

FOCUS ISSUE: HYPERTROPHIC CARDIOMYOPATHY

Risk Factors and Mode of Death in Isolated Hypertrophic Cardiomyopathy in Children

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Objectives	This study was designed to review outcomes of pediatric isolated hypertrophic cardiomyopathy (HCM) managed uniformly at a single institution and assess whether reported adult risk factors for sudden death are predictive in pediatric HCM.
Background	Cardiac death in HCM occurs suddenly (SCD) or may be nonsudden (non-SCD). Little data exists on non-SCD in children. Risk factors for SCD in adult HCM are characterized and consensus management strategies detailed. Their application to children is uncertain and treatment strategies vary.
Methods	A retrospective cohort study of children with HCM was performed. Primary end points were cardiac death and transplantation. Frequency and outcomes of known adult risk factors were assessed. Outcomes analysis was performed using Kaplan-Meier curves and Cox regression analysis.
Results	Ninety-six patients were included. The average age at diagnosis was 10.6 ± 5.4 years, and mean follow-up was 6.4 ± 5.2 years. Primary end points occurred in 11 patients over the 20-year follow-up (11%), 4 underwent cardiac transplant and 7 died (3 suddenly). Extreme left ventricular hypertrophy (z-score: >6) and an abnormal blood pressure response to exercise were predictive of non-SCD ($p < 0.02$ and $p < 0.03$, respectively). Kaplan-Meier survival analysis predicts an 82% survival over a 20-year period.
Conclusions	In children with isolated HCM managed primarily with exercise restriction and medication, cardiac death occurred infrequently. Non-SCD or transplant was at least as common as SCD. Extreme left ventricular hypertrophy and blunted blood pressure response to exercise were associated with an increased risk of non-SCD. (J Am Coll Cardiol 2009;54:250-4) © 2009 by the American College of Cardiology Foundation

Patients with hypertrophic cardiomyopathy (HCM) are at risk of death, in the form of sudden cardiac death (SCD) or progressive heart failure (non-SCD). Previous studies have reported that children with HCM have up to a 6% annual mortality rate (1), although more recent data suggest the mortality rate is closer to 1% (2,3).

Risk factors for SCD have been identified in large cohorts of adult patients with HCM (4). Although several studies have attempted to risk-stratify children with HCM by identifying clinical and laboratory risk factors (3-8), most have not been validated. Even less data exist as to risk factors for the development of end-stage systolic and/or

diastolic heart failure in isolated pediatric HCM. Once systolic dysfunction is noted, progression to end-stage heart failure and death occurs rapidly (9). As limited data are available to identify pediatric patients with HCM at risk for cardiac death, current treatment strategies are often based on reported risk factors for SCD in adults. As a result, no consensus on the management of pediatric patients exists.

The purpose of this study was to review the clinical characteristics and outcomes of our pediatric population with isolated HCM who have been managed in a standard manner and to determine whether reported adult risk factors for SCD are predictive of outcome in these affected children. In addition, we assessed progression to death and transplant to determine if any other risk factors for cardiac death could be identified.

Methods

Study patients. A retrospective review of patients between January 1, 1985, and November 1, 2006, with the diagnosis of HCM was performed through our institutional database,

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Manuscript received January 29, 2009; revised manuscript received March 16, 2009, accepted March 24, 2009.

including patients enrolled from our institution in the National Institutes of Health–supported PCMR (Pediatric Cardiomyopathy Registry) database (2). Criteria for inclusion in the study were age <18 years at the time of diagnosis and echocardiographic evidence of either concentric left ventricular hypertrophy or asymmetric septal hypertrophy (defined as a diastolic septal thickness or left ventricular diastolic wall thickness z-score >2) with no other cause. This study was approved by the Baylor College of Medicine institutional review board. Individual consent was waived.

Echocardiography. Two-dimensional, Doppler, and M-mode echocardiography was performed at rest using standard methods. Left ventricular outflow tract obstruction was defined as a peak resting gradient ≥ 16 mm Hg (peak velocity ≥ 2 m/s). All studies were read by a pediatric cardiologist.

