Long-term Outcome and Prognostic Determinants in Children With Hypertrophic Cardiomyopathy

ANJI T. YETMAN, MD, ROBERT M. HAMILTON, MD, LEE N. BENSON, MD, FACC, BRIAN W. MCCRINDLE, MD, FACC
Toronto, Canada

Objectives. We sought to determine clinical, angiographic, and echocardiographic predictors of survival in children with isolated hypertrophic cardiomyopathy (HCM) in a large pediatric centre.

Background. Sudden death is a catastrophic outcome of HCM in childhood but has been difficult to predict. Current therapies might provide for improved outcome if factors identifying high risk can be identified.

Methods. Records of 99 patients diagnosed with HCM from 1958 to 1997 at <18 yr were reviewed for clinical, angiographic (n = 62) and echocardiographic (n = 83) predictors of survival outcome. The effects of clinical characteristics on sudden death (including resuscitated sudden death) were individually tested in Cox's proportionate hazard modeling.

Results. Seventy-one subjects were male. Median age at diagnosis was 5.0 yr with a medical follow-up interval of 4.8 yr. Thirty-seven of 97 patients had a family history of HCM. Ambulatory electrocardiograms (ECG) in 78 patients demonstrated supraventricular tachycardia in 16 and ventricular tachycardia in 21. Death or resuscitated sudden death occurred in 18 patients. Sudden death rate was 2.7%/yr after age 8 yr. Cox's proportionate survival modeling revealed increased corrected QT interval (QTc) dispersion on ECG (relative risk [RR] 1.61 per 20 ms increment, p < 0.0003), ventricular tachycardia (VT) on ambulatory ECG (RR 3.75, p < 0.006) and myocardial bridging of the LAD coronary (RR 12.0, p < 0.003) to be associated with reduced time to death or resuscitated sudden death.

Conclusions. Detailed assessment of ECGs, ambulatory ECGs, and coronary angiography can assist in identifying which children with HCM are at risk for sudden death.

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Hypertrophic cardiomyopathy (HCM), a heterogeneous disease of sarcomeric contractile proteins, was initially identified in adults (1) and is thought to be uncommon in the pediatric population (2,3). It is characterized by left-ventricular hypertrophy not attributable to another cause (4–6). Left-ventricular hypertrophy can be manifest even shortly after birth (7–13), or may develop in children with previously normal echocardiographic evaluations (14).

Although the outcomes and effects of treatment have been well characterized in adults (15–19), the pediatric literature features smaller series (7–9,20) sometimes limited to children with an older age at presentation (21,22). The data that does exist on infants and young children varies with mortality rates ranging from 0 to 50% (8,9). There is no consensus on predictors of mortality in this population (8,9,21,22) which makes risk stratification difficult.

To improve risk stratification in this group of patients, we sought to describe the long-term outcomes of a large series of infants and children with HCM and to assess possible clinical, angiographic and echocardiographic predictors of mortality.

Methods

Patients. The cardiology database at a single tertiary pediatric centre was reviewed to identify patients diagnosed with HCM. Hypertrophic cardiomyopathy was defined by the presence of a hypertrophied, nondilated ventricle in the absence of cardiac or systemic diseases that could produce ventricular hypertrophy (4–6). Between 1958 and 1997, 99 patients at our centre had been diagnosed with HCM before the age of 18 years. The initial diagnosis was confirmed by echocardiography in 83 patients and by angiography in 16 patients diagnosed before the availability of echocardiography.

