

Prevention of sudden cardiac death in childhood-onset hypertrophic cardiomyopathy

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Abstract

Sudden cardiac death (SCD) is the most common cause of death in children with HCM. Although recent population-based studies have shown that SCD rates are lower than previously thought, it still occurs more frequently than in adult patients, highlighting the importance of accurate identification of those at risk. The traditional approach to risk prediction in childhood-onset HCM, using cumulative risk factor thresholds and adopted by current international guidelines, has involved extrapolation of adult data, but recent evidence has demonstrated that this approach does not accurately discriminate high-risk from low-risk individuals. In response to this knowledge gap, novel paediatric-specific risk stratification models have been developed that allow calculation of individualised estimates of SCD risk and enable a personalised and shared decision-making approach to ICD implantation.

Introduction

Hypertrophic cardiomyopathy (HCM), defined as left ventricular hypertrophy (LVH) in the absence of abnormal loading conditions¹, has an estimated population prevalence in childhood of approximately 3 per 100,000² and an annual incidence of less than 0.5/100,000²⁻⁴. Although the underlying aetiology, particularly in childhood, is heterogeneous, including malformation syndromes (e.g. Noonan syndrome and related disorders), inborn errors of metabolism (e.g. Pompe disease and storage disorders), and neuromuscular disease (e.g. Friedreich ataxia), most cases, even in very young children, are caused by variants in one or more cardiac sarcomere protein genes⁵⁻⁹. Age at presentation and aetiology are major determinants of natural history and overall outcome; children with non-syndromic HCM generally have a good prognosis (estimated 5-year survival above 80%) but those with metabolic or malformation syndromes, and those presenting with heart failure symptoms in infancy (in the first year of life) have substantially poorer outcomes^{5, 7, 8}. Beyond infancy, sudden cardiac death (SCD) is the most common cause of death during childhood and adolescence^{5, 10} and identifying those individuals with HCM at highest risk of SCD is a major aspect of clinical care in specialist paediatric HCM centres.

Pathophysiology of SCD in HCM

Hypertrophic cardiomyopathy is characterised histologically by the presence of myocyte disarray, interstitial fibrosis and small vessel disease. These features are thought to act as a substrate for ventricular arrhythmia, and the extent of myocyte disarray has been associated with SCD at post-mortem evaluation¹¹. The pathophysiological mechanisms leading to the generation of malignant arrhythmias are likely multifactorial, and include dispersion of repolarisation caused by LVH; disruption of cell alignment due to myocyte disarray; and localised conduction block and altered calcium sensitivity related to fibrosis^{12, 13}. This combination of structural and biochemical abnormalities would be expected to result in an almost universal incidence of ventricular arrhythmia; the fact that the overall incidence of SCD in HCM is relatively low suggests that additional transient electrical (e.g. premature ventricular ectopy or atrial arrhythmias) or structural changes (e.g. myocardial ischaemia) are required to trigger malignant ventricular arrhythmias and SCD.

Preventing SCD in childhood HCM

Early studies in small, highly selected childhood cohorts reported an annual incidence of SCD of up to 7%^{14, 15}, leading to HCM being considered a highly malignant disease in children. The advent of data from larger, more representative population-based studies has shown SCD rates between 0.8-2% per year^{10, 16, 17}, much lower than the initial reports but nevertheless substantially higher than those seen in adults with HCM (<0.8%),^{18, 19}. Recent longitudinal datasets from the Sarcomeric Human Cardiomyopathy Registry (SHaRE) have demonstrated that in childhood-onset HCM patients, arrhythmic events are responsible for more than 50% of adverse events occurring within 10 years of diagnosis, with a cumulative incidence of 8.8%, and that children with HCM are 36% more likely to experience an arrhythmic event during follow up compared to those diagnosed in adulthood¹⁰.

Although high dose beta-blockade has been reported to reduce the risk of SCD in a small single-centre study²⁰, this has not been independently confirmed in other paediatric populations and there is no convincing evidence that pharmacological therapy alone can prevent sudden cardiac death. The mainstay of preventative therapy, therefore, is the implantable cardioverter-defibrillator (ICD), which has been shown to be effective at terminating malignant ventricular arrhythmias in both children and adults with HCM^{21, 22}. However, compared to adults, ICD implantation in children is associated an increased risk of device-related complications (including lead fracture or migration, infective endocarditis or venous occlusion) and inappropriate therapies. Data from retrospective population studies suggest that ICD-related complications occur in up to 30% of childhood cohorts over a relatively short follow-up time (mean 5-7 years)^{22, 23}. Previous childhood ICD studies have raised concerns regarding high rates of inappropriate therapies^{21, 22, 24, 25}, but recent data from a national cohort study of children with HCM and an ICD from the United Kingdom (UK) suggest that, with current management strategies, this risk may not be as high as previously thought and is comparable to that reported in adults (\approx 8%)^{23, 26}. Nevertheless, it is clear that, as children with an ICD will have a lifelong exposure to these risks and no device or programming strategies have been identified to reduce this risk²³, accurate identification of those children at highest risk who would benefit most from ICD implantation while minimising the risk of complications is essential.

