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Research Letter

Benefit of Cardiac Resynchronization Therapy in End-Stage Nonobstructive Hypertrophic Cardiomyopathy

End-stage nonobstructive hypertrophic cardiomyopathy (HCM), with systolic dysfunction and adverse left ventricular (LV) remodeling due to extensive myocardial scarring, is associated with high risk for progressive heart failure and mortality (1-5). Currently, heart transplantation is the only definitive therapeutic option for advanced heart failure symptoms in this relatively young patient group (1,2). However, the potential benefit of cardiac resynchronization therapy (CRT) in end-stage HCM to improve symptoms and alter clinical course remains uncertain, with conflicting results reported from several centers (6-8). Therefore, we believe it is timely to examine our experience with CRT to better determine the potential role of this therapeutic option in end-stage HCM.

Of 150 consecutive patients with end-stage nonobstructive HCM presenting to the Tufts HCM Institute from 2004 to 2017, we identified 20 (13% of patients with systolic dysfunction; 1% of total HCM cohort) with advanced drug refractory heart failure symptoms (New York Heart Association [NYHA] functional classes III/IV), systolic dysfunction (ejection fraction ≤50%; 35 ± 14%), and prolonged intraventricular conduction (QRS duration >120 ms) who elected to undergo CRT treatment.

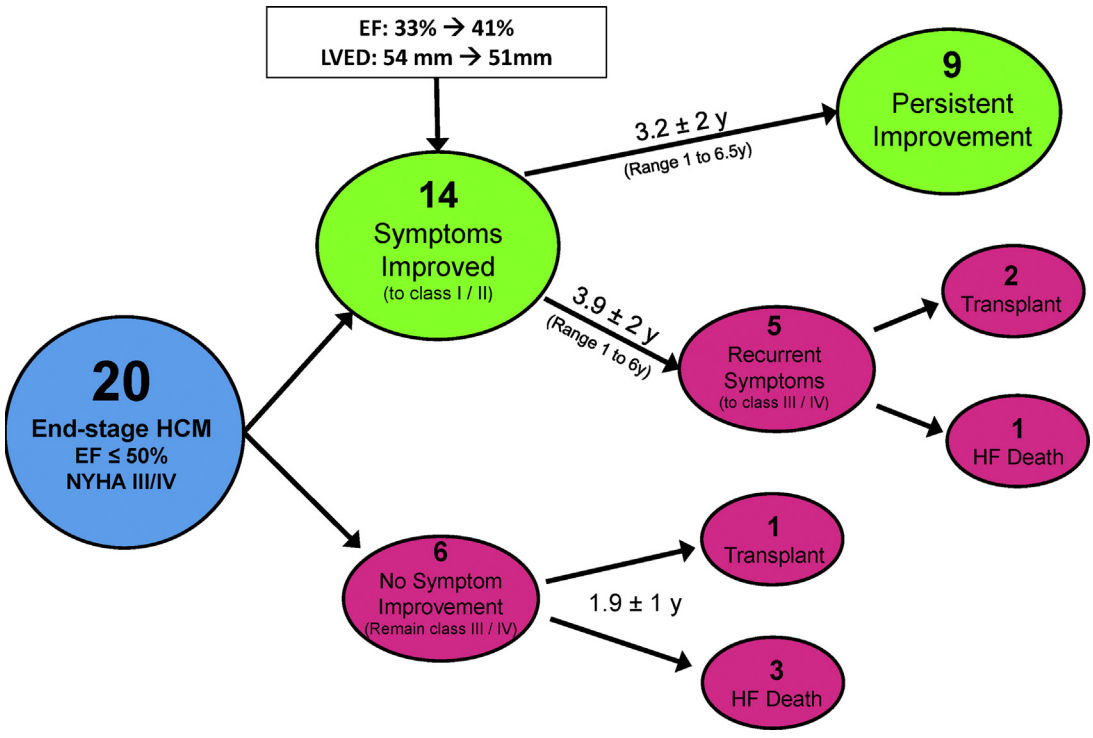
CRT was implanted at 49 ± 14 years of age, with QRS duration of 156 ± 17 (range 130 to 182) ms, with LV lead placed in the most accessible branch of the coronary sinus in a lateral or posterolateral location (while avoiding an apical position). Favorable response to CRT therapy was defined as functional improvement to NYHA functional classes I/II at 1 year post-implantation; nonresponders had persistent advanced heart failure symptoms from time of implantation.

