Clinical Features and Outcomes of Childhood Hypertrophic Cardiomyopathy
Results From a National Population-Based Study

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Background—Population-based studies have provided insight into the natural history of adult hypertrophic cardiomyopathy, but comparable information for affected children is lacking.

Methods and Results—All Australian children who presented with primary cardiomyopathy at 0 to 10 years of age between January 1, 1987, and December 31, 1996, were enrolled in a longitudinal cohort study. A single cardiologist reviewed serial cardiac investigations on each subject. A total of 80 subjects with hypertrophic cardiomyopathy were identified. An underlying syndromal, genetic, or metabolic condition was identified in 46 subjects (57.5%). There were no cases of sudden death at presentation. Left ventricular outflow tract obstruction was present in 32 subjects (40%); right ventricular outflow obstruction was present in 10 (12.5%). Freedom from death or transplantation was 83% (95% CI, 73 to 90) 5 years after presentation and 76% (95% CI, 62 to 86) 10 years after presentation. By proportional-hazards regression analysis, risk factors for death or transplantation included concentric left ventricular hypertrophy, age at presentation, lower initial fractional shortening Z score, and increasing left ventricular posterior wall thickness relative to body surface area. At the latest follow-up, 54 of 65 surviving subjects had no symptoms, and 46 were receiving no regular medication.

Conclusions—Syndromal, genetic, and metabolic causes predominate in children with hypertrophic cardiomyopathy. Ventricular outflow tract obstruction is common. The clinical status of long-term survivors is good. This population-based study identifies children with hypertrophic cardiomyopathy who are at risk of adverse events. (Circulation. 2005;112:1332-1338.)

Key Words: cardiomyopathy ■ pediatrics ■ sudden death

Hypertrophic cardiomyopathy resulting from sarcomeric protein mutations is the commonest genetically determined cardiovascular disease and the commonest cause of sudden cardiac death in fit young adults. In children, hypertrophic cardiomyopathy is characterized by diverse causes and has a peak incidence during the first year of life.

Previous reviews based on institutional experience have suggested a poor outcome for childhood hypertrophic cardiomyopathy. In adults, population-based reviews of hypertrophic cardiomyopathy have corrected misconceptions about disease severity and outcomes. However comparable studies of childhood hypertrophic cardiomyopathy are currently lacking. This study examines the clinical characteristics and outcomes for children with hypertrophic cardiomyopathy enrolled in the National Australian Childhood Cardiomyopathy Study.

Methods
Cases were recruited as part of the National Australian Childhood Cardiomyopathy Study, a population-based cohort study of all children in Australia who presented with primary cardiomyopathy at 0 to 10 years of age between January 1, 1987, and December 31, 1996. Data from inpatient and outpatient records were collected during a series of site visits performed by the same 3 investigators to all 9 pediatric cardiology centers and 12 hospitals caring for children.
with cardiac disease. Additional cases were recruited from rural pediatricians and cardiologists caring primarily for adults. Ethics committee approval was obtained from all participating institutions. The methodology and major epidemiological findings have previously been described. Children with cardiac dysfunction secondary to other organ abnormalities were excluded.

Cardiomyopathies were categorized according to the current World Health Organization cardiomyopathy classification by a single pediatric cardiologist after review and analysis of all available investigations. Children with cardiac hypertrophy secondary to progressive neuromuscular disorders and inborn errors of metabolism with multiple organ involvement were excluded. Hypertrophic cardiomyopathy was defined by otherwise unexplained septal and/or left ventricular free wall hypertrophy (Z score >2 for either). Right ventricular involvement was defined by a right ventricular free wall thickness >4 mm in the absence of pulmonary valve stenosis. The morphology of left ventricular involvement was classified as either asymmetric septal hypertrophy if the interventricular septum was predominantly involved or concentric left ventricular hypertrophy if both the left ventricular free wall and interventricular septum were affected to a similar degree. Left ventricular outflow tract obstruction was defined as anatomic narrowing, together with a measured systolic gradient at cardiac catheterization or a peak instantaneous gradient of >15 mm Hg from echocardiography. The presence of congestive heart failure was based on signs and symptoms recorded by the attending physician. The diagnosis of Noonan syndrome was made if characteristic phenotypic features were identified at clinical genetic review. Familial hypertrophic cardiomyopathy was considered present if there was an affected first- or second-degree relative in the absence of Noonan syndrome, a mitochondrial disorder, or metabolic condition. Routine genotyping was performed for sarcomeric protein mutations and Noonan syndrome was not available during the study period.

