The risk of sudden death in children with hypertrophic cardiomyopathy

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Key points

- Sudden cardiac death (SCD) is the most common cause of death in childhood HCM and occurs more frequently than in adult patients
- Important differences between childhood and adult cohort have been described with the implication the paediatric specific risk stratification methods are needed.
- Current guidelines using cumulative risk factors to guide ICD implantation have been shown to have limited discrimination
- New paediatric models have been developed to allow clinicians to calculate individualised estimates of 5-year risk of SCD

Clinics care points

- Ensure systematic risk stratification for SCD events is performed for all childhood patients with HCM
- Risk stratification for childhood HCM should be systematic and include assessment of left ventricular hypertrophy, left atrial diameter, left ventricular outflow tract gradient, presence of malignant arrhythmias on ambulatory ECG monitoring and unexplained syncope.
- Consider using a paediatric specific risk model (HCM Risk-Kids or PRiMACY) to calculate individualised estimates of 5-year SCD risk.

Abstract

Sudden cardiac death (SCD) is the most common cause of death in childhood HCM and occurs more frequently than in adult patients. Risk stratification strategies have traditionally been extrapolated from adult practice but newer evidence has highlighted important differences between childhood and adult cohorts, with the implication that paediatric-specific risk stratification strategies are required. Current guidelines use cumulative risk factor thresholds to recommend ICD implantation but have been shown to have limited discriminatory ability. Newer paediatric models have been developed that allow clinicians to calculate individualised estimates of 5-year risk allowing, for the first time, personalisation of ICD implantation decision making. This article describes the pathophysiology, risk factors and approach to risk stratification for SCD in childhood HCM and highlights unanswered questions.

Introduction

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular hypertrophy (LVH) in the absence of abnormal loading conditions[1]. The prevalence of HCM during childhood is estimated at 3 in 100,000[2] births, with a reported annual incidence of less than 0.5/100,000[2-4] from population registry studies, making it the second most common cardiomyopathy presenting during childhood. The underlying aetiology is heterogeneous and includes inborn errors of metabolism (IEM), RASopathy syndromes and neuromuscular disease, but most cases of childhood-onset HCM, even in very young children, are caused by variants in sarcomere protein genes[5-9]. The natural history and overall outcome of childhood HCM is highly variable and largely dependent on the underlying aetiology and age of presentation. Children with presumed sarcomeric HCM have a relatively good prognosis, with an estimated 5-year survival above 80% but patients with syndromic disease (IEM or RASopathy syndromes) or infantile onset (in the first year of life) are recognised to have a worse overall prognosis[5, 7, 8]. The majority of deaths occurring in infancy are heart failure-related but sudden cardiac death (SCD) is the most common cause of death during childhood[5, 10]. Identifying those at highest risk of malignant ventricular arrhythmias is therefore an important part of clinical care. This article describes the pathophysiology, risk factors and approach to risk stratification for SCD in childhood HCM.

Pathophysiology of sudden death in HCM

The hallmark macroscopic and histological features of HCM include myocyte disarray, fibrosis and small vessel disease. The extent of myocyte disarray was associated with SCD in a post-mortem study of HCM[11] but the mechanism by which this pro-arrhythmic substrate translates into an increased risk of ventricular arrhythmias is incompletely understood. It is likely that the pathophysiology is multifactorial, with LV hypertrophy causing dispersion of repolarisation, myocardial disarray disrupting cell alignment, and areas of fibrosis creating a localised conduction block and altered calcium sensitivity[12, 13]. The observation that the overall incidence of SCD in HCM is low[16,17] despite these universal underlying structural and biochemical abnormalities suggests that transient

electrical (such as premature ventricular ectopics, supraventricular tachycardias) or structural changes (such as ischaemia, or dynamic outflow tract obstruction) in the context of a pro-arrhythmic substrate are the trigger for ventricular arrhythmias. The primary underlying arrhythmia resulting in SCD is usually ventricular fibrillation (VF) or ventricular tachycardia (VT) in the majority of cases.

