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Epidemiology and Cause-Specific Outcome of Hypertrophic Cardiomyopathy in Children

Findings From the Pediatric Cardiomyopathy Registry

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Background—Current information on the epidemiology and outcomes of hypertrophic cardiomyopathy (HCM) in children is limited by disease diversity and small case series.

Methods and Results—The Pediatric Cardiomyopathy Registry has collected prospective and retrospective data on children diagnosed with HCM since 1990. We identified the various causes of HCM in childhood and determined the relationship between outcomes, cause, and age at presentation. Of 855 patients <18 years of age with HCM, 8.7% (n=74) had inborn errors of metabolism, 9.0% (n=77) had malformation syndromes, 7.5% (n=64) had neuromuscular disorders, and 74.2% (n=634) had idiopathic HCM. Children with HCM associated with inborn errors of metabolism and malformation syndromes have significantly worse survival than the other 2 groups. Patients with idiopathic HCM diagnosed before 1 year of age (n=227) had worse survival from the time of diagnosis than those diagnosed after 1 year of age (n=407). Patients with idiopathic HCM who survived to at least 1 year of age, however, had an annual mortality rate of 1% that was similar regardless of whether they were diagnosed before or after 1 year of age.

Conclusions—In children, HCM is a diverse disorder with outcomes that depend largely on cause and age. Patients presenting before 1 year of age have the broadest spectrum of causes and the poorest outcome. In those children with idiopathic HCM who survive beyond age 1, however, survival is independent of age at diagnosis, with an annual mortality rate (1%) that is much lower than previously reported in children and is not different from has been found in population-based studies in adults. **(*Circulation*. 2007;115:000-000.)**

Key Words: cardiomyopathy ■ death, sudden ■ heart diseases ■ heart failure ■ hypertrophy ■ pediatrics ■ survival

The Pediatric Cardiomyopathy Registry (PCMR) was initiated in 1994 to study the epidemiology and clinical course of cardiomyopathies in children.[1] Regardless of cause, the cardiomyopathies are generally categorized according to the dominant pathophysiology as dilated, hypertrophic, restrictive, or arrhythmogenic right ventricular dysplasia. Despite the limitations of this purely descriptive nomenclature, it is used by most pediatric cardiologists because it provides a clinically useful framework,[2] and for this reason, it was adopted by the PCMR.

Clinical Perspective p ●●●

The clinical hallmark of hypertrophic cardiomyopathy (HCM) is ventricular hypertrophy without an identifiable hemodynamic cause. This phenotype represents a heterogeneous group of disorders, and this diversity is most apparent in childhood. Results of molecular studies conducted in adults with familial isolated HCM have implicated sarcomeric protein defects in a high percentage of patients, leading some investigators to suggest that use of the term HCM should be restricted to only patients with documented or suspected sarcomeric defects.[3] This convention has not been adopted in pediatric cardiology, in which the overwhelming majority of cases are genetically uncharacterized and most cases are not familial. Even in adults, systematic screening for sarcomeric defects accounts for only 40% to 60% of cases,[4–6] and cause other than nonsarcomeric defects has been increasingly rec-

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TABLE 1. Annual Incidence of Pure HCM

	Annual Incidence (or Estimated Range) of Pediatric HCM per 1 000 000 Children*								
	Region		Sex		Race			Age Group	
	New England (N=96)	Central Southwest (N=150)	Boys (N=158)	Girls (N=88)	White (N=157)	Black (N=33)	Hispanic (N=46)	<1 y (N=87)	1 to <18 y (N=159)
Overall	5.9	4.2†	5.9	3.4‡	3.6 to 4.9	5.3 to 5.7	3.6 to 198.0	30.0	3.2‡
95% CI	4.8 to 7.2	3.5 to 4.9	5.0 to 6.9	2.8 to 4.2	…	…	…	24.0 to 37.0	2.7 to 3.8
95% CI for lower estimate	…	…	…	…	3.0 to 4.2	3.6 to 7.4	2.6 to 4.8	…	…
95% CI for upper estimate	…	…	…	…	4.2 to 5.8	3.9 to 8.0	144.9 to 267.0	…	…
By region									
New England	…	…	7.8	3.9	5.2 to 5.7	5.3 to 6.4	7.7 to 292.7	…	…
Central Southwest	…	…	5.0	3.2	2.8 to 4.4	5.3 to 5.5	3.1 to 179.7	…	…
By sex									
Boys	…	…	…	…	4.4 to 6.1	6.6 to 7.1	4.4 to 246.2	…	…
Girls	…	…	…	…	2.7 to 3.7	3.9 to 4.2	2.7 to 148.4	…	…
By race									
White	…	…	…	…	…	…	…	19.2 to 28.6	2.7 to 3.6
Black	…	…	…	…	…	…	…	39.6 to 43.9	3.4 to 3.6
Hispanic	…	…	…	…	…	…	…	27.2 to 1776.7	1.9 to 104.8

*Data are from 246 children in the prospective cohort of the PCMR.
†$P=0.009$; ‡$P<0.001$.

ognized.[3,7–9] We have therefore used the term HCM to imply phenotype and used the system of classification that has been recommended in the 2 systematic published nomenclatures in pediatric heart disease.[10,11] The present article reports the PCMR data for epidemiology and outcome in HCM, including its primary (isolated) and secondary (systemic) forms.

Methods

The PCMR study design and implementation are described in detail elsewhere.[1,12] In brief, patients <18 years of age newly diagnosed with cardiomyopathy are eligible for inclusion in the registry. Diagnosis of HCM is based on the finding of regional or global left ventricular hypertrophy based on strict criteria (wall thickness >2 SD above the normal population mean for body surface area[1]) in the absence of a defined hemodynamic cause such as hypertension, congenital heart disease, or exposure to drugs known to cause cardiac hypertrophy. Patients with normal systolic ventricular function (defined as above the lower limits of normal for age[1]) were classified as "pure" HCM; patients with depressed ventricular function were defined as having a "mixed" form of cardiomyopathy. We report in the present study only the data for patients with pure HCM.

