Treatment of Obstructive Hypertrophic Cardiomyopathy Symptoms and Gradient Resistant to First-Line Therapy with Beta-Blockade or Verapamil

Sherrid et al: Obstructive HCM Resistant to First-Line Therapy

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Abstract

Background—There is controversy about preferred methods to relieve obstruction in hypertrophic cardiomyopathy (HCM) patients still symptomatic after beta-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 mmHg, followed 4.8 years. Disopyramide was added in 221 (74%) and pharmacologic control of symptoms was achieved in 141 (64%). 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 mmHg, p<0.0001; NYHA 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 non-obstructed patients (p=0.28). Only one patient had sudden death, a low annual rate of 0.06%/year. KM 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 pharmacologic therapy with beta-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.

Key Words: hypertrophic cardiomyopathy, surgery, pharmacologic treatment
Left ventricular outflow tract (LVOT) obstruction at rest or after physiologic provocation occurs in approximately 2/3 of patients with HCM, usually from systolic mitral-septal apposition and is associated with adverse outcomes. In symptomatic obstructed patients pharmacologic therapy is the first-line approach. Using recommendations from the previous two decades we selected treatment paths for patients with obstruction resistant to first-line pharmacotherapy with beta-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 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.

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 hypertrophied (≥ 15 mm) non-dilated LV in the absence of a cause of hypertrophy sufficient to cause that observed.

For each patient heart failure symptoms were assessed based on NYHA classification and the Minnesota Living with Heart Failure Questionnaire (MLHF QOL). All patients signed informed consent approved by the IRB 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 (MR). 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.1

Echocardiographic maximal LV wall thickness was measured from parasternal long axis and short axis views3. Since 2004 cardiac magnetic resonance imaging was performed in patients with ambiguous or suboptimal echocardiograms3. The length of the anterior mitral valve leaflet was measured on the echocardiographic apical three chamber view in diastole from the tip of the anterior leaflet to the insertion of the non-coronary aortic cusp12,13.

**Stepped treatment**

After year 2000 all patients were stratified for sudden death (SCD) risk4. Patients who were deemed to be at increased risk for SCD 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 ≤ 30 years old were counseled about the benefits and risks of the implanted defibrillator (ICD) and, given consent, were implanted3,4. 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.

Based on their treatment path patients were divided into 3 groups.
Group 1: Obstructed, beta-blocker or verapamil. These patients had LVOT obstruction ≥30 mm Hg, either at rest or after physiologic provocation and symptoms could be managed with beta-blocker or verapamil, or they were asymptomatic and required no pharmacologic therapy. In all obstructed patients vasodilator medications for hypertension or renal disease were stopped³. Group 2: Obstructed, advanced-care: These obstructed patients required advanced-care because they had both limiting symptoms and had rest or provoked gradients ≥50 mm Hg despite treatment with beta-blockade, verapamil, or both. 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.

1) The largest group of these obstructed, advanced-care patients were started on disopyramide. Time-release disopyramide 250 mg 2x/day was added to either beta-blocker or verapamil. If patient weight was <100 pounds, or for mild degree of renal failure (creatinine 1.3-2.0) initial dose was decreased to 200 mg 2x/day. Disopyramide was initiated during a 3 day hospitalization under continuous ECG monitoring⁷,¹⁴. Additionally during hospitalization, daily ECGs were performed to assess the expected QTc prolongation. In patients with an inadequate echocardiographic response (resting LVOT gradient > 40 mm Hg after 2 days) the dose of disopyramide was titrated up to 600 mg/day and beta-blockade was optimized to a resting heart rate of 50-60 bpm.

After hospital discharge patients were seen after 3 weeks and then every 4 months in follow-up for drug titration and 12 lead ECG monitoring. Follow-up visits were at our center in 85% of patients; the remaining patients saw their local cardiologists. Regular disopyramide dosing was continued unless QTc exceeded 525 msec in patients with initial normal QRS duration, or 550-560 msec in patients with initial intraventricular conduction delay¹⁴. Patients who experienced
improvement in their limiting symptoms were continued on pharmacologic therapy. To mitigate vagolytic side effects of dry mouth or constipation, sustained-release pyridostigmine, a cholinesterase inhibitor, was administered as needed in doses of 90-180 mg, 2x/day. This allows continuation of adequate disopyramide dosing\textsuperscript{15}. Patients who had no symptom improvement, or who experienced drug side effects were referred for surgical septal myectomy, unless they had significant medical co-morbidity or refused surgery\textsuperscript{3}.

