Published in final edited form as:

Prog Pediatr Cardiol. 2018 June ; 49: 31–37. doi:10.1016/j.ppedcard.2018.03.001.

Risk stratification in pediatric hypertrophic cardiomyopathy: Insights for bridging the evidence gap?

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Abstract

Identification of children with hypertrophic cardiomyopathy (HCM) who are at high risk for sudden cardiac death (SCD) remains challenging. Although a large number of risk factors have been implicated in HCM associated SCD, evidence for individual risk factors are not robust. Current risk prediction models are extrapolated from adult HCM and have low positive predictive value when applied to the pediatric HCM population. Clinical factors that are strongly associated with SCD in children with HCM are limited to previous adverse cardiac event, prior syncope and extreme left ventricular hypertrophy; there are variable conclusions regarding the utility of other conventional risk factors. Additionally, while implantable cardioverter defibrillators (ICDs) are effective in aborting malignant arrhythmias, ICD complication rates are higher in children than in adults. Although echocardiography derived parameters like left atrial volume, diastolic function indices, severity of left ventricular outflow tract obstruction and abnormalities in deformation imaging (strain and strain rate) have been associated with SCD risk in childhood HCM, these echocardiographic predictors have low specificity and sensitivity. More recently, cardiac magnetic resonance (CMR) imaging derived perfusion and viability (delayed gadolinium enhancement) abnormalities have been associated with SCD in childhood HCM and warrant further investigation. Given that myocyte disarray and fibrosis are prominent histological features of HCM, novel imaging modalities that allow for improved tissue characterization may provide additional insight into HCM phenotypes that are at higher risk for SCD. T₁ mapping, cardiac diffusion tensor imaging (cDTI), and assessment of a phosphocreatine/adenosine triphosphate (PCr/ATP) ratio by ³¹P magnetic resonance spectroscopy (³¹P-MRS) are future avenues of myocardial imaging that may provide additional prognostic benefit when used in conjunction with traditional assessments. Further investigations of disease pathogenesis, genotype-phenotype correlations, genetic modifiers and circulating biomarkers specific to children with HCM hold promise for a more effective and refined risk stratification model in pediatric HCM.

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Conflicts of interest

Authors declare there is no conflict of interest.

Keywords

Hypertrophic cardiomyopathy; Sudden cardiac death; Risk stratification; Children

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1. Introduction

Hypertrophic cardiomyopathy (HCM) is a heterogeneous disorder characterized by abnormal left ventricular hypertrophy in the absence of proportionate loading condition, with variability in etiology, clinical presentation, and outcomes. In both adults and children with HCM, there is a sub-population that is at high risk for sudden cardiac death (SCD), largely attributed to malignant ventricular arrhythmias. Myocardial fibrosis, microvascular ischemia and cellular disarray are inherent to HCM pathogenesis and predispose patients with HCM to ventricular arrhythmias and SCD [1]. Estimates for SCD rates in childhood HCM vary widely, and epidemiological studies have reported rates of between 1% and 7.2% per year [2–7], although more recent SCD rates are closer to 1% per year. Implantable cardioverter defibrillators (ICDs) are effective at aborting malignant arrhythmias in childhood HCM [3,8] but this is at the expense of a relatively high rate of ICD complications (9.5% per year), requirement for multiple generator changes, some quality of life restrictions and the possible psychological burden imposed by ICDs [9]. Thus, identifying children in which the risk for SCD is higher than the potential risks of ICD placement remains challenging. Additionally, the estimated prevalence of phenotypically positive HCM in childhood is relatively low at 2.9 per 100,000 [10–12] when compared to a prevalence of 1 in 500 [13] or even 1 in 200, based on contemporary genetic testing and advanced imaging [14], in adults. Therefore, the ability to conduct large prospective HCM studies focused on children has been limited and risk stratification has been extrapolated from adult data. Similar to adult HCM, the majority of cases of childhood HCM are caused by mutations in genes encoding sarcomere proteins [15,16]; however, there are sub-populations of children in whom HCM develops secondary to inborn errors of metabolism, malformation syndromes and neuromuscular disorders [17]. HCM is a complex pathophysiologic process that includes impaired myocardial energetics, myocardial fibrosis, and structural remodeling [18], features that may be further investigated with novel tissue characterization modalities. As presented at the 4th International Conference on Cardiomyopathy in Children, we will discuss opportunities to utilize advancements in non-invasive imaging to enhance our ability to precisely characterize pediatric HCM patients at risk for SCD.