Identifying those at risk

Implantation of a secondary prevention ICD in children who have previously experienced a sustained malignant arrhythmia is a class I indication in European and North American guidelines^{1, 27} and recent data from the UK have shown that almost two thirds of patients undergoing secondary prevention ICD implantation received an appropriate ICD therapy for a ventricular tachyarrhythmia within 5 years of follow up²³. Identifying those patients who have not yet had a sustained ventricular arrhythmia but are at risk of SCD, however, is more challenging. Until recently, data on clinical risk factors for SCD events in childhood-onset HCM were scarce and largely extrapolated from adult cohorts. In 2017, we performed the first systematic review and meta-analysis of risk factors in children with HCM, identifying four major risk factors associated with SCD events in two or more univariable analyses (table 1): previous VF or sustained VT; unexplained syncope; nonsustained ventricular tachycardia (NSVT); and extreme LVH (defined as a LV maximal wall thickness ≥ 30 mm 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 and heterogeneous cohorts, but suggested important differences between adult and paediatric risk factors. In particular, there was insufficient evidence to consider a family history of SCD as a risk factor in children with HCM, possibly related to a higher prevalence of *de novo* variants in childhood HCM; the inclusion of non-sarcomeric disease; under-reporting of family history in paediatric cohorts; or the fact that follow-up times in paediatric studies tend to be relatively short and children with HCM may not express their full phenotype until they reach adult age.

Current risk stratification recommendations in childhood HCM

Current guidelines from the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology (AHA/ACC) use a cumulative risk factor approach to recommend ICD implantation in children with HCM (≥ 1 risk factor in the AHA/ACC guideline²⁷ and ≥ 2 risk factors in the ESC guidelines¹, as class II indications). This approach is based on clinical risk factors largely extrapolated from adult practice (extreme LVH, unexplained syncope, NSVT and family history of SCD)^{1, 27} and provides relative rather than absolute estimates of risk. However, the only study to externally validate this approach

showed that it has only modest discriminatory ability [c-statistic 0.62 (95% CI 0.55-0.70)], leading to unnecessary ICD implantation in many children²⁹. The 2020 AHA/ACC guidelines suggest that additional risk factors, including the presence of LGE on CMRI and LV systolic function, may help to improve the performance of the current recommendations, but this has not been evaluated in children.

A new individualised approach to SCD risk stratification in childhood HCM

In response to the lack of paediatric-specific evidence and the limited ability of current guidelines to accurately discriminate between high and low risk patients, a large multicentre international collaboration was established (the International Paediatric Hypertrophic Cardiomyopathy Consortium - IPHCC) to develop a more personalised approach to risk stratification for children with HCM, mimicking the move towards individualised risk prediction in adult HCM. The HCM Risk-SCD model, adopted by the ESC HCM guidelines, uses readily available clinical risk factors to calculate individualised estimated for 5-year SCD risk to guide ICD implantation, but crucially is not validated for use in children < 16 years of age¹⁹. External validation of the HCM Risk-SCD model in IPHCC cohort showed it to have poor correlation between predicted and observed risk, underestimating for all risk groups, confirming that should not be used in childhood HCM patients¹⁶. In 2019, the first validated paediatric-specific risk model for SCD was developed (HCM Risk-Kids), based on data from 1024 children with non-syndromic HCM from the IPHCC¹⁶. This new paediatric model uses 5 readily available clinical predictors assessed at the time of baseline clinical evaluation, selected *a priori* from the published literature (MLVWT Z score, LA Z score, LVOT gradient, NSVT and unexplained syncope), to calculate personalised estimates of 5-year SCD risk. Internal validation of HCM Risk-Kids showed it to have superior discriminatory ability than the current international guidelines, with good calibration between the expected and observed risk (Figure 1), and an overall performance similar to that reported for the adult HCM Risk-SCD model (C-Index 0.69 vs 0.70)³⁰. External validation of HCM Risk-Kids has been completed (currently under review) and the model is available online (<https://hcmriskkids.org>), allowing clinicians to calculate individualised estimates of risk for the first time.

Following the publication of HCM Risk-Kids, an alternative paediatric specific risk model (PRIMaCY) was developed using a largely North American cohort (n=572)¹⁷ and externally validated in a small cohort of 285 patients from the SHaRe consortium. Performance of the model was superior to current guidelines and similar to the HCM Risk-Kids model (C-statistic 0.707). Despite differences in risk factor selection approaches, the clinical parameters included in PRIMaCY are very similar to those in HCM Risk-Kids, with the exception that PRIMaCY includes two measures of LVH (septal and posterior wall thickness, rather than MLVWT) and age as independent predictors (table 2). Age was not included in the HCM Risk-Kids model as its role in prognosis remains unclear beyond infancy^{10, 31} and its inclusion in post-hoc did not improve its performance. It is likely, however, that any effect of age on risk may be accounted for by the use of body surface area-corrected (rather than absolute) echocardiographic measurements.