2) Selected patients were referred for surgical septal myectomy without an intervening disopyramide trial. These patients had SAM, mitral-septal contact but also had either: a) significant coexisting conditions that required combined surgical repair, b) Selected patients who had the combination of anterior mitral leaflet length $\geq 33$ 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\textsuperscript{13}. c) 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 while the remaining 20% had their operations at other North American centers\textsuperscript{16}.

Operative technique and results of the resect-plicate-release (RPR) modification of the standard Morrow myectomy as performed at SLR have been described previously\textsuperscript{10}. Individual components of the operation are 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 pre-operative echocardiogram, intraoperative transesophageal echocardiography and direct surgical inspection.

3) DDD pacing with short AV delay and complete ventricular capture was applied sparingly and selectively in specific conditions\textsuperscript{3}.
Dyslipidemia was treated with appropriate pharmacologic therapy, usually a statin\textsuperscript{17}.

**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 the intervention, 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 CDC for the general US population in 2005, matched for age of diagnosis, gender, and race\textsuperscript{18}. A Microsoft Excel 2007 program (Microsoft Inc. Redmond WA) developed by Finkelstein\textsuperscript{19} for calculating a one sample log rank test was used to test for a difference. SAS 9.1 (SAS, 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 for median 4.5 years (IQR=2.2-7.6). In groups 1, 2 and 3 the follow-ups were 3.9 years (IQR=1.9-6.4), 4.8 years (IQR=2.6-8.1), and 4.9 years IQR=(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 beta-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 beta-blockade (235) or verapamil (64) or both (38). Compared to 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 (AF) and coronary disease (CAD). 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 supplemental online material. 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 NYHA classification and MLHF QOL after the final treatment selected in all patient groups.

**Disopyramide** was administered to 221 patients, mean daily dose 501 ±30 mg, followed 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; but, 141 (64%) were successfully continued on therapy and followed 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 mmHg (p<0.0001). In the 141 patients (64%) successfully managed with pharmacologic therapy including disopyramide, without need for septal reduction, the average resting gradient was 18 mmHg at final evaluation demonstrating long-term gradient reduction; additionally, symptoms improved as shown in Table 3. In contrast, in the 80 patients (36%) who eventually required septal reduction, the final gradients achieved with pharmacologic treatment were lower than
initial values (p<0.0001), but were inadequate to control symptoms, and averaged 40 mmHg, higher than in the patients who could be managed without septal reduction therapy (p<0.0001) Table 2.

**Septal reduction:** 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 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 co-morbidities and 3 because of patient choice. As expected, gradient reduction was most complete in the surgical group, gradient at follow-up 3+9 mmHg 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 between the 3 HCM groups, graphed in Figure 2, showed no difference in survival between 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 over the 5.6 years of follow-up. Fifteen deaths were judged to be non-cardiac, while 10 deaths were from cardiovascular cause including 4 patients who died after cerebrovascular accidents (mean age 81, 3 with AF). In the obstructed advanced-care group there was only one 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% /year 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% /year.

Comparison with age-matched US survival: There were 25 deaths observed in the
advanced-care group while 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 United States 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 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 one patient 2 years after disopyramide. Two patients implanted for
secondary prevention (both with mid-LV 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 pt), successfully resuscitated ventricular tachycardia (1 pt), post-
operative prolonged non-sustained ventricular tachycardia (1 pt) and appropriate ICD discharge
in primary prevention patients (3 pts). The combined annual rate of lethal and potentially lethal
arrhythmic events was 0.4% /year.

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 pharmacologic therapy and were followed for
6.3 ± 3.9 years. Only ten (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 non-cardiac and 4 cardiovascular deaths.

Complications in the 299 obstructed-advanced care patients are shown in Table 5.