Measurements. Medical records were reviewed to determine patients’ ages at time of presentation for medical evaluation, onset of cardiovascular symptoms and diagnosis; the presence or absence of symptoms including loss of consciousness, resuscitated sudden death, presyncope, chest pain, shortness of breath on exertion, exercise limitation and palpitations; and family history of HCM or sudden cardiac death. Data from standard 12-lead electrocardiograms (ECGs), ambulatory ECGs, exercise testing, thallium-201 scintigraphy, echocardiography and cardiac catheterization were collected where

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was defined as blood pressure from the resting value; a hypotensive response age. Blood pressure was recorded as absolute peak value and peak heart rate and as a percentage of the predicted value for protocol (26) using standard indications for termination of day). tractions/day), or frequent (1440 premature contractions per day), occasional (240 –1440 premature con-

Supraventricular or ventricular ectopic activity in the face of an adjoining U wave, the intersection of a tangent to the downslope of the major repolarization wave with the isoelectric line. The end of the QT interval was defined as the return of the repolarization trace to the isoelectric line, or the return of the repolarization trace to the downslope of the major repolarization wave with the isoelectric line. Supraventricular or ventricular ectopic activity on ambulatory ECG was defined as rare (24 –240 premature contractions per day), occasional (240 –1440 premature contractions/day), or frequent (>1440 premature contractions/day).

In patients undergoing exercise testing, a Bruce treadmill protocol (26) using standard indications for termination of exercise was used (27). Heart rate was recorded as absolute peak heart rate and as a percentage of the predicted value for age. Blood pressure was recorded as absolute peak value and as absolute change (either positive or negative) in systolic blood pressure from the resting value; a hypotensive response was defined as <20 mm Hg rise in blood pressure at peak exercise (28). Exercise duration was recorded as an absolute value as well as a percentage of that predicted for age.

Among patients who underwent thallium-201 exercise single photon emission tomography (SPECT) scintigraphy, a bicycle ergometer exercise test was performed with the James protocol (29), with exercise continued until chest pain, fatigue, presyncope, arrhythmia or >3 mm ST segment alteration occurred.

For echocardiography, asymmetric septal hypertrophy was defined as a septal to posterior left-ventricular free-wall ratio of greater than 1.5 (30). In patients receiving medical management for obstructive disease, response to treatment was identified as no response (change in gradient <10 mm Hg), a transient response (reduction in gradient achieved for <3 months) or a sustained response (reduction in gradient >3 months). Gradient reduction was noted to be mild (10–15 mm Hg), moderate (16–25 mm Hg) or major (>25 mm Hg).

Statistical analysis. Patient characteristics are expressed as frequencies, medians with ranges, or means ±1 standard deviation, as appropriate. Group comparisons were performed with student t test or Mann–Whitney U test as appropriate. Where data was missing for a given variable, the number of nonmissing values is provided. Kaplan-Meier estimates of sudden death or resuscitated sudden death were plotted. Patients lost to follow-up were censored at the time that they were last known to be alive. The effect of clinical characteristics on sudden death or resuscitated sudden death was tested with Cox’s proportionate hazard modeling. A p value of less than 0.05 was considered significant.

Results

Between 1958 and 1997, 99 children from 93 families were diagnosed with HCM, of which 71 were male (72%) and 28 female. Median age at diagnosis was 5.0 years (range, 1 day to 17 yr), with 30 patients diagnosed at less than 1 year of age.

Presentation and family history. Features prompting presentation included presence of a heart murmur in 41 patients, a family history of HCM in 23 (14 other subjects with a family history had symptoms prompting presentation), an abnormal ECG in three and documented episode(s) of dysrhythmia in five. Symptoms prompted presentation in 39 patients (39%). Presenting symptoms included shortness of breath with exertion in 23, chest pain in 8, resuscitated sudden death in 6, syncope in 4 and presyncope in 1, palpitations in 4, shortness of breath at rest in 3 and failure to thrive in 2. Of 99 patients, 70 (71%) were symptomatic at some point during follow-up. Median age at onset of symptoms was 8.9 years (range, 0 to 18.1 yr).

Thirty-seven patients had a positive family history of HCM in first or second degree relatives; 11 had one affected family member; 13, two affected family members; 3, three affected family members; and 10 had four or more family members with HCM. Twenty-one had an associated family history of sudden death in up to seven family members. Sixty children had no family history of HCM. Family history was not available for two patients.