Data collection. Demographic information and the reported adult risk factors for sudden death (4), including extreme left ventricular hypertrophy, abnormal blood pressure response to exercise, history of prior cardiac arrest or sustained ventricular tachycardia, documented nonsustained ventricular tachycardia, non-neurocardiogenic syncope, and a family history of HCM with associated sudden death were collected. In addition, left ventricular posterior wall and septal echocardiographic measurements, degree of left ventricular outflow tract obstruction, exercise stress testing results,

Holter results, clinical symptoms, and treatment strategies, including medications prescribed, pacemaker or implantable cardioverter-defibrillator (ICD) placement, septal myectomy, and cardiac transplantation were also collected.

Exercise testing. Exercise testing was performed on a Marquette pediatric treadmill (Marquette Electronics, Milwaukee, Wisconsin), using a standard or modified Bruce protocol. Blood pressure measurements were recorded with a manual sphygmomanometer in the upper extremities during testing. An abnormal blood pressure response to exercise was defined as either a hypotensive response or a minimal increase in the systolic blood pressure to increased workload compared with baseline (<20 mm Hg). Continuous electrocardiograms were recorded in all cases. Peak oxygen consumption was measured when possible.

Management algorithm. Patients diagnosed with HCM were evaluated in the Cardiomyopathy Clinic. The management strategy is outlined in Figure 1. Some patients had multiple clinical characteristics that fell into more than 1 category in the management algorithm.

Abbreviations and Acronyms

- HCM** = hypertrophic cardiomyopathy
- ICD** = implantable cardioverter-defibrillator
- RSCD** = resuscitated sudden cardiac death
- SCD** = sudden cardiac death

