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ORIGINAL ARTICLE

Long-Term Follow-Up of Children and Adolescents Diagnosed with Hypertrophic Cardiomyopathy: Risk Factors for Adverse Arrhythmic Events

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Abstract Our aim was to identify prognostic factors for an arrhythmic event (AE) in children with hypertrophic cardiomyopathy (HCM) without a previous AE. One hundred thirty-one nonconsecutive patients (≤20 years) with HCM but no previous AE were evaluated at the NIH Clinical Center from 1980 to 2001. At a median follow-up of 6.4 years, 22 patients experienced an AE [sudden death (SD) ($n = 12$), resuscitated cardiac arrest ($n = 3$), clinical sustained ventricular tachycardia (VT) ($n = 2$), and implantable cardiac defibrillator discharge ($n = 5$)], resulting in a 2% annual AE rate. Baseline factors that were most predictive in univariate risk analysis included ventricular septal thickness (ST) ($P = 0.01$), VT induction by programmed ventricular stimulation (PVS) ($P = 0.01$), age ($P = 0.05$), and presyncope/syncope ($P = 0.05$). In multivariate analysis, ST, age, presyncope/syncope, and PVS were not independently predictive of risk for an AE. However, the 5-year event rates for AE was 15% (95% CI: 5–23%) if ST ≥ 20 mm, 19% (95% CI: 6–31%) when age ≥ 13 years and ST ≥ 20 mm were combined together, and 23% (95% CI: 3–39%) when PVS and ST ≥ 20 mm were combined together. Of the various risk factors that were considered in our pediatric HCM cohort, ST and inducible VT were the most significant univariate predictors of risk for an AE. More traditional risk factors identified in older patients (family history of SD, VT on Holter, and exercise-induced hypotension) were not predictive of an AE in patients age under 21 years.

Keywords Hypertrophic cardiomyopathy · Arrhythmia event · Children

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Introduction

Hypertrophic cardiomyopathy (HCM) is the commonest inherited cardiomyopathy, with a prevalence of 0.2% [11]. It is an important cause of arrhythmic events (AEs) in young people with an estimated annual mortality varying between 1 and 6% [5, 11, 14, 17, 29, 33]. Implantable cardiac defibrillator (ICD) therapy can be life-saving. On the other hand, ICD therapy can result in considerable morbidity and psychological burden if used indiscriminately [2, 5, 23, 29, 30]. Recent reports have shown ICD lead failure rates varying from 2 to 21% in children and young adults [2, 23, 30] and a very high rate of inappropriate shock rates in the HCM population (23–33% of patients) [28, 52], highlighting the importance of selecting the highest risk population of children most likely to benefit from defibrillator therapy.

Traditional risk factors for sudden death (SD) in adult HCM patients include a family history of SD, young age, nonsustained ventricular tachycardia (VT) on Holter, increased septal thickness (ST), abnormal blood pressure (BP) response to exercise, and syncope [17].

The purpose of this study was to determine (1) whether risk factors for AE in adults would have predictive value in children and (2) if not, what clinical parameters would identify subgroups of children and adolescents that might benefit the most from ICD implantation.

Methods

Patient Population

Between 1980 and 2001, 144 children (≤20 years of age) with HCM were evaluated in the Cardiology Branch, National Heart Lung and Blood Institute (NHLBI), National Institutes of Health (NIH), Bethesda, MD and underwent an electrophysiology study (EPS). Two patient subsets were of interest: (Group 1) 131 patients who did not have a prior (preclinical presentation at the NIH) AE and who had an EPS and (Group 2) 13 patients who had a prior AE and who had an EPS. These two patient groups were identified retrospectively from our larger clinical database of patients with HCM who had undergone clinical evaluation. Study inclusion criteria were (1) clinical evaluation at the NIH between 1980 and 2001, (2) age ≤ 20 years, (3) consent to participate in a research protocol, (4) consent for publication of clinical data, and (5) an EPS. The primary focus of this article is the first group of 131 patients. This research study was conducted under a separate NHLBI Institutional Review Board approved protocol.

Hypertrophic cardiomyopathy was diagnosed by echocardiographic demonstration of a hypertrophied nondilated left ventricle (LV) in the absence of another cause of LV hypertrophy.

Baseline evaluation included an electrocardiogram and a two-dimensional echocardiogram. Ventricular ST was measured in mm and also indexed to body surface area (BSA) (mm/m^2). Patients undertook additional tests depending on patient age, clinical presentation, patient/family willingness to participate in protocols, and year of presentation. These studies included 24–48-h ambulatory electrocardiographic monitoring, exercise stress test, myocardial perfusion scan, cardiac catheterization and angiography, and EPS.