Data are collected in 2 ways. First, 98 private and institutional centers in the United States and Canada voluntarily submit data to the registry.[1] In addition, 2 geographic regions were targeted for comprehensive patient recruitment: the central Southwest (Arkansas, Oklahoma, and Texas) and New England (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont). Data in these regions are collected by an outreach team that regularly travels to the participating centers, enrolling new cases and abstracting relevant data from medical records.

Patients fall into 2 cohorts. The prospective cohort consists of patients diagnosed on or after January 1, 1996. Within the 2 geographic regions, the goal is to identify all children with cardiomyopathy. The retrospective cohort comprises patients with cardiomyopathy who were first diagnosed on or after January 1, 1990, but before 1996. The retrospective nature of enrollment in this group precludes assurance of complete capture, but the observation period is longer. Follow-up data are available up to February 25, 2003.

Details of the data collection methods for the PCMR have been previously published.[1] Collected data include demographic descriptors and all information relevant to the cardiomyopathy, including personal history, family history, clinical data, laboratory data, and outcome. Patients in whom no specific origin had been established were classified as idiopathic HCM (IHCM; n=634) and for purposes

TABLE 2. Annual Incidence of IHCM

	Annual Incidence (or Estimated Range) of IHCM per 1 000 000 Children*								
	Region		Sex		Race			Age Group	
	New England (N=73)	Central Southwest (N=117)	Boys (N=127)	Girls (N=63)	White (N=122)	Black (N=26)	Hispanic (N=35)	<1 y (N=63)	1 to <18 y (N=127)
Overall	4.5	3.2	4.7	2.5†	2.8 to 3.8	4.1 to 4.5	2.7 to 150.6	21.7	2.6†
95% CI	3.5 to 5.7	2.7 to 3.9	3.9 to 5.6	1.9 to 3.2				16.7 to 27.8	2.1 to 3.1
95% CI for lower estimate					2.3 to 3.3	2.7 to 6.1	1.9 to 3.8		
95% CI for upper estimate					3.2 to 4.6	2.9 to 6.6	104.9 to 209.4		

*Data are from 190 children in the prospective cohort of the PCMR.
†$P<0.001$.

TABLE 3. Characteristics at Diagnosis of Pure HCM by Cause of Disease

	Types of HCM				
	IEM (n=74)	MFS (n=77)	NMD (n=64)	IHCM (n=634)	Pairwise $P \leq 0.01$
Description of population at diagnosis of HCM*					
Prospective cohort, % ($P=0.003$)	50.0	61.0	50.0	67.0	1/3 vs 4
Male sex, % ($P=0.044$)	63.5	54.6	57.8	68.3	NS
Age at diagnosis, % (MH $P<0.001$)					
<1 y	64.9	64.9	4.7	35.8	1 vs 3/4
1 to <6 y	20.3	18.2	10.9	12.3	2 vs 3/4
6 to <12 y	8.1	13.0	51.6	18.3	3 vs 4
12 to <18 y	6.8	3.9	32.8	33.6	...
Median age at diagnosis, y (Q1, Q3) ($P<0.001$)	0.42 (0.23, 2.61)	0.41 (0.03, 2.05)	10.10 (7.56, 13.75)	7.07 (0.28, 13.17)	1 vs 3/4
	...	...	...	...	2 vs 3/4
	...	...	...	...	3 vs 4
Race, % ($P=0.003$)					
White	64.4	65.3	93.7	69.8	1/2 vs 3
Black	16.4	10.7	1.6	12.1	3 vs 4
Hispanic	12.3	18.7	4.8	14.0	...
Other	6.9	5.3	0.0	4.0	...
CHF present at diagnosis, % ($P<0.001$)	40.3	23.4	6.4	9.9	1 vs 3/4
	...	...	...	...	2 vs 0.3/4
Echocardiographic data at diagnosis of HCM*					
Echocardiography done, % ($P=0.526$)	96.0	93.5	98.4	96.1	NS
Median septal thickness to free wall thickness ratio ($P<0.001$)	1.00	1.23	1.08	1.42	1/3 vs 4
Q1, Q3	0.92, 1.24	1.00, 1.67	1.00, 1.30	1.04, 2.00	...
n	56	53	55	509	...
Median free wall thickness to EDD ratio ($P=0.013$)	0.31	0.31	0.30	0.27	No significant pairwise
Q1, Q3	0.23, 0.42	0.25, 0.38	0.27, 0.36	0.21, 0.36	...
n	57	53	54	483	...
EDD z score ($P<0.001$)	0.08±3.05	−3.01±2.39	−1.14±1.60	−1.80±2.21	1 vs 2/3/4
n†	53	45	52	445	2 vs 0.3/4
	...	...	...	...	3 vs 4
Fractional shortening z score ($P<0.001$)	−1.11±5.65	5.42±4.31	3.01±3.40	3.62±5.15	1 vs 2/3/4
n†	59	48	57	480	2 vs 3
Free wall thickness z score ($P<0.001$)	4.06±3.52	1.67±2.49	3.21±1.77	1.80±2.89	1 vs 2/4
n†	55	50	53	470	2 vs 3
	...	...	...	...	3 vs 4
Septal thickness z score ($P=0.017$)	3.01±2.83	2.38±2.26	2.92±1.59	3.44±2.54	NS
n†	50	49	51	475	...
LV mass z score ($P<0.001$)	3.55±3.37	0.14±2.75	2.33±1.94	1.87±2.56	1 vs 2/4
n†	53	48	49	440	2 vs 3/4

MH indicates Mantel-Haenszel test for linear trend; EDD, end-diastolic dimension; and LV, left ventricular. Data are from 849 children in the combined retrospective and prospective cohorts of the PCMR.

