Treatnent of Obstructive Hypertrophic Cardiomyopathy Symptoms and Gradient Resistant to First-Line Therapy With β-Blockade or Verapamil

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Background—There is controversy about preferred methods to relieve obstruction in hypertrophic cardiomyopathy patients still symptomatic after β-blockade or verapamil.

Methods and Results—Of 737 patients prospectively registered at our institution, 299 (41%) required further therapy for obstruction for limiting symptoms, rest gradient 61±45, provoked gradient 115±49 mm Hg, and followed up for 4.8 years. Disopyramide was added in 221 (74%) patients and pharmacological control of symptoms was achieved in 141 (64%) patients. Overall, 138 (46%) patients had surgical relief of obstruction (91% myectomy) and 6 (2%) alcohol septal ablation. At follow-up, resting gradients in the 299 patients had decreased from 61±44 to 10±25 mm Hg (P<0.0001); New York Heart Association class decreased from 2.7±0.7 to 1.8±0.5 (P<0.0001). Kaplan–Meier survival at 10 years in the 299 advanced-care patients was 88% and did not differ from nonobstructed patients (P=0.28). Only 1 patient had sudden death, a low annual rate of 0.06%/y. Kaplan–Meier survival at 10 years in the advanced-care patients did not differ from that expected in a matched cohort of the US population (P=0.90).

Conclusions—Patients with obstruction and symptoms resistant to initial pharmacological therapy with β-blockade or verapamil may realize meaningful symptom relief and low mortality through stepped management, adding disopyramide in appropriately selected patients, and when needed, by surgical myectomy. (Circ Heart Fail. 2013;6:694-702.)

Key Words: cardiac surgical procedures ■ cardiomyopathy, hypertrophic ■ disopyramide ■ drug therapy

Left ventricular outflow tract (LVOT) obstruction at rest or after physiological provocation occurs in approximately two third of patients with hypertrophic cardiomyopathy (HCM), usually from systolic mitral-septal apposition and is associated with adverse outcomes. In symptomatic-obstructed patients pharmacological therapy is the first-line approach. Using recommendations from the previous 2 decades, we selected treatment paths for patients with obstruction resistant to first-line pharmacotherapy with β-blockade or verapamil, based on their cardiac pathology, risk stratification for sudden death, and symptoms. There have been case series describing the response of obstructed patients to treatments such as disopyramide, surgery, alcohol ablation, or dual chamber (DDD) pacing with short atrioventricular (AV) delay. However, given the heterogeneous presentation and anatomy of obstructive HCM, and the wide age range of presentation from youth to old age, a “one size fits all” approach cannot be applicable or practical.

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Methods

St. Luke’s-Roosevelt Hospital Center (SLR) has offered organized consultation services for referred HCM patients since 1985; we have maintained a prospective registry of evaluated patients. The current report includes all patients initially evaluated from 1985 to June 30, 2011.

The diagnosis of HCM was confirmed by demonstrating a hypertrophy (>15 mm) nondilated left ventricle in the absence of a cause of hypertrophy sufficient to cause that observed.

For each patient heart failure symptoms were assessed based on New York Heart Association classification and the Minnesota Living with Heart Failure Questionnaire. All patients signed informed consent approved by the institutional review board of SLR for use of their clinical data for research purposes and for annual questionnaire or scripted telephone follow-up. If patients could not be reached, their survival was determined by interrogation of the Social Security death index.

Echocardiography

Echocardiograms with standard imaging planes were performed at initial evaluation and last follow-up. Continuous wave Doppler was used to measure LVOT gradient from the apical 5- and 3-chamber views to record maximum velocity parallel to the systolic LVOT flow. Care was taken to separate LVOT signal from that of mitral regurgitation. Gradient was measured during 3 Valsalva maneuvers and after standing. The simplified Bernoulli equation was used to calculate gradient. After 1994, capable patients underwent treadmill testing with Bruce protocol and had gradients acquired after exercise. Echocardiographic maximal left ventricle wall thickness was measured from parasternal long axis and short axis views. Since 2004, cardiac MRI was performed in patients with ambiguous or suboptimal echocardiograms. The length of the anterior mitral valve leaflet...
was measured on the echocardiographic apical 3-chamber view in diastole from the tip of the anterior leaflet to the insertion of the non-coronary aortic cusp.12,13