Electrophysiologic Study

EPS was performed under fasting conditions and conscious sedation. Cardioactive drugs were discontinued five half-lives prior to study. Details of the EP protocol have been described [5, 16]. Programmed ventricular stimulation (PVS) involved up to three premature extrastimuli delivered during drive cycle lengths (600, 500, and 400 ms) at the right ventricular (RV) apex and RV outflow tract (OT). The end point of the stimulation protocol was induction of a sustained ventricular arrhythmia or shortening of the coupling intervals down to ventricular refractoriness. PVS was only performed in the baseline state; isoproterenol was not administered. VT was defined as three or more consecutive ventricular beats at a rate of >100 beats/min. Nonsustained VT was defined as VT terminating spontaneously in less than 30 s. Sustained VT was defined as VT lasting greater than 30 s in duration or requiring termination because of hemodynamic compromise. VT with continuously changing QRS morphology was termed polymorphic and that with uniform QRS complexes was termed monomorphic.

Patient Management

Therapy was based on the patient's clinical presentation, cardiac catheterization, and EP findings. Treatment was initiated with the intent of relieving symptoms and treating identified mechanisms of syncope or AE. The study population dated back to 1980, when ICD therapy was very rarely used in children. Over time, with changes in technology and indications for device implantation, the frequency of ICD implantation increased. In the early era, only drug therapy was readily available. A total of 40 Group 1 subjects underwent ICD implantation. ICD implantation was also advised in 10 patients whose families refused. Beta-blockers were used in 70 of 125 (56%) patients for whom such data were available. However, only 46 of 70 (66%) patients continued beta-blocker therapy long term. Five patients underwent septal myomyectomy.

Follow-Up

Follow-up included annual visits to the NIH, reassessment by the community cardiologist, and telephone calls to the patient and local physicians. When possible, ICDs were interrogated to review electrograms, event markers, and counter data for VT or ventricular fibrillation (VF). Episodes of VT/VF associated with ICD discharge were considered to be an AE if coincident with a clinical event (e.g., lightheadedness, rapid palpitations, or loss of consciousness).

Definitions

A modified Hinkle–Thaler system was used to classify AEs [20]. AEs included sudden unwitnessed deaths, sustained VT, successful resuscitation from a cardiac arrest (CA), and ICD therapy for appropriately treated episodes of

VT/VF. Exercise-induced hypotension was defined as a lack of increase in systolic BP by more than 10 mmHg during treadmill exercise. LV outflow tract obstruction was defined as a subvalvular gradient >30 mmHg at rest or ≥50 mmHg after provocation (isoproterenol or premature ventricular complex).

Predictors of Arrhythmic Events

Clinical features examined as potential predictors included: age at presentation to the NIH, family history of SD, presyncope or syncope, exercise-induced hypotension, ST, LV outflow obstruction, elevated LV end diastolic pressure, QRS duration, QT interval, VT on ambulatory electrocardiographic monitoring, myocardial ischemia on stress nuclear perfusion imaging, inducible VT, intracardiac conduction intervals, and ventricular refractory periods.

Statistical Analysis

The time of first NIH attendance was used as the baseline in the time-to-AE analyses. Statistical significance for the univariate time-to-event analyses was assessed using the log rank statistic for dichotomous variables and Cox's score statistic for continuous variables. Statistical significance for the multivariate time-to-event analyses was assessed using Cox's Wald statistic. Baseline differences between inducible VT and electrophysiologic findings were assessed using the *t*-test. For all analyses, a two-sided *P*-value ≤ 0.05 was deemed statistically significant. Unless otherwise indicated, data are reported as median ± standard deviation.

Results

Baseline Characteristics and Follow-Up

The baseline clinical characteristics and risk factors for AE are summarized in Table 1. The median follow-up was 6.4 years (interquartile range: 3.0–9.6; maximum: 21.3). Twenty-two patients experienced AEs that included SD ($n = 12$), resuscitated CA ($n = 3$), clinical sustained VT ($n = 2$), and ICD discharge ($n = 5$). Twenty of the 22 patients were ≥14 years of age at the time of their AE (mean age: 20.1 ± 6.2 years).

Forty patients had an ICD, 11 of whom had an AE. AEs occurred subsequent to ICD implantation in seven patients (ICD discharge = 5 and SD = 2).