*Probability values included with characteristic name are for the comparisons of IEM vs MFS vs NMD vs IHCM.

†All echocardiographic z scores in all causal groups have been tested for statistical difference from normal (z score=0). Only the following echocardiographic z scores were not statistically different from normal ($P>0.01$): for IEM, EDD z score and fractional shortening z score; for MFS, LV mass z score.

of analysis were subclassified according to age at diagnosis into infantile IHCM (IHCM <1YR; n=227) for patients <1 year of age at diagnosis and noninfantile IHCM (IHCM ≥1YR; n=407) for older patients. Patients with known cause were grouped into inborn errors of metabolism (IEM; n=74), malformation syndromes (MFS; n=77), or neuromuscular disorders (NMD; n=64). Patients with a first-degree relative with HCM were defined as familial isolated HCM. As discussed above, although adult patients with familial HCM often are presumed to have sarcomeric gene defects, this association has been documented in only a tiny fraction of the pediatric population with familial HCM. Therefore, 109 patients with familial isolated HCM who did not have a confirmed gene defect were considered idiopathic for purposes of analysis. Six patients who had a defect in cardiac myosin β-heavy chain and are members of the familial isolated cardiomyopathy group are excluded from the IHCM group.

TABLE 4. Characteristics at Diagnosis of IHCM by Age at Diagnosis

	Infantile IHCM (n=227)	Noninfantile IHCM (n=407)	*P*
Description of population at diagnosis of HCM			
Prospective cohort, %	66.1	67.6	0.725
Male sex, %	58.2	74.0	<0.001
Race, %	...	...	0.313
White	71.0	69.2	...
Black	9.1	13.8	...
Hispanic	15.8	13.0	...
Other	4.1	4.0	...
CHF present at diagnosis, %	20.5	4.0	<0.001
Echocardiographic data at diagnosis			
Echocardiography done, %	96.9	95.6	0.525
Median septal thickness to free wall thickness ratio [Q1,Q3] (n)	1.44 [1.11, 2.10] (173)	1.39 [1.00, 1.96] (336)	0.155
Median free wall thickness to EDD ratio [Q1,Q3] (n)	0.28 [0.21, 0.40] (166)	0.26 [0.21, 0.34] (317)	0.217
EDD *z* score (n)*	−2.03±2.62 (153)	−1.68±1.95 (292)	0.143
Fractional shortening *z* score (n)*	2.09±5.75 (166)	4.43±4.61 (314)	<0.001
Free wall thickness *z* score (n)*	1.67±3.31 (160)	1.86±2.65 (310)	0.514
Septal thickness *z* score (n)*	3.21±2.67 (159)	3.56±2.46 (316)	0.157
LV mass *z* score (n)*	1.49±2.82 (150)	2.07±2.39 (290)	0.030

EDD indicates end-diastolic dimension; LV, left ventricular. Data are from 634 children with IHCM in the combined retrospective and prospective cohorts of the PCMR.

*All echocardiographic *z* scores in both groups have been tested for statistical difference from normal (*z* score=0). At the 0.01 significance level, all *z* scores in both groups are statistically different from normal.

Statistical Methods

Body surface area was calculated from height and weight.[13] Left ventricular end-diastolic dimension, free wall thickness, septal thickness, and mass were expressed as *z* scores relative to the distribution of these measurements versus body surface area in normal children,[14] and fractional shortening was expressed as the *z* score relative to age.[15] Incidence estimates are based on the prospective cohort from the 2 geographic regions for 1996 through 2000 using methods described elsewhere.[12]

The distributions of categorical variables by groups were compared using the Fisher exact test unless otherwise noted. Two- and 3-group comparisons for normal continuous variables were conducted using Student *t* test and ANOVA, respectively, whereas skewed data were compared using the Wilcoxon rank sum and Kruskal-Wallis tests. Comparisons of 3 or more groups of normal continuous variables were analyzed using the ANOVA test, whereas skewed data were compared using the Kruskal-Wallis test.

The Mantel-Haenszel test for linear trend was used to examine the age at diagnosis by cause of HCM. Survival curves and estimates were calculated using the Kaplan-Meier method for time since diagnosis. Outcomes were death (with transplanted patients censored at the date of transplantation) and transplantation. Group differences in survival were assessed using the log-rank test. Cumulative incidence competing risk estimates,[16] which do not assume independence between transplant and death, also were calculated but were nearly identical to the Kaplan-Meier estimates and are not included in the present report.

To control for the large number of subgroup analyses and for multiple comparisons, a significance level of 0.01 was used. All analyses were conducted with the Statistical Analysis System, version 9.1, and S-Plus 6.1.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

As of February 25, 2003, 855 children who met the entrance criteria for "pure" HCM had been enrolled in the PCMR. Of these, 542 (63.4%) were enrolled prospectively, and 313 (36.6%) were enrolled retrospectively. The prospective and retrospective cohorts were compared with respect to cause and clinical characteristics obtained at the time of diagnosis. The frequency of different causes, clinical characteristics, and family history were similar in the 2 groups, except that a family history of arrhythmia was more common in the prospective cohort (8.2% versus 2.3%; $P=0.005$). Echocardiographic findings were similar in the 2 cohorts, except that both mean septal thickness *z* score and mean left ventricular mass *z* score were lower in the prospective cohort than in the retrospective cohort (3.08±2.51 versus 3.73±2.41, $P=0.002$; and 1.65±2.68 versus 2.46±2.66, $P<0.001$, respectively). There were no significant differences in outcomes between the prospective and retrospective cohorts. Because of the similarity of the 2 groups, only the data on the combined groups are presented, except for the incidence data, which pertain exclusively to cases from the 2 geographic regions in the prospective cohort.