Risk of SCD in paediatric HCM

Early studies in small, highly selected patient groups from tertiary centres reported a high incidence of SCD during childhood of up to 7% per year[14, 15]. Over time, data from larger, more representative population cohort studies have suggested much lower SCD incidence rates, with current estimates between 0.8-2% per year[10, 16, 17]. Outside of infancy, SCD is the most common cause of death in paediatric HCM and recent population studies have reported that arrhythmic events are responsible for more than 50% of adverse events occurring within 10 years of diagnosis, with a cumulative incidence of 8.8%[10]. A single study has described a higher incidence of SCD in the pre- and early adolescent years (aged 9-14yrs), but this has not been confirmed in other populations[18]. It is clear, however, that the incidence of SCD reported in paediatric population studies is substantially higher than that seen in similar sized adult cohorts (<0.8%),[19, 20] with the result that children are considered to be at higher risk of arrhythmic events. This perception has recently been confirmed using longitudinal datasets from the Sarcomeric Human Cardiomyopathy Registry (SHaRE), in which paediatric onset-HCM patients (aged 1-18 years) were 36% more likely to experience an arrhythmic event during follow up compared to those diagnosed in adulthood[10].

SCD prevention

No medical treatment is currently recommended as preventative therapy for SCD in HCM. High dose beta-blockade (up to 23mg/kg propranolol daily) has been described to reduce the risk of SCD in a single centre study[51] but these results have not been independently confirmed in either paediatric or adult populations. The mainstay of preventative therapy is the implantable cardioverter defibrillator (ICD), which has been shown to be effective at terminating malignant ventricular arrhythmias in children and adults with HCM[21, 22]. Children who have previously

experienced a malignant arrhythmia are widely accepted to be at high risk of future arrhythmic events and are recommended for a secondary prevention ICD implantation as a class I indication[1, 23]. In a recent national cohort study of children with HCM and an ICD from the United Kingdom (UK), almost two thirds of patients with a secondary prevention device received an appropriate ICD therapy for a ventricular tachyarrhythmia within 5 years of follow up[24]. However, this is at the expense of an increased risk of device-related complications (including lead fracture or migration, infective endocarditis or venous occlusion) and inappropriate therapies compared to adult patients. Retrospective population studies have reported that, over a relatively short follow-up time (mean 5-7 years), ICD-related complications occur in up to 30% of childhood cohorts, most commonly system infection, lead fracture/failure or need for lead repositioning/replacement due to somatic growth[22, 24]. Historically, this group of patients have been considered to be at high risk of inappropriate therapies, which have been reported to occur in up to one third of patients from population series[21, 22, 25, 26]. More recent data from the United Kingdom suggests that this risk may not be as high as previously thought and comparable to adult patients (≈8%)[24, 27]. However, as this younger group of patients has an ongoing lifetime exposure to these risks and no device or programming strategies have been identified to reduce this risk[24], the balance between benefit and harm for primary prevention ICD implantation is particularly important. In this context, it is essential to accurately identify those children at highest risk who would benefit most from ICD implantation.

Risk factors for SCD in paediatric HCM

Until recently, our understanding of the clinical risk factors for SCD events in childhood HCM was limited and largely extrapolated from adult literature. The first systematic review and meta-analysis of risk factors in childhood disease was performed in 2017 and identified four major clinical risk factors associated with SCD events in two or more univariable analyses: previous VF or sustained VT; unexplained syncope; nonsustained ventricular tachycardia (NSVT); and extreme LVH (defined as a LV maximal wall thickness ≥30mm or Z score ≥6)[28]. The number of studies available for inclusion in this meta-analysis was small (n=23) and

individual studies reported small, often heterogeneous, patient cohorts (all but 3 had less than 150 participants). Nonetheless, this provided the first paediatric-specific systematic assessment of risk factors for SCD events. This study also suggested important differences between adult and paediatric risk factors. In particular, although there is robust evidence to support the use of family history of SCD in adult patients, there is insufficient evidence to support its use during childhood. Only one study reported a significant association in a small cohort of patients with an ICD who had *a priori* been determined to be at high risk of malignant arrhythmias by treating clinicans[25]. Possible explanations for this include a higher prevalence of *de novo* variants in childhood HCM, low proportion of sarcomeric disease in the included cohorts, or incomplete reporting of family history. Recent multi-centre collaborative population studies (including HCM Risk-Kids[16], PRiMACY[17] and SHaRE[10]) have provided further evidence and novel insights into the risk factors identified by this meta-analysis, as well as evidence for additional risk factors, such as left atrial diameter and left ventricular outflow tract obstruction (LVOTO). A brief description of the main risk factors for SCD in childhood HCM can be found below and in table 1.