2. Lack of Robust Risk Prediction Models in Children

Current risk stratification of children with HCM are extrapolated from the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines from 2011, focusing on the clinical factors that increase the risk of SCD (Table 1) [19]. However, even in the adult HCM population, the only risk marker with excellent positive predictive value is a prior cardiac arrest; adults that receive an ICD for secondary prevention have an annual rate of subsequent events of 10% per year [20–22]. A recent clinical risk model/calculator (HCM Risk-SCD) has been developed in Europe to provide individualized risk estimates for the probability of SCD at 5 years (Table 2), with recommendations for ICD

placement being: < 4% generally not indicated, 4–6% may be considered, and > 6% should be considered [23]. Notably, the HCM Risk-SCD incorporates two additional echocardiographic measures (left atrial diameter and fractional shortening) which are not included in the 2011 ACCF/AHA guidelines. Nevertheless, this model is not validated for patients under 16 years of age.

A recent systematic literature review and meta-analysis of clinical risk factors for SCD specifically in childhood HCM was performed by Norrish et al., which concluded that: [1] previous adverse cardiac event (pooled hazard ratio [HR] 5.4, 95% confidence interval [CI] 3.67–7.95, $p < 0.001$), [2] non-sustained ventricular tachycardia (pooled HR 2.13, 95% CI 1.21–3.74, $p = 0.009$), [3] unexplained syncope (pooled HR 1.89, 95% CI 0.69–5.16, $p = 0.22$), and [4] extreme left ventricular hypertrophy (maximum LV wall thickness > 30 mm or z-score > 6, pooled HR 1.80, 95% CI 0.75–4.32, $p = 0.19$) are each individually likely to be associated with an increased risk of SCD [17]. However, the authors noted that the evidence base for individual risk factors is not robust and there was not sufficient data to substantiate numerous other minor risk factors, including family history of SCD, gender, age at presentation, symptoms, ECG changes, abnormal blood pressure response to exercise, LV outflow tract obstruction, left atrial size, restrictive physiology, strain, 24-hour blood pressure monitoring, and late gadolinium enhancement on CMR imaging [17]. Specifically, echocardiography derived parameters like left atrial volume, diastolic function indices and abnormalities in deformation imaging (strain and strain rate) (Fig. 1 and 2) have been associated with risk of SCD in children with HCM (Table 3); however, these echocardiographic predictors have low specificity and sensitivity. CMR imaging derived perfusion and viability (delayed gadolinium enhancement) abnormalities have also been associated with SCD in childhood HCM (Fig. 3) (Table 3) and will be discussed in more detail below. Similarly, an international, multi-center retrospective study reported that in childhood HCM, the only two risk factors for SCD that were significant by multivariate analysis were a personal history of syncope and higher z-score of the posterior wall thickness [24]. The authors also reported that, in this population, the presence of significant LV outflow tract obstruction (> 36 mm Hg) appeared to be protective against SCD [25]. Nevertheless, both studies concluded that large, prospective studies of risk stratification for SCD in children with HCM are needed. Thus, our current recommendations regarding risk stratification of SCD in pediatric HCM are imprecise, have low positive predictive value, are not additive, and are not updated (inclusive of current technologies).