Incidence

The incidence data reported in the present study include the data from 1996 to 2000 for pure HCM.[12] The overall annual incidence of pure HCM (n=246) in the prospective regional cohort was 4.7 (95% CI, 4.1 to 5.3) per 1 million children (Table 1). There was a higher incidence in the New England

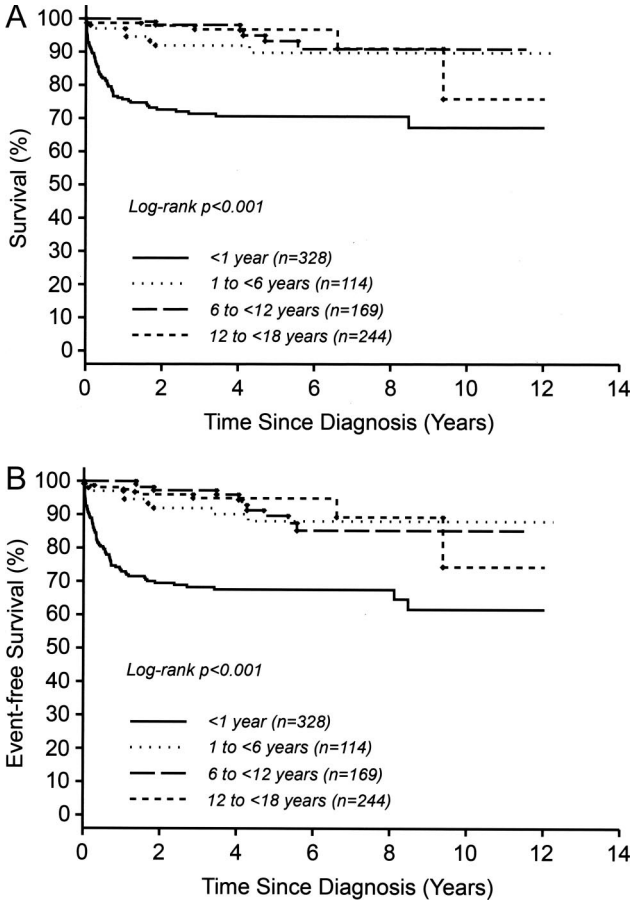

Figure 1. Survival rates from diagnosis of cardiomyopathy to death (A; log-rank $P<0.001$) and death or transplantation (B; log-rank $P<0.001$) in the combined prospective and retrospective cohorts (N=855) by age at diagnosis (<1, 1 to <6, 6 to <12, and 12 to <18 years).

than in the central Southwest region ($P=0.009$), in boys than in girls ($P<0.001$), and in children diagnosed at <1 year of age than in older children ($P<0.001$). The interaction between sex and age was significant ($P=0.007$), with no sex difference in infants but a higher incidence of HCM in boys than in girls ≥1 year of age (4.4 versus 1.9 cases per 1 million children per year).

The annual incidence of IHCM (n=190) was 3.6 (95% CI, 3.1 to 4.2) per 1 million children. Subgroup differences in incidence for the IHCM patients were similar to those of the group as a whole, except that the regional difference was not present (Table 2).

Patient Characteristics

The combined retrospective and prospective cohorts were classified according to cause over all available follow-up (Table 3). The IHCM group accounted for 74.2% of cases (n=634), with the remainder divided nearly equally among the other 3 categories. For all patients who presented before 1 year of age, 48 (14.6%) had IEM, 50 (15.2%) had MFS, 3 (0.9%) had NMD, and 227 (69.2%) had IHCM. There were significant differences among the etiologic categories for age at diagnosis, congestive heart failure (CHF) at diagnosis, and nearly all echocardiographic z scores. Patients with IEM or MFS were diagnosed with HCM earlier in life than those with NMD or IHCM (all $P<0.001$), and those with NMD were diagnosed later than those with IHCM ($P<0.001$). Children with IEM, compared with those with NMD and those with IHCM, also had a higher rate of CHF at diagnosis (both $P<0.001$), higher end-diastolic dimension z scores ($P=0.012$ and $P<0.001$, respectively), and lower fractional shortening z scores (both $P<0.001$). As a group, patients with IEM and NMD were characterized by concentric hypertrophy, whereas the IHCM group had a median septal thickness 1.4 times that of the posterior wall.

The diversity of diagnoses in childhood HCM is illustrated by the observation that a total of 42 specific causes were identified in this cohort. The frequency, number of deaths, and age at death for each of these 42 causes are presented in Table I of the online Data Supplement. Of interest, a single cause predominated within each of the disease categories: Pompe disease accounted for 33.8% of the cases with IEM, Noonan syndrome accounted for 77.9% of the cases with MFS, and Friedreich ataxia accounted for 87.5% of the cases with NMD.

Of the 634 patients with IHCM, 227 (35.8%) were diagnosed before 1 year of age (IHCM <1YR group), and 407 (64.2%) presented after 1 year of age (IHCM ≥1YR group). Comparison of the retrospective (n=209) and prospective (n=425) IHCM cohorts demonstrated no significant differences for echocardiographic data (Table II of the online Data Supplement). These groups were therefore pooled for the remainder of the analysis. The IHCM group comprised 109 familial and 525 sporadic cases. The familial and sporadic groups demonstrated no significant differences with regard to race, age at diagnosis, sex distribution, frequency of CHF at

TABLE 5. Survival Rate From Time of HCM Diagnosis by Etiology

	Survival Rate After HCM Diagnosis, % (95% CI)			
	1 y	2 y	5 y	10 y
IEM	53.6 (41.3 to 66.0)	44.9 (31.9 to 57.9)	41.7 (28.2 to 55.2)	*
MFS	82.4 (73.0 to 91.9)	76.6 (65.8 to 87.5)	74.4 (63.0 to 85.7)	74.4 (63.0 to 85.7)
NMD	98.2 (94.7 to 100)	98.2 (94.7 to 100)	98.2 (94.7 to 100)	91.7 (78.9 to 100)
IHCM	94.4 (92.4 to 96.4)	92.8 (90.5 to 95.1)	89.8 (86.5 to 93.1)	85.3 (77.4 to 93.2)
Infantile IHCM	85.8 (80.7 to 90.9)	84.3 (78.8 to 89.7)	82.2 (76.2 to 88.2)	82.2 (76.2 to 88.2)
Noninfantile IHCM	99.2 (98.3 to 100)	97.6 (95.7 to 99.4)	93.9 (90.0 to 97.9)	85.9 (72.7 to 99.2)

*Maximum follow-up observation in this group is only 9.0 years.

