Cardiac resynchronization therapy in patients with end-stage hypertrophic cardiomyopathy

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Aims

A dilated/end-stage phase of hypertrophic cardiomyopathy (HCM) is rare but well-recognized. The role for cardiac resynchronization therapy (CRT) in this subset of patients remains unexplored. We aimed to clarify the impact of bi-ventricular pacing CRT in dilated/end-stage HCM.

Methods and results

The Mayo Clinic HCM database was interrogated to identify patients with ejection fraction (EF) < 50% and CRT. Control subjects were identified in 1:1 manner. Clinical outcomes were determined. Of 2073 patients with HCM, 9 (8 male) had EF < 50% and received CRT. The average age at CRT-D implant was 44.8 ± 14.8 years, an average of 17.3 ± 10.3 years after HCM diagnosis. The indication for CRT was based on New York Heart Association class II symptoms (mean 2.7 ± 0.4) and EF < 50% in all patients (EF 34.7 ± 7.1% at implant), with electrocardiographic evidence of abnormal ventricular conduction. At 6-month, 12-month, and long-term follow-up, EF was 39.9 ± 8.4%, 37.9 ± 9.8%, and 33.3 ± 7.6%, respectively (P > 0.05 for all). There was no difference in the combined end-point of left ventricular assist device (LVAD), cardiac transplant, or death between groups (P = 0.90). At last follow-up [mean duration 12.9 ± 8.3 (median 10.7) years], 8 (89%) in the CRT group were alive. Three and 2 patients underwent LVAD implantation and cardiac heart transplantation, respectively, 15.0 ± 10.1 years from HCM diagnosis and 2.6 ± 0.9 years from CRT implant. In the control group, 4 (44.4%) patients were alive at last follow-up [mean duration 12.0 ± 7.1 (median 12.7) years]. One patient each had LVAD and cardiac transplant.

Conclusions

CRT in patients with dilated/end-stage HCM does not appear to confer a salutary effect on ventricular function. In medium-term follow-up, however, left ventricular function did not appear to deteriorate further, yet advanced heart failure therapy was common in this group.

Keywords

Hypertrophic cardiomyopathy • Cardiac resynchronization therapy • Biventricular pacing • Dilated cardiomyopathy

Introduction

A well-recognized, yet infrequent complication of hypertrophic cardiomyopathy (HCM) is the development of an end-stage cardiomyopathic phenotype.1,2 Occurring in around 3–5% of patients, it is recommended that these patients be managed as per standard heart failure guideline strategies3 but the overall prognosis of this group of patients remains poor.1 Evolving from normal or hyperdynamic systolic ventricular function and defined by a left ventricular ejection fraction (EF) < 50%, some patients will develop wall thinning with cavity dilatation, commonly with delayed electrical activation of the left ventricle. Over and above the standard histological signature of HCM (which includes myocyte hypertrophy, fibrosis and myofibrillar disarray6) this group of patients appear to develop more fibrosis, potentially driven by severe microvascular dysfunction.5

Although current guidelines provide a class Ib (class IIa, American guidelines) indication for septal reduction therapy (SRT) with either septal alcohol ablation or surgical myectomy for patients with HCM,
What’s new?

- A dilated/end-stage phase of hypertrophic cardiomyopathy (HCM) is rare but well-recognized.
- The incidence of a dilated/end-stage phase in HCM in this study is lower than previously reported.
- Cardiac dyssynchrony may contribute to disease progression – yet biventricular pacing is not associated with sustained ventricular functional improvement.

Methods

Patient population
Following institutional review board approval, we analysed patients with HCM and systolic dysfunction (defined as EF <50%) despite optimal medical therapy that underwent implantation of a CRT device between 2001 and 2013. A control group of patients with HCM and systolic dysfunction but no CRT was identified in a 1:1 fashion, matched for age and EF.