Electrocardiography. The initial ECG was available in 93 patients and demonstrated left ventricular hypertrophy in 57 patients (61%) and right ventricular hypertrophy in 20 (22%). Other abnormalities included prominent inferolateral Q-wave in 59 patients, isolated ST segment changes in 36, left axis deviation in 18, left bundle branch block in 9, right bundle branch block in 4, left atrial enlargement in 10, right atrial enlargement in 8, pre-excitation in 4, and right axis deviation in 7. Mean QT interval, corrected for heart rate using Bazett’s equation (31), was 440 ± 43 ms (n = 40). Mean calculated QT dispersion was 54 ± 39 ms (n = 78). The mean calculated QT dispersion available for 65 surviving patients was 47.7 ± 35.1 compared to 83.2 ± 46.7 for 13 patients with sudden death or resuscitated sudden death (p = 0.0024).

Ambulatory ECGs. Ambulatory electrocardiograms (AECGs) were performed for 78 patients and demonstrated episodes of supraventricular tachycardia in 16 children (20%) and ventricular tachycardia in 21 children (27%) including 9
with associated symptoms. Ventricular ectopy or couplets were noted in 22 additional patients. Ischemic ST segment changes were evident in 10 patients (13%).

**Stress testing.** Exercise-treadmill testing was performed in 43 patients, all without fatigue. Mean exercise duration was 8.4 ± 2.3 min (66 ± 19% of that predicted for age). Percentages of predicted heart rate averaged 90% ± 10%. Median ST segment depression was 2 mm (range, 0 to 10 mm). Chest pain was induced in eight patients, who had a median ST depression of 4 mm compared to 0 mm for asymptomatic patients (p = 0.006). Dysrhythmias included increasing ventricular ectopy in six, ventricular tachycardia (VT) in two and second-degree heart block in one. Mean systolic blood pressure change was +27 ± 35 mm Hg, with 18 patients having a hypotensive response to exercise. Stress thallium myocardial imaging, done for 23 patients, showed fixed perfusion defects in 2 children, reversible perfusion defects in 8, and no evidence of ischemia in 13.

**Echocardiography.** Initial echocardiograms were available for 83 patients. Left-ventricular hypertrophy was noted in 65 patients (78%), with 13 (16%) additional children having both right- and left-ventricular hypertrophy, and 5 (6%) having normal initial echocardiograms but subsequently developing left-ventricular hypertrophy during follow-up. Mean ratio of interventricular septum to left-ventricular free-wall thickness was 2.3 ± 1.1, with 68 patients (82%) having asymmetric septal hypertrophy. Systolic anterior motion of the mitral valve was noted in 58 children (70%). Right-ventricular outflow tract obstruction was noted in 13 patients (16%), with a mean peak instantaneous gradient of 23 ± 16 mm Hg. Left-ventricular outflow tract obstruction was noted in 49 patients (59%), with a mean peak instantaneous gradient of 44 ± 33 mm Hg. Provocation with amyl nitrate in 27 patients resulted in an increase in left-ventricular gradient in 11, 3 of whom had no gradient at rest. Mitral regurgitation was qualitatively mild in 18 children, moderate in 4, and severe in 1. Mean ejection fraction (n = 63) was 78% ± 12%. Progressive left-ventricular obstruction on echocardiography occurred in 43 patients (43%) at a mean age of 9.7 ± 5.4 yr.

Diastolic function was assessed in 32 patients, and the pattern of left-ventricular diastolic filling was abnormal in 18 (56%). Mean isovolumic relaxation time was 87 ± 29 ms (n = 25); c/a ratio, 1.7 ± 0.9 (n = 26); deceleration time, 157 ± 41 ms (n = 19); and median a-wave reversal velocity, 0.18 m/s (range, 0.0 to 0.80 m/s; n = 23). Although diastolic abnormalities in HCM may relate more directly to symptomatic status or exercise endurance (17), they did not predict survival in our study.

**Cardiac catheterization.** Cardiac catheterization was performed in 62 patients. Mean left-ventricular end-diastolic pressure (n = 48) was 15 ± 8 mm Hg. Median left-ventricular outflow peak-to-peak gradient (n = 61) was 10 mm Hg (range, 0 to 149). Left-ventricular systolic function was qualitatively graded as normal in 60 patients, and significantly reduced in 2. Median right-ventricular outflow tract peak-to-peak systolic gradient was 0 (range, 0 to 52 mm Hg). Coronary angiography in 36 patients showed evidence of myocardial bridging with compression of the left anterior descending coronary artery in ten patients.