Prospective follow-up was arranged for patients who had not been seen within the preceding 12 months. Presenting deaths were those in which there had been no prior symptoms. Autopsy records for cases presenting with sudden death were identified from centralized records compiled by the Australian Bureau of Statistics using the same diagnostic codes as for hospital medical records. In this way, autopsy reports were obtained for subjects who had never had contact with a physician.

Prognostic factors sought included clinical features at presentation and results of relevant investigations. The earliest available ECG was read by a single observer, and measurements were converted to age-appropriate Z scores. Serial echocardiographic measurements of left ventricular dimensions, diastolic free wall and septal thickness, and fractional shortening (in those without regional wall motion abnormalities) were expressed as Z scores based on body surface area. Echocardiograms were usually available at presentation; after 3, 6, 12, and 24 months; and at the latest follow-up. Among subjects with at least 2 suitable echocardiograms available from the time of presentation, the change in echocardiographic wall thickness or fractional shortening Z score at each subsequent occasion of measurement was calculated by subtracting the initial Z score from the subsequent value.

**Statistical Analysis**

Age at presentation was summarized through the use of median and interquartile range (IQR), and comparisons between different subgroups were made with the Wilcoxon rank-sum test. Paired peak echocardiographic gradients before surgery and at the latest follow-up were compared with the Wilcoxon matched-pairs signed-rank test. Standard methods of survival analysis were used for the end point of surgical left ventricular outflow resection and the combined end point of death or transplantation. Important prognostic factors from the univariable analysis were included in a multivariable Cox proportional-hazards model. Changes in echocardiographic left ventricular posterior wall and fractional shortening Z score were entered into the multivariable model as continuous predictors, with the latter a time-dependent covariate defined using the most recent available echocardiographic value.

**Results**

A total of 80 subjects with hypertrophic cardiomyopathy were identified. Table 1 summarizes the clinical characteristics of the study population. The median age at presentation, 5.7 months (IQR, 1.48 to 30.4 months), was unrelated to the morphology of left ventricular involvement. Children with Noonan syndrome tended to be younger at presentation than the remaining study subjects (median age, 2.79 months [IQR, 0.26 to 21.3 months] versus 6.6 months [IQR, 2.14 to 36.0 months], respectively; *P*=0.07), as did those with biventricular involvement.