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 beta-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 U.S. population. Additional major observations from this experience are 1) patients whose symptoms and gradients can be successfully controlled by disopyramide and beta-blockade have a low mortality, and a very low sudden death mortality. A similar disopyramide/beta blockade experience has recently been reported by Ball and colleagues. In their report, patients who responded to conservative pharmacologic 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 nearly 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\textsuperscript{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 like severe CAD, moderate aortic valve disease, or MR from intrinsic mitral abnormalities more than SAM, had surgery sooner in their course\textsuperscript{17}; 3) We have observed that patients who fail to respond to disopyramide have a combination of adverse physiologic and anatomic features: both very high resting gradients and long anterior mitral leaflets as described above. Patients with this combination (\textasciitilde15\% of considered individuals) have a mechanical problem; in recent years we have referred patients with this combination directly to surgery if they fail beta-blockade \textit{/}verapamil, without an intervening disopyramide trial, particularly if they are less than 45 years of age\textsuperscript{13,14}. 4) patients otherwise were treated by adding disopyramide to their pharmacologic regimen, usually with beta-blockade\textsuperscript{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\textsuperscript{20}.

\textbf{Survival:} Overall, mortality in our advanced-care obstructed patients was low; survival did not differ from the expected mortality observed an age, gender and race matched cohort of the United States population. Kaplan-Meier survival at 10 years was 88\%. These results are similar to that previously reported when surgical therapy was employed for resistant cases\textsuperscript{8}. Mortality has previously been reported higher in obstructive HCM patients than in patients without obstruction\textsuperscript{2}. In sharp contrast, we observed no difference in mortality between our advanced-care obstructed patients and our non-obstructed patients, Figure 2. There was only one sudden death in the 299
patients in the obstructed advanced-care group, a very low annual incidence of 0.06% / year. The combined annual rate of sudden death, resuscitated ventricular tachycardia and appropriate ICD discharge in primary prevention patients was low, 0.4% / year. 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 mmHg\textsuperscript{21}.

There are few randomized trials of treatments in HCM\textsuperscript{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 should pharmacologic therapy fail\textsuperscript{3,5-7,11,14}. We 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 nearly two thirds continue on pharmacologic 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 to other agents\textsuperscript{23,24}, and that it has no vasodilator effect\textsuperscript{25}. In direct head-to-head comparisons of its effect on gradient, it is more potent than verapamil or beta-blockade\textsuperscript{24}. It is usually given in combination with beta-blockade to blunt the exercise-related rise in gradient, for synergistic negative inotropic effect, and to provide AV delay should AF occur. Despite its 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% / year. This low sudden death incidence may most likely be attributed to gradient lowering, though we cannot exclude a beneficial intracellular metabolic effect. Nevertheless, we continue the surveillance described above in our disopyramide-
treated patients\textsuperscript{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 vs. 432 mg/day)\textsuperscript{7} because there is a prominent dose-response relationship with disopyramide, with more effective gradient reduction at higher dose\textsuperscript{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\textsuperscript{15}. Half of our patients received pyridostigmine timespan at least temporarily. The safety of the combination in obstructive HCM is shown in the present study.

Though disopyramide is a mainstay of pharmacologic therapy at UK and Canadian programs with national scope\textsuperscript{6,11} it has seen less use in the US. For example, it had been prescribed in 11\% of patients before surgical myectomy in one study\textsuperscript{8} and in 11\% of patients before ablation in another\textsuperscript{26}. The current experience is unique in the US as 74\% of patients received disopyramide, at higher dose than previously, and pyridostigmine sustained release was used to control vagolytic side effects.

Surgical septal myectomy: A third of our patients failed their trial of disopyramide/beta-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\textsuperscript{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\textsuperscript{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 RPR repair grew out of prior surgical innovations and its results have been reported previously. 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-pharmacologic and surgical patients would not be a valid comparison because of selection bias: the pharmacologic group included more patients with advanced age and severe comorbidities.

**Alcohol septal ablation:** The myectomy vs. alcohol ablation controversy cannot be resolved by a prospective randomized trial. ten Cate found late sudden death and appropriate ICD discharge in 14% of ablation patients after 5.4 years, 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 can be obtained by a strategy that reserves alcohol ablation for patients in whom surgical myectomy is contraindicated, or when informed patients are reluctant to undergo surgery.

DDD pacing with short AV delay, though not a primary therapeutic option for young patients with obstructive HCM has a limited positive role in selected patients such as the elderly or those already implanted with an ICD. There is a synergistic beneficial effect for gradient reduction when DDD pacing is used with disopyramide.