Patient assessment
Baseline clinical evaluation prior to CRT implantation was via office interview and included assessment of New York Heart Association (NYHA) class. Six-minute walk test, exercise treadmill test with oxygen consumption, and quality of life (Minnesota Living with Heart Failure Questionnaire) assessment were not routinely performed. Comprehensive two-dimensional and Doppler echocardiographic assessment was performed at baseline and following CRT. Left ventricular (LV) EF was calculated using the modified Simpson’s formula. The peak instantaneous left ventricular outflow tract (LVOT) gradient was measured by continuous wave Doppler echocardiography. Mitral inflow velocity was measured by pulse-wave Doppler echocardiography at the level of the mitral leaflet tips. The degree of mitral regurgitation (MR) was assessed and graded via integration of colour flow and Doppler data.

Medical therapy and cardiac resynchronization therapy
Once LV dysfunction was identified, medical therapy for heart failure was typically initiated and maintained prior to/following CRT. For CRT implantation, standard implant techniques were used; the LV lead position was prioritized as lateral/posterolateral whenever possible as dictated by pacing thresholds, diaphragmatic stimulation, and ability to cannulate the veins. The apical region and anterior interventricular vein were avoided. Atroventricular or interventricular optimization was not routinely performed in the pacing laboratory at the time of implant. Non-responders were consistently evaluated in our CRT clinic, being exposed to a variety of different LV–RV offsets based with simultaneous 2D echocardiography ± 12 lead electrocardiography.

Follow-up
The Mayo Clinic electronic medical record was reviewed to determine outcomes including change in EF and NYHA class score. Outcomes included the combined endpoint of left ventricular assist device (LVAD) implantation, cardiac transplantation, or death from the time of CRT implantation (or time of determination of a low EF in controls).

Statistical analysis
Results are presented as mean (standard deviation) for continuous measures or median (range) for skewed distributions. Categorical measures are presented as number (percentage). Fisher’s exact test was used for comparison of dichotomous variables and 2-sample t-test was used for continuous variables. Paired t-test was used to determine change in EF and QRS pre- and post-CRT. Endpoints were estimated using the Kaplan–Meier method using the time of CRT implantation or determination of low EF as time zero. Comparison between the case and control groups for each of these endpoints was completed using log-rank tests.

Results

Baseline clinical characteristics
Of 2073 patients with HCM, 42(2%) were identified as having a low EF and 9 received CRT (Figure 1). Baseline characteristics are shown in Table 1 and Table 2. Eight patients were male. At initial diagnosis, the mean age was 27.7 ± 14.5 (median 25, range 7–53) years and mean EF was 51.9 ± 11.8% (median 55, range 35–69%). The LV mass index was 418.9 grams/m² and average septal thickness was 18 ± 4.8 mm (median 20 mm, range 9–24). At the time of initial diagnosis, 3 patients (Patients 2, 6, and 7) had LVOT obstruction. However, at the time of CRT, only 1 patient had a provable LVOT gradient—Patient 6 had...
a resting LVOT gradient of 16 mmHg which increased to 49 mmHg with amyl nitrite inhalation. Moderate MR was evident only in Patient 7; the remaining patients had no more than mild MR. Mean NYHA class at the time of the initial diagnosis was 1.7 ± 0.8 (median 1, range 1–3). In terms of comorbidities, 1 had known coronary artery disease, 5 patients had paroxysmal atrial fibrillation, and 3 had a history of ventricular tachycardia/ventricular fibrillation at the time of CRT implant.