**Table 1. Demographic Characteristics of the Patients Studied**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of total cases in NACCS (n=314)</td>
<td>25.5</td>
</tr>
<tr>
<td>Male/female, n (%)</td>
<td>55/25 (69/31)</td>
</tr>
<tr>
<td>Age ≤1 y at presentation, n (%)</td>
<td>48 (60)</td>
</tr>
<tr>
<td>Age &gt;1 and ≤5 y, n (%)</td>
<td>19 (23.8)</td>
</tr>
<tr>
<td>Age &gt;5–10 y, n (%)</td>
<td>13 (16.2)</td>
</tr>
<tr>
<td>Noonan syndrome, n (%)</td>
<td>23 (28.8)</td>
</tr>
<tr>
<td>Familial hypertrophic cardiomyopathy, n (%)</td>
<td>17 (21.3)</td>
</tr>
<tr>
<td>Presence of metabolic disease, n (%)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Morphology of left ventricular involvement, n (%)</td>
<td></td>
</tr>
<tr>
<td>Asymmetric septal hypertrophy</td>
<td>56 (70)</td>
</tr>
<tr>
<td>Concentric left ventricular hypertrophy</td>
<td>24 (30)</td>
</tr>
<tr>
<td>Biventricular involvement, n (%)</td>
<td>18 (22.5)</td>
</tr>
<tr>
<td>Left ventricular outflow obstruction, n (%)</td>
<td>32 (40)</td>
</tr>
<tr>
<td>Surgical left ventricular myectomy, n (%)</td>
<td>18 (22.5)</td>
</tr>
<tr>
<td>Right ventricular outflow obstruction, n (%)</td>
<td>10 (12.5)</td>
</tr>
<tr>
<td>Death or transplantation, n (%)</td>
<td>15 (18.8)</td>
</tr>
<tr>
<td>Follow-up from presentation for all patients (n=80), y</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.25</td>
</tr>
<tr>
<td>IQR</td>
<td>2.42 to 8.54</td>
</tr>
<tr>
<td>Follow-up from presentation for surviving patients (n=65), y</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6.23</td>
</tr>
<tr>
<td>IQR</td>
<td>4.29 to 9.04</td>
</tr>
<tr>
<td>Fractional shortening at presentation (n=72*), %</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>46</td>
</tr>
<tr>
<td>IQR</td>
<td>41 to 52</td>
</tr>
<tr>
<td>Fractional shortening Z score at presentation (n=72*)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.38</td>
</tr>
<tr>
<td>IQR</td>
<td>1.21 to 5.51</td>
</tr>
<tr>
<td>Left ventricular posterior wall Z score at presentation (n=77*)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.27</td>
</tr>
<tr>
<td>IQR</td>
<td>−1.28 to 2.70</td>
</tr>
</tbody>
</table>

NACCS indicates National Australian Childhood Cardiomyopathy Study, n=80.

Eight subjects did not have a suitable echocardiogram for measurement of fractional shortening and/or posterior wall thickness at presentation.

Survival curves were plotted using Kaplan-Meier survival estimates with accompanying Greenwood confidence bands. Cumulative incidence estimates for first left ventricular myectomy were calculated with the Nelson-Aalen approach accounting for the competing risk of death/transplant. Analysis was undertaken using Stata software. The 95% CIs are given for estimated hazard ratios, and all reported probability values are 2 sided.
ular involvement (median presenting age, 2.32 months [IQR, 0.43 to 14.4 months] versus 6.60 months [IQR, 2.1 to 37.3 months], respectively; \( P < 0.08 \)).

**Presenting Symptoms**
Congestive heart failure was present in 6 subjects (7.5%) at presentation, and 2 subjects (2.5%) had arrhythmic symptoms. The remaining subjects were diagnosed after being screened for a cardiac murmur (42 of 80, 52.5%), a family history of hypertrophic cardiomyopathy (12 of 80, 15%), an underlying syndrome (5 of 80, 6.3%), or nonspecific symptoms (13 of 80, 16.3%). There were no cases in whom sudden death was the first manifestation of hypertrophic cardiomyopathy.

**Etiological Considerations**
Noonan syndrome was present in 23 subjects (28.8%), and there was 1 case each of Costello, Beckwith-Wiedemann, and Fukuyama syndromes. Seventeen subjects (21.3%) had familial hypertrophic cardiomyopathy, all with at least 1 prior affected adult family member. Seven subjects with familial cardiomyopathy were diagnosed before 12 months of age. Two children with familial cardiomyopathy who were diagnosed at 3 years of age were found to have myosin binding protein-C mutations. Two children with initial cardiac findings that were indistinguishable from those of other study subjects were subsequently found to have a myocardial respiratory chain enzyme deficiency. Parental consanguinity as a potential marker of a recessively inherited condition was present in 2 cases, including 1 with a complex IV respiratory chain enzyme defect. At least 1 of the conditions listed above was present in 46 of the 80 study subjects (57.5%).

**Morphology of Hypertrophic Cardiomyopathy**
Asymmetric septal hypertrophy was present in 56 subjects (70%); concentric left ventricular hypertrophy was seen in 24 (30%). There was a strong association between the presence of biventricular involvement and the pattern of left ventricular hypertrophy. Eleven of 18 subjects (61.1%) with biventricular involvement had concentric left ventricular hypertrophy compared with 13 of 62 subjects (21%) in whom only the left ventricle was involved (\( P = 0.003 \) by Fisher’s exact test).