Treatment of obstructive HCM has evolved over 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.
Conclusion: Patients with obstruction and symptoms unresponsive to initial pharmacologic therapy with beta-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


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 Beta Blocker or Verapamil n=210</th>
<th>Group 2, Obstructed advanced care n=299</th>
<th>Group 3, Non-obstructed n=214</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</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>
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<td>Gender (%m)</td>
<td>57</td>
<td>65</td>
<td>51</td>
<td>59</td>
<td>0.003</td>
</tr>
<tr>
<td>Rest LVOT Gradient mmHg</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 mmHg</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>
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<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>
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<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>
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<td>Syncope (%)</td>
<td>26</td>
<td>21</td>
<td>28</td>
<td>28</td>
<td>0.16</td>
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<tr>
<td>FH SCD first degree relative (%)</td>
<td>16</td>
<td>21</td>
<td>14</td>
<td>22</td>
<td>0.10</td>
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<td>NSVT (%)</td>
<td>26</td>
<td>21</td>
<td>31</td>
<td>26</td>
<td>0.28</td>
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<tr>
<td>BB (%)</td>
<td>66</td>
<td>64</td>
<td>76</td>
<td>55</td>
<td>&lt;0.001</td>
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<td>CCB (%)</td>
<td>22</td>
<td>26</td>
<td>21</td>
<td>18</td>
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<td>FH of HCM (%)</td>
<td>39</td>
<td>36</td>
<td>35</td>
<td>48</td>
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<td>AF (%)</td>
<td>19</td>
<td>12</td>
<td>24</td>
<td>19</td>
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<td>CAD (%)</td>
<td>10</td>
<td>8</td>
<td>15</td>
<td>5</td>
<td>&lt;0.001</td>
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<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>
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</table>

BB=beta blocker; EF=ejection fraction; FH=family history; MWT=Maximal LV wall thickness; NSVT=non-sustained ventricular tachycardia
Table 2. Gradient reduction after treatment in 299 patients with advanced-care for obstructive HCM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial resting gradient mmHg</th>
<th>Gradient at follow-up mmHg</th>
<th>Interim gradient after disopyramide but before septal reduction n=80</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All obstructed pts receiving advanced care, n=299</td>
<td>61 ±44</td>
<td>10 ±23</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Disopyramide, all pts n=221</td>
<td>63 ±45</td>
<td>25 ±32*</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Disopyramide without septal reduction n=141†</td>
<td>59 ±46</td>
<td>18 ±31</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Septal reduction after disopyramide=80§</td>
<td>69 ±41</td>
<td>7 ±17**</td>
<td>40 ±27‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All surgical pts n=138</td>
<td>65 ±42</td>
<td>3 ±9*</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*Gradient reported here includes that measured before intervention in 80 patients who had subsequent septal reduction.
†43 (30%) patients had DDD pacing for gradient as well.
§surgery in 75 and septal reduction in 5.
**final gradient after septal reduction in 80 patients who first received disopyramide.
‡interim gradient after disopyramide but before septal reduction, lower compared with their initial gradients, but higher than the final gradients in the 141 patients who could be managed without septal reduction, both p<0.0001.
*less than final gradient in 221 patients treated with disopyramide (p<0.0001), and less than final gradient in 141 patients treated with disopyramide but without septal reduction (p<0.0001)
### 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 Score Init 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 ±.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 ±.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 pts without septal reduction n=141</td>
<td>2.7 ±0.6</td>
<td>1.9 ±.5</td>
<td>&lt;0.0001</td>
<td>40 ±23</td>
<td>27 ±23</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 4. Characteristics of 63 patients with LVOT obstruction due to SAM, mitral-septal contact referred directly for surgery without a trial of disopyramide

<table>
<thead>
<tr>
<th>Characteristics</th>
<th># of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant cardiac surgery (n=23)</td>
<td></td>
</tr>
<tr>
<td>Coronary bypass</td>
<td>9</td>
</tr>
<tr>
<td>MVR to relieve MR due to intrinsic abnormality more than SAM, i.e., 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 pharmacologic therapy, long anterior mitral leaflet and high resting gradient *</td>
<td>20</td>
</tr>
<tr>
<td>Contraindications (n=11)</td>
<td></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.
MVR=mitral valve replacement; RVOT=right ventricular outflow tract
Table 5. Complications of therapy in 299 patients in the obstructed, advanced-care group