The average age at CRT-D implant was 44.8 ± 14.8 years, an average of 17.3 ± 10.3 years after HCM diagnosis. Three patients had previously undergone SRT (2 surgical myectomy, 1 alcohol septal ablation followed by surgical myectomy) an average of 15.0 ± 11.4 years prior to CRT implantation. None of these patients developed a need to require pacing following SRT. With regards to medical therapy, 6 patients were taking beta-blockers, 2 calcium-channel blockers, and 7 were taking renin-angiotensin-aldosterone system antagonists. No patients were taking disopyramide. Four patients were using anti-arrhythmic drugs. The indication for CRT was based on a reduced EF in all patients plus NYHA class II or greater heart failure symptoms. Notably, 6 patients had clinical cardiac failure within the preceding 6 months. In addition, three patients required defibrillators for primary prevention while the remaining six patients underwent defibrillator implant for secondary prevention. At the time of implant, average EF was 34.7 ± 7.1%; average NYHA class was 2.7 ± 0.4. The implant in 5 patients involved upgrade from a dual chamber implantable-cardioverter defibrillator (ICD); in the remaining 4 patients, CRT was a de novo implant. Prior to biventricular upgrade, 4 patients demonstrated a paced QRS morphology on their electrocardiogram; 2 had non-specific intraventricular conduction delay, 2 had left bundle branch block and 1 had right bundle branch block. Baseline QRS duration was 182 ± 39 ms. In individuals with right ventricular pacing, the pacing percentage at last device check prior to CRT was 100%, 100%, 0%, 52%, and 100% in Patients 1, 5, 6, 8, and 9, respectively. The coronary sinus LV lead was placed in an anterolateral position in 2, posterolateral position in 4, and lateral position in 3 patients.

The control group was relatively well matched to the CRT group (Table 1). Of 9 controls, 7 were male. The average age at HCM diagnosis was 32.1 ± 13.3 years. The average age at diagnosis with EF < 50% was 46.0 ± 14.1 years—at that time, the average EF 36.1 ± 6.3%. Six patients had previously undergone SRT (all with surgical myectomy). Seven patients had ICDs. In terms of comorbidities at the time of EF < 50%, 2 patients had coronary artery disease, 5 had atrial fibrillation, and 3 patients had a history of ventricular tachycardia/ventricular fibrillation. With regards to medical therapy, 8 patients were on beta-blockers, 1 on calcium-channel blockers, and 6 patients were on renin-angiotensin-aldosterone system antagonists. No patients were taking disopyramide or anti-arrhythmic drugs.

### Post-cardiac resynchronization therapy defibrillator

**ECG and echocardiography**

The mean LV EF at implant was 34.7 ± 7.1%. The temporal change in EF following CRT is shown in Figure 2. Following CRT therapy, all

<table>
<thead>
<tr>
<th>Variable(mean ± SD, unless stated otherwise)</th>
<th>CRT-group(n=9)</th>
<th>Control group(n=9)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>27.4 ± 14.5</td>
<td>32.1 ± 13.3</td>
<td>0.86</td>
</tr>
<tr>
<td>At diagnosis</td>
<td>44.8 ± 14.8</td>
<td>46.0 ± 14.1</td>
<td>0.85</td>
</tr>
<tr>
<td>Male gender, n(%)</td>
<td>8 (89)</td>
<td>7 (78)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>115.4 ± 18</td>
<td>118 ± 13</td>
<td>0.76</td>
</tr>
<tr>
<td>Diastolic</td>
<td>71.3 ± 11</td>
<td>72 ± 8</td>
<td>0.85</td>
</tr>
<tr>
<td>EF, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>51.9 ± 11.8</td>
<td>N/A</td>
<td>–</td>
</tr>
<tr>
<td>De novo CRT implant, n (%)</td>
<td>(44.4)</td>
<td>N/A</td>
<td>–</td>
</tr>
<tr>
<td>NYHA class pre-CRT implant(%)</td>
<td>2.7 ± 0.4</td>
<td>2.2 ± 0.9</td>
<td>0.24</td>
</tr>
<tr>
<td>NYHA class post-CRT implant(%)</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.8</td>
<td>0.77</td>
</tr>
<tr>
<td>QRS duration at baseline, ms</td>
<td>182 ± 39</td>
<td>122 ± 39</td>
<td>0.02</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>5 (55)</td>
<td>5 (55)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Coronary artery disease, n(%)</td>
<td>1 (11)</td>
<td>2 (22)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Prior SRT, n(%)</td>
<td>3 (33)</td>
<td>6 (67)</td>
<td>0.35*</td>
</tr>
<tr>
<td>Beta-blocker, n(%)</td>
<td>6 (67)</td>
<td>8 (89)</td>
<td>0.58*</td>
</tr>
<tr>
<td>Calcium channel blocker, n(%)</td>
<td>2 (22)</td>
<td>1 (11)</td>
<td>1.0*</td>
</tr>
<tr>
<td>RAAS blocker, n(%)</td>
<td>7 (78)</td>
<td>6 (67)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Antiarrhythmic therapy, n(%)</td>
<td>4 (44)</td>
<td>0</td>
<td>0.08*</td>
</tr>
<tr>
<td>Family history of HCM, n(%)</td>
<td>6 (67)</td>
<td>3 (33)</td>
<td>0.35*</td>
</tr>
</tbody>
</table>