Left ventricular hypertrophy

Recent large paediatric cohort studies have confirmed the importance of LVH for risk stratification, but the most appropriate measure of LVH is unknown as published studies vary widely in their definition and measure [including interventricular septal thickness (IVST), LV posterior wall thickness (LVPWT), septal thickness:cavity ratio, BSA-corrected measurements and absolute maximal left ventricular wall thickness (MLVWT)[16, 17, 29, 30]]. Extreme LVH (defined as maximal left ventricular wall thickness (MLVWT ≥ 30mm or Z score ≥6) is recommended as a threshold for ICD implantation decisions in current North American and European risk stratification guidelines[1, 23]. The evidence for using this particular threshold is limited and the interpretation of all z-score thresholds is inherently hampered by the use of different normative population data, each of which will provide a different z-score for the same individual. The meta-analysis identified extreme LVH as a major risk factor with a combined hazard ratio of 1.8 (95% CI 0.75-4.32), although this did not reach threshold for significance (p value

0.19). Nonetheless the implication of using a threshold is that risk increases linearly with increasing LVH. Recent publications from large population studies (HCM Risk-Kids[16] and PRIMaCY[17]) have challenged this view, showing that a non-linear relationship exists between measures of LVH and SCD risk, with the result that beyond a particular threshold, risk plateaus or starts to fall. The mechanism behind these observations is unknown but it is in keeping with the relationship between MLVWT and SCD risk in a large adult HCM study[31].

Non-sustained ventricular tachycardia (NSVT)

NSVT is defined as ≥3 consecutive ventricular beats occurring at a rate greater than 120bpm lasting less than 30 seconds[1]. The true prevalence of NSVT in childhood HCM is unknown, with estimates from retrospective cohorts between 8-30%[16, 17, 22, 30, 32]. It was identified as a major risk factor in the meta-analysis with a pooled hazard ratio of 2.13 (95% CI 1.21-3.74, p value 0.0009)[28]. No study has assessed the importance of frequency, rate or length of NSVT detected on ambulatory ECG in childhood and the significance of exercise induced arrhythmias is also unknown.

Unexplained syncope

Unexplained syncope, presumed secondary to malignant arrhythmias, has been identified as a risk factor for SCD in childhood HCM with a pooled odds ratio of 2.64 (95% CI 1.21-5.79, p value 0.02). The timing of a syncopal event has been shown to be important in adult HCM cohorts (recent syncope (within 6 months) associated with a 5-fold increased risk[33]) but has not been explored in paediatric cohorts.

Traditional approach to risk stratification

The traditional approach to risk stratification in childhood HCM is based on conventionally accepted risk factors largely extrapolated from adult practice (extreme LVH, unexplained syncope, NSVT and family history of SCD)[1, 23]. As has been discussed above, some of these traditional risk factors have insufficient evidence to support their use in childhood disease. Reflecting the finding in adult cohorts that coexistence of multiple risk factors was associated with an increased

risk of SCD[34], cumulative risk factor thresholds are recommended in current guidelines to guide ICD implantation decisions. This approach to risk stratification provides relative rather than absolute estimates of risk and has been shown in an external validation study from UK to have only moderate discriminatory ability [c-0.62 (95% CI 0.55-0.70)], leading to unnecessary ICD implantation in many[35]. Current risk stratification guidelines continue to recommend this practice although the number of risk factors required to meet the threshold for considering ICD implantation differs (≥1 risk factor in the AHA/ACC guideline[23] and ≥2 risk factors in the ESC guidelines[1]). The newer North American guidelines published in 2020 suggest that additional risk factors, including the presence of LGE on CMRI and LV systolic function, could also be helpful in select paediatric patients. Figure 1 shows the current guidelines for risk stratification in childhood disease.