3. Future Evolution of Pediatric HCM Risk Stratification

Current SCD risk stratification guidelines focus on clinical features of the disease, however HCM is a complex pathophysiologic process including impaired myocardial energetics, edema, myocardial fibrosis, and structural remodeling [18]. Recent advances in CMR imaging and genetic testing allow for more detailed, non-invasive phenotyping of the myocardium that may help with risk-stratification in this challenging population.

3.1. Fibrosis and Extracellular Volume Evaluation

Late gadolinium enhancement (LGE) has been used to detect and quantify the degree of focal myocardial fibrosis, which is present in 67% of adult HCM patients [26]. The pattern of LGE in adult HCM is predominantly located within the mid-myocardium and always located in the area of hypertrophy [26]. Adult patients with scar by LGE had a higher burden of hypertrophy [26] and a recent meta-analysis found that the risk of SCD increased in the presence of LGE [27]. However, other studies suggest that the extent of LGE, rather than simply its presence, is associated with the risk of ventricular arrhythmias or SCD [28–30]. Accordingly, the predictive value of LGE as a risk factor for SCD in childhood HCM has been evaluated in 3 studies [31–33], and although an increased incidence of LGE in patients with adverse outcomes has been reported, this did not reach statistical significance. Similar to adult HCM studies, however, the presence of LGE was statistically associated with increased LV wall thickness/mass.

Quantification of fibrosis by LGE, however, is limited to focal myocardial fibrosis and is unable to detect diffuse fibrosis since it relies on a comparison between unaffected normal myocardium and regions of focal myocardial damage. Thus, post-contrast T1 mapping (Fig. 4) techniques can assist in detection of diffuse myocardial fibrosis [34]; adult patients with HCM have abnormal T1 indices concordant with diffuse myocardial disease, even in the absence of LGE and in areas outside overt LGE [35–38]. Additionally, diffuse ventricular fibrosis by T1 mapping has been shown to be a predictor of non-sustained ventricular tachycardia and aborted SCD in adult HCM patients [39], however further studies are required to assess whether diffuse myocardial fibrosis in HCM offers additional prognostic benefit regarding SCD compared to LGE alone.

3.2. Apical LV Aneurysms

In adults with HCM, the presence of apical LV aneurysms portends a higher risk for arrhythmic sudden death; specifically, a cohort with apical LV aneurysms had an arrhythmic event rate of almost 5% per year, which is > 5-fold greater than that of the cohort of HCM patients without aneurysms [40]. While the incidence of LV apical aneurysms was only 4.8% in adults with HCM, the data suggests that this is a subset of patients who is at higher risk for SCD and may benefit from prophylactic ICD placement regardless of other clinical risk factors. Notably, standard echocardiographic assessment is often insufficient in identifying the presence of apical LV aneurysms, with 46% of adult HCM patients requiring cardiac MRI or computed tomography for diagnosis of an aneurysm [40]. Nevertheless, the incidence and outcome of apical LV aneurysms in pediatric HCM is unknown.

3.3. Functional and Metabolic Assessments

On a functional level, a common property of myocytes affected by known HCM-causing mutations in sarcomeric proteins include an increase in myofilament or myosin ATPase calcium sensitivity [41–44], resulting in increased cardiomyocyte tension and slowed or limited diastolic relaxation kinetics [45]. Cardiac diffusion tensor imaging (cDTI) measures the magnitudes and directions of intramyocardial water diffusion, which are consistent with hypercontraction in systole and failure of relaxation in diastole in HCM [45]. Further in vivo investigations of myocardial structural dynamics may assist with risk stratification for SCD

in the future. From a metabolic energetics perspective, the phosphocreatine/adenosine triphosphate (PCr/ATP) ratio measured by ^{31}P magnetic resonance spectroscopy (^{31}P -MRS) is decreased in HCM [46], suggesting that there is myocardial energy depletion secondary to inefficient force generation in all HCM subjects [47]. Future studies may be able to utilize ^{31}P -MRS to phenotype different HCM genotypes based on PCr/ATP ratio in response to physiologic and pharmacologic stress. The metabolic responses of patients, in combination with the detailed anatomical, functional, and scar imaging provided by cardiac MRI, may identify prognostic indicators that could aid in risk stratification and family screening of HCM patients [48].