Risk Factors for an Arrhythmic Event

Table 2 describes the univariate prognostic significance of baseline characteristics for a subsequent AE. Inducible VT and ST were most strongly associated with an AE. Other risk factors found significant in univariate analysis were older age at the time of initial NIH evaluation and presyncope/syncope. Multivariate analysis did not reveal ST ($P = 0.13$), age ($P = 0.10$), presyncope/syncope ($P = 0.29$), or inducible VT ($P = 0.21$) to be independently predictive of an AE. The traditional risk factors for AE in adult HCM patients of family history of SD, nonsustained VT on Holter, and abnormal BP response to exercise were not significantly related to the occurrence of AE.

Patients with inducible VT had a significantly higher AE rate than those with noninducible VT (5-year rates of 22 vs. 6%, respectively; log rank $P = 0.01$; Fig. 1a).

Patients with ST < 20 mm were at significantly lower risk for an AE than were patients with ST ≥ 20 mm (Five-year event rates of 0 vs. 14%, respectively; $P = 0.01$; Fig. 1b). In particular, among the 51 patients with ST < 20 mm (median follow-up: 5.9 years), only 2 patients had an AE during follow-up (16 and 20 years after baseline evaluation). ST increased from 18 to 20 mm by year 15 of follow-up in the first patient and from 14 to 28 mm by year 14 of follow-up in the second patient. ST was ≥20 mm in 19 of 21 patients who developed an AE and had baseline ST data; ST data were missing in one patient who developed an AE.

When analyzed as a continuous variable, larger absolute ST (mm), as well as larger ST divided by BSA (mm/m^2) were significantly predictive of an AE (Table 2). There was no statistical difference in age between patients with ST < 20 mm and patients with ST ≥ 20 mm (13.2 ± 5.1 vs. 13.9 ± 4.1 years, $P = 0.37$). ST ≥ 20 mm was independently predictive of age for an AE ($P = 0.003$).

When combined, children ≥ 13 years of age and a ST ≥ 20 mm had a 5-year event rate of 19% (95% CI: 6–31%). Children <13 years of age and ST ≥ 20 mm had a 5-year event rate of 6% (95% CI: 0–16%) (see Fig. 2).

The probability of AE curves stratified according to VT inducibility and ST ≥ 20 mm are shown in Fig. 3. In particular, children without inducible VT but ST ≥ 20 mm had a 5-year event rate of 10% (95% CI: 4–25%). Children with inducible VT and ST ≥ 20 mm had a 5-year event rate of 23% (95% CI: 10–47%). Children with ST < 20 mm had a 5-year AE rate of 0%.

By comparison, there were 13 children (Group 2) referred because of a prior AE during the same time period as the 131 patients who did not have a prior AE reported here. Six of those 13 patients had an AE during follow-up (5-year rate = 43%), making that group a higher AE risk group ($P < 0.0001$) than the 131 patients (5-year rate = 9%). In those 13 patients, VT was induced during EPS in 3 of the 6 patients (50%) who had a subsequent AE. Ventricular ST in the patient group with a prior AE did not

Table 1 Baseline characteristics of 131 children with HCM without prior AE

Age (years) at EP study	14.4 ± 3.9 (range: 3–20)
Male gender	92/131 (70%)
First degree relatives with HCM	23/131 (18%)
Presentation	
Chest pain	46/111 (41%)
Dyspnea	46/112 (41%)
Candidate risk factors for an AE	
Family history of SD	35/117 (29%)
Presyncope/syncope	56/112 (50%)
Myocardial perfusion defect	83/112 (74%)
Lack of BP response to exercise	33/122 (27%)
VT on Holter	23/128 (18%)
Cardiac catheterization	
LVOT obstruction	66/128 (52%)
Elevated LVEDP (>15 mmHg)	61/128 (48%)
Electrophysiologic	
QRS duration (>100 ms)	38/129 (29%)
HV interval (≥55 ms)	45/128 (35%)
RVOT VERP (≥290 ms)	23/79 (29%)
Inducible VT	
Sustained or nonsustained	28/131 (21%)
Sustained only	17/131 (13%)
Echocardiograhic ventricular ST	
<20 mm	51/127 (41%)
20–29 mm	39/127 (31%)
≥30 mm	37/127 (29%)
Patients with at least one traditional risk factor[a]	112/131 (85%)
Patients with more than one traditional risk factor[a]	70/131 (53%)
Follow-up duration (years)	6.4 ± 4.8 (range: 0.0–21.3)

Note: Denominators are given to indicate the amount of missing data

HV His to ventricular conduction time, *LVEDP* left ventricular end diastolic pressure, *LVOT* left ventricular outflow tract obstruction, *VERP* ventricular effective refractory period

[a] Traditional risk factors include family history of SD, presyncope/syncope, VT on Holter, ST ≥ 20 mm, and lack of BP response to exercise

differ significantly from the EPS patient group without a prior AE (24.6 ± 6.6 vs. 23.8 ± 9.4 mm; $P = 0.76$).