SD, standard deviation; CRT, cardiac resynchronization therapy; EF, ejection fraction; SRT, septal reduction therapy; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association. RAAS blocker, renin-angiotensin-aldosterone system.

*Fisher’s exact test.
Table 2
Clinical characteristics and outcomes of patients with HCM at the time of CRT-D implantation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at CRT-D (years)</th>
<th>Gender</th>
<th>Coronary artery</th>
<th>LV lead position</th>
<th>LVOT disease</th>
<th>NYHA class</th>
<th>EF, % (pre, post)</th>
<th>SRT type</th>
<th>De novo</th>
<th>QRS duration, ms (pre, post)</th>
<th>QRS morphology</th>
<th>Ventricular tachycardia/fibrillation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60±1</td>
<td>N</td>
<td>Y</td>
<td>Postero-lateral</td>
<td>N/A</td>
<td>2/3</td>
<td>37, 41</td>
<td>LVAD</td>
<td>Well</td>
<td>172, 132</td>
<td>Lateral</td>
<td>Pacemaker</td>
<td>Well</td>
</tr>
<tr>
<td>2</td>
<td>57±2</td>
<td>M</td>
<td>Y</td>
<td>Antero-lateral</td>
<td>RBBB</td>
<td>3</td>
<td>39, 22</td>
<td>LVAD</td>
<td>Well</td>
<td>174, 186</td>
<td>Antero-lateral</td>
<td>RBBB, right bundle branch block</td>
<td>Well</td>
</tr>
<tr>
<td>3</td>
<td>62±3</td>
<td>F</td>
<td>N</td>
<td>Antero-lateral</td>
<td>IVCD</td>
<td>2</td>
<td>32, 22</td>
<td>LVAD</td>
<td>LVAD Transplant</td>
<td>160, 144</td>
<td>Postero-lateral</td>
<td>LVAD</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>60±4</td>
<td>M</td>
<td>Y</td>
<td>Paced</td>
<td>LBBB</td>
<td>2</td>
<td>40, 22</td>
<td>LVAD</td>
<td>LVAD Transplant</td>
<td>268, 220</td>
<td>Postero-lateral</td>
<td>LVAD</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>62±5</td>
<td>M</td>
<td>N</td>
<td>N/A</td>
<td>LBBB</td>
<td>3</td>
<td>30, 33</td>
<td>LVAD</td>
<td>Myectomy</td>
<td>182, 176</td>
<td>Postero-lateral</td>
<td>LVAD, heart transplant</td>
<td>LVAD</td>
</tr>
<tr>
<td>6</td>
<td>47±6</td>
<td>M</td>
<td>N</td>
<td>N/A</td>
<td>LBBB</td>
<td>2</td>
<td>40, 44</td>
<td>LVAD</td>
<td>—</td>
<td>192, 152</td>
<td>N/A</td>
<td>Alcohol ablation</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>31±7</td>
<td>M</td>
<td>N</td>
<td>N/A</td>
<td>IVCD</td>
<td>3</td>
<td>44, 30</td>
<td>LVAD</td>
<td>—</td>
<td>122, 196</td>
<td>N/A</td>
<td>LVAD, heart transplant</td>
<td>LVAD</td>
</tr>
<tr>
<td>8</td>
<td>43±8</td>
<td>M</td>
<td>Y</td>
<td>Paced</td>
<td>LBBB</td>
<td>3</td>
<td>40, 33</td>
<td>LVAD</td>
<td>—</td>
<td>212, 196</td>
<td>N/A</td>
<td>LVAD, heart transplant</td>
<td>LVAD</td>
</tr>
</tbody>
</table>