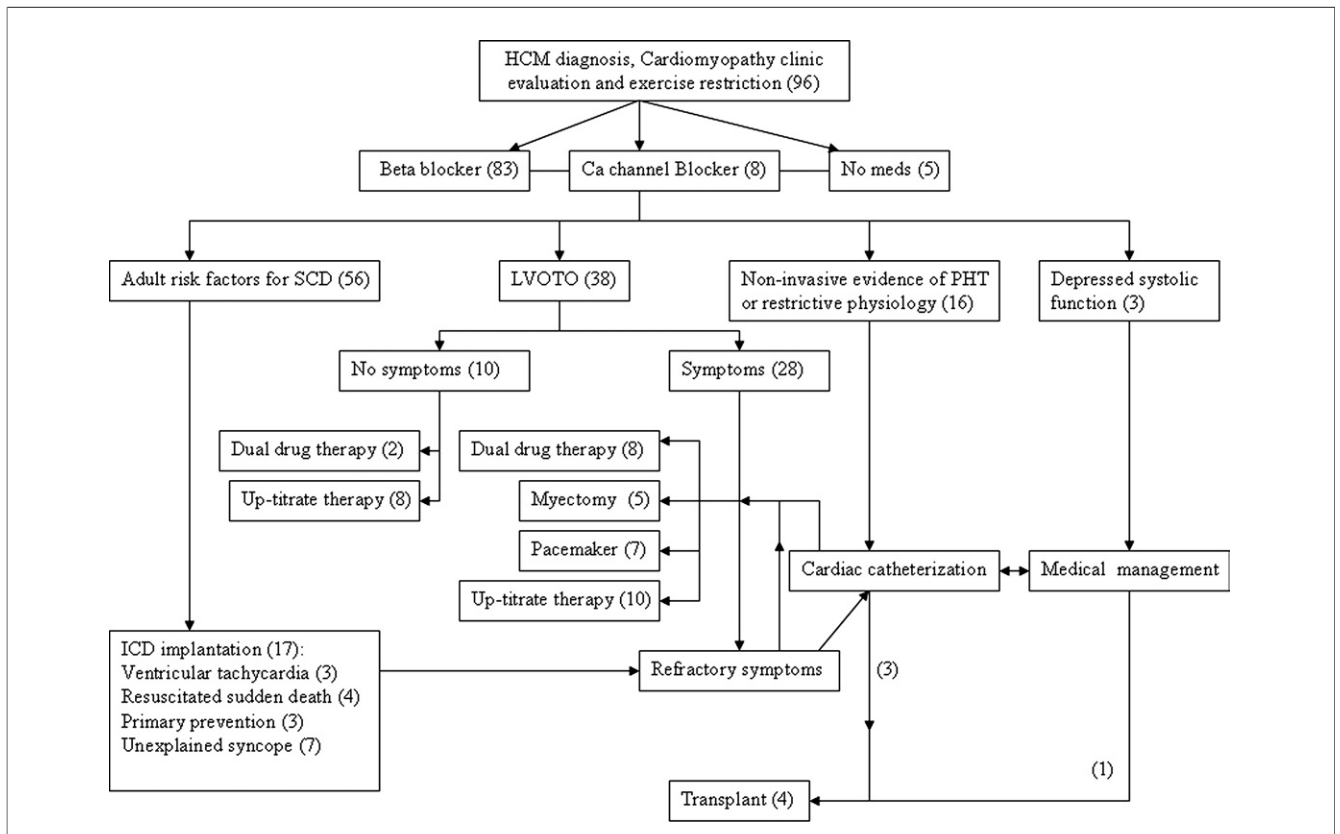


Figure 1. Texas Children's Hospital Management Algorithm for HCM

Schematic approach to treatment of pediatric hypertrophic cardiomyopathy (HCM). ICD = implantable cardioverter-defibrillator; LVOTO = left ventricular outflow tract obstruction; PHT = pulmonary hypertension; SCD = sudden cardiac death.

Statistics. Death and cardiac transplantation were the primary end points. Statistical analysis was performed using SPSS for Windows version 16.0 (SPSS, Inc., Chicago, Illinois). Clinical variables were converted into groups and univariate analysis using the log-rank test was performed. Kaplan–Meier survival curves were generated. Individual z-score measurements were run in Kaplan–Meier survival analysis to determine a statistically significant z-score. Cox regression analysis was used to perform univariate analysis. Baseline data were reported as a mean ± 2 SD, or a median with an interquartile range. Statistical significance was taken as $p \leq 0.05$. No adjustments were made for a type I error.

Table 1 Patient Characteristics

Demographic data, n (%)	
Female	30 (31)
Caucasian	51 (53)
Hispanic	22 (23)
African American	17 (18)
Age at diagnosis	
Cohort mean, yrs, ± 2 SD	10.6 ± 5.4
Cohort median, yrs (IQR)	12.2 (7.8–14.8)
Age ≤1 yr, n (%)	10 (10)
Age >1 and ≤5 yrs, n (%)	8 (8)
Age >5 and ≤10 yrs, n (%)	19 (20)
Age >10 and ≤18 yrs, n (%)	59 (62)
Family history, n (%)	
HCM	41 (43)
HCM-related sudden death	16 (17)
Presenting sign/symptom, n (%)	
Murmur	43 (45)
Family history of HCM	18 (19)
Syncope/near-syncope	9 (9)
Chest pain	7 (7)
Dyspnea on exertion	4 (4)
Resuscitated sudden death	4 (4)
Palpitations	1 (1)
Heart failure	1 (1)
Follow-up, yrs	
Mean ± 2 SD	6.4 ± 5.2
Median (IQR)	5 (1 month to 24 yrs)
Death/cardiac transplant, n (%)	
	11 (11)
Echocardiographic data	
Left ventricular morphology, n (%)	
Asymmetric septal hypertrophy	68 (71)
Concentric left ventricular hypertrophy	28 (29)
Septal wall z-score in diastole	
Mean ± 2 SD	4.2 ± 2.3
Median (IQR)	4.3 (2.5–5.9)
Posterior wall z-score in diastole	
Mean ± 2 SD	2.2 ± 2.6
Median (IQR)	2.2 (0.5–3.7)
Fractional shortening (n = 90)*	
Mean ± 2 SD	46 ± 8.8
Median (IQR)	45 (40–51)

*Quantitative echocardiographic functional analysis not available in all patients.
HCM = hypertrophic cardiomyopathy; IQR = interquartile range.

Table 2 Prevalence of Adult Risk Factors of Sudden Death

Risk Factor (Overall % of Patients)	Survivor (n = 85)	Death/Transplant (n = 11)	p Value*
Syncope (18%)	14	3	0.57
Family history of premature HCM-related death (22%)	20	1	0.35
Nonsustained VT (10%)	9	1	0.76
Prior cardiac arrest (6%)	6	1	0.92
Extreme LVH (z-score >6) (24%)	17	6	<0.04
Left ventricular outflow tract obstruction (40%)	35	3	0.35
Inappropriate BP response to exercise (20%)†	16	3	<0.03

*Log-rank test; †58% of total patients underwent exercise testing.
BP = blood pressure; HCM = hypertrophic cardiomyopathy; LVH = left ventricular hypertrophy;
VT = ventricular tachycardia.