Electrophysiologic Findings and Inducible VT

Ventricular tachycardia was induced in 28/131 (21%) patients (nonsustained 11; sustained 17). The combination of sustained or nonsustained VT was significantly predictive of an AE ($P = 0.01$), as was sustained VT alone ($P = 0.03$). VT was induced using two extrastimuli in nine and three extrastimuli in 18 patients. The number of extrastimuli needed for VT induction was unknown in one patient studied outside of the NIH. There was no difference in AE outcome whether VT was induced using two extrastimuli or three extrastimuli ($P = 0.39$). Induced VT was polymorphic in 24 patients, monomorphic in 3 patients, and of unknown morphology in 1 patient. Ventricular extrastimulus testing was performed down to ventricular refractoriness. At a drive cycle length of 400 ms, the V1V2, V2V3, and V3V4 coupling intervals in the noninducible group were 268 ± 21, 228 ± 21, and 212 ± 21 ms, respectively; in the inducible group, they were 268 ± 19, 220 ± 20, and 209 ± 18 ms, respectively. Although statistically significant ($P = 0.04$), the 8-ms difference in the V2V3 coupling interval was not clinically significant.

Patients with inducible VT were older (15.7 ± 2.3 vs. 12.9 ± 4.7 years, $P = 0.003$); nevertheless, inducible VT was nearly independent of age as an AE predictor ($P = 0.06$). Patients with inducible VT had a prolonged HV interval (55 ± 11 vs. 49 ± 10 ms, $P = 0.01$) and a marginally prolonged QT_C interval (433 ± 27 vs. 419 ± 31 ms, $P = 0.04$). There were no significant relationships between inducible VT and AH interval, QRS interval, or ventricular refractory period in the RV apex or RVOT.

Discussion

In this study, the AE rate (SD, resuscitated CA, sustained VT, or defibrillator discharge) in children with HCM but no previous AE was 2% per year, quite comparable to the rate recently reported in a large pediatric cardiomyopathy registry (1.4% per year) [11]. Univariate analysis identified ST (either in absolute terms or indexed to BSA) and inducible VT as significantly associated with AE risk. Age, presyncope or syncope, QT_C, and RVOT ERP were marginally predictive in univariate analysis for an AE; family history of SD, exercise-induced hypotension, nonsustained VT on Holter, and myocardial ischemia were not significant. Multivariate analysis did not reveal ST, inducible VT, age, or presyncope/syncope to be independently significant for an AE. This might be due to the relatively small number of AEs as well as the possible correlation among these risk factors. The combination of inducible VT and ST ≥ 20 mm or patient age ≥ 13 years and ST ≥ 20 mm had the highest 5-year AE rates. In contrast, patients with a ST < 20 mm had a 5-year event rate of 0%.

The 13 children in our database with a prior AE had a significantly higher subsequent AE rate than the 131 patients without a prior AE, despite similar ventricular ST at time of presentation. This identifies a previous AE as one of the highest risk factors for a subsequent AE. Maron et al. [31] found similar data for high risk of AE recurrence (53%) in HCM individuals who suffered a previous AE.

Table 2 Baseline characteristics of 131 patients considered as possible risk factors for the subsequent occurrence of an AE

Variable	Hazard ratio (95% CI)	*P* value
Inducible VT		
Sustained or nonsustained	3.1 (1.2–8.1)	0.01
Sustained only	3.2 (1.0–9.7)	0.03
Septal thickness (mm)	1.3 (1.1–1.6)[a]	0.01
Septal thickness/BSA (mm/m^2)	1.6 (1.1–2.3)[b]	0.01
Age (years)	1.1 (1.0–1.2)	0.05
+ Myocardial perfusion defect	1.2 (0.8–3.2)	0.65
Family history of SD	1.0 (0.4–2.5)	0.96
Lack of BP increase during exercise	0.8 (0.3–2.3)	0.68
Presyncope or syncope	2.4 (1.0–5.9)	0.05
VT on Holter	1.3 (0.5–3.4)	0.60
QRS duration (ms)	1.1 (0.9–1.3)[c]	0.30
QT_C interval (ms)	1.07 (1.0–1.15)[c]	0.05
HV interval (ms)	1.2 (1.0–1.4)[c]	0.07
AH interval (ms)	0.97 (0.88–1.1)[c]	0.56
RVOT VERP (ms)	1.1 (1.0–1.3)[c]	0.05
RV apex VERP (ms)	1.0 (0.91–1.1)[c]	0.75