CRT-D, cardiac resynchronization therapy-defibrillator; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; RBBB, right bundle branch block; EF, ejection fraction; SRT, septal reduction therapy.

Although some patients had initial improvement in EF of >5%, only 1 patient maintained such an improvement at long-term follow-up. Patients demonstrated a paced rhythm on their ECG with a mean QRS duration of 165.3 ± 28.9 ms—a reduction of 16.4 ± 25 ms from baseline (P = 0.10). At 6 months, after implant, the average EF was 39.9 ± 8.4%, reflecting a mean increase of 5.9 ± 4.9% from baseline. At 12 months, mean EF was 37.9 ± 9.8%, a mean increase of 3.9 ± 9.8% from baseline. At last measurement (mean duration 5.0 ± 3.7 years), the EF was 33.3 ± 7.6%, a mean reduction of 0.8 ± 7.2% from baseline levels (P = 0.04, 0.33, 0.79 at 6-months, 12-months, and long-term follow-up versus baseline, respectively). At 6-months, 12-months and, last follow-up, 6, 3, and 1 Patient, respectively, had improved EF >5%; 2 patients had a >5% reduction in EF at last follow-up. At last EF follow-up (mean duration 4.9 ± 3.7 years), the control group EF dropped from 36.1 ± 6.3% to 31.3 ± 9.0%, reflecting a drop of 4.8 ± 5.7% (P = 0.05 compared to baseline EF, and P = 0.33 compared to change in EF of CRT group at long-term follow-up).

Left ventricular assist device/heart transplantation/death
There was no difference in the combined endpoint of LVAD, cardiac transplantation, or death between groups [50% in those with CRT vs. 81.3% in controls (P = 0.90)]. Similarly, there was no difference in death between those with or without CRT (16.7% vs. 66.7%, respectively, [P = 0.16]) although patient numbers were small and LVAD/cardiac transplant utilization variable. In the CRT group, 3 patients ultimately underwent LVAD implantation and 2 underwent heart transplantation (1 of which was preceded by LVAD). The mean time of LVAD or heart transplant was 15.0 ± 0.1 years from HCM diagnosis and 2.6 ± 0.9 years from CRT implant. At last follow-up (mean 12.9 ± 8.3 years), 8(89%) CRT patients were alive. Death occurred in 1 patient who was being managed with an LVAD as destination therapy 1.8 years after implant. The death was non-cardiac, secondary to intracranial haemorrhage. In the control group, 1 patient had LVAD and 1 patient had heart transplant at a mean time of 24.7 ± 3.9 years from diagnosis and 4.7 ± 4.2 years from identification of low EF. At last follow-up (mean 12.0 ± 7.1 years), 4 (44.4%) of the control group patients were alive. Of the 5 deaths, 1 patient died due to multisystem organ failure in the setting of LVAD, 1 died due to end-stage heart failure, 2 died of non-cardiac causes, and 1 was undetermined.

Discussion
The experience from this cohort reveals that in a large tertiary referral practice for HCM, progressive LV dysfunction reaching an end-stage is rare. In lieu of this, biventricular pacing is rarely indicated and was implanted in <1% of individuals with this form of the disease. This therapeutic tool was utilized specifically in those patients with failing LV function with heart failure symptoms despite maximal medical therapy. Noteworthy is the relatively young age of these patients, nearly all of whom are male, a finding in keeping with an earlier report.