Left ventricular outflow obstruction with a resting gradient was present in 32 subjects (40%) during the study period. It was present at the time of initial evaluation in 25 subjects (31.3%) and developed in an additional 7 subjects (8.7%) during follow-up. Six more subjects had left ventricular midcavity obstruction with systolic cavity obliteration in association with an outflow gradient. Ten subjects had right ventricular outflow obstruction caused by pulmonary valve stenosis and/or muscular infundibular narrowing.

**Outcomes**

**Death/Transplantation**
Freedom from death or transplantation was 83% (95% CI, 73 to 90) 5 years after presentation and 76% (95% CI, 62 to 86) at 10 years (Figure 1A). Fourteen subjects died, and 1 underwent cardiac transplantation. The average annual mortality for the entire study population was 3.39% during the follow-up period and 1.52% for subjects diagnosed after the first year of life. The causes of death included congestive heart failure in 7 subjects, 6 of whom had normal systolic function on echocardiography, diffuse bronchomalacia (1 case), bacterial sepsis (2 cases), aspiration of food (2 cases), metabolic decompensation (1 case), and sudden unexpected death caused by presumed ventricular arrhythmia (1 case). Both children with consanguineous parents died, as did 1 subject with a respiratory chain enzyme deficiency and 2 subjects who had undergone previous septal myectomy 6 and 58 months earlier. The median time between presentation and death among subjects who died of congestive heart failure was 7.6 months (range, 1.7 to 98.7 months).

Table 2 shows risk factors for the combined end point of death or cardiac transplantation. Familial cardiomyopathy was predictive of survival on univariable analysis (\( P = 0.03 \) by log-rank test), but a hazard ratio could not be calculated because all patients with this characteristic were free from...
death or transplantation (Figure 1B). Left ventricular outflow obstruction was not related to the risk of death or transplantation (hazard ratio, 0.68; 95% CI, 0.23 to 1.99). By multivariable analysis, the risk factors for death or transplantation included the presence of concentric left ventricular hypertrophy at presentation (Figure 1C), age/<1 year at diagnosis (Figure 1D), lower initial fractional shortening Z score, and increasing left ventricular posterior wall Z score from presentation. For each of these risk factors, the highest mortality was during the first 12 months after presentation. The 5-year survival for children diagnosed during the first year of life was 76.7% (95% CI, 61.9 to 86.4) compared with 93.2% (95% CI, 75.5 to 98.3) for those diagnosed between 1 and 10 years of age (Figure 1D).

**Relief of Ventricular Outflow Obstruction**

Nineteen subjects (23.8%) have undergone a total of 22 surgical procedures to relieve left and/or right ventricular outflow obstruction. Six surgical procedures involved simultaneous relief of biventricular outflow obstruction, and only 1 subject underwent surgery for isolated right ventricular outflow tract obstruction. The median age at the time of the first surgical procedure was 2.1 years (IQR, 0.61 to 4.3 years) a median of 1.1 years (IQR, 0.36 to 3.9 years) after presentation.

A septal myectomy with or without resection of a subaortic membrane for relief of ventricular outflow obstruction was performed in 18 subjects, 3 of whom underwent a repeated surgical procedure for the same indication at 1.1, 1.5, and 2.9 years after the initial procedure. The commonest indications for septal myectomy included outflow tract obstruction associated with symptoms (congestive heart failure, exercise intolerance) or a large outflow tract gradient that persisted despite therapy with a β-blocker or a calcium channel blocker. Risk factors for first left ventricular myectomy included younger age at presentation, systolic anterior mitral valve motion on the initial echocardiogram, peak instantaneous left ventricular outflow tract gradient on initial echocardiography, and change in peak instantaneous left ventricular outflow tract gradient from presentation. Multivariable analysis provided strong evidence of independent effects of initial peak echocardiographic gradient (hazard ratio per 10-mm Hg gradient, 1.32; 95% CI, 1.17 to 1.5) and change in peak echocardiographic gradient from presentation (hazard ratio per 10-mm Hg increase in peak echocardiographic gradient, 1.32; 95% CI, 1.12 to 1.55). Figure 2 shows the cumulative probability of initial left ventricular myectomy from time of presentation, given that the patient had not died or undergone transplantation by that time. The medians for the peak echocardiographic gradient before surgery and at latest follow-up among 15 subjects in whom both measurements were available were 85 and 15 mm Hg (IQR, 70 to 110 and 0 to 36 mm Hg), respectively (*P*<0.004).