**Therapies and outcome.** Sixty-four patients (65%) received medical therapy for symptoms, outflow tract obstruction, or arrhythmia. Forty-one patients received a β-blocking drug; eighteen (44%) had no change in gradient despite apparent compliance in taking a therapeutic dose. Only 10 children (24%) experienced a sustained decrease, with a major reduction in 6 (15%). Four patients had a reduction in VT on

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**Table 1. Summary of Patients Dying (n = 12)**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age at dx</th>
<th>Age at death</th>
<th>Symptoms</th>
<th>Family mbs with SD/HCM</th>
<th>QTcD (ms)</th>
<th>Holter monitor results</th>
<th>LVOTO/ RVOTO (mm Hg)</th>
<th>Maximum septal thickness</th>
<th>Exercise BP response</th>
<th>Medications</th>
<th>Myectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 yr</td>
<td>7 yr</td>
<td>SOBOE</td>
<td>4</td>
<td>100</td>
<td>No data</td>
<td>Normal</td>
<td>111/23</td>
<td>No data</td>
<td>None</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>1 wk</td>
<td>3 mo</td>
<td>CHF, failure to wean from ventilator</td>
<td>0</td>
<td>61</td>
<td></td>
<td></td>
<td>90/77</td>
<td>5 mm</td>
<td>No data</td>
<td>Disopyramide, propranolol</td>
</tr>
<tr>
<td>3</td>
<td>8 yr</td>
<td>9 yr</td>
<td>None</td>
<td>0</td>
<td>100</td>
<td>No data</td>
<td>VT/</td>
<td>0/0</td>
<td>50 mm</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1 day</td>
<td>4 mo</td>
<td>SVT/CHF</td>
<td>0</td>
<td>150</td>
<td>VT/</td>
<td>0/0</td>
<td>6 mm</td>
<td>No data</td>
<td>Propranolol, digoxin</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>8 yr</td>
<td>9 yr</td>
<td>SOBOE</td>
<td>0</td>
<td>51</td>
<td>No data</td>
<td>20/0</td>
<td>15 mm</td>
<td>No data</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>10 yr</td>
<td>18 yr</td>
<td>Resuscitated SD</td>
<td>3</td>
<td>88</td>
<td>VT</td>
<td>14/0</td>
<td>10 mm</td>
<td>10 mm Hg</td>
<td>Propranolol</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>10 yr</td>
<td>13 yr</td>
<td>None</td>
<td>0</td>
<td>128</td>
<td>Normal</td>
<td>0/0</td>
<td>24 mm</td>
<td>No change</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>11 yr</td>
<td>14 yr</td>
<td>SOBOE</td>
<td>0</td>
<td>79</td>
<td>Normal</td>
<td>0/0</td>
<td>23 mm</td>
<td>No change</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>6 yr</td>
<td>17 yr</td>
<td>SOBOE, palpitations, pre-syncope</td>
<td>0</td>
<td>90</td>
<td>VT</td>
<td>102/8</td>
<td>20 mm</td>
<td>No change</td>
<td>Disopyramide, propranolol</td>
<td>+ + +</td>
</tr>
<tr>
<td>10</td>
<td>5 yr</td>
<td>5 yr</td>
<td>None</td>
<td>0</td>
<td>85</td>
<td>No data</td>
<td>0/0</td>
<td>21 mm</td>
<td>No data</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>11 yr</td>
<td>17 yr</td>
<td>Syncope</td>
<td>2</td>
<td>100</td>
<td>VT</td>
<td>0/0</td>
<td>26 mm</td>
<td>No change</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>1 wk</td>
<td>2 yr</td>
<td>Resuscitated SD, CHF</td>
<td>0</td>
<td>50</td>
<td>SVT</td>
<td>0/0</td>
<td>26 mm</td>
<td>No change</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

Pt = patient number; dx = diagnosis; SOBOE = shortness of breath on exertion; CHF = congestive heart failure; SVT = supraventricular tachycardia; SD = sudden death; mbs = members; HCM = hypertrophic cardiomyopathy; QTcD = corrected QT dispersion; VT = ventricular tachycardia; LVOTO/RVOTO = left/right-ventricular outflow tract obstruction; BP = blood pressure.
AECG. Two patients with unobstructed HCM had symptomatic improvement, whereas three others had deteriorating clinical symptoms that necessitated discontinuation of the drug.