Personalised approach to risk stratification for childhood HCM

The limited ability of current guidelines to discriminate between high and low risk patients has led to interest in developing a more personalised approach to risk stratification for these patients. Current risk stratification practice for adults with HCM has moved away from the traditional approach of using cumulative risk factors in favour of using a validated risk prediction model that provides individualised estimates of risk. The HCM Risk-SCD model uses readily available clinical risk factors to calculate individualised estimated for 5-year SCD risk to guide implantation decisions, but is not validated for use in paediatric populations (< 16 years of age)[20]. External validation of the adult risk model in a childhood cohort showed it to have poor correlation between predicted and observed risk (under-estimated for all risk groups), confirming that it's use should not be extrapolated to childhood patients[16]. In 2019, the first validated paediatric-specific risk model for SCD was developed and published (HCM Risk-Kids) in a large (n=1024), international cohort of children with non-syndromic HCM[16]. The new paediatric model uses 5 readily available clinical predictors pre-selected from over 3 decades of published literature (MLVWT Z score, LA Z score, Maximal LVOT gradient, NSVT and unexplained syncope) assessed at the time of baseline clinical evaluation to calculate personalised estimates of 5-year SCD risk. Age was not included as a predictor variable in the model as, outside of infancy, its role in

prognosis remains unclear[10, 18]. However, the effect of age may have been mitigated by accounting for somatic growth using body surface area corrected, rather than absolute 2D, echocardiographic measurements. Internal validation of HCM Risk-Kids showed that the model had better discrimination between high- and low-risk patients than current paediatric guidelines with good calibration between the expected and observed risk (Figure 2). The performance is similar to that reported in adult cohorts for the adult HCM Risk-SCD model (C-Index 0.69 vs 0.70)[36]. The HCM Risk-Kids model is available online (https://hcmriskkids.org) allowing clinicians to calculate individualised estimates of risk for the first time and external validation studies have been completed to confirm the superior performance of this model in an independent study population.

Following the publication of HCM Risk-Kids, an alternative paediatric specific risk model (PRIMaCY) was developed and published using a largely North American cohort (n=572)[17]. The final models are similar despite differences in their approaches to risk factor selection, with the exception that PRIMaCY includes two measures of LVH (IVST and LVPWT) and age as an independent predictor. External validation of this model in a small cohort of 285 patients from the SHaRe consortium confirmed that the performance of the model was superior to current guidelines (C-statistic 0.707) and similar to the HCM Risk-Kids model. No direct comparison of the two models has been performed, although given their similarities, it is plausible that their performance will be similar. A comparison of the two models is shown in table 2.

A final alternative model that has been proposed for use in childhood HCM is the ECG risk score, which is comprised of 8 parameters (deviation in QRS axis, pathological T wave inversion in limb or precordial leads, ST-segment depression, dominant S wave inV4, limb-lead amplitude sum, 12-lead amplitude duration product and QTc). The 12 lead ECG provides valuable quantitative and qualitative information about a patient's phenotype and the ECG risk score has been described to predict arrhythmic events with a high negative and positive predictive value (99% and 45% respectively)[37]. Until recently, these findings had not been confirmed or refuted in an external validation study. However, a recent external validation

study in 356 children from HCM Risk-Kids cohort showed the ECG risk score had only moderate discriminatory ability (similar to the current guidelines but lower than HCM Risk-Kids or PRIMaCY) to predict 5-year SCD events with a low positive predictive value (10%)[38]. Despite the majority of patients having ECG abnormalities, no individual or combined ECG score was associated with arrhythmic events in this independent population. This suggests that the ability of the 12 lead ECG to improve risk stratification in childhood HCM is limited.

Future directions

In the past 5 years, the development of paediatric-specific risk models has allowed clinicians to calculate individualised estimates of risk for the first time and deliver personalised care. This represents a significant advance for risk stratification of childhood disease and patient management. These models have not yet been adopted by clinical guidelines and further validation studies are required to assess performance in real world clinical practice, which will be facilitated by the availability of both models on freely available public websites. Such studies would also help determine if a 5-year risk threshold is appropriate for recommending ICD implantation in childhood HCM analogous to that seen in the adult guidelines. Although both models outperform current risk stratification guidelines, they remain imperfect and additional risk factors are likely to be important for prognosis. Late gadolinium enhancement (LGE) on CMRI is a marker of fibrosis and has been shown to be a risk factor for SCD in adult cohorts independently of traditional clinical risk factors with an apparent linear association between risk and proportion of LGE[39]. In childhood disease, LGE has been shown to be associated with the degree of LV hypertrophy and to increase during follow up[40, 41]. Its role as an independent risk factor has not clearly been established but a single centre study has reported improved discriminatory performance of both the current guidelines and the HCM Risk-Kids model with the addition of LGE as either a binary or continuous variable[42]. Future multi-centre studies are required to investigate the role of LGE in paediatric risk stratification.