Note: *P* values are from univariate analyses using the log rank statistic for dichotomous variables and Cox's score statistic for continuous variables

AH atrial to His conduction time, + positive

[a] Hazard ratio corresponds to 5-mm increments

[b] Hazard ratio corresponds to 5-mm/m^2 increments

[c] Hazard ratio corresponds to 5-ms increments

Left Ventricular Hypertrophy

Recent reports provide conflicting data on the association between the magnitude of LV hypertrophy and SD risk in adult HCM patients. Some authors have reported an increased SD risk when LV ST exceeds 15 mm [49], whereas others could not identify any relationship between LV ST and SD [15, 39]. The current data provide evidence for increased risk of AEs in children when ST is ≥20 mm. This risk was compounded in the presence of inducible VT and older age.

Östman-Smith et al. [40] reported that ST over 190% of the 95th percentile for age was a significant risk marker for AE in children with HCM (odds ratio = 6.2, 95% CI = 1.5–25.1). Östman-Smith et al. [40] used the following equation from their earlier work for the 95th percentile of ST in mm: 6.25 + (age in years × 0.0269). In the age group 14–21 years, a ST of 19–22 mm defines ST over 190% of the 95th percentile for age, agreeing with our finding of 20 mm as being associated with higher AE risk.

Basso et al. [4] studied morphologically the hearts from 19 patients with HCM in the age group ≤35 years who died suddenly. ST averaged 21.8 mm and measured ≥20 mm in 12 of 19 patients. Our results are concordant with these findings. In our study, ST measured at the time of clinical presentation was ≥20 mm in 19 of 21 patients who developed AE and had ST data (ST was unknown for one patient who had a subsequent AE).

Absence of LV hypertrophy on an electrocardiogram has been shown to have a lower SD rate in HCM [34]. ST averaged 17.3 mm in the group presenting with a normal ECG (CM). Similar to our study, patients with a ST < 20 mm had a 5-year event rate of 0%.

Induction of VT at EP Study and Polymorphic VT

In previous studies of children with congenital heart disease, inducible VT predicted a threefold increased risk

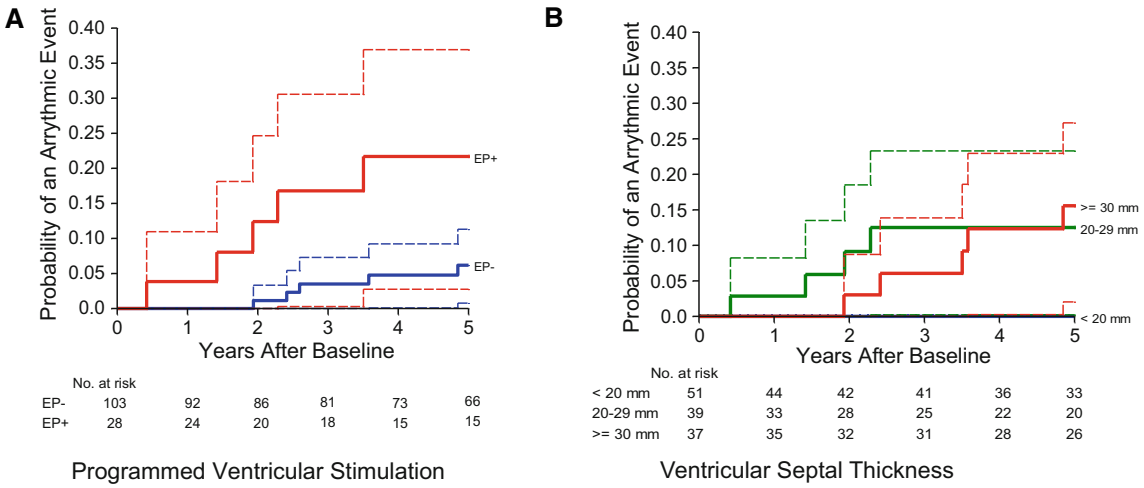

Fig. 1 Cumulative probability, with 95% Greenwood confidence intervals, of an AE according to baseline inducibility of VT **(a)** and ventricular ST **(b)**. **a** Log rank *P*-value = 0.01 for the difference between the EP+ and the EP− group for follow-up to 5 years. **b** Log rank *P*-value = 0.01 for the difference between the ≥20-mm group and the <20-mm group for follow-up to 5 years. Log rank *P*-value = 0.94 for the difference between the 30-mm group and the 20–29 mm group for follow-up to 5 years