**Stepped Treatment**

After year 2000, all patients were stratified for sudden death risk.4 Patients who were deemed to be at increased risk for sudden death because of prior sustained ventricular tachycardia or resuscitated ventricular fibrillation, massive thickening ≥30 mm, sudden death in first degree relative, unexplained syncope, or non-sustained ventricular tachycardia in patients aged ≤30 years were counseled about the benefits and risks of the implanted cardioverter defibrillator (ICD) and, given consent, were implanted.3,4 ICD follow-ups were obtained either at our own clinic or through questionnaires and scripted phone calls. The nature of ICD interventions were confirmed by analysis of stored electrograms in all cases by a SLR-attending electrophysiologist.

On the basis of their treatment path, patients were divided into 3 groups: (1) Group 1: obstructed, β-blocker, or verapamil. These patients had LVOT obstruction ≥30 mm Hg, either at rest or after physiological provocation and symptoms could be managed with β-blocker or verapamil, or they were asymptomatic and required no pharmacological therapy. In all obstructed patients vasodilator medications for hypertension or renal disease were stopped.3 (2) Group 2: obstructed, advanced-care. These obstructed patients required advanced-care because they had both limiting symptoms and had rest or provoked gradients ≥250 mm Hg, despite treatment with β-blockade, verapamil, or both. (3) Group 3: patients without obstruction at rest or after provocation.

The treatment paths for the 299 obstructed, advanced-care patients are shown in Figure 1.

The largest group of these obstructed, advanced-care patients were started on disopyramide. Time-release disopyramide 250 mg 2x per day was added to either β-blocker or verapamil. If patient weight was <100 pounds, or for mild degree of renal failure (creatinine 1.3–2.0) mide dosing was continued unless QTc exceeded 525 ms in patients with initial normal QRS duration, or 550 to 560 ms in patients with initial intraventricular conduction delay. Patients who experienced improvement in their limiting symptoms were continued on pharmacological therapy. To mitigate vagolytic side effects of dry mouth or constipation, sustained-release pyridostigmine, a cholinesterase inhibitor, was administered as needed in doses of 90 to 180 mg 2x per day. This allows continuation of adequate disopyramide dosing.

Patients who had no symptom improvement, or who experienced drug side effects were referred for surgical septal myectomy, unless they had significant medical comorbidity or refused surgery.

Selected patients were referred for surgical septal myectomy without an intervening disopyramide trial. These patients had systolic anterior motion, mitral-septal contact and also had (1) significant coexisting conditions that required combined surgical repair; (2) selected patients who had the combination of anterior mitral leaflet length ≥33 mm plus resting gradients >85 mm Hg were also referred to surgery without disopyramide trial because of our experience that such patients have a mechanical problem that does not respond to pharmacotherapy; (3) patients with symptomatic prostatism (hesitancy, dribbling) were referred for surgery as disopyramide is contraindicated in this setting. Depending on patient choice, surgery was performed at SLR in 80% of patients, whereas the remaining 20% had their operations at other North American centers. The operative technique and results of the resect-plicate-release modification of the standard Morrow myectomy as performed at SLR have been described previously. Individual components of the operation are

![Figure 1. Treatment paths in 299 obstructed advanced-care patients. ASA indicates alcohol septal ablation; Ant. Leaf, anterior leaflet of mitral valve; DDD paced, atrioventricular (AV) sequential paced with short AV delay; and verap, verapamil. A total of 43 (30%) of the 141 patients who were successfully treated with disopyramide were DDD paced as well.](http://circheartfailure.ahajournals.org/Downloaded from)
extended myectomy, horizontal plication of the anterior mitral leaflet, and release of the papillary muscles. Components are selectively applied, as necessary, depending on scrutiny of the preoperative echocardiogram, intraoperative transesophageal echocardiography, and direct surgical inspection.

DDD pacing with short AV delay and complete ventricular capture was applied sparingly and selectively in specific conditions. Dyslipidemia was treated with appropriate pharmacological therapy, usually a statin.  