Eighteen patients were treated with disopyramide, either primarily (n = 10) or in addition to beta-blockade (n = 8). Five patients (28%) experienced no change in gradient; nine patients (50%) had a sustained reduction in gradient, which was major in six (33%). One patient was noncompliant because of dry mouth, a side-effect. Eight patients were treated with calcium channel blockers (diltiazem or verapamil). A mild sustained decrease in gradient was noted in two patients. All patients reported an improvement in exercise-limitation symptoms. There were no adverse complications.

Six patients were started on amiodarone treatment for prevention of ventricular arrhythmias. Four had clinical improvement and a decrease in the frequency of arrhythmia on AECG recording and two patients had an increase in the frequency of arrhythmia, in association with a marked increase in the corrected QT interval. Eight patients were started on sotalol for treatment of ventricular arrhythmias with 7 having an improved clinical status associated with a decrease in ventricular arrhythmia (AECG) and no change in the remaining patient.

Twenty-four children underwent one or more left-ventricular myectomies; two underwent both left- and right-ventricular myectomies; three patients underwent isolated right-sided myectomy. Sixteen of 29 patients (55%) had complete resolution of outflow tract gradients following surgical intervention; eight (28%) had a moderate reduction in gradient; and five patients (17%) experienced no change in gradient following surgery. Following left-ventricular myectomy, five patients developed complete heart block requiring permanent pacemaker implantation. Three patients were left with greater-than-mild aortic insufficiency; none required surgical intervention. Two patients had a neurologic insult at the time of surgery. One patient, having undergone two previous left-ventricular myectomies, died in the immediate post-operative period.

Six children had insertion of an implantable cardioverter defibrillator because of resuscitated sudden death with two of these patients also undergoing unroofing of a myocardial bridge because of evidence of ischemia-induced ventricular dysrythmias. One underwent unroofing of a myocardial bridge during a separate procedure because of recurrent defibrillator discharges into what appeared to be ischemia-induced ventricular tachycardia. An additional patient had isolated unroofing of a myocardial bridge. One patient underwent cryoablation of an accessory pathway, with concomitant pacemaker implantation, for intractable supraventricular tachycardia. Two patients went on to cardiac transplantation after developing end-stage heart failure.

Characteristics of the 12 patients who died are listed in Table 1. Two of these patients had a previous resuscitated sudden death. An additional six patients experienced resuscitated sudden death but continue to survive. Patients were followed up to their last clinic visit at 18 yr or until death. Two patients were lost to follow-up. The remainder were followed to a mean age of 12.1 ± 6.3 years, for a median interval from diagnosis of 4.8 years. Kaplan–Meier estimates of freedom from death or resuscitated sudden death are graphed, from birth in Figure 1 and from time of diagnosis in Figure 2. The yearly combined incidence of death or resuscitated sudden death between 8 and 18 years of age has been constant at 2.7% per yr.

When variables (Table 2) were tested individually with Cox’s proportionate hazard modeling to determine their effect on time from diagnosis to death or to resuscitated sudden death, those significantly associated with an increased risk included increased QT dispersion on baseline ECG (relative risk [RR], 1.61 per 20 ms incremental increase; 95% confidence interval [CI], 1.24 to 2.08), presence of ventricular tachycardia on ambulatory monitoring (RR 3.75, CI 1.48 to 9.50), and the presence of myocardial bridging on coronary angiography (RR 12.0, CI 2.47 to 58.3). The presence of ST segment depression on exercise testing approached but did not reach significance. History of symptoms, age at diagnosis,
positive family history of HCM or HCM-associated sudden death, ECG voltage criteria for hypertrophy, left-ventricular outflow tract obstruction, diastolic dysfunction and treatment with medication or surgery did not correlate with an increased risk of mortality (Table 2).