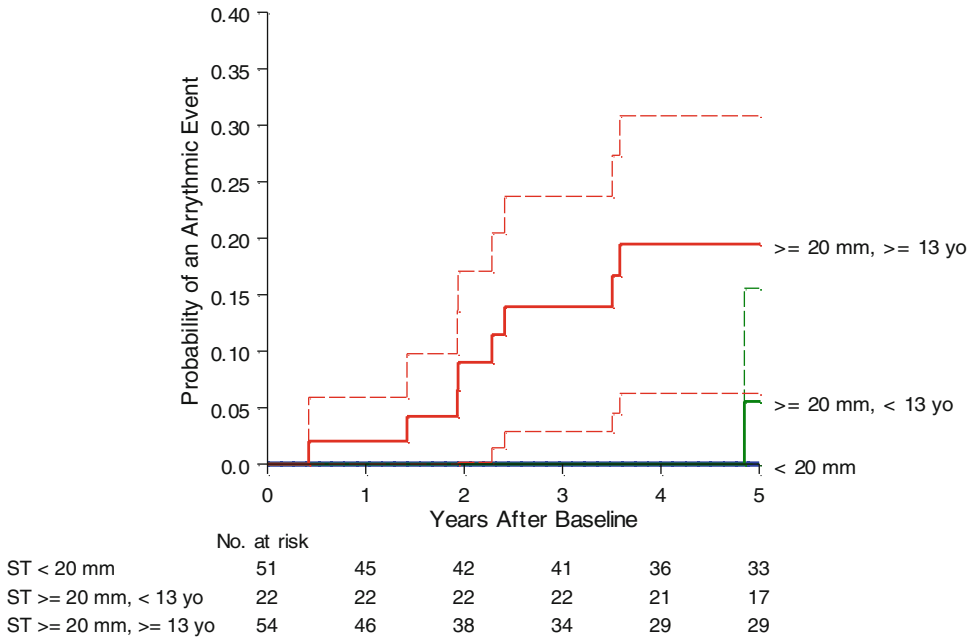

Fig. 2 Cumulative probability, with 95% Greenwood confidence intervals, of an AE according to baseline age and ventricular ST. Log rank *P*-value = 0.11 for the difference between the ≥20-mm and ≥13-year-old group and the ≥20-mm and <13-year-old group for follow-up to 5 years. Log rank *P*-value = 0.18 for the difference between the ≥20 mm and <13-year-old group and the <20-mm group for follow-up to 5 years