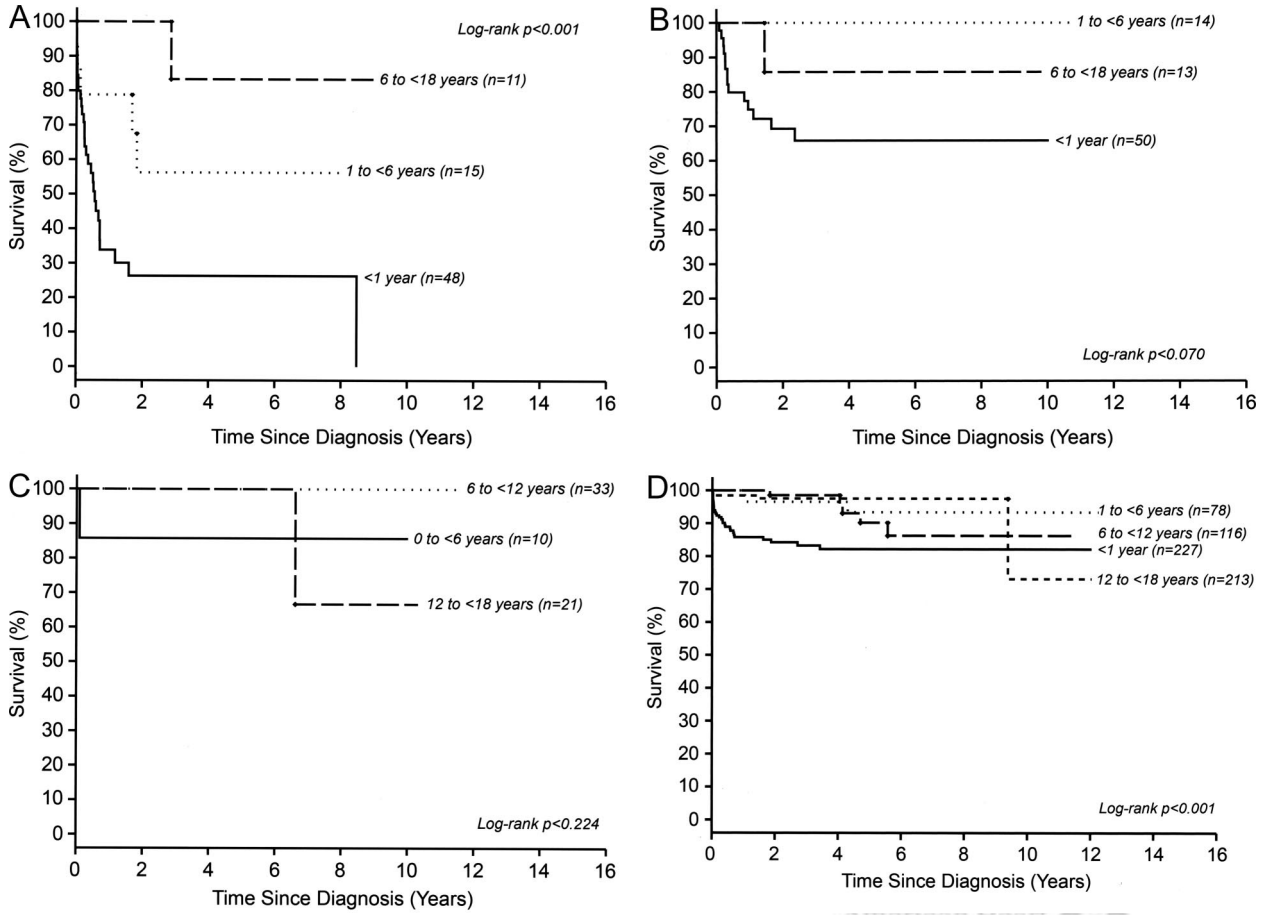

Figure 2. Survival rates from the diagnosis of cardiomyopathy in IEM (A; n=74; log-rank $P<0.001$), MFS (B; n=77; log-rank $P=0.070$), NMD (C; n=64; log-rank $P=0.224$), and IHCM (D; n=634; log-rank $P<0.001$) by age at diagnosis.

diagnosis, or survival. Racial distribution was not different for the IHCM <1YR and IHCM ≥1YR groups (Table 4), but there was a male predilection in the IHCM ≥1YR group. CHF was significantly more common at the time of diagnosis in the IHCM <1YR group, and fractional shortening *z* score was higher in the IHCM ≥1YR group (both $P<0.001$).

Outcomes

The median follow-up period for patients who did not die or undergo cardiac transplantation was 2.1 years (25th to 75th percentile, 6.2 months to 12.3 years). There were 96 deaths, 18 cardiac transplantations, and 11 patients who developed dilated cardiomyopathy in the combined prospective and retrospective cohorts. There were 36 deaths in the IEM group, 15 in the MFS group, 2 in the NMD group, and 43 in the IHCM group. Within the IHCM group, 30 deaths occurred in the IHCM <1YR group and 13 in the IHCM ≥1YR patients. Mode of death, when known, was sudden in 8 of 18 in the IHCM <1YR group and 8 of 8 in the IHCM ≥1YR. The 328 patients diagnosed as infants had significantly poorer survival (Figure 1A) and event-free survival (Figure 1B) from the time of diagnosis than children presenting after age 1 year (log-rank $P<0.001$). Eighty-eight (36%) of the HCM <1YR presented with CHF; of these, 36 (41%) died.