**Table 2. Postulated Risk Factors for Reduced Time to Death or Resuscitated Sudden Death**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
<th>p value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of symptoms</td>
<td>1.45</td>
<td>0.46</td>
<td>99</td>
</tr>
<tr>
<td>Syncope</td>
<td>0.33</td>
<td>0.29</td>
<td>99</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0.77</td>
<td>0.65</td>
<td>99</td>
</tr>
<tr>
<td>Age at diagnosis (per 1 yr increment)</td>
<td>1.06</td>
<td>0.23</td>
<td>99</td>
</tr>
<tr>
<td>Family history of HCM</td>
<td>1.34</td>
<td>0.54</td>
<td>99</td>
</tr>
<tr>
<td>Family history of sudden death</td>
<td>1.86</td>
<td>0.22</td>
<td>99</td>
</tr>
<tr>
<td>Interventricular septal thickness</td>
<td>1.03</td>
<td>0.11</td>
<td>80</td>
</tr>
<tr>
<td>Left-ventricular outflow gradient</td>
<td>0.92</td>
<td>0.22</td>
<td>98</td>
</tr>
<tr>
<td>Medication</td>
<td>1.63</td>
<td>0.36</td>
<td>99</td>
</tr>
<tr>
<td>Surgery</td>
<td>1.78</td>
<td>0.23</td>
<td>99</td>
</tr>
<tr>
<td>ST segment depression on exercise test</td>
<td>2.45</td>
<td>0.06</td>
<td>99</td>
</tr>
<tr>
<td>QTc dispersion (per 20 ms increment)</td>
<td>1.61</td>
<td>*0.0003</td>
<td>78</td>
</tr>
<tr>
<td>Ventricular tachycardia on ambulatory ECG</td>
<td>3.75</td>
<td>*0.006</td>
<td>99</td>
</tr>
<tr>
<td>Myocardial bridging of LAD coronary artery</td>
<td>12.0</td>
<td>*0.003</td>
<td>36</td>
</tr>
</tbody>
</table>

*Statistically significant. HCM = hypertrophic cardiomyopathy; inc. = increment; QTc = corrected QT interval; ECG = electrocardiogram; LAD = left anterior descending.

Discussion

The clinical course of HCM in children is variable; asymptomatic or mildly symptomatic patients may die unexpectedly (5,32,33). Although it has been postulated that the best determinant of outcome may be the specific molecular genetic defect (6), current patient management relies on clinical predictors of outcome. Although literature on outcome determinants in adults is ample, data on risk factors for mortality in children is sparse, and that which is available is controversial. In previous studies, increased risk of mortality in children with HCM has been associated with a history of syncope on presentation (21,34), the presence of congestive heart failure in the first year of life (9), malignant family history (35), high-grade ventricular ectopy on ambulatory recording (19) and evidence of ischemia on noninvasive testing (36). In contrast, we found that only the last two of these factors were predictive of death or resuscitated sudden death in our patients, plus two others (presence of increased QTc dispersion and myocardial bridging). The explanations for our contrasting findings may be related to methodology, statistical power, differences in practice or patient population.

Comparison of our study to that of McKenna and Deanfield (21) demonstrates differing methodology and practice. They found a history of syncope to be a risk factor for sudden death with four of four patients who presented with loss of consciousness subsequently experiencing sudden death. In contrast, within our population there was no association between a history of loss of consciousness and sudden death. We defined syncope as a brief loss of consciousness requiring no resuscitative efforts and analyzed these patients separately from those who presented with resuscitated sudden death, whereas McKenna and Deanfield (21) did not distinguish between these two forms of consciousness loss. None of their patients received a defibrillator, while six of our eight patients with resuscitated sudden death had implantation of an internal defibrillator. Many were also treated with a class III antiarrhythmic agent or unroofing of a myocardial bridge. Most of the patients who developed a defibrillator subsequently experienced appropriate discharge, suggesting that such treatment was, in fact, protective. The remaining two patients not implanted with a defibrillator died suddenly. It would appear that while a history of syncope may not confer an increased risk of mortality, a history of resuscitated sudden death does.