A surgical infundibular resection with or without pulmonary valvuloplasty to relieve right ventricular outflow obstruction was performed in 1 subject.

**Table 2. Survival Analysis of Predictors of Death or Transplantation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample Size, n</th>
<th>Univariable Survival Analysis</th>
<th>Multivariable Survival Analysis (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting age &lt;1 y</td>
<td>80</td>
<td>2.94 (0.83–10) 0.10</td>
<td>6.2 (1.44–26) 0.01</td>
</tr>
<tr>
<td>Congestive heart failure at presentation</td>
<td>80</td>
<td>3.46 (0.97–12) 0.06</td>
<td></td>
</tr>
<tr>
<td>Concentric left ventricular hypertrophy</td>
<td>80</td>
<td>5.4 (1.8–16) 0.002</td>
<td>8.0 (1.33–48) 0.02</td>
</tr>
<tr>
<td>Biventricular involvement</td>
<td>80</td>
<td>4.4 (1.57–12) 0.005</td>
<td></td>
</tr>
<tr>
<td>Familial hypertrophic cardiomyopathy</td>
<td>80</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Parental consanguinity</td>
<td>73</td>
<td>12.5 (2.68–58) 0.001</td>
<td></td>
</tr>
<tr>
<td>Left ventricular posterior wall Z score at presentation</td>
<td>77</td>
<td>1.23 (1.03–1.46) 0.02</td>
<td>1.02 (0.76–1.37) 0.91</td>
</tr>
<tr>
<td>Change in left ventricular posterior wall Z score from presentation</td>
<td>77</td>
<td>1.19 (0.94–1.50) 0.14</td>
<td>1.36 (1.03–1.81) 0.03</td>
</tr>
<tr>
<td>Fractional shortening Z score at presentation</td>
<td>72</td>
<td>1.16 (0.99–1.36) 0.07</td>
<td>1.31 (1.08–1.6) 0.01</td>
</tr>
<tr>
<td>Change in fractional shortening Z score from presentation</td>
<td>72</td>
<td>1.02 (0.89–1.16) 0.79</td>
<td>1.14 (0.99–1.31) 0.06</td>
</tr>
</tbody>
</table>

Only variables that achieved a value of *P*<0.10 are included in the table. For each echocardiographic variable that was included at baseline, the respective time-varying variable was also included in the multivariable model. Probability values were calculated with the log-rank test. *n=80.

*Familial cardiomyopathy was predictive of survival, but a hazard ratio could not be calculated because all patients with this characteristic were free from death or transplant.

†Per unit Z score increase.

‡Per unit (percent fractional shortening or Z score) decrease.
struction was undertaken on 8 occasions in 7 subjects, including 5 with Noonan syndrome.

Additional cardiac interventions in the study cohort included permanent pacemaker implantation in 7 subjects for postsurgical complete heart block (4 cases) or short-interval AV pacing (3 cases), all of whom also underwent septal myectomy. Surgical ligation or transcatheter closure of a patent ductus arteriosus was undertaken in 3 cases; repair of a vascular ring was done in 1 case; and surgical pulmonary valve replacement with closure of an atrial septal defect was performed in 1 case.

