Risk of sudden cardiac death in childhood hypertrophic cardiomyopathy: Time to solve the mystery

Gabrielle Norrish,[1,2] Juan Pablo Kaski[1,2]

[1]Great Ormond Street Hospital;
[2]Institute of Cardiovascular Sciences University College, London, UK

Abstract

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular hypertrophy in the absence of loading conditions sufficient to cause the observed abnormality. The true prevalence in childhood is unknown; the aetiology is more heterogeneous than that seen in adult populations, and includes inborn errors of metabolism, malformation syndromes and neuromuscular syndromes. However, one of the greatest clinical challenges in managing young patients with HCM is identifying those at greatest risk of sudden cardiac death.

Childhood hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular hypertrophy in the absence of loading conditions (hypertension, valve disease, congenital heart disease) sufficient to cause the observed abnormality.[1] The true prevalence in childhood is unknown, however population based studies from USA, Australia and Finland have reported an annual incidence between 0.24-0.47 per 100,000 children.[2-4] The aetiology is more heterogeneous than that seen in adult populations, and includes inborn errors of metabolism, malformation syndromes and neuromuscular syndromes.[5]

The long-term prognosis of HCM in childhood is highly variable and depends partly on the age of presentation and underlying aetiology.[6] However, one of the greatest clinical challenges in managing young patients with HCM is identifying those at greatest risk of sudden cardiac death.

Hypertrophic cardiomyopathy (HCM) has been reported as the most common cause of SCD in young athletes,[7] however published estimates of the SCD rate in childhood HCM have varied widely. Early publications reported rates of up to 7% per year.[8] However, these estimates were obtained from small, highly selective populations derived from tertiary referral centres, which may not have been representative of the whole population. Over time, reflecting what has been seen in the adult literature, reported SCD rates have fallen, and the most recent, large population based studies have reported an annual SCD of 1-2% per year.[5,9] Nevertheless, there is a subgroup of children with HCM who do have a higher risk of SCD[10] and may benefit from implantable cardioverter defibrillator (ICD) therapy. Although it is a rare event, ICDs have been shown to be effective at aborting malignant arrhythmias in childhood HCM.[11] However, these younger patients experience a higher rate of complications, reinforcing the need to robustly identify patients most likely to benefit from device implantation.

Risk factors for SCD in adult patients are well described and include prior ventricular fibrillation or sustained ventricular tachycardia; family history of sudden cardiac death; unexplained syncope; non-sustained ventricular tachycardia (NSVT); maximal left ventricular wall thickness >30 mm; and an abnormal blood pressure response to exercise. These conventional clinical risk factors are used in two alternative, validated approaches to risk stratification for adult patients with HCM. The American College of Cardiology Foundation/American Heart Association[12] currently recommends that ICD implantation is reasonable if one major clinical risk factors is present, and could be considered if two or more other risk factors are present. This approach provides relative rather than absolute risks for non-homogenous groups, and necessarily converts continuous variables (such as maximal wall thickness) into binary variables (*e.g.*, maximal wall thickness >30 mm or <30 mm) for the purpose of risk stratification, the validity of which may be questioned. Additionally, cohort studies have shown that this approach may have a low predictive power for SCD and lead to unnecessary ICD implantation in some patients.[13] In comparison, the European Society of Cardiology[14] has endorsed the use of a SCD risk prediction model (HCM Risk-SCD)[15] that provides an individualised estimate for 5-year SCD risk utilising clinical predictor variables associated with SCD in multivariable analysess. Independent, external comparison of these two approaches has shown that the HCM-risk SCD model improves the risk stratification of patients with HCM (C statistic 0.69) compared to 2011 ACCF/AHA guidelines (C-statistics 0.6).[16]

However, whilst advances have been made in risk stratification for adult patients, little progress has been made in risk stratification for childhood HCM. Indeed, although a large number of potential risk factors for SCD have been reported in the literature over the past 30 years, the lack of consistent definitions and well-designed, large population studies means that the evidence for individual risk factors is not robust. In a recently published systematic review and meta-analysis by the authors,[17] only twenty five studies were identified that explored associations between twenty three separate clinical risk factors and SCD in childhood HCM. The majority of studies identified were retrospective and reported small, heterogeneous populations; all but 3 had less than 150 participants. Four clinical risk factors were identified as being *Major risk factors* and likely to be associated with SCD in childhood HCM (Table 1): previous aborted cardiac arrest or sustained VT; unexplained syncope; NSVT; and extreme left ventricular hypertrophy. Left atrial diameter did not meet the major risk factor criteria, however was likely to be an additional significant risk factor and was associated with SCD in two out of three studies. *Minor risk factors* included a family history of SCD, gender, age, symptoms, electrocardiograph findings, blood pressure response to exercise and left ventricular outflow tract obstruction.