In contrast to the multi-institutional NIH study of Maron and colleagues, 21 of our 23 patients diagnosed under the age of one yr survived. This may be due to improvements in therapies for these infants which have occurred since this earlier study.

The frequency of a positive family history of HCM in our patients was 38%, somewhat less than that found by Greaves et al. (37). However, many of the patients may have been investigated when family screening was not routinely performed. While 22% of our patients had a positive family history of HCM associated with sudden death, such a history was not predictive of childhood mortality. Previous studies have found an association between a malignant family history and sudden death (35,38,39). The lack of such an association within our patient population may reflect a follow-up duration confined to the childhood and adolescent years or an aggressive treatment approach in those with a family history of sudden death (40).

Frenneaux et al. (41) previously reported an increased risk of resuscitated sudden death in adult patients with HCM who had documented exercise-induced hypotension. The six patients in this study series who had undergone formal exercise testing and then died suddenly had, in concordance with the findings of others, failed to elevate their blood pressure with exercise (Table 1), but this did not reach statistical significance. ST segment depression on exercise approached statistical significance as a predictor of sudden death, supporting a similarly reported association between ischemia (on exercise thallium study) and sudden death (36).

Ventricular dysrhythmias have long been postulated as the mechanism of sudden death in children with HCM (16,19,42). We documented a high incidence of sudden death in those patients with ventricular tachycardia on ambulatory recording. This is in keeping with the findings of two previous independent studies associating nonsustained VT with sudden cardiac...
sustained relief of left-ventricular outflow tract obstruction in to its negative inotropic effect. We report the successful potentially useful in reducing subaortic obstruction secondary and left-ventricular outflow tract obstruction has only been patient population, the effect of beta-blockade on left-
outflow tract obstruction by blocking sympathetic tone is also thought to lead to an improvement in symptoms. Within our present study population, greater QT dispersion on ECG was strongly associated with an increased risk of mortality. The etiology of this increase in QT dispersion has not been well defined, but may relate to ischemia-induced alteration in myocardial repolarization (51).

Additional evidence supporting the role of regional myocardial ischemia in sudden death in children with HCM has included increasing myocardial lactate production with rapid atrial pacing (52), appearance of reversible exercise-induced perfusion defects on thallium scanning (36) and transmural infarcts on autopsy (53). We have shown an association between increased risk of mortality and ischemic ECG changes on exercise testing which approaches statistical significance. Few patients underwent thallium scanning, and we were unable to demonstrate an association between reversible perfusion defects with exercise and subsequent mortality. The mechanism of ischemia remains undefined, but proposed factors include intramural small-vessel abnormalities (6,15,32), septal perforator artery compression (6,15,32), abnormal myocellular architecture (6), massive hypertrophy (54), or myocardial bridging with systolic compression of the left anterior descending coronary artery (50,55).

Management. The role of β-blockers in the treatment of children with HCM is controversial (8,9,18,22,56,57). β-blocking drugs have been shown to improve exertional angina and dyspnea in patients with HCM by inhibiting sympathetic stimulation of the heart and diminishing myocardial oxygen requirements (15). β-blockers are thought to improve diastolic function through a reduction in heart rate and a reduction in myocardial ischemia (15,36). Relief of outflow tract obstruction by blocking sympathetic tone is also thought to lead to an improvement in symptoms. Within our patient population, the effect of beta-blockade on left-ventricular outflow tract obstruction was inconsistent.

The role of disopyramide in pediatric patients with HCM and left-ventricular outflow tract obstruction has only been assessed in a small series (58). The drug is thought to be potentially useful in reducing subaortic obstruction secondary to its negative inotropic effect. We report the successful sustained relief of left-ventricular outflow tract obstruction in half of the children treated. Disopyramide may also have an antihypertrophic effect when administered to patients, although we have not deliberately used it for this indication.