3.4. Genetic Predictors of SCD in Pediatric HCM

A survey of genetic etiologies in children with HCM revealed, similar to adult HCM, that the majority of pediatric patients with mutation-positive HCM had at least one mutation in MYH7 (encoding beta-myosin heavy chain) or MYBPC3 (encoding myosin-binding protein C) [16]. Despite the suggestion that rarer forms of the MYH7 mutation can increase the risk of SCD [49,50], single mutations in genes encoding proteins of the cardiac sarcomere cannot be used to predict SCD risk in HCM [51–55]. However, HCM patients with multiple mutations are described to have early disease onset, marked LV hypertrophy, and advanced heart failure due to systolic dysfunction requiring heart transplantation [56–60]. Double mutations, modifier genes, and environmental factors likely influence a patient's clinical course [49]. Thus, although the percentage of HCM patients that carry two disease-causing mutations is small (up to 5% in adult HCM [60]), genetic testing could identify those with a greater risk for severe disease progression, including SCD, even in the absence of conventional risk factors [49]. Lastly, the influence of syndrome-related HCM, non-sarcomere genetic mutations (*PRKAG2*, *LAMP2*), and myectomy in determining risk of SCD in childhood HCM still needs to be evaluated further.

3.5. Utility of Predictive Biomarkers in Pediatric HCM

Further investigation is needed to identify putative biomarkers in HCM; a combination of circulating miRNAs, for example, has been shown to correlate with diffuse myocardial fibrosis by post-contrast T_1 mapping in HCM patients [61]. Validation of circulating biomarkers in the pediatric HCM population may be of particular clinical application in patients who are too young or unable to undergo cardiac MRI without sedation. Lastly, the influence of syndrome-related HCM, nonsarcomere genetic mutations (*PRKAG2*, *LAMP2*), and myectomy in determining risk of SCD in childhood HCM still needs to be evaluated further.

4. Summary

Despite lack of validation, in our current practice, risk models for SCD in children with HCM are often extrapolated from adult risk models. Many of the conventional SCD risk factors lack robust prognostic capabilities in children with HCM. There is a clear need for larger studies aimed at improving our understanding of risk factors for primary prevention of SCD in childhood HCM. Incorporation of novel and emergent imaging modalities, especially CMR imaging, can provide new insights into myocardial tissue characterization

and mechanics, which may ultimately assist in improving prediction of SCD in childhood HCM.

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Fig. 1. Myocardial deformation imaging in HCM can be performed using echocardiogram (panel A: Velocity Vector Imaging; panel B: Speckle Tracking) or cardiovascular magnetic resonance feature tracking (panel C and D) and can provide valuable insights in to global and regional myocardial mechanics in HCM.

Fig. 2. Myocardial deformation imaging showing reduced regional peak systolic strain in the left ventricular apex in apical HCM (blue area).

Fig. 3.

Delayed enhancement (late gadolinium enhancement) magnetic resonance imaging showing fibrosis in the interventricular septum (arrow). The distribution pattern of hyper-enhancement in hypertrophic cardiomyopathy (HCM) does not typically correspond to a coronary artery distribution and is usually patchy mid-wall enhancement with multiple foci. Delayed enhancement has been associated with severity of hypertrophy and risk of ventricular arrhythmia.

Fig. 4. Pre (panel A and B) and post (panel C and D) contrast T1 mapping using cardiac magnetic resonance (CMR) imaging techniques shows clinical promise in the evaluation of diffuse fibrosis in HCM.

Table 1

Recommendations for ICD placement based on 2011 ACCF/AHA risk factors for SCD in HCM.

Adapted from 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy
Gersh et al., Circulation (2011) 124:e783–e831.