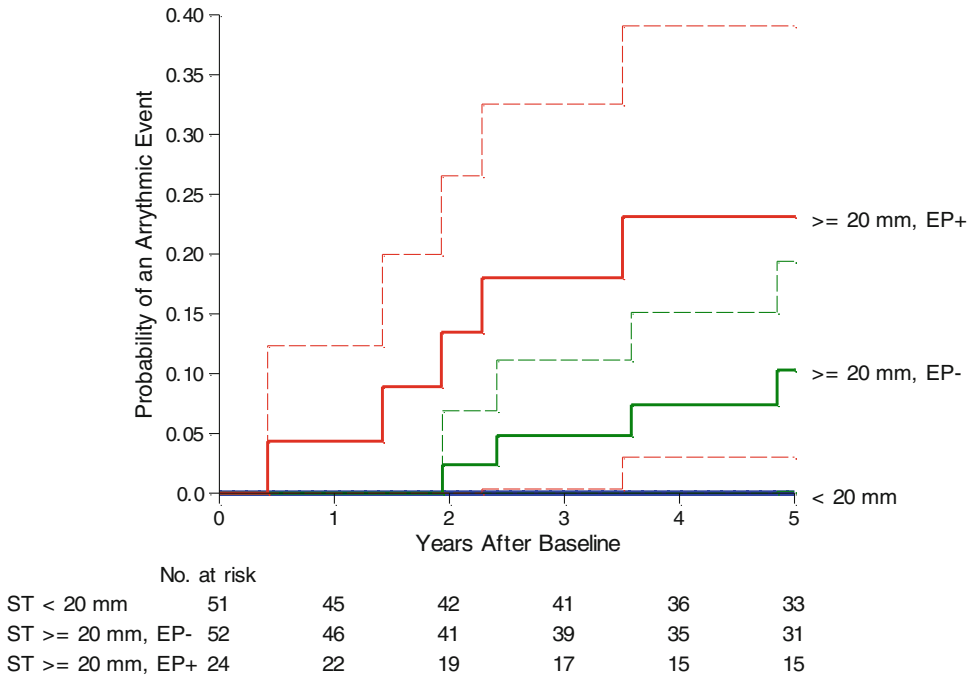

Fig. 3 Cumulative probability, with 95% Greenwood confidence intervals, of an AE according to baseline inducibility of VT and ventricular ST. Log rank *P*-value = 0.12 for the difference between the ≥20-mm EP+ group and ≥20-mm EP− group for follow-up to 5 years. Log rank *P*-value = 0.04 for the difference between the ≥20-mm EP− group and the <20-mm group for follow-up to 5 years

of AEs, whereas noninducibility favored a good outcome (3% false negative rate) [1, 22]. In this study of children with HCM, inducible VT was an important univariate predictor of an AE (hazard ratio = 3.1, 95% CI = 1.2–8.1).

Previous studies have shown the value of EPS in adult patients with HCM and other forms of cardiomyopathy. Induction of VT during EPS was associated with increased risk for ICD firing in adult subjects with arrhythmogenic RV dysplasia (odds ratio = 11.2, 95% CI = 1.23–101.24) [43]. Although EPSs in adults with HCM have limited predictive value during short-term follow-up [3, 18, 21, 24, 26, 47, 54], a negative test predicted a better prognosis in studies with longer follow-up [54].

Anatomic studies have described myocardial fiber disarray and patchy fibrosis in HCM. Fragmentation of electrograms was detected at long premature ventricular coupling intervals in patients with previous VT/VF [46], which could provide the substrate for unstable conduction and reentry and, hence, polymorphic VT/VF.

Traditionally, inducible polymorphic VT was thought to have little predictive value. However, in the Multicenter UnSustained Tachycardia Trial, patients with coronary artery disease and inducible sustained VT/VF had higher mortality from CA than noninducible patients, irrespective of VT morphology [7]. The 2-year adverse AE rate was slightly higher in patients with sustained monomorphic or polymorphic VT/VF induced with two extra stimuli (18%) compared with sustained polymorphic VT induced using three extra stimuli (14%) [8]. More recently, Greenberg et al. [19] showed no difference in appropriate ICD discharge rate or mortality between patients dichotomized by type of arrhythmia induced during PVS (monomorphic VT = 20 vs. polymorphic VT/VF = 21%). Similarly, in congenital heart disease, sustained polymorphic VT trended toward the worse outcome [1].

In our study, polymorphic VT was the predominant morphology of VT induced. Pablo Kaski et al. [42] reviewed the type of ventricular arrhythmias resulting in appropriate ICD shocks in 22 children with HCM. Arrhythmia morphology identified from 15 appropriate shocks were ventricular fibrillation ($n = 11$), polymorphic VT ($n = 2$) and monomorphic VT ($n = 2$), confirming the importance of ventricular fibrillation and polymorphic VT as a clinically significant arrhythmia in children with HCM [42]. These results differ from what has been reported in the adult HCM population in whom monomorphic VT and ventricular fibrillation predominate [10].

The safety of EPSs has been questioned following reports of HCM patients refractory to defibrillation [25, 51]. No complication related to failure of defibrillation was encountered in the current pediatric study or in an earlier adult study [16].

Other Risk Factors for Sudden Death

Risk factors for SD vary between different adult age groups with HCM [6, 9, 27, 32, 37, 38, 45, 50], but most studies include few patients aged less than 21 year of age. As in our study, Decker et al. [12] were unable to show that risks factors identified for SD in adults predicted SD in a pediatric HCM cohort of 96 patients. However, this might have been due to the limited statistical power of the two studies.

Syncope

Syncope has been regarded as an important predictor of SD in children given the low predictive value of other clinical/laboratory findings [32]. By comparison, syncope in adults had low predictive value except in combination with a family history of SD [14]. In this study, syncope/presyncope was of marginal statistical significance in univariate analysis.