Survival rates from the time of HCM diagnosis (Table 5, Figures 1 and 2) were poorer in patients with IEM and MFS compared with NMD or IHCM patients (all log-rank $P<0.001$). Survival from the time of diagnosis differed significantly by age at diagnosis for children with IEM and IHCM (both log-rank $P<0.001$) but not for children with MFS or NMD (Figure 2). Overall, patients with IHCM who were alive at >1 year of age had an annual mortality of 1.0 per 100 patient-years. This group was made up of the IHCM ≥1YR group, who had an annual mortality of 1.1 per 100 patient-years, and children diagnosed at age <1 year who survived past 1 year of age, who had an annual mortality of 0.7 per 100 patient-years (log-rank $P=0.386$). The distribution of age at death in IHCM (Figure 3) for all HCM (Figure 3A) and for IHCM (Figure 3B) appears to be bimodal, with highest frequencies during infancy and adolescence. Children with HCM associated with IEM and MFS presenting with HCM before 1 year of age have a particularly poor prognosis, with a 5-year survival post-HCM diagnosis of 26.3% (95% CI, 11.4 to 41.1) and 65.8% (95% CI, 50.9 to 80.7), respectively.

Discussion

In the PCMR, we enrolled a cohort of pediatric patients with HCM that is much larger than previously reported, particularly with respect to the number of younger children.[17–25] The present study identified several characteristics of the disease

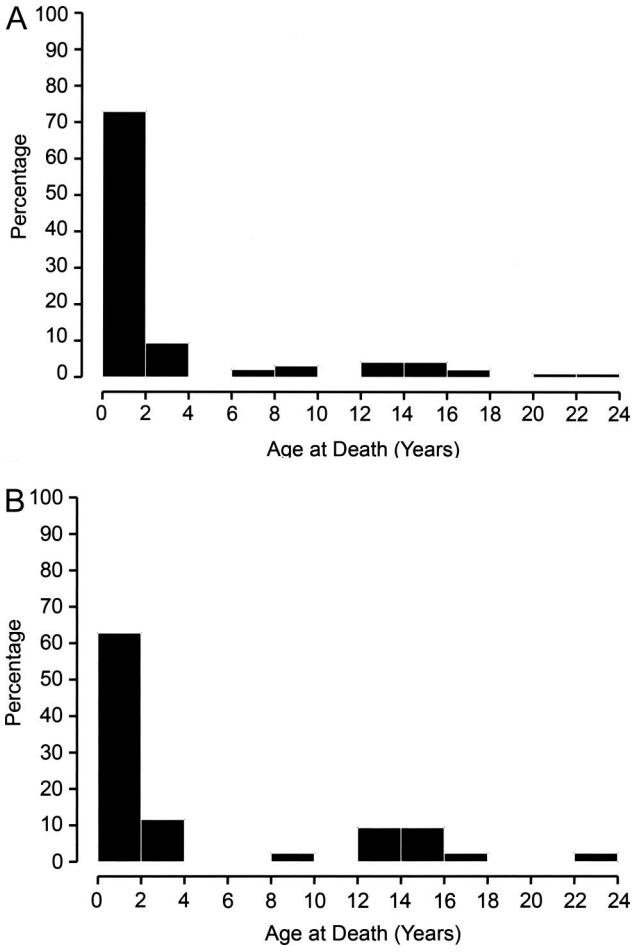

Figure 3. Age at death expressed as a percentage of deaths for all HCM patients (A; N=96) and for those with IHCM (B; n=43).

in children. The incidence of both pure HCM and IHCM is highest in the first year of life. The heterogeneity of the disorder, as demonstrated in these results, is particularly notable in infants. Although nearly two thirds of pediatric HCM cases are idiopathic, a significant number are caused by IEM, MFS, and NMD. There are 2 important new findings in this study. First, overall, survival in pediatric patients with IHCM is much better than previously reported. Second, although, as previously reported, diagnosis of IHCM during infancy carries a worse prognosis, those children who survive beyond 1 year of age have similar survival rates regardless of age at diagnosis.

Outcome in IHCM

In this large series of pediatric patients with IHCM diagnosed or surviving past 1 year of age, we found a mortality rate of 1.0 per 100 patient-years. A recent population-based study of outcome in children diagnosed at <10 years of age from Australia[26] found an annual mortality of 1.5% in children diagnosed at >1 year of age, including patients with MFS. The survival rates in these 2 studies are much better than previously reported in children with HCM (3% to 8%) thought to be idiopathic.[22,23,25] Our experience parallels that in adults, in which the annual incidence of sudden death in HCM patients referred to tertiary care centers was reported to be 3% to 5%, but subsequent population studies in adults indicated a much lower annual mortality of 0.1% to 1%,[27–31] with asymptomatic adults at even lower risk.[32] Referral bias appears largely responsible for these differences.

Relationship of Outcome to Age at Diagnosis

The prognosis for infants with HCM is worse than in older children, and 36 of 328 of children (11%) diagnosed at <1 year of age died, including 36 of 88 (41%) who presented with CHF. Several prior reports have indicated that HCM presenting in infancy carries a worse prognosis than in older age groups, but the reported mortality rates have varied dramatically from 0% to 89% (9 of 11,[17] 10 of 19,[18] 1 of 13,[20] and 0 of 22[19]). These disparities likely are due to small series that fail to reflect the wide variation in cause-specific survival. The poor survival in patients with IEM implies that survival statistics will be highly dependent on the number of patients with these diseases who are included in the cohort. Perhaps the most significant new finding reported here is the nonlinear hazard associated with diagnosis of IHCM during infancy; although the 1-year survival from the time of diagnosis of HCM in the IHCM <1YR cohort is 85.8% compared with 99.2% in IHCM ≥1YR, there is no difference in annual mortality between these 2 groups for those patients who survive beyond 1 year of age.