At 1 year, 14 of the 20 patients (70%) had experienced a positive response to CRT with symptom improvement to NYHA functional class I (n = 4) and class II (n = 10), associated with increased ejection fraction (33 ± 13% to 41 ± 13%; p = 0.02) and decreased LV end-diastolic dimension (54 ± 9 mm to 51 ± 9 mm; p = 0.02) (**Figure 1**). Nine of these 14 patients have remained in NYHA functional class I or II to the end of follow-up (mean 3.2 ± 2 years, with 2 patients improved to 6.5 years). Five of the 14 responders, after an initial 3.9 ± 2.1 years of improvement following implantation, experienced recurrence of advanced symptoms (including 2 patients with symptom improvement for 6 years). Of these 5 patients, 2 went on to heart transplantation and 3 either declined or did not qualify.

The remaining 6 patients (30%) were nonresponders to CRT therapy: without significant improvement in symptoms, ejection fraction, or LV end-diastolic dimension; 1 received a transplant, 1 is active on the transplant list, and 4 declined or did not qualify for transplant (including 3 with heart failure death). Time from CRT to transplantation or death was 1.9 ± 1.0 years, compared with 7.2 ± 1.0 years for responders (p = 0.03) (**Figure 1**). Nonresponders had more advanced symptoms at time of device implantation compared with responders (NYHA functional class IV: 50% vs. 7%, p = 0.06), but without differences in age, LV ejection fraction, LV end-diastolic dimension, or degree of intraventricular conduction delay (Online Table 1).

In 70% of our end-stage HCM patients, CRT was effective in providing symptomatic benefit associated with improved ejection fraction and LV cavity size. Furthermore, the proportion of our HCM patients who responded favorably to CRT was similar to the benefit reported in non-HCM heart failure populations (9,10). However, given that extensive LV myocardial fibrosis is the primary pathophysiologic abnormality leading to LV remodeling and dysfunction in end-stage HCM (1-4), it is unlikely that CRT alone can be regarded as an effective long-term treatment option eliminating the need for a transplant in this relatively young patient subgroup. In this regard, 5 of the 14 patients with initial response to CRT had recurrent advanced symptoms over follow-up, substantiating the value of close clinical

FIGURE 1 Benefit of CRT in Patients With End-Stage HCM



Effectiveness of cardiac resynchronization therapy (CRT) in improving advanced drug refractory heart failure (HF) symptoms and survival free of transplant for 20 patients with end-stage nonobstructive hypertrophic cardiomyopathy (HCM). EF = ejection fraction; LVED = left ventricular end-diastolic; NYHA = New York Heart Association.

surveillance, and low threshold for transplant listing.

Most importantly, CRT allowed for improved quality of life, achieving for these patients an average of 3.9 years (and at least 6 years in 20%) with no or only mild symptoms, and creating a substantial and valuable delay in the timing of heart transplantation for this subset of young patients without alternative treatment options (1,2). Indeed, overall, CRT provided a total of 47 additional years of symptom improvement, free of transplant, for the treatment group.

Our data also suggest that the optimal benefit of CRT may occur earlier in the clinical course of end-stage HCM patients. For example, 50% of CRT nonresponders had progression to NYHA functional class IV at time of implantation (7-fold more than responders), likely with irreversible LV remodeling and more extensive myocardial fibrosis at a late stage in the clinical course (3,4).

In conclusion, CRT can be beneficial to end-stage HCM patients with systolic dysfunction and wide QRS with the capability of extending the pre-transplant period with reasonable quality of life for patients with no other options.

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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APPENDIX For a supplemental table, please see the online version of this paper.