Results

A total of 426 patients were diagnosed with hypertrophic cardiomyopathy between January 1, 1985, and November 1, 2006. Ninety-six patients met inclusion criteria for isolated HCM. Clinical characteristics of the patient population are listed in Table 1. Sixteen patients had a hemodynamic assessment in the cardiac catheterization laboratory due to noninvasive assessments suggesting restrictive physiology or pulmonary hypertension. Eight of these patients had pulmonary hypertension (average pulmonary artery mean pressure: 34.1 ± 8.4 mm Hg), all of whom had an elevated end-diastolic ventricular pressure consistent with restrictive physiology (average: 23 ± 7.3 mm Hg). Three patients had an elevated end-diastolic ventricular pressure (average end-diastolic ventricular pressure: 21.3 ± 6.1 mm Hg) without pulmonary hypertension.

Symptoms. One patient presented with symptomatic heart failure due to systolic dysfunction. The reason for the diagnostic echocardiogram in the other patients is listed in Table 1. The presenting symptom was not documented in the medical record in 9 (9%) patients. Twenty-seven patients (28%) remained asymptomatic throughout follow-up. The remaining 69 patients complained of chest pain, fatigue, dyspnea on exertion, palpitations, or a combination of these during follow-up. No single symptom or constellation of symptoms was a risk factor for cardiac death.

Adult risk factors for SCD. The frequency of reported adult risk factors for SCD is summarized in Table 2. No single or multiple risk factors were predictive of SCD. However, a left ventricular wall thickness z-score >6 and an abnormal response to exercise were predictive of non-SCD. **Arrhythmias.** Seventeen patients had arrhythmias. Five children had atrial tachyarrhythmias and 12 had ventricular tachyarrhythmias. The presence of any arrhythmias, including nonsustained ventricular tachycardia on Holter monitor was not significant for cardiac death.

Resuscitated sudden cardiac death (RSCD). Of the 7 patients with an RSCD event, the average age at diagnosis of HCM was 10.3 ± 4.9 years. The rhythm at the time of the arrest was documented in 4 patients, 2 of whom had ventric-

ular tachycardia and 1 had ventricular fibrillation. One patient with an ICD discharge had ventricular tachycardia. This was the presenting symptom in 4 patients. The 3 patients with a prior diagnosis of HCM were engaged in restricted physical activity at the time of the arrest. The average septal diastolic wall thickness z-score of this group was 4.9 ± 3.8 and the average posterior wall thickness z-score was 2.19 ± 1.5 .

Echocardiographic analysis. The echocardiographic characteristics of the patient population are summarized in Table 1. Twenty-three patients (27%) had severe hypertrophy with a diastolic left ventricular posterior wall or diastolic septal wall thickness z-score >6 . This included 2 patients who underwent heart transplantation and 4 who died. A left ventricular diastolic wall thickness z-score >6 predicted cardiac death ($p < 0.02$) (Fig. 2A). The calculated hazard ratio of cardiac death was 3.8 (95% confidence interval: 1.1 to 12.5). Two patients who died had qualitatively severely depressed left ventricular systolic function. One additional patient had depressed systolic function before transplantation. The presence, degree, or absence of left ventricular outflow tract obstruction did not predict cardiac death.

Exercise testing. Fifty-six patients had at least 1 exercise treadmill test. Nineteen (34%) had an abnormal blood pressure response to exercise. Of those undergoing exercise testing, 48 (86%) were on beta-blockers and 5 (9%) were on calcium-channel blocker therapy, comprising 95% of those tested. Despite these medications, 37 (66%) had a normal blood pressure response to exercise. An abnormal blood pressure response to exercise was a risk factor for cardiac death ($p < 0.03$) (Fig. 2B). The calculated hazard ratio for cardiac death if there was an abnormal blood pressure response to exercise was 9.6 (95% confidence interval: 1.0 to 93.7).