The causal classification of HCM has been seriously impeded by the inability to diagnose IHCM genetically and to diagnose the various forms of IEM reliably. Ultimately, causal diagnosis of HCM depends on molecular identification of the gene or the abnormal gene product. Until such testing is widely available, diagnosis depends almost exclusively on recognition of the clinical phenotype. This limitation has important implications for our present findings. First, our incidence estimates represent the number of children who manifest the phenotype, but they necessarily underestimate the number of genetically affected children. Second, HCM in infants presents unique issues in differential diagnosis. Patients with secondary forms of HCM often cannot be classified as to cause during the first year of life because etiologic diagnosis based on phenotype often is unreliable, laboratory-based diagnosis may require months or years to complete, and death frequently occurs before laboratory diagnosis. As a result, a large fraction of patients under 1 year of age with metabolic and mitochondrial disorders never achieve a laboratory diagnosis. In various patient series, diseases other than IHCM have accounted for 30% to 70% of HCM cases in patients <2 years of age.[20] Among our patients presenting before 1 year of age, 14.6% had IEM, 15.2% had MFS, 0.9% had NMD, and 69.2% were idiopathic.

Unlike in adults,[33] HCM in children is associated with numerous disorders other than those due to sarcomeric gene defects, as reported in the present study and elsewhere.[34] Although isolated case reports have described many disorders associated with HCM, several are seen with sufficient frequency to indicate that HCM is an intrinsic element of the disease. The classic infantile form of Pompe disease typically is associated with a severe and progressive HCM resulting in death by 2 years of age. Between 25% and 50% of patients with Friedreich ataxia have been reported to have HCM, but

we found the clinical characteristics of the heart disease to be different from IHCM, with all patients in this cohort surviving to 20 years of age. HCM is seen in up to 30% of patients with Noonan's syndrome,[35,36] with a significant risk for CHF and death. Even in the absence of other evidence of noncardiac involvement, nonsarcomeric abnormalities may be responsible. For example, the increased incidence of HCM in male individuals suggests that x-linked disorders such as Fabry disease, which was reported in 1 series to account for 4% of HCM in adults,[9] may account for a significant number of these patients.

Conclusions

HCM in children is a diverse disorder with origin-specific outcomes. Infants have a worse outcome, with HCM associated with IEM and MFS having a particularly poor prognosis. Infants with IHCM have a much better survival than previously reported, however, and for those who survive beyond 1 year of age, survival rates are not different from survival rates in patients diagnosed after 1 year of age. Overall, pediatric patients with IHCM who survive beyond or are diagnosed at >1 year of age have a mortality rate of 1.0 per 100 patient-years.

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Disclosures

None.