ICD Recommended	Prior cardiac arrest or sustained VT
ICD Reasonable	Family history of sudden death in first-degree relative OR LV wall thickness ≥ 30 mm OR recent unexplained syncope
ICD can be useful	Non-sustained VT OR abnormal BP response AND other SCD risk modifiers (resting LV outflow tract gradient ≥ 30 mm Hg, late gadolinium enhancement on CMR imaging, presence of LV apical aneurysm, genetic mutations)
ICD not recommended	Absence of risk factors

Regardless of the level of recommendation put forth in these guidelines, the decision for placement of an ICD must involve prudent application of individual clinical judgment, through discussions of the strength of evidence, the benefits, and the risks (including but not limited to inappropriate discharges, lead and procedural complications) to allow active participation of the fully informed patient in ultimate decision making.

Table 2

European Society of Cardiology HCM-risk SCD algorithm.

Adapted from 2014 ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy. O'Mahoney C et al., Eur Heart J (2014) 35 (30): 2010–2020.

Predictor variable	Definition	Coding
Age	Age at evaluation	Continuous, years
Family history of SCD	History of SCD in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post- or ante-mortem diagnosis).	Binary (yes = 1/no = 0)
Maximal wall thickness	The greatest thickness in the anterior septum, posterior septum, lateral wall, and posterior wall of the LV, measured at the level of the mitral valve, papillary muscles, and apex using parasternal short-axis plane using 2D echocardiography at the time of evaluation	Continuous, mm
Fractional shortening	(LV end-diastolic dimension-LV end-systolic dimension)/LV end-diastolic dimension measured by M-Mode or 2D echocardiography at time of evaluation	Continuous, %
Left atrial diameter	Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation	Continuous, mm
Maximal LV outflow tract gradients	The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three- and five-chamber views. Peak outflow tract gradients were determined using the modified Bernoulli equation: Gradient = $4v^2$, where v is the peak aortic outflow velocity	Continuous, mm Hg
Non-sustained ventricular tachycardia	3 consecutive ventricular beats at a rate of 120 bpm and <30 s in duration on Holter monitoring (minimum duration 24 h) at or prior to evaluation	Binary (yes = 1/no = 0)
Unexplained syncope	History of unexplained syncope at or prior to evaluation	Binary (yes = 1/no = 0)

Notably, the HCM Risk-SCD should not be used in: [1] pediatric patients (< 16 years), [2] elite/competitive athletes, [3] HCM associated with metabolic diseases (e.g. Fabry disease) and syndromes (e.g. Noonan syndrome), and [4] patients with a previous history of aborted SCD or sustained ventricular arrhythmia who should be treated with an ICD for secondary prevention. Caution should be exercised when assessing the SCD in patients following invasive reduction in LV outflow tract obstruction with myectomy or alcohol septal ablation.

Table 3

Imaging findings associated with increased risk of SCD in childhood HCM.

Adapted from Norrish et al., Eur J Prev Cardiol (2017) 24:1220–1230.

Left atrial size	Increased left atrial size (HR 3.125, 95% CI 1.45–6.74, $p = 0.001$ [62] and HR 3.4, 95% CI 1.1–11.2, $p = 0.049$ [63])
Diastolic function	Early transmitral LV filling velocity (E)/septal E/A ratio (HR 6, $p < 0.001$ [64]); echocardiographic findings associated with restrictive physiology (HR 3.8, $p = 0.302$ [63])
Strain	Reduced global strain (OR 1.13, 95% CI 1.00–1.27 [65])
LGE on CMR imaging	Increased incidence of LGE in patients with adverse outcomes (not statistically significant). Presence of LGE statistically associated with increased LV wall thickness/mass. [31–33]

HR = hazard ratio. CI = confidence interval. LV = left ventricular. OR = odds ratio. LGE = late gadolinium enhancement. CMR = cardiac magnetic resonance.