Knowledge gaps

The development of paediatric-specific individualised risk prediction models represents a significant advance in the management of childhood HCM. Although superior to current paediatric risk stratification guidelines, it is likely that their performance can be refined by the inclusion of additional risk factors. Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) has been shown to be an independent risk factor for SCD in adults with HCM³². Data in children are limited, but recent studies have suggested that LGE is associated with the degree of LVH and correlates with disease progression^{33, 34}. Its role as an independent risk factor has not been established, but a recent 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 variable³⁵. Future multi-centre studies are required to investigate the role of LGE in paediatric risk stratification.

In contrast, a recent study from the IPHCC cohort did not show an improvement in the performance of the HCM Risk-Kids model with the addition of individual and combined electrocardiographic (ECG) parameters, suggesting a limited role for the ECG in risk stratification in childhood HCM³⁶.

The role of genotype in risk stratification for childhood HCM remains unclear, and recent data from the SHaRE registry did not find a higher lifetime risk of arrhythmic events for genotype positive children with HCM compared to those without a genetic variant identified¹⁰. Furthermore, inclusion of genotype in the PRIMaCY model did not significantly improve its performance¹⁷. It is likely that as yet unidentified genetic and epigenetic modifiers play a role in the expression of sarcomere protein gene variants and a variant-specific approach, including assessment of the contribution of common genetic variants, is likely to be needed³⁷. This will require further multicentre collaborative efforts.

Finally, there are very little data on risk stratification in patients with syndromic disease. Current risk stratification algorithms and models, including HCM Risk-Kids and PRIMaCY, exclude patients with RASopathy syndromes and metabolic HCM, and whether these are applicable to nonsyndromic disease has not yet been evaluated, in part related to the relative rarity of these aetiologies, but also because SCD has been reported infrequently in this context. However, there are data emerging to suggest that SCD can occur in children and teenagers with RASopathy syndromes and inborn errors of metabolism⁵. The limited available suggest that the degree of LVH may be a strong predictor of SCD in patients with RASopathy syndromes³⁸, but future studies will need to determine if risk stratification methods developed for non-syndromic disease can be extrapolated to syndromic patients and to identify disease-specific risk factors.

Conclusions

SCD is the most common cause of death in childhood HCM and occurs more frequently than in adult patients. Recently developed paediatric-specific risk prediction models allow clinicians to calculate individualised estimates of 5-year risk and are an important novel tool for shared decision making in relation to ICD implantation. Future studies are required to provide real world validation and to further refine risk stratification for SCD in children with HCM in the current era of personalised medicine.

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Table 1: Risk factors for sudden cardiac death in childhood HCM. Adapted from Norrish et al²⁸

	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, 39, 40} .
	LVOT gradient	The definition of LVOT obstruction varies in the literature. Increasing LVOT gradient has been linked to SCD ^{40, 41} 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 ²⁴ . 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) ³¹ and children presenting in infancy are believed to be at lower risk ^{7, 42}
	12 lead ECG	Proposed 12 lead ECG features include; measures of LV hypertrophy ⁴³ and abnormal repolarisation ⁴⁴ but a recent large study showed no association between individual ECG parameters and risk ³⁶ . An ECG risk score has been developed by Ostman-Smith et al ⁴⁴ but this was shown to have only moderate discriminatory ability in an external validation study ³⁶ .
	LGE on CMRI	LGE has been shown to increase during childhood and is associated with left ventricular hypertrophy ³³ . It is unclear if LGE is an independent risk factor for SCD ^{34, 45} .

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 prognosis⁴⁶ and certain genotypes associated with higher arrhythmic risk⁴⁷.

Table 2: Comparison between HCM Risk-Kids and PRIMaCY risk prediction models for sudden cardiac death in childhood hypertrophic cardiomyopathy

	HCM Risk-Kids	PRIMaCY
n (development and internal validation)	1024	572
Risk factors		
LVH	✓ (MLVWT z-score)	✓ (IVS and LVPW z-scores)
LA z-score	✓	✓
Unexplained syncope	✓	✓
NSVT	✓	✓
LVOT gradient	✓	✓
Age at diagnosis	✗	✓
Model performance		
Internal validation C-statistic	0.69 (0.66-0.72)	0.75 (CI not provided)
External validation C-statistic	<i>Under review</i>	0.71 (CI not provided)

LVH – left ventricular hypertrophy; MLVWT – maximal left ventricular wall thickness; IVS – interventricular septum; LVPW – left ventricular posterior wall; LA – left atrium; NSVT – nonsustained ventricular tachycardia; LVOT – left ventricular outflow tract

Figure 1: 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