<table>
<thead>
<tr>
<th>Class of therapy, number of patients treated</th>
<th>Complication</th>
<th>Number of patients</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical, n=138</td>
<td>Large ventricular septal defect and early post-op heart failure</td>
<td>1</td>
<td>Required reoperation for complete closure, NYHA I outcome</td>
</tr>
<tr>
<td></td>
<td>Post-operative stroke</td>
<td>1</td>
<td>Disability</td>
</tr>
<tr>
<td></td>
<td>Post-operative TIA</td>
<td>1</td>
<td>Complete resolution</td>
</tr>
<tr>
<td></td>
<td>Large Pericardial Effusion</td>
<td>4 (3%)</td>
<td>Pericardial windows with complete resolution</td>
</tr>
<tr>
<td></td>
<td>Post-operative respiratory failure in patients with pulmonary disease</td>
<td>2</td>
<td>Prolonged ICU course</td>
</tr>
<tr>
<td></td>
<td>Heart block</td>
<td>7 (5%)</td>
<td>Permanent pacemaker</td>
</tr>
<tr>
<td></td>
<td>Wound infection</td>
<td>2</td>
<td>Resolved with drainage and antibiotics</td>
</tr>
<tr>
<td>Disopyramide, n=221</td>
<td>Torsade de pointes in female, age 82 with 96 mmHg resting gradient who</td>
<td>1</td>
<td>ICD discharge terminated arrhythmia which completely subsided after</td>
</tr>
<tr>
<td></td>
<td>developed diarrhea-induced hypokalemia.</td>
<td></td>
<td>K+ repletion. Disopyramide resumed</td>
</tr>
<tr>
<td></td>
<td>Heart block (age 88)</td>
<td>1</td>
<td>Permanent pacemaker</td>
</tr>
<tr>
<td></td>
<td>Urinary hesitancy (age 53)</td>
<td>1</td>
<td>Discontinued diso</td>
</tr>
<tr>
<td></td>
<td>Urinary retention (age 88)</td>
<td>1</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></td>
<td>Inappropriate shock</td>
<td>12 (20%)</td>
<td>Specifically targeted responses</td>
</tr>
<tr>
<td></td>
<td>Inappropriate ATP</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD infection</td>
<td>1</td>
<td>System extraction</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1. Treatment paths in 299 obstructed advanced-care patients. ASA=alcohol septal ablation; Ant. Leaf=anterior leaflet of mitral valve; DDD paced=AV sequential paced with short AV delay; Diso = diso; verap = verapamil; *43 (30%) of the 141 patients who were successfully treated with disopyramide were DDD paced as well.

Figure 2. Kaplan Meier plot comparing survival in 3 groups of HCM patients. Survival in the obstructed advanced-care patients did not differ from non-obstructed patients.

Figure 3. Kaplan Meier plot comparing observed survival in the obstructed advanced-care group (n=299, solid line) versus the expected survival based on 2005 US survival matched for age, sex and race (dashed line).
Symptomatic Obstructive HCM Unresponsive to β-Blockade or Verap, n=299

Other cardiac pathology, or (Combination of both Ant. Leaf ≥ 33mm + Gradient > 85 mm Hg), or Contraindication to diso

Surgery, n=63

Add disopyramide, n=221

Symptoms persist or drug side effects

Intervention, n=80

Continue pharmacologic therapy, n=141*

Surgery, n=75

ASA, n=1

DDD Paced, n=14

ASA, n=5
Treatment of Obstructive Hypertrophic Cardiomyopathy Symptoms and Gradient Resistant to First-Line Therapy with Beta-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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Supplemental Material

![Graph showing outflow gradient mm Hg for different groups.](image)

- **All pts n=299**
  - Before: 61
  - After: 10

- **All diso pts n=221**
  - Before: 63
  - After: 25

- **Diso pts w/o septal reduction n=141**
  - Before: 59
  - After: 18

- **Septal reduction after diso trial n=80**
  - Before: 69
  - After: 40

- **All surgical pts n=138**
  - Before: 65
  - After: 7

* p < 0.0001
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.