Ventricular function
These findings suggest that CRT in this context was not associated with any significant, sustained benefit in LV systolic function or mortality. Although some patients had initial improvement in EF of >5%, only 1 patient maintained such an improvement at long-term follow-
up. Furthermore, the change in EF at long-term follow-up was not different than that in the control group patients. The clinical paradigm whereby hypertrophic myocardium with hyperdynamic systolic function deteriorates into a dilated poorly contracting myocardium has been observed in small series—occurring in up to 10% of HCM cases (although this is less frequent in our experience). This form of HCM does not seem to be a hallmark of a particular genetic substrate and likely is the combination of a genetically coordinated maladaptation in the context of other clinical influences or polymorphisms. In this cohort alone, the patients were relatively young and a substantial proportion ultimately required advanced heart failure therapies such as ventricular assist device implantation or cardiac transplantation. This is distinctly different from the bulk of patients with HCM that maintain their LV function throughout life and are symptomatic predominantly from LV filling abnormalities and outflow tract obstruction. It is therefore difficult to know whether these findings can be extrapolated to the older HCM patient with a less aggressive disease pattern.

This investigation confirms findings seen in other studies assessing end-stage HCM in that the time duration from onset of symptoms to the development of end-stage HCM is long and independent of prior SRT. In one study, the mean duration from HCM symptoms to development of end-stage disease was 14 years. However, once end-stage disease developed, death or transplantation occurred within 3 years. In this cohort, patients required destination therapy with LVAD or heart transplantation an average of 15 years after HCM diagnosis and 2–3 years after CRT implantation. Coupled with the findings of the study cited above, our study suggests that while CRT may have limited salutary effects on symptoms and EF, it does not seem to retard or ameliorate the disease progression in comparison to the control group.

Although still poorly understood, it is likely that the benefit conferred by CRT in other forms of acquired heart disease is mediated through improved electrical and mechanical coupling while the fundamental abnormality is the degree of dysynchrony from abnormal electrical activation of the left ventricle. Many patients with HCM present with a wide left bundle branch block ECG signature yet do not develop worsening systolic function, despite the delayed activation of the lateral wall. Furthermore, SRT will result in abnormal activation of the septum, and thereby conceptually further delay conduction from the right bundle to the lateral LV wall. This does suggest that ventricular systolic function can be improved with CRT by ameliorating the electro-mechanical coupling with this iatrogenic conduction delay, yet there is insufficient data to draw a firm conclusion.

Interestingly, a significant number of patients had a high burden of right ventricular pacing prior to CRT. Prior randomized controlled trials evaluating dual-chamber pacing for HCM demonstrated limited benefits of symptom relief and reduction of gradients whereas others demonstrated symptom and hemodynamic improvements. It is possible that some patients with HCM exhibit some type of ‘molecular response’ that causes faster progression of LV systolic dysfunction than that which happens in patients with other forms of cardiomyopathy. In addition, it is conceivable that in previous studies resolution of outflow tract gradient with dual-chamber pacing was in fact due to adverse remodelling with LV enlargement and decreased systolic function. Further studies carefully assessing the effect of right ventricular pacing in patients with HCM are warranted.

