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Review

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. T_1 mapping, cardiac diffusion tensor imaging (cDTI), and assessment of a phosphocreatine/adenosine triphosphate (PCr/ATP) ratio by ^{31}P magnetic resonance spectroscopy (^{31}P-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.

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

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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.

in genes encoding sarcomere proteins [15,16]; however, there are subpopulations 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

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 ina 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.