Statistical Methods
Normally distributed data are described as mean±SD and categorical data as frequency (percent). Baseline characteristics were compared by ANOVA. In patients who first received disopyramide and then septal reduction therapy, gradients after disopyramide are reported both before and after the intervention. Changes in gradient and symptoms were compared using paired t tests. Cox proportional hazards test was used to compare survival in the 3 treatment groups. Survival rate for the obstructed advanced-care group was compared with survival rate published by the Centers for Disease Control for the general US population in 2005, matched for age of diagnosis, sex, and race. A Microsoft Excel 2007 program (Microsoft Inc, Redmond, WA) developed by Finkelstein et al for calculating a one sample log-rank test was used to test for a difference. Statistical Analysis System version 9.1 (SAS Institute, Inc, Cary, NC) was used for all other analyses.

Results
Patients and Treatment Paths
Of the 737 patients in the registry, 14 patients who received surgical myectomy before our initial evaluation were excluded from survival analysis. The whole group of registry patients (n=723) were followed up for a median of 4.5 years (interquartile range, 2.2–7.6). In groups 1, 2, and 3 the follow-ups were 3.9 years (interquartile range, 1.9–6.4), 4.8 years (interquartile range, 2.6–8.1), and 4.9 years (interquartile range, 2.1–8.1), respectively. Characteristics of the 723 patients in the 3 treatment groups are shown in Table 1. There were 299 obstructed advanced-care patients (group 2) who had gradients and symptoms unresponsive to β-blockade or verapamil requiring further treatment. The interquartile age range was wide (45.8–68.2 years). They had been treated before initial evaluation with β-blockade (235) or verapamil (64) or both (38). Compared with the other 2 groups the obstructed advanced-care patients were older, more frequently had rest obstruction, had greater maximal wall thickness, were more symptomatic, and more frequently had atrial fibrillation and coronary artery disease. The treatment paths for the advanced-care group are shown in Figure 1.

Change in gradient depending on the treatment selected is shown in Table 2 and in the Figure in the online-only Data supplement. In the whole patient group (n=299), resting gradient decreased from 61±44 to 10±23 mm Hg (P<0.0001). Table 3 shows the change in symptoms by final therapy selected. Symptom management was an iterative process. Patients who did not respond to disopyramide were offered septal reduction. There was improvement in New York Heart Association classification and Minnesota Living with Heart Failure Questionnaire after the final treatment selected in all patient groups. Disopyramide was administered to 221 patients, mean daily dose 501±30 mg, followed up for 5.1±3.8 years. This dose was higher than that used in the multicenter registry of obstructive HCM patients reported in 2005 (432±181 mg; P<0.0001). To mitigate the vagolytic effects of disopyramide, 117 (53%) patients received pyridostigmine timespan, at least temporarily. The 221 patients who were begun on disopyramide might otherwise have been candidates for septal reduction; however, 141 (64%) patients were successfully continued on therapy and followed up 4.5±3.6 years with a favorable response without need for septal reduction. In the whole group of 221 patients in whom it was used, disopyramide lowered resting gradients, from 63±45 to 25±32 mm Hg (P<0.0001). In the 141 patients (64%) successfully managed with pharmacological therapy including disopyramide, without need for septal reduction, the average resting gradient was 18 mm Hg at final evaluation demonstrating long-term gradient reduction; in addition, symptoms improved as shown in Table 3. In the 80 patients (36%) who eventually required septal reduction, the final gradients achieved with pharmacological treatment were lower than initial values (P<0.0001), but were inadequate to control symptoms, and averaged 40 mm Hg, higher than in the patients who could be managed without septal reduction therapy (P<0.0001) Table 2.

Septal Reduction Centers for Disease Control
In 63 obstructed HCM patients, surgical myectomy was judged to be the best treatment without a disopyramide trial. Table 4 shows the characteristics of these patients. The balance of the septal reduction patients (n=80) were those who received disopyramide but failed to respond adequately or had drug side effects and who then underwent septal reduction (75 surgical and 5 alcohol ablation). The 138 patients who underwent surgery were followed up for 5.5±3.6 years; 125 (91%) patients had surgical septal myectomy and 13 (9%) had mitral valve replacement for calcific disease. In this series only 6 (2%) patients received ablation, 3 because of severe medical comorbidities and 3 because of patient choice. As expected, gradient reduction was most complete in the surgical group, gradient at follow-up was 3±9 mm Hg, and symptoms improved in parallel as shown in Table 3.

Survival
Survival follow-up was complete in 718 (99.3%) patients; 5 (0.7%) patients were lost to follow-up (only 1 in the advanced-care group). Survival comparison among the 3 HCM groups, graphed in Figure 2, showed no difference in survival among the 3 groups; 10 year survival was 87% in group 1, 88% in group 2, and 85% in group 3 (P=0.28).