The role of genotype in risk stratification for childhood HCM remains unclear, with studies reporting conflicting findings. Although patients with a disease-causing sarcomeric variant have been reported to have a higher cumulative life time risk of

adverse events[43], recent data, including over 1000 children with HCM, from the SHaRE registry did not find a higher lifetime risk of arrhythmic events for genotype positive patients[10]. Inclusion of genotype status (positive or negative) in the PRIMaCY model did not significantly improve model predictions[17]. Efforts to explore genotype-phenotype correlations in HCM have been limited by significant genetic heterogeneity and variable or incomplete age-related penetrance, but insufficient evidence currently exists to support the use of genotype at the level of the gene or gene region in risk stratification for childhood disease. As yet unidentified genetic and epigenetic modifiers are likely to play an important role in the expression of sarcomeric disease and a variant specific approach, including assessment of the contribution of common genetic variants, is likely to be needed[44]. Such analysis will be limited by small numbers of patients with individual variants and will require multicentre collaborative efforts.

Finally, work to date has focused on patients with HCM secondary to sarcomeric protein variants and little is known about risk stratification in patients with non-syndromic disease (eg RASopathy or inborn errors of metabolism). This group of patients is traditionally considered to be at lower risk for arrhythmic events, although population studies have reported SCD events in an important minority[5, 52, 53]. Future studies are required to determine if risk stratification methods developed in sarcomeric disease can be extrapolated to non-syndromic patients and identify disease-specific risk factors.

Conclusions

SCD is the most common cause of death outside of infancy in childhood HCM and occurs more frequently than in adult patients. Systematic evaluation of individual risk factors has revealed important differences between childhood- and adult-onset disease and led to the development of paediatric specific risk models. These models allow clinicians to calculate individualised estimates of 5-year risk for the first time and are an important tool for shared ICD implantation decision making. Future studies are required to investigate additional risk factors and provide real-life validation to further improve risk stratification for childhood HCM.

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Major risk factor	Clinical risk factor	Comment
Major risk factors	Previous VF/VT	Pooled HR 5.4 (95% CI 3.67-7.95, P value <0.001). Pooled OR 5.06 (95% 2.11-12.17, P value <0.001)
	Unexplained syncope	Pooled HR 1.89 (0.69-5.16, p value 0.22). Pooled OR 2.64 (1.21-5.79, p value 0.02)
	NSVT	Pooled HR 2.13 (95% CI 1.21-3.74, p value 0.0009). Pooled OR 2.05 (96% CI 0.98-4.28, p value 0.06).
	Extreme LVH	Pooled HR 1.8 (95% CI 0.75-4.32, p value 0.19). Pooled OR 1.70 (95% CI 0.85-3.40, p value 0.13). The most useful measure of LVH for risk stratification is unknown.
Other putative risk factors	LA dilatation	Left atrial size was not included as a major risk factor in the meta-analysis but a significant association has subsequently been reported in four studies [16, 17, 30, 45].
	LVOT gradient	The definition of LVOT obstruction varies in the literature. Increasing LVOT gradient has been linked to SCD[30] [46]and two large studies have described an inverse relationship between LVOT gradient and risk in childhood[16, 17].
	Family history of SCD	Only 1/10 studies reported a significant association between a family history of SCD and SCD event[25]. Limited evidence to support its use as a risk factor during childhood.
	Age	The role of age in SCD is not fully understood. SCD risk has been reported to be increased in pre-adolescent years (9-14yrs)[18] and children presenting in infancy are believed to be at lower risk [7, 47]
	12 lead ECG	Proposed 12 lead ECG features include; measures of LV hypertrophy[29] and abnormal repolarisation[37] but a recent large study showed no association between individual ECG parameters and risk[38]. An ECG risk score has

	been developed by Ostman-Smith et al[37] but this was shown to have only moderate discriminatory ability in an external validation study[38].
LGE on CMRI	LGE has been shown to increase during childhood and is associated with left ventricular hypertrophy[40]. It is unclear if LGE is an independent risk factor for SCD[41, 48].
Genotype	The role of genotype in SCD risk during childhood is not fully understood. In small cohorts, the presence of a pathogenic sarcomeric mutation has been described to be associated with worse prognosis[49] and certain genotypes associated with higher arrhythmic risk[50].