Whilst some of the risk factors for SCD in childhood appear to be the same as the conventional adult risk factors, this meta-analysis highlights possible important dif-

Correspondence: Gabrielle Norrish, Centre for Inherited Cardiovascular Diseases, Great Ormond Street Hospital, London, WC1N 3JH, UK.
E-mail: g.norrish@ucl.ac.uk

Key words: Hypertrophic cardiomyopathy; childhood; sudden cardiac death.

Funding: This work was supported by the British Heart Foundation (grant number FS/16/72/32270) to GN and JPK.

Contributions: GN, JPK contributed to the conception and design of the work. GN drafted the manuscript, JPK critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Received for publication: 20 November 2017.
Revision received: 18 December 2017.
Accepted for publication: 30 December 2017.

Cardiogenetics 2018; 8:7201
doi:10.4081/cardiogenetics.2018.7201

ferences between risk stratification in children and adults. In particular, a family history of SCD was not identified as a major risk factor in this study as it was only associated with SCD in one out of seven studies. There is some evidence supporting a family history of SCD as a risk factor in adult HCM, but there is currently a lack of data to support its role in childhood HCM. Possible explanations for this include a higher prevalence of de novo mutations in childhood HCM, or insufficient reporting of family history in the included studies. Similarly, there is evidence that an abnormal blood pressure response to exercise and left ventricular outflow tract obstruction may be less important for risk stratification during childhood. Further evaluation of the association between these clinical risk factors and SCD in childhood HCM is needed in large-scale studies.

Not surprisingly, given the sparsity of evidence, the current European and American guidelines[12,14] contain only short sections on the risk of SCD in childhood HCM. Both guidelines recommend the use of four major risk factors to predict SCD (maximum LV wall thickness >30 mm (or Z score >6), unexplained syncope, NSVT or family history of SCD) and recommend implantation of an ICD for primary prevention in those with two or more risk factors. As has already been discussed, the evidence supporting the use of some of these risk factors is not robust. In addition, whilst left ventricular hypertrophy has been shown to be associated with SCD in several studies, only one has shown a significantly increased risk with a LV wall thickness >30 mm/z-score >6,[18] which is the definition endorsed by the guidelines. The most clinically important measure of LVH and appropriate cut off for measuring increased risk needs further investigation. Importantly, this approach to risk stratification has the same inherent limitations as the traditional adult models providing only an estimate of relative risk. However, the HCM-risk SCD model is not currently validated for use in patients under 16 years of age, and although it can be used for patients aged 16-18 years, this group of young adults constituted a small proportion of the development cohort (n=82/3675, 2%), and so further evaluation of their risk may be required. Indeed, given that the risk factors for SCD in childhood HCM do not appear to be the same as in adulthood, the application of this model without further validation would be inappropriate.

Conclusions

In summary, risk stratification in childhood HCM remains a significant challenge. Compared to adults with HCM, patients presenting during childhood are more heterogeneous in terms of their age, symptoms and underlying aetiology. Our current understanding regarding the risk factors for SCD in childhood is limited by the lack of consistent definitions and well-designed, large population studies. Childhood is also a time of considerable somatic growth meaning that a patient's phenotype may change considerably. This may have important implications for risk stratification during childhood but has not yet been systematically explored. In our own clinical practice, risk stratification is currently performed at each out-patient review and is largely based upon disease severity and the presence or absence of traditional risk factors for SCD. The difficulties in this approach however are described above. As childhood HCM is a rare disease and SCD is a rare outcome, the challenge of improving risk stratification in childhood HCM can only be addressed through multi-centre, large-scale, collaborative projects. In response to this, the authors have established an International Paediatric Hypertrophic Cardiomyopathy Consortium consisting of 38 cardiac centres worldwide caring for paediatric patients with hypertrophic cardiomyopathy. A cohort of over 1400 patients has been created which will allow us to systematically investigate the role of individual risk factors for SCD in childhood HCM and improve risk stratification for these patients. Identifying which patients are most at risk is unlikely to be simple, however through international collaboration there is an opportunity to finally solve the mystery of the risk of SCD in childhood HCM.

Table 1. Risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy.

Major clinical risk factor*	Hazard ratio (95% confidence interval)
Previous aborted cardiac event	5.4 (3.67-7.95), P<0.001
Non-sustained ventricular tachycardia	2.13 (1.21-3.74), P=0.009
Unexplained syncope	1.89 (0.69-5.16), P=0.22
Extreme left ventricular hypertrophy°	1.8 (0.75-4.32), P=0.19
***Minor* risk factor#**	
Left atrial diameter, Family history SCD, Gender, Age, Symptoms, ECG changes, Abnormal blood pressure response to exercise, LVOTO	

**Major* risk factor defined as being investigated in at least 4 studies and significantly associated with SCD in ≥ 2 statistical analysis; °Maximum LV thickness >30 mm, or Z-score >6; #*Minor* risk factor defined as being associated with SCD in 1 analysis. Adapted from Norrish *et al.*, 2017.[17]

References

1. Elliott P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270-6.
2. Arola A, et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents. A nationwide study in Finland. Am J Epidemiol 1997;146: 385-93