Deaths in the Obstructed Advanced-Care Group
Of the 299 patients, there were 25 deaths during the 5.6 years of follow-up. Fifteen deaths were judged to be noncardiac, whereas 10 deaths were from cardiovascular cause, including 4 patients who died after cerebrovascular accidents (mean age 81 years, 3 with atrial fibrillation). In the obstructed advanced-care group, there was only 1 sudden death, in a 77 female heavy smoker who died suddenly 7 years after beginning disopyramide. Annual rate of sudden death was very low 0.06%/y in the whole advanced-care group. There were no in-hospital deaths in our surgical patients, and long-term survival was 95% at 10 years. In the 221 disopyramide-treated patients the annual rate of sudden death was 0.1%/y.
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Table 1. Baseline Characteristics of 723 Patients With HCM

<table>
<thead>
<tr>
<th>Variable</th>
<th>All HCM (N=723)</th>
<th>Group 1: Obstructed</th>
<th>Group 2: Advanced Care (n=210)</th>
<th>Group 3: Non-obstructed (n=299)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53.8±17</td>
<td>54.1±18</td>
<td>56.7±15</td>
<td>48.4±17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>57</td>
<td>65</td>
<td>51</td>
<td>59</td>
<td>0.003</td>
</tr>
<tr>
<td>Rest LVOT gradient, mm Hg</td>
<td>33±42</td>
<td>26±31</td>
<td>61±45</td>
<td>1±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obstructed at rest, %</td>
<td>41</td>
<td>38</td>
<td>71</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Provoked gradient, mm Hg</td>
<td>74±64</td>
<td>89±41</td>
<td>115±49</td>
<td>2.5±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obstructed at rest or after provocation, %</td>
<td>68</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.3±0.8</td>
<td>2.1±0.9</td>
<td>2.7±0.7</td>
<td>1.7±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MLHF QOL</td>
<td>27±24</td>
<td>22±23</td>
<td>37±23</td>
<td>19±21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MWT, mm</td>
<td>22±6</td>
<td>20.8±6</td>
<td>22.7±6</td>
<td>22.4±7</td>
<td>0.02</td>
</tr>
<tr>
<td>Syncope, %</td>
<td>26</td>
<td>21</td>
<td>28</td>
<td>28</td>
<td>0.16</td>
</tr>
<tr>
<td>FH SCD first degree relative, %</td>
<td>16</td>
<td>21</td>
<td>14</td>
<td>22</td>
<td>0.10</td>
</tr>
<tr>
<td>NSVT, %</td>
<td>26</td>
<td>21</td>
<td>31</td>
<td>26</td>
<td>0.28</td>
</tr>
<tr>
<td>BB, %</td>
<td>66</td>
<td>64</td>
<td>76</td>
<td>55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCB, %</td>
<td>22</td>
<td>26</td>
<td>21</td>
<td>18</td>
<td>0.14</td>
</tr>
<tr>
<td>FH of HCM, %</td>
<td>39</td>
<td>36</td>
<td>35</td>
<td>48</td>
<td>0.005</td>
</tr>
<tr>
<td>AF, %</td>
<td>19</td>
<td>12</td>
<td>24</td>
<td>19</td>
<td>0.002</td>
</tr>
<tr>
<td>CAD, %</td>
<td>10</td>
<td>8</td>
<td>15</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF, %</td>
<td>64.6±13</td>
<td>63.5±16</td>
<td>66.5±9</td>
<td>63.3±13</td>
<td>0.33</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; BB, β-blocker; CAD, coronary artery disease; CCB, calcium channel blocker; EF, ejection fraction; FH, family history; LVOT, left ventricular outflow tract; MLHF QOL, Minnesota Living with Heart Failure Questionnaire; MWT, Maximal LV wall thickness; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; and SCD, sudden cardiac death.

Comparison With Age-Matched US Survival

There were 25 deaths observed in the advanced-care group, whereas 24 were expected based on the general population. As shown in Figure 3 the observed rate of survival for the 299 obstructed advanced-care patients did not differ from the expected survival in the general US population (P=0.90).