Table 1: Risk factors for sudden cardiac death in childhood HCM. Adapted from Norrish et al[28]

	HCM Risk-Kids	PRiMACY
Development cohort		
Sample size	1024	572
Age	≤ 16	≤ 18
Number of SCD events		
Predictor Variables		
LVMWT Z score	X	
IVST Z score		X
LVPWT Z score		X
LA Z score	X	X
Maximal LVOT gradient (mmHg)	X	X
NSVT	X	X
Unexplained syncope	X	X
Age		X
Model Validation		
Internal	0.69 (95% CI 0.66-0.72)	0.75 (CI not provided)
External	Ongoing	0.71 (CI not provided)
Model website	https://hcmriskkids.org	https://primacycalculator.com

Table 2: Comparison of personalised risk models for SCD risk stratification in childhood HCM[16, 17].

	Recommendations	Class
ACCF/AHA	An ICD is recommended if prior event (SCD, VF, sustained VT)	1
	An ICD is reasonable if one or more risk factors (family history SCD, massive hypertrophy, unexplained syncope, apical aneurysm, ejection fraction ≤50%, NSVT	2a
	An ICD may be considered if extensive LGE on CMR	2b
ESC	An ICD is recommended if prior cardiac arrest or sustained VT	1
	An ICD should be considered in children with two or more major paediatric risk factors (extreme LVH, unexplained syncope, NSVT, Family history of SCD)	2a
	An ICD may be considered in children with a single major paediatric risk factor if overall considered to be a net benefit from ICD therapy	2b

Figure 1: Risk stratification guidelines for SCD for childhood HCM a) American College of Cardiology
Foundation/American Heart Association (2020) b) Eurooean Society of Cardiology (2014)

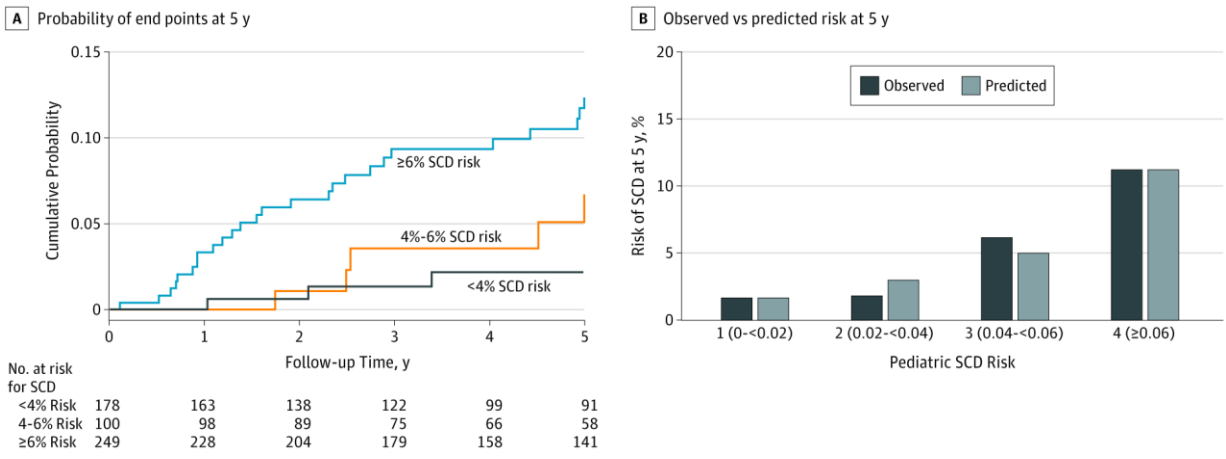

Figure 2: Performance of HCM Risk-Kids model A) Kaplan Meier curve showing cumulative probability of meeting SCD end point within 5 years by estimated clinical risk group b) Comparison of observed and predicted risk by clinical risk group. Reproduced with permission from Norrish et al.[16]