ICDs. Seventeen patients received ICDs (Fig. 1). The mean follow-up time after implantation was 3.6 ± 2.1 years. One patient, who had an ICD placed for a history of ventricular

tachycardia and syncope, had 2 appropriate discharges for ventricular tachycardia and 2 inappropriate discharges for atrial tachycardia/fibrillation. This patient was not included in the end point analysis as this patient was conscious and this was considered the same as an RSCD event. Two other patients underwent cardiac transplantation after ICD placement due to persistent heart failure symptoms.

Outcomes. Over the 21-year period, there were 11 cardiac deaths, which consisted of 7 deaths and 4 cardiac transplantations. Of the patient deaths, 3 had sudden cardiac death and 3 had non-SCD (2 from systolic heart failure, 1 from a massive stroke). One cause of death was unknown. Of the transplanted patients, 3 (75%) had elevated end-diastolic pressures and 2 had pulmonary hypertension measured by cardiac catheterization. All had intractable heart failure symptoms, most commonly chest pain, fatigue, and dyspnea on exertion. One patient had systolic dysfunction at the time of transplantation. Kaplan-Meier survival analysis shows an 82% survival for the entire group at 21 years (Fig. 3).

Discussion

Predicting which patients with HCM are at greatest risk of sudden cardiac death has been the major focus of investigation in adults and children. Risk factors in adult studies are well described. Studies have been inconsistent in children, which may reflect the varying etiologies of HCM (2,3,5,7,8), as well as the low incidence of cardiac death (2), also noted in this study. Prior studies have documented the importance of non-SCD in infants <1 year of age (2). However, in older children, other modes of death are not well documented. In this study, non-SCD was more common than SCD in children. Therefore, although none of the previously identified adult risk factors predicted SCD in our pediatric cohort, the identification of risk factors for non-SCD is at least as important in children as identifying risk factors for SCD.

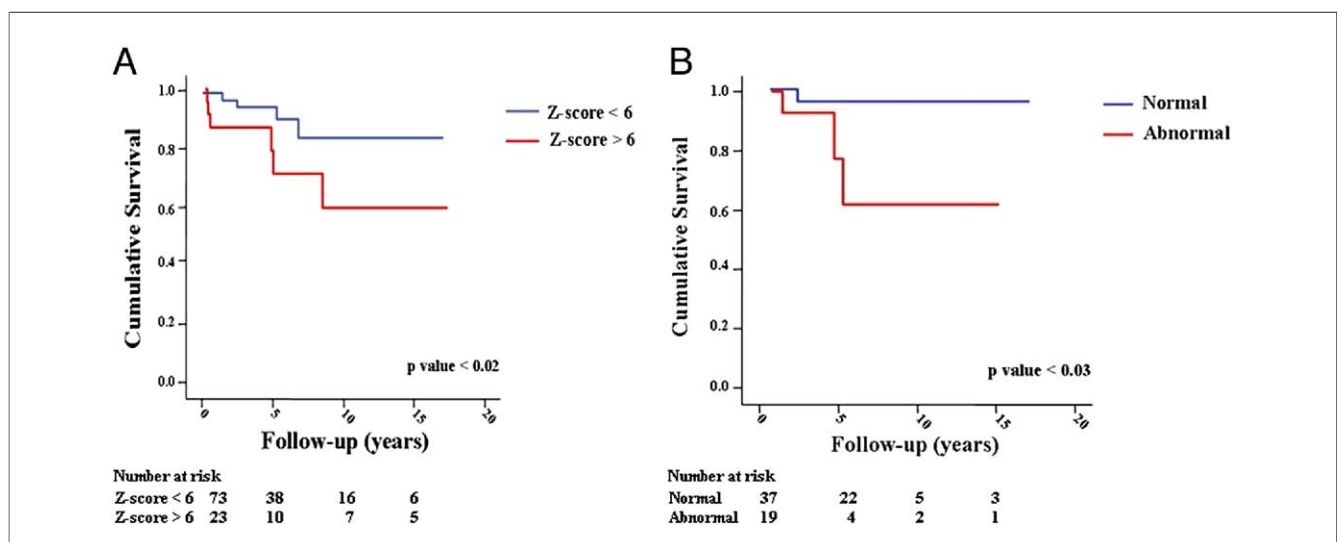
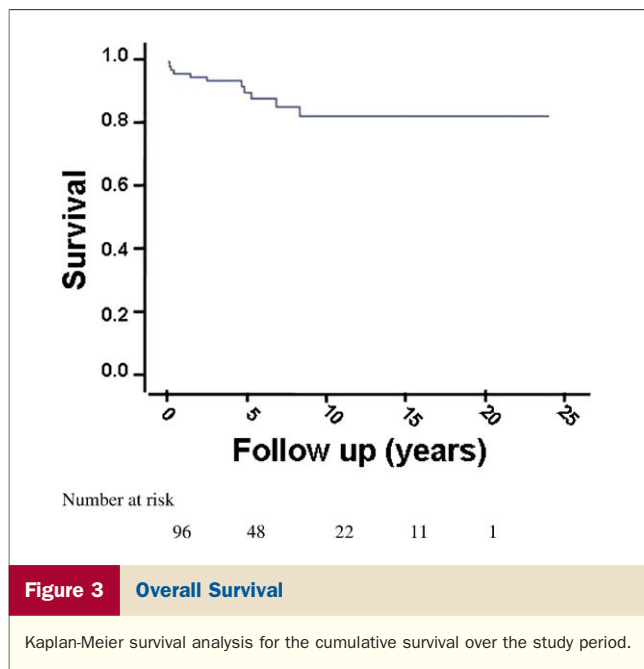