Device Therapy

In the obstructed advanced-care group, 56 (19%) patients had ICD implanted at SLR for primary prevention, and 3 for secondary prevention. ICD patients were followed up for 6.1±3.5 years. There were appropriate discharges in 3 (5%) patients implanted for primary prevention. These discharges occurred in 2 patients at 2 months and 5 years after surgery, respectively, and in 1 patient 2 years after disopyramide. Two patients were implanted for secondary prevention (both with mid-left ventricle obstruction and an apical akinetic chamber also had appropriate discharges).

Lethal and Potentially Lethal Arrhythmias

In the whole advanced-care group, events included sudden death (1 patient), successfully resuscitated ventricular tachycardia (1 patient), postoperative prolonged nonsustained ventricular tachycardia (1 patients), and appropriate ICD discharge in primary prevention patients (3 patients). The combined annual rate of lethal and potentially lethal arrhythmic events was 0.4%/y.

Of the patients with ICD, 38 patients were also DDD paced with short AV delay for gradient reduction. An additional 19 patients had DDD pacemaker inserted specifically for gradient reduction, but without an ICD. Thus, overall, 57 (19%) of the obstructed advanced-care patients were DDD paced for gradient in combination with pharmacological therapy and were followed up for 6.3±3.9 years. Only 10 (18%) of these patients required surgical myectomy for control of gradient and symptoms. At follow-up in the paced patients there had been 8 deaths, 4 noncardiac, and 4 cardiovascular deaths.

Discussion

A relatively common clinical dilemma that confronts physicians caring for obstructive HCM patients is how to manage patients whose symptoms and gradients are resistant to first-line therapy with β-blockade or verapamil. These patients represent a subset of HCM patients who often are referred for advanced care. In this study, we applied a stepped approach to this widely heterogeneous group, in whom therapy was individually tailored for sudden death prevention and for symptom relief. We found that such an approach can result in a meaningful improvement in functional status, very low
sudden death mortality, and overall mortality that did not differ from that expected in a matched cohort of the general US population. Additional major observations from this experience are (1) patients whose symptoms and gradients can be successfully controlled by disopyramide and β-blockade have a low mortality, and a very low sudden death mortality. A similar disopyramide/β-blockade experience has recently been reported by Ball et al. In their report, patients who responded to conservative pharmacological therapy with symptom relief had an 87% HCM-related survival at 10 years. In their report, >150 patients achieved symptom relief with disopyramide but without septal reduction. In the present report a similar number achieved symptom relief without septal reduction and together, this experience numbers >300 patients with excellent survival. In both reports patients who responded to pharmacotherapy were maintained on their successful regimens, and those who did not were referred for septal reduction. (2) In the present study, carefully selected patients preferentially underwent surgical myectomy rather than alcohol ablation.3,4 There were no in-hospital deaths in our 138 surgical patients, and survival at 10 years was 95% with no late sudden deaths.

### Stepped Management

In our therapy we were guided by additional maxims (1) all patients regardless of obstruction and category had formal risk stratification for sudden death; in patients with high risk implanted defibrillators were placed; (2) patients with concomitant cardiac pathology such as severe coronary artery disease, moderate aortic valve disease, or mitral regurgitation from intrinsic mitral abnormalities more than systolic anterior motion had surgery sooner in their course1; (3) we have observed that patients who fail to respond to disopyramide have a combination of adverse physiological and anatomic features: both very high resting gradients and long anterior mitral leaflets as described above. Patients with this combination (≈15% of considered individuals) have a mechanical problem; in recent years, we have referred patients with this combination directly to surgery if they fail β-blockade/verapamil, without an intervening disopyramide trial, particularly if they are <45 years of age.13,14 (4) Patients otherwise were treated by adding disopyramide to their pharmacological regimen, usually with β-blockade.5-7,11,14 (5) For elderly or frail patients resistant to disopyramide DDD pacing with short AV delay was preferred. Disopyramide was continued because of the previously reported positive synergy between DDD pacing and disopyramide.20

### Survival

Overall, mortality in our advanced-care obstructed patients was low; survival did not differ from the expected mortality observed an age-, sex-, and race-matched cohort of the US population. Kaplan–Meier survival at 10 years was 88%. These results are similar to that previously reported when surgical therapy was used for resistant cases.6 Mortality has previously been reported higher in obstructive HCM patients than in patients without obstruction.2 In sharp contrast, we observed no difference in mortality between our advanced-care obstructed patients and our nonobstructed patients (Figure 2). There was only 1 sudden death in the 299 patients in the obstructed advanced-care group, a very low annual incidence of 0.06%/y. The combined annual rate of sudden death, resuscitated ventricular tachycardia, and appropriate ICD discharge in primary prevention patients was low (0.4%/y). We posit that these low rates of mortality, sudden death, and potentially fatal arrhythmias occurred because of the stepped treatment herein described that yielded a mean final resting gradient of 10 mm Hg.21

There are few randomized trials of treatments in HCM.22 In their absence, below are comments pertinent to our choices for therapy.