Calcium channel blockers have previously been shown to be effective agents in the management of children with HCM (20,59,60), improving cardiac symptoms and exercise capacity in most HCM patients, regardless of whether obstruction is present (15,20). Mechanisms thought to underlie this beneficial effect include a mild negative inotropic effect (15) and an improvement in diastolic function (15,59).

Amiodarone and sotalol may assume increasing importance as therapeutic agents in children with HCM and documented VT. Both drugs have been shown to reduce QT dispersion (49,61) and to protect against malignant ventricular dysrhythmias in this group of patients. Six of eight patients experiencing resuscitated sudden death in our series had implantation of an automatic defibrillator. All patients are alive at follow-up. In addition to a history of resuscitated sudden death, other indications for defibrillator implantation may include symptomatic ventricular tachycardia uncontrolled by medical or surgical management. We have not had a patient receiving either drug experience sudden death.

When medical management is ineffective or not tolerated in symptomatic children with obstructive cardiomyopathy, surgical myectomy should be undertaken. A persistent left-ventricular outflow tract gradient >60 mm Hg despite medication is also suggested as an indication for surgery, regardless of symptomatology (62). Surgical complications in our series included aortic insufficiency, complete heart block, and neurologic sequelae (63).

Surgical unroofing of a myocardial bridge in the setting of angiographically documented coronary compression may prove valuable in reducing ischemia (64). All patients with a myocardial bridge who did not undergo surgical unroofing had evidence of ongoing ischemia and repeat episodes of resuscitated sudden death or death. There was no evidence of ischemia on exercise testing or perfusion scanning in those undergoing surgical relief of the obstruction, as well as no recurrence of resuscitated sudden death (50).

Recommendations. All patients with evidence for ischemia, based on clinical history or laboratory findings such as chest pain, resting or exercise-induced ST segment changes, excessive QT dispersion or ventricular dysrhythmias should be evaluated with nuclear exercise testing and coronary angiography to rule out septal perforator artery compression or myocardial bridging with systolic compression of the left anterior descending artery (50). Patients with documented ischemia from myocardial bridging should undergo coronary unroofing, in addition to implantation of an automatic implantable cardioverter defibrillator if there is a history of resuscitated sudden death. Patients with evidence of ischemia, but no surgically correctable lesion, may benefit from medical management with β-blockers or calcium-channel blockers (6,50).

All patients with loss of consciousness should be evaluated as to other potential manifestations of ischemia (angina or exercise-induced syncope) and undergo Holter ambulatory monitoring, echocardiographic evaluation of systolic and dia-
stolic function, measurement of left-ventricular outflow tract gradient at rest and with provocation, cardiac catheterization with coronary angiography to evaluate for the presence of myocardial bridging (50) and radionuclide exercise testing to assess for the presence of ischemia or ischemia-induced arrhythmias. Dispersion of refractoriness should be specifically assessed on ECG.

Limitations. Although this is one of the largest reported series of children with hypertrophic cardiomyopathy, it is also therefore retrospective over a long period of evolving practice. The development of surgical excellence in relief of outflow tract obstruction may have led to some referral bias, although probably not to the extent of other large series. The presence of a stable coding system and clinical database throughout the period of study provided for the study of all cases and their investigations, although no consistent investigative strategy was maintained throughout this period. Only selected investigations were performed in each patient. Therefore, predictors could only be assessed independently, and their interrelationships could not be explored in multivariate analysis.

Interpretation. Mortality in this large series of children with HCM is lower than that previously reported. Sudden death continues to be the primary cause of death in these patients. Evidence is increasing that the underlying cause of sudden death is myocardial ischemia, often secondary to myocardial bridging. Ventricular tachycardia, increased QT dispersion, and ST segment changes on exercise testing appear to be markers of an increased risk of mortality and may all reflect ongoing ischemia. An aggressive diagnostic evaluation to detect ischemia and the use of a multifaceted treatment approach to prevent ischemia may be beneficial.

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References

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