Figure 2 Risk Factors for Cardiac Death

Kaplan-Meier survival analysis for left ventricular wall thickness (A) and blood pressure response to exercise (B).



One risk factor was extreme left ventricular hypertrophy, which is defined in adult studies as an absolute left ventricular wall thickness of 30 mm (4). Absolute values in children are not as useful due to changing body surface area. This study is the first to show a significant association between left ventricular wall thickness indexed to body surface area, defined as a z-score >6, and premature death or transplantation in children with isolated HCM.

The second risk factor predictive of cardiac death in children was an abnormal blood pressure response to exercise. Although the majority of children were on a potentially blood pressure-lowering agent, 66% still maintained a normal blood pressure response. Children with a blunted blood pressure response to exercise or a hypotensive response to exercise had a higher incidence of cardiac death.

Although both of these risk factors were predictive of cardiac death, neither was associated with SCD. This may be due to the small number of sudden deaths in our population, but it may also be due to the fact that SCD or RSCD is often a presenting symptom in children. In the 7 patients with RSCD, the event was the presenting symptom for 4. Three patients had an RSCD event after the diagnosis of HCM was made. All of these patients were noncompliant, engaging in some form of physical activity at the time of cardiac arrest. The low incidence of SCD seen in this study is similar to that recently reported in the PCMR (2). The reason for the lower incidence of sudden death in the multicenter PCMR cohort is unknown, because management approaches and patient compliance could not be addressed. In our study, the low incidence of SCD after diagnosis may be, in part, secondary to the management strategy of exercise restriction and beta-blockade for virtually all patients, starting at the time of diagnosis, with further treatment based on symptoms and the presence of potential risk factors for sudden cardiac death.

Study limitations. This study is a retrospective survival analysis and has limitations intrinsic to such an analysis. There were a low number of cardiac deaths, and therefore the study may not be powered to detect all risk factors. In addition, the number of patients who underwent catheterization was not enough for statistical analysis. The number of end points was also small and limited valid multivariate analysis. Controlled exercise testing is not possible in young children and infants, and a blunted blood pressure response to exercise can be normal in pre-pubescent children, making interpretation of such data in these patients difficult.

Conclusions

Patients managed with our treatment algorithm demonstrated >80% survival over 20 years of follow-up. Cardiac death was at least as likely to be from non-SCD as SCD. Therefore, the ability to predict non-SCD is as important as the ability to predict SCD. A left ventricular wall thickness z-score >6 and an abnormal blood pressure response to exercise were found to be risk factors for non-SCD and therefore warrant close follow-up and further study in a large multicenter cohort.

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Key Words: pediatrics ■ hypertrophy ■ cardiomyopathy ■ ventricular tachycardia ■ sudden cardiac death ■ implantable cardioverter-defibrillator.