Noonan Syndrome
Two of 23 subjects (8.7%) with Noonan syndrome had congestive heart failure at presentation; 8 children (34.8%) had biventricular involvement; and 5 subjects (21.7%) had concentric left ventricular hypertrophy. Three subjects with Noonan syndrome had biventricular involvement with concentric left ventricular hypertrophy. Freedom from death or transplantation was similar for children with and without Noonan syndrome (hazard ratio, 1.65; 95% CI, 0.59 to 4.6). In total, 10 subjects (43.5%) with Noonan syndrome underwent a transcatheter or cardiac surgical intervention to relieve outflow tract obstruction. Balloon pulmonary valvuloplasty for treatment of severe pulmonary valve stenosis was undertaken in 5 subjects, 2 of whom had a subsequent surgical pulmonary valvuloplasty. An additional 5 subjects with Noonan syndrome underwent surgical relief of right and/or left ventricular outflow tract obstruction.

Arrhythmias
Episodes of supraventricular tachycardia were documented in 4 subjects. One of these underwent radiofrequency catheter ablation of a concealed accessory pathway. One subject with Wolff-Parkinson-White syndrome has not experienced any arrhythmia. Four adolescent subjects underwent prophylactic insertion of an implantable cardioverter-defibrillator. The individual indications for implantable cardioverter-defibrillator insertion included an episode of aborted sudden death, recurrent syncpe, easily inducible ventricular fibrillation at electrophysiological study (in the subject with an accessory pathway), and a family history of hypertrophic cardiomyopathy associated with sudden death. None of these subjects has died or undergone transplantation. One subject died suddenly and unexpectedly from a presumed ventricular arrhythmia at the age of 84 months.

At the latest follow-up, 46 of 65 surviving subjects (70.8%) were receiving no regular medication, and the remaining 19 (29.2%) were receiving a β-blocking agent (n = 17), a calcium channel blocker (n = 2), or a diuretic (n = 2). Of the 63 surviving subjects with a known New York Heart Association functional status, 54 (85.7%) had no symptoms (class I), and 9 had symptoms with moderate exercise (class II). Left ventricular outflow tract obstruction with a resting gradient was present in 20 subjects, with a peak echocardiographic gradient of at least 30 mm Hg in 14 cases.

Discussion
Hypertrophic cardiomyopathy has a prevalence of 0.2% among unselected populations. The pattern of left ventricular hypertrophy is variable but typically involves the interventricular septum. In affected adult subjects, left ventricular outflow tract obstruction is present in ≈25% of cases. Inheritance usually follows an autosomal dominant pattern, with about half of all cases representing spontaneous mutations. Almost all the mutations uncovered so far encode for sarcomeric proteins.

Etiological Considerations
The causes of pediatric hypertrophic cardiomyopathy have not been well defined. Sarcomeric protein mutations, particularly those involving the β-myosin heavy chain, may present before adult life. Although most commonly inherited in an autosomal dominant manner, autosomal recessive inheritance has also been described. Metabolic and mitochondrial diseases may become manifest during this time. In the present study, a syndromal, metabolic, or genetic explanation was identified in ≈60% of subjects, including Noonan syndrome in 28.8%. The unexpectedly high incidence of Noonan syndrome may reflect adherence to systematic screening protocols that were in place during the study period, genetic differences within the Australian population, or underreporting in previous studies. Higher-than-expected incidence of patent ductus arteriosus may be attributable to the young age of the study population and the abnormal genetic background of many subjects. Familial hypertrophic cardiomyopathy involving an adult relative was identified in 21.3% of subjects. Although a sarcomeric protein mutation was documented in 2 cases, the origin of familial hypertrophic cardiomyopathy in the youngest subjects remains speculative.