Abnormal Blood Pressure Response to Exercise

In approximately one-third of HCM patients, systolic BP does not change or decreases during exercise, consistent with the current report. Lack of BP response to exercise has been attributed to exaggerated vasodilatory responses [27] and to abnormal reflex responses in venous capacitance [50], increasing LVOT obstruction, myocardial ischemia or abnormal diastolic relaxation. Abnormal BP response to exercise might be an independent predictor of CA in adults <40 years but not >40 years [17, 45]. Consistent with previous reports, the current study failed to show an association between exercise-induced hypotension and an AE [5, 38].

Family History of Sudden Death

A malignant family history of SD has been associated with increased adverse events [17], but detection of "malignant" genetic mutations did not always predict adverse outcomes [6]. In this study, a family history of SD was not predictive of an AE.

Nonsustained VT on Holter

Ventricular tachycardia on Holter occurred in 18% of children in this study and was not a risk marker. The incidence of VT on Holter is generally higher in adult HCM patients (14–50%) [9, 17, 21, 37] and has variable prognostic significance [9].

Myocardial Ischemia

Myocardial ischemia detected by thallium-201 scintigraphy was a frequent finding in this study. An earlier report suggested that myocardial ischemia was common in children with a history of CA or syncope [13]. It remains uncertain whether myocardial bridging contributes to ischemia and SD in both children and adults [36, 44, 48, 53].

Time-Limited Nature of Risk Stratification

Risk stratification for AEs should be considered a time-limited process in children. In medicine, risk is thought to evolve over time, usually increasing. Because of age-related changes in the myocardial substrate (changes in OT gradients, ST, and fibrosis), the substrate for AEs is likely to alter. The median age of our EP group was 14.4 ± 3.9 years, representing early adolescence. A 5-year time frame represents the transition to late adolescence and early adulthood, when myocardial septal hypertrophy might be nearing a plateau. We envisioned but do not have the data

to support a reassessment at 18–21 years of age. Consequently, for smaller/younger patients for whom ICD implantation is technically unattractive, noninducibility, age < 13 years, and a ST < 20 mm might be viewed as good justification for delaying implant, but only until the patient is older and larger, when the patient should be reassessed. However, initial risk assessment should not be delayed to late adolescence because for the 13 patients who presented with an AE prior to NIH evaluation, their mean age at NIH evaluation was 13.8 ± 3.5 years.

Limitations

The effect of patient choice on enrollment, testing, and data collection cannot be quantified. Not all children evaluated at the NHLBI underwent PVS; technical limitations and younger patient age affected decisions as to whether to perform certain invasive procedures. Most patients were symptomatic at presentation and were treated with what was considered to be the best available therapy for hemodynamic and electrophysiologic abnormalities. The effect of such therapy on outcome is also unknown, although recent data have confirmed the absence of efficacy of pharmacologic treatment in the prevention of sudden death in HCM [35]. The small number of adverse events in our study group somewhat limited the predictive power of our analysis.

Whereas the children evaluated at the NHLBI might be considered a referral population, our study group is not unlike other reported pediatric HCM series. The incidence of an AE in the study reported by Östman-Smith et al. [41] from a multicenter European HCM study group was 39/150 (26%), higher than what was observed in our study population 22/131(17%). Olivotto et al. [39] found the incidence of severe ST ($\geq$30 mm) in patients $\leq$15 years to be 24%, which was lower than in our study 33%.

Conclusions

One hundred thirty-one children and adolescents with HCM but no prior AE had an annualized AE rate of 2% per year. Patients with an AE prior to evaluation continued to have a high incidence of subsequent AEs (11% per year). The current study found in univariate analyses that ST and VT induced at EPS were significant predictors of AEs in children with HCM. Older age and presyncope or syncope were of marginal statistical significance. However, perhaps due to the limited statistical power of our study, ST, age, presyncope/syncope, and inducible VT were not independently predictive of risk for an AE.

Our data suggest that ICD implantation has stronger justification when both ST is $\geq$20 mm and there is a positive EP test (5-year event rate for AE = 23%) than when either factor occurs alone. Nevertheless, the ST $\geq$ 20 mm and EP negative group had a 5-year event rate of 10% and was at significantly greater risk ($P = 0.04$) than the ST < 20 mm group. Thus, newer technologies using smaller ICD leads and devices with improved algorithms for VT detection might suggest that ST $\geq$ 20 mm alone is sufficient to justify ICD implantation.

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