References

1. Grenier MA, Osganian SK, Cox GF, Towbin JA, Colan SD, Lurie PR, Sleeper LA, Orav EJ, Lipshultz SE. Design and implementation of the North American Pediatric Cardiomyopathy Registry. *Am Heart J*. 2000; 139:S86–S95.
2. Keren A, Popp RL. Assignment of patients into the classification of cardiomyopathies. *Circulation*. 1992;86:1622–1633.
3. Arad M, Maron BJ, Gorham JM, Johnson WH, Saul JP, Perez-Atayde AR, Spirito P, Wright GB, Kanter RJ, Seidman CE, Seidman JG. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med*. 2005;352:362–372.
4. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, Benaiche A, Isnard R, Dubourg O, Burban M, Gueffet JP, Millaire A, Desnos M, Schwartz K, Hainque B, Komajda M, EUROGENE Heart Failure Project. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation*. 2003;107:2227–2232.
5. Van Driest SL, Vasile VC, Ommen SR, Will ML, Tajik AJ, Gersh BJ, Ackerman MJ. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2004; 44:1903–1910.
6. Van Driest SL, Ommen SR, Tajik AJ, Gersh BJ, Ackerman MJ. Sarcomeric genotyping in hypertrophic cardiomyopathy. *Mayo Clin Proc*. 2006;80:463–469.
7. Charron P, Villard E, Sebillon P, Laforet P, Maisonobe T, Duboscq-Bidot L, Romero N, Drouin-Garraud V, Frebourg T, Richard P, Eymard B, Komajda M. Danon's disease as a cause of hypertrophic cardiomyopathy: a systematic survey. *Heart*. 2004;90:842–846.
8. Murphy RT, Mogensen J, McGarry K, Bahl A, Evans A, Osman E, Syrris P, Gorman G, Farrell M, Holton JL, Hanna MG, Hughes S, Elliott PM, MacRae CA, McKenna WJ. Adenosine monophosphate-activated protein kinase disease mimicks hypertrophic cardiomyopathy and Wolff-Parkinson-White syndrome: natural history. *J Am Coll Cardiol*. 2005;45: 922–930.
9. Sachdev B, Takenaka T, Teraguchi H, Tei C, Lee P, McKenna WJ, Elliott PM. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation*. 2002;105:1407–1411.
10. Franklin RCG, Anderson RH, Elliott M, Gewillig MHML, Ghisla R, Krogmann ON, Ulmer HE, Stocker FP. The European paediatric cardiac code. *Cardiol Young*. 1999;9:633–657.
11. Delius RE. Congenital heart surgery and database project: pediatric cardiomyopathies and end-stage congenital heart disease. *Ann Thorac Surg*. 2000;69:S180–S190.
12. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, Lurie PR, McCoy KL, McDonald MA, Messere JE, Colan SD. The incidence of pediatric cardiomyopathy in two regions of the United States. *N Engl J Med*. 2003;348:1647–1655.
13. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr*. 1978;93:62–66.
14. Sluysmans T, Colan SD. Theoretical and empirical derivation of cardiovascular allometric relationships in children. *J Appl Physiol*. 2005;99: 445–457.
15. Colan SD, Parness IA, Spevak PJ, Sanders SP. Developmental modulation of myocardial mechanics: age- and growth-related alterations in afterload and contractility. *J Am Coll Cardiol*. 1992;19:619–629.
16. Tai BC, Machin D, White I, Gebski V. Competing risks analysis of patients with osteosarcoma: a comparison of four different approaches. *Stat Med*. 2001;20:661–684.
17. Maron BJ, Tajik AJ, Ruttenberg HD, Graham TP, Atwood GF, Victorica BE, Lie JT, Roberts WC. Hypertrophic cardiomyopathy in infants: clinical features and natural history. *Circulation*. 1982;65:7–17.
18. Suda K, Kohl T, Kovalchin JP, Silverman NH. Echocardiographic predictors of poor outcome in infants with hypertrophic cardiomyopathy. *Am J Cardiol*. 1997;80:595–600.
19. Schaffer MS, Freedom RM, Rowe RD. Hypertrophic cardiomyopathy presenting before 2 years of age in 13 patients. *Pediatr Cardiol*. 1983;4: 113–119.
20. Moran AM, Colan SD. Verapamil therapy in infants with hypertrophic cardiomyopathy. *Cardiol Young*. 1998;8:310–319.
21. McKenna WJ, Goodwin JF. The natural history of hypertrophic cardiomyopathy. *Curr Probl Cardiol*. 1981;6:1–26.
22. McKenna WJ. The natural history of hypertrophic cardiomyopathy. *Cardiovasc Clin*. 1988;19:135–148.
23. McKenna WJ, Deanfield JE. Hypertrophic cardiomyopathy: an important cause of sudden death. *Arch Dis Child*. 1984;59:971–975.
24. Bruno E, Maisuls H, Juaneda E, Moreyra E, Alday LE. Clinical features of hypertrophic cardiomyopathy in the young. *Cardiol Young*. 2002;12: 147–152.
25. Yetman AT, Hamilton RM, Benson LN, McCrindle BW. Long-term outcome and prognostic determinants in children with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1998;32:1943–1950.
26. Nugent AW, Daubeney PE, Chondros P, Carlin JB, Colan SD, Cheung M, Davis AM, Chow CW, Weintraub RG. Clinical features and outcomes of childhood hypertrophic cardiomyopathy: results from a national population-based study. *Circulation*. 2005;112:1332–1338.
27. Spirito P, Chiarella F, Carratino L, Berisso MZ, Bellotti P, Vecchio C. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. *N Engl J Med*. 1989;320:749–755.
28. Agnarsson UT, Hardarson T, Hallgrimsson J, Sigfusson N. The prevalence of hypertrophic cardiomyopathy in men: an echocardiographic population screening study with a review of death records. *J Intern Med*. 1992;232:499–506.
29. Cecchi F, Olivotto I, Montereggi A, Santoro G, Dolara A, Maron BJ. Hypertrophic cardiomyopathy in Tuscany: clinical course and outcome in an unselected regional population. *J Am Coll Cardiol*. 1995; 26:1529–1536.
30. Cannan CR, Reeder GS, Bailey KR, Melton LJ, Gersh BJ. Natural history of hypertrophic cardiomyopathy: a population-based study, 1976 through 1990. *Circulation*. 1995;92:2488–2495.
31. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA*. 1999;281:650–655.
32. Takagi E, Yamakado T, Nakano T. Prognosis of completely asymptomatic adult patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1999;33:206–211.
33. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH, III, Spirito P, ten Cate FJ, Wigle ED. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Car-

diology Committee for Practice Guidelines. *J Am Coll Cardiol*. 2003;42:1687–1713.
34. Schwartz ML, Cox GF, Lin AE, Korson MS, Perez-Atayde A, Lacro RV, Lipshultz SE. Clinical approach to genetic cardiomyopathy in children. *Circulation*. 1996;94:2021–2038.
35. Nishikawa T, Ishiyama S, Shimojo T, Takeda K, Kasajima T, Momma K. Hypertrophic cardiomyopathy in Noonan syndrome. *Acta Paediatr Jpn*. 1996;38:91–98.
36. Noonan J, O'Connor W. Noonan syndrome: a clinical description emphasizing the cardiac findings. *Acta Paediatr Jpn*. 1996;38:76–83.

CLINICAL PERSPECTIVE

The information concerning hypertrophic cardiomyopathy (HCM) in children is based on small case series and is limited by disease diversity. The Pediatric Cardiomyopathy Registry has collected prospective and retrospective data on children diagnosed with HCM since 1990, including a prospective comprehensive capture of all newly diagnosed cases from 2 regions of the United States. We identified the various causes for HCM in childhood and determined the relationship between outcomes, cause, and age at presentation. Of 855 patients, 8.7% (n=74) had inborn errors of metabolism, 9.0% (n=77) had malformation syndromes, 7.5% (n=64) had neuromuscular disorders, and 74.2% (n=634) had idiopathic HCM. Children with HCM associated with inborn errors of metabolism and malformation syndromes have significantly worse survival than the other 2 groups. Patients with idiopathic HCM had a 10-year survival from the time of diagnosis of 85.3% (95% CI, 77.4 to 93.2). Patients with idiopathic HCM diagnosed before 1 year of age had worse survival from the time of diagnosis than those diagnosed after age 1. Yet patients with idiopathic HCM diagnosed before 1 year of age who survived to at least 1 year of age had survival rates that were not different from the survival rate in idiopathic HCM patients who were diagnosed beyond 1 year of age. Overall, patients with idiopathic HCM who are older than 1 year of age, regardless of age at diagnosis, have an annual mortality of 1%, a rate that is much lower than previously reported in children and is not different from that found in population-based studies in adults.