Outcomes
Death or Transplantation
Pediatric institutional reviews have suggested a high mortality for hypertrophic cardiomyopathy diagnosed during infancy and childhood. An annual mortality of ≈5% has been reported in some series, with overall mortality rates exceeding 50% for subjects presenting during infancy. Population-based studies in adults have demonstrated annual mortality rates of ≈1%, but comparable data have been lacking for children with hypertrophic cardiomyopathy. The National Australian Childhood Cardiomyopathy Study is the largest population-based study of pediatric cardiomyopathy. Recruitment of subjects from multiple sources, including pediatric cardiologists, regional pediatricians, and adult physicians caring for children, minimized the possibility of referral bias, which may have skewed outcomes among study subjects. The highest mortality for subjects with identifiable risk factors was during the first 12 months after diagnosis. Despite the young age of the study population, the average annual mortality for all subjects was ≈3.4% and 1.5% for subjects diagnosed after the first year of life. This compares to an all-cause average annual mortality rate for children 1 to 9 years of age in the general Australian population of <0.5 per 1000 at-risk population since the beginning of the study period. Our study demonstrates that mortality among children with hypertrophic cardiomyopathy is better than previously reported.
The morphological, clinical, and genetic heterogeneity of familial hypertrophic cardiomyopathy complicates risk stratification. Proposed risk factors for sudden death in adults with familial hypertrophic cardiomyopathy include prior cardiac arrest or a family history of sudden death,21 spontaneous sustained ventricular tachycardia,1,16,24,25 exercise-induced hypotension,1,23 repetitive syncope,26 and some high-risk genotypes.1 Several studies have identified a maximal left ventricular wall thickness >30 mm as a risk factor for sudden death,27,28 although the predictive value of this factor in isolation is low.28,29 Recently, left ventricular outflow tract obstruction with a peak gradient >30 mm Hg has been linked to both death and symptom progression among older subjects.30 Specific risk factors identified in pediatric reviews include congestive heart failure17 and increasing left ventricular posterior wall thickness.19 There are conflicting data for other proposed risk factors, including the presence of coronary myocardial bridging.31,32

In the present study, familial hypertrophic cardiomyopathy conferred an obvious survival benefit, although a hazard ratio could not be calculated because all subjects with familial cardiomyopathy survived. Conversely, earlier age at diagnosis and concentric left ventricular hypertrophy were associated with an increased rate of death or transplantation. Concentric left ventricular hypertrophy was also associated with right ventricular involvement. These observations suggest that nonsarcoid childhood hypertrophic cardiomyopathy is characterized by earlier and more diffuse cardiac hypertrophy, with worse outcomes for the most severely affected subjects. Other variables associated with a poor outcome included the severity of left ventricular systolic dysfunction and the magnitude of left ventricular hypertrophy relative to body surface area. Similar preliminary findings have been reported from the North American Pediatric Cardiomyopathy Registry.

Sudden cardiac death was uncommon as a presenting feature or during follow-up in this study population, whereas congestive heart failure was by far the commonest mode of death. Although serial echocardiographic assessment of diastolic function was unavailable for many subjects, diastolic dysfunction and/or minor decreases in systolic function may have a disproportionate effect on symptoms and survival in the setting of considerable cardiac hypertrophy. A longer follow-up in similar study cohorts is required to determine the incidence and risk factors for sudden death.

Surgery
Ventricular outflow tract obstruction was common and was not related to death or transplantation. In adults with hypertrophic cardiomyopathy, surgical relief of left ventricular outflow obstruction has been shown to be safe and effective in reducing symptoms.23,34 In the present study, the indications for surgical relief of left and/or right ventricular outflow obstruction were variable but usually centered around symptoms or the presence of a large gradient that was refractory to medical therapy. As in other reported pediatric series, there was a significant reduction in the gradient, and surgical mortality was low.35,36 However, the benefit of left ventricular myectomy in young patients is still unclear.

Study Limitations
Variable diagnostic protocols and limitations in existing knowledge have restricted the proportion of study subjects with cardiomyopathy of known origin. In addition, the inclusion age limited the number of subjects with potential sarcomeric protein mutations. However, the proportion of subjects with a known cause remains high compared with other published pediatric studies. The results of the present study cannot be extrapolated to children who have not yet developed overt cardiac hypertrophy. The duration of follow-up in this young study cohort was insufficient to determine the ongoing risk of late sudden death.

Conclusions
Childhood hypertrophic cardiomyopathy is characterized by early onset, and ventricular outflow tract obstruction is common. Syndromal, genetic, and metabolic causes account for most identifiable causes. Sudden death is an uncommon presenting symptom during the first decade of life. The mortality among subjects diagnosed beyond infancy is comparable to that of adult subjects, and the clinical status of long-term survivors is good. This population-based study identifies children with hypertrophic cardiomyopathy who are at risk of adverse events.

Acknowledgments
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References


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