### Disopyramide

Introduced by investigators from Toronto, disopyramide is often administered to patients whose next option would be septal reduction therapy, if pharmacological therapy fails.3,5-7,11,14 We

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### Table 3. Improvement in Symptoms in the Obstructed, Advanced-Care Group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NYHA Initial Evaluation</th>
<th>NYHA Last Visit</th>
<th>P Value</th>
<th>MLHF QOL Initial Evaluation</th>
<th>MLHF QOL Last Visit</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N=299)</td>
<td>2.7±0.7</td>
<td>1.8±0.5</td>
<td>&lt;0.0001</td>
<td>37±23</td>
<td>27±23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All surgical patients (n=138)</td>
<td>2.7±0.7</td>
<td>1.7±0.5</td>
<td>&lt;0.0001</td>
<td>39±23</td>
<td>27±22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All disopyramide-treated patients without septal reduction (n=141)</td>
<td>2.7±0.6</td>
<td>1.9±0.5</td>
<td>&lt;0.0001</td>
<td>40±23</td>
<td>27±23</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

MLHF QOL indicates Minnesota Living with Heart Failure Questionnaire; and NYHA, New York Heart Association.

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### Table 4. Characteristics of 63 Patients With LVOT Obstruction Because of SAM, Mitral-Sепtal Contact Referred Directly for Surgery Without a Trial of Disopyramide

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant cardiac surgery (n=23)</td>
<td>9</td>
</tr>
<tr>
<td>Coronary bypass</td>
<td>9</td>
</tr>
<tr>
<td>MVR to relieve MR because of intrinsic abnormality more than SAM (ie, calcified leaflet)</td>
<td>7</td>
</tr>
<tr>
<td>Aortic valve replacement for moderate aortic valve disease</td>
<td>4</td>
</tr>
<tr>
<td>Aortic root replacement for aortic aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>RVOT myectomy for RV outflow obstruction</td>
<td>1</td>
</tr>
<tr>
<td>ICD lead extraction</td>
<td>1</td>
</tr>
<tr>
<td>Unfavorable anatomy thought not likely to respond to any pharmacological therapy; both long anterior mitral leaflet and high resting gradient*</td>
<td>20</td>
</tr>
<tr>
<td>Contraindications (n=11)</td>
<td>6</td>
</tr>
<tr>
<td>Symptomatic prostatism</td>
<td>6</td>
</tr>
<tr>
<td>Amiodarone therapy for AF</td>
<td>5</td>
</tr>
<tr>
<td>Patient choice</td>
<td>7</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>2</td>
</tr>
</tbody>
</table>

*Including 5 patients with syncope and 1 with cardiogenic shock.
found a 60% reduction in resting gradient in the 221 patients initiated on disopyramide and a corresponding improvement in symptoms. Of the patients begun on disopyramide who might otherwise have been candidates for septal reduction, 141 patients, nearly two thirds of those initiated, continue on pharmacological therapy 4.5 years without need for septal reduction.

Disopyramide’s particular efficacy in obstructive HCM is due to its marked negative inotropic effect compared with other agents,23,24 and that it has no vasodilator effect.25 In direct head-to-head comparisons of its effect on gradient, it is more potent than verapamil or β-blockade.24 It is usually given in combination with β-blockade to blunt the exercise-related rise

Figure 2. Kaplan–Meier plot comparing survival in 3 groups of hypertrophic cardiomyopathy patients. Survival in the obstructed advanced-care patients did not differ from nonobstructed patients. BB indicates β-blocker.