Figure 2 Time line of EF post CRT-D implantation in patients with end-stage HCM. Patient 8 returned home following CRT and was lost for follow-up until returning 28 months following CRT for heart transplantation. Of note, he had undergone LVAD implantation 18 months following CRT. Long-term represents mean duration of 5.0 ± 3.7 years.
Lusitropy and left ventricular outflow tract obstruction

More recently, biventricular resynchronization has been considered as a treatment modality for reducing LVOT obstruction in patients with HCM and a preserved LV function.\textsuperscript{10,22,23} Histologically, HCM is characterized by myocyte hypertrophy, fibrillar disarray, and various amount of interstitial fibrosis.\textsuperscript{5} This heterogeneity is thought to lead to a regional difference in electrical conduction and thereby delay in both contraction and relaxation.\textsuperscript{24,25} As such, CRT is felt to hold promise by improving the local variation in contraction and, potentially, also relaxation by improved diastolic ventricular interaction.\textsuperscript{25} Furthermore, alterations in the contractile sequence by CRT whereby the posterolateral/lateral LV is activated simultaneously with the RV and prior to the septum may change the shape and diameter of the LVOT and subsequent LVOT gradient. Moreover, positioning the LV lead near the anterolateral papillary muscle may alter the timing of anterior mitral leaflet closure, and therefore reduce its contact with the septum.\textsuperscript{23} Interestingly, evaluation of the optimal pacing strategy in a small cohort of HCM patients with preserved ventricular function, substantial outflow tract obstruction, and severe heart failure symptoms identified biventricular pacing as the most beneficial configuration in the majority; LV pacing alone and right ventricular pacing appeared more beneficial in the remainder.\textsuperscript{22} In this group, at one year follow-up, there remained continued improvement in symptoms and reduction in LVOT gradient. Longer term follow-up after successful CRT implantation has also demonstrated salutary effects on symptoms and LVOT gradients.\textsuperscript{23}

Clinical outcomes

CRT has previously been shown to be of potential clinical benefit in non-obstructive, end-stage HCM by improving heart failure symptoms in around 40% of a small cohort of 20 patients. The patients studied in this particular investigation had on average significantly higher EFs (45 ± 14% with a range from 21 to 64%),\textsuperscript{10} and at relatively short-term follow-up mixed results were suggestive of a disease-stabilizing effect as opposed substantial improvements noted typically in other non-HCM patients. Our data suggest similarly that LV resynchronization may temporarily stabilize the disease yet does not result in long-lasting improvements in ventricular function in patients with HCM. Overall, this suggests that disease progression is ongoing and restoration of synchrony does not significantly retard such progression. In addition, diastolic dysfunction and restrictive filling may not be adequately addressed by CRT and may in part explain the limited benefit. Despite optimal medical therapy, these patients frequently evolve to require more advanced heart failure therapy, such as LVAD and heart transplant, and it remains unclear as to whether CRT can stave off decline if begun prior to LV dilatation in patients with or without LVOT obstruction.\textsuperscript{9}

Limitations

This small study has several intrinsic limitations secondary to its retrospective nature. Patients were managed at a tertiary referral centre and results may not be applicable outside of similar centres. HCM is a heterogeneous disease; therefore it may be difficult to account for certain confounders. Several patients had undergone prior SRT and had non-obstructive physiology at the time of CRT. Additionally, although pre- and post-CRT EF and long term outcomes were available, we did not routinely have objective assessment of functional capacity (6-min walk test, maximum oxygen consumption) post-CRT implantation. In spite of a control group, there are likely to be inherent differences between groups that may affect outcomes. Only 2 patients had LBBB with QRS duration > 150 ms (4 others were paced) which may account for the attenuated benefit seen in this population; however, 7 had QRS duration > 150 ms. The cohort was predominately male, a group known to have a lower degree of response to CRT in non-HCM populations compared to females. Given that this report is observational, the control group may not be representative and the comparison futile; yet the authors feel there is utility to reporting a larger group with a single unusual phenotypic expression of HCM. Finally, the lack of benefit seen with CRT may be due to lack of power.

Conclusion

An end-stage form of dilated cardiomyopathy develops in a small minority of patients with HCM. These findings suggest that this phenotype is a more aggressive manifestation of the disease, and continues to evolve, with associated clinical decline. Cardiac dyssynchrony may contribute to disease progression—and biventricular pacing is not associated with sustained ventricular functional improvement.

Conflict of interest: none declared.

References


