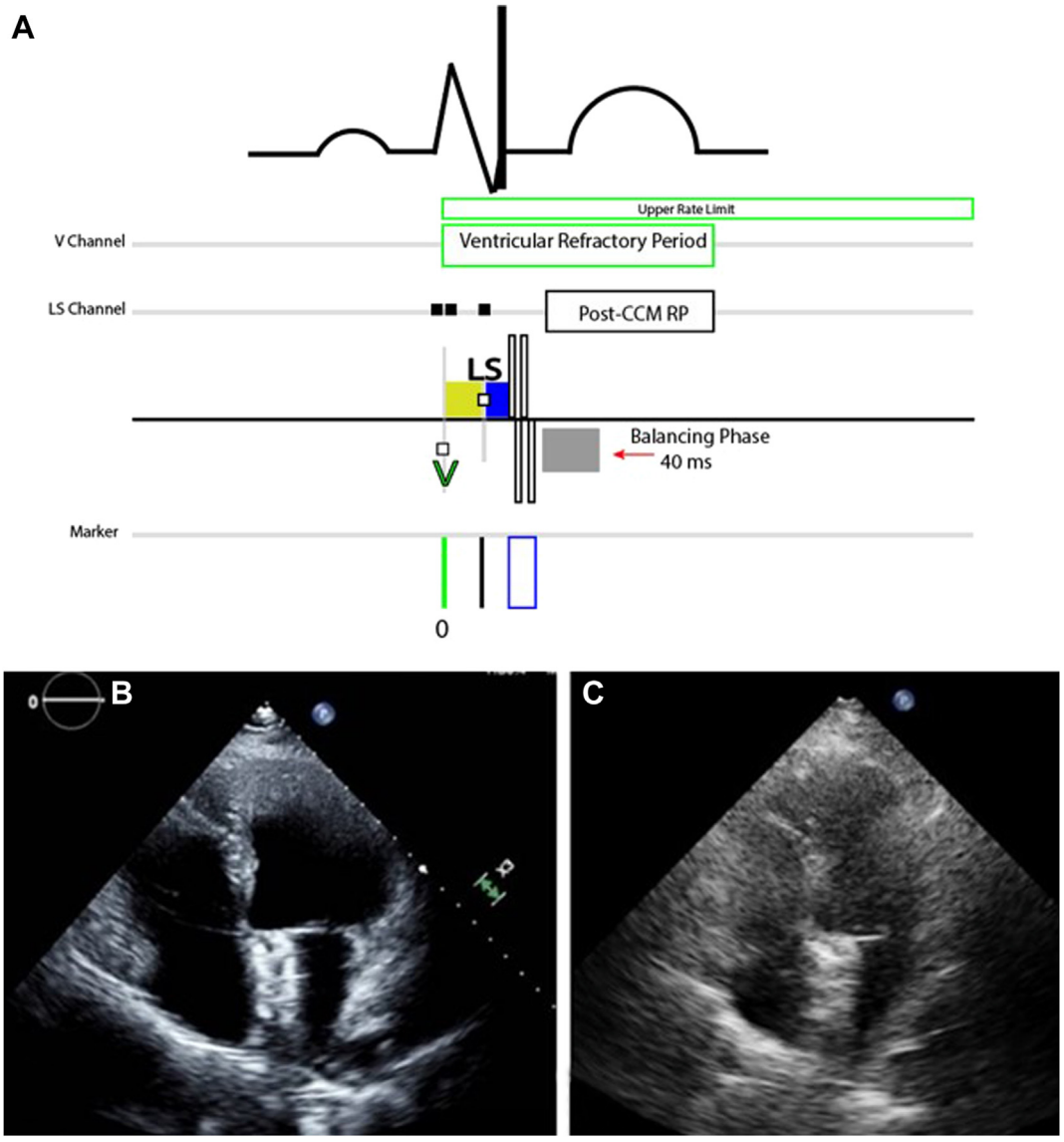

Figure 2 Cardiac contractility modulation (CCM) therapy with patient 7. A: CCM timing diagram. Four-chamber echocardiogram view pre-CCM (B) and post-CCM (B). LS = local sense; RP = refractory period; V = ventricular.

GCM as a whole, and additionally including such rigorous endpoints of postimplant magnetic resonance imaging volume changes, heart failure questionnaire scoring, exercise capacity, gene expression, and oxygen consumption that were not included in this study, would help clarify a possible relation to CCM response in GCM.

Individualized shared decision making is still required at this time regarding primary prevention ICD insertion given the paucity of data for CCM in GCM to date, regardless of LVEF improvement, and absence of ventricular arrhythmia. Coordinated efforts within the spectrum of basic and clinical science will ultimately be needed beyond present findings to determine if there may be enhanced response to CCM therapy within different genetic patient cohorts.

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