Figure 3. Kaplan–Meier plot comparing observed survival in the obstructed advanced-care group (n=299, solid line) vs the expected survival based on 2005 US survival matched for age, sex, and race (dashed line).
Table 5. Complications of Therapy in 299 Patients in the Obstructed, Advanced-Care Group

<table>
<thead>
<tr>
<th>Class of Therapy, No. of Patients Treated (n=138)</th>
<th>Complication</th>
<th>No. of Patients</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>Large ventricular septal defect and early postoperative heart failure</td>
<td>1</td>
<td>Required reoperation for complete closure, NYHA I outcome</td>
</tr>
<tr>
<td>Postoperative stroke</td>
<td>1</td>
<td>Disability</td>
<td></td>
</tr>
<tr>
<td>Postoperative TIA</td>
<td>1</td>
<td>Complete resolution</td>
<td></td>
</tr>
<tr>
<td>Large pericardial effusion</td>
<td>4 (3%)</td>
<td>Pericardial windows with complete resolution</td>
<td></td>
</tr>
<tr>
<td>Postoperative respiratory failure in patients with pulmonary disease</td>
<td>2</td>
<td>Prolonged ICU course</td>
<td></td>
</tr>
<tr>
<td>Heart block</td>
<td>7 (5%)</td>
<td>Permanent pacer</td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>2</td>
<td>Resolved with drainage and antibiotics</td>
<td></td>
</tr>
<tr>
<td>Disopyramide (n=221)</td>
<td>Torsade de pointes in female, age 82 y with 96 mm Hg resting gradient who developed diarrhea-induced hypokalemia</td>
<td>1</td>
<td>ICD discharge terminated arrhythmia which completely subsided after K+ repletion. Disopyramide resumed</td>
</tr>
<tr>
<td>Heart block (age 88 y)</td>
<td>1</td>
<td>Permanent pacemaker</td>
<td></td>
</tr>
<tr>
<td>Urinary hesitancy (age 53 y)</td>
<td>1</td>
<td>Discontinued diso</td>
<td></td>
</tr>
<tr>
<td>Urinary retention (age 88)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device therapy ICD (n=59); DDD pacemaker (n=24)</td>
<td>Tamponade</td>
<td>2</td>
<td>Pericardial window with complete resolution</td>
</tr>
<tr>
<td>Inappropriate shock (20%)</td>
<td>12</td>
<td>Specifically targeted responses</td>
<td></td>
</tr>
<tr>
<td>Inappropriate ATP</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD infection</td>
<td>1</td>
<td>System extraction</td>
<td></td>
</tr>
</tbody>
</table>

DDD indicates dual chamber; ICD, implanted cardioverter defibrillator; ICU, Intensive Care Unit; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; and TIA, transient ischemic attack.

in gradient, for synergistic negative inotropic effect, and to provide AV delay, if atrial fibrillation occurs. Despite this type I antiarrhythmic effects, proarrhythmia with disopyramide is very rare in patients with HCM; we found a very low rate of sudden death mortality (0.1%/y). This low sudden death incidence may most likely be attributed to gradient lowering, although we cannot exclude a beneficial intracellular metabolic effect. Nevertheless, we continue the surveillance described above in our disopyramide-treated patients.3,7 We did not observe any organ toxicity from disopyramide, no renal, hepatic, hematologic, or central nervous system adverse effects. This makes it suitable for long-term use.

We administered a higher dose disopyramide in the present cohort than in the multicenter registry of 2005 (501 versus 432 mg/d)7 because there is a prominent dose-response relationship with disopyramide, with more effective gradient reduction at higher dose.14 Pyridostigmine-controlled release (Mestinon timespan) administered with disopyramide attenuates side effects, such as dry mouth and constipation, and we offer it, as needed, to all patients.13 Half of our patients received pyridostigmine timespan at least temporarily. The safety of the combination in obstructive HCM is shown in the present study.

Although disopyramide is a mainstay of pharmacological therapy at United Kingdom and Canadian programs with national scope,6,11 it has seen less use in the United States. For example, it had been prescribed in 11% of patients before surgical myectomy in 1 study8 and in 11% of patients before ablation in another.26 The current experience is unique in the United States as 74% of patients received disopyramide, at higher dose than previously, and pyridostigmine-sustained release was safely used to control vagolytic side effects.

Surgical Septal Myectomy

One third of our patients failed their trial of disopyramide/β-blockade, or had adverse side effects, and required septal reduction. Surgical septal myectomy is the gold standard treatment for such patients and has been performed for 40 years.3,16 In recent years because of improved understanding about the cause of mitral-septal contact, appreciation of the role of the mitral valve and the papillary muscles, and because of improved surgical technique, excellent outcomes are now reported with in-hospital mortalities <1% and excellent long-term survival.3,8,10,27,28 In the 80% of patients operated at SLR we applied a patient-tailored individualized modification of the classic Morrow myectomy that we have termed the resect- plicate-release operation. The surgical techniques of the resect-plicate-release repair grew out of prior surgical innovations,27 and its results have been reported previously.10 A unique aspect of this surgical cohort is the application of horizontal anterior mitral leaflet plication in selected patients with long, redundant slack mitral anterior leaflets. Within the advanced-care group, a subgroup analysis of survival between aggressive-pharmacological and surgical patients would not be a valid comparison because of selection bias; the pharmacological group included more patients with advanced age and severe comorbidities.

Alcohol Septal Ablation

The myectomy versus alcohol ablation controversy cannot be resolved by a prospective randomized trial.3,22,26 ten Cate29 found that 14% of ablation patients had late sudden death or appropriate ICD discharge occurring ≥30 days post procedure after 5.4 years of follow up. This was substantially higher than in their surgically treated patients. From the prospective data in the current study, we can at least conclude that excellent overall results may be obtained by a strategy that reserves alcohol ablation only for patients in whom surgical myectomy is contraindicated, or when informed patients are reluctant to undergo surgery.

DDD pacing with short AV delay, although not a primary therapeutic option for young patients with obstructive HCM,30 has a limited positive role in selected patients such as the elderly or those already implanted with an ICD.3 There is a
synergistic beneficial effect for gradient reduction when DDD pacing is used with disopyramide. Treatment of obstructive HCM has evolved during the 26 years encompassed in this study. Comparing the first with the second half of the time period under consideration, the annual number of surgical myectomies performed for resistant symptoms nearly tripled, the number of ICD implants more than doubled, and DDD pacing for gradient reduction declined, to the benefit of our most severely affected patients.

Conclusions
Patients with obstruction and symptoms unresponsive to initial pharmacological therapy with β-blockade or verapamil may realize meaningful symptom relief and low mortality through stepped management by adding disopyramide in appropriately chosen patients, and when needed, by surgical septal myectomy.

Disclosures
None.

References


CLINICAL PERSPECTIVE

Patients with obstructive hypertrophic cardiomyopathy with symptoms and left ventricular outflow gradients refractory to β-blockade or verapamil present the clinician with challenges and choices. There are multiple potential therapeutic modalities that can potentially be selected for these patients, including disopyramide pharmacotherapy, surgical septal myectomy, and alcohol septal ablation. In the absence of randomized clinical trials there is controversy about best practices. Moreover, because of the wide age range and variation of anatomy in obstructive hypertrophic cardiomyopathy no one of the treatments can be universally applied. In the current study, the authors present their experience with a cohort of 299 advanced-care patients generally treated with disopyramide and, when necessary, with surgical septal myectomy. Specifically, disopyramide was added in 221 (74%) patients and pharmacological control of symptoms was achieved in 141 (64%) patients. Overall, 138 (46%) patients required surgical relief of obstruction. At follow-up, resting gradients in the 299 patients had decreased from 61 to 10 mm Hg; New York Heart Association class decreased from 2.7 to 1.8. Kaplan–Meier survival at 10 years in the 299 advanced-care patients was 88% and did not differ from nonobstructed patients ($P=0.28$). Only 1 patient had sudden death, a low annual rate of 0.06%/y. Kaplan–Meier survival at 10 years did not differ from that expected in a matched cohort of the US population. Patients with obstruction and symptoms resistant to first-line pharmacological therapy may realize meaningful symptom relief and low mortality through patient-tailored stepped management, adding disopyramide in appropriately selected patients, and when needed, by surgical myectomy.
Treatment of Obstructive Hypertrophic Cardiomyopathy Symptoms and Gradient Resistant to First-Line Therapy With β-Blockade or Verapamil
Mark V. Sherrid, Aneesha Shetty, Glenda Winson, Bette Kim, Dan Musat, Carlos L. Alviar, Peter Homel, Sandhya K. Balaram and Daniel G. Swistel

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Figure Legend

Echocardiographic resting LVOT gradients in 299 patients in the obstructed advanced-care group at initial evaluation and at last measurement after treatment. In the patients who received a disopyramide trial, but then required septal reduction, interim gradients obtained just before the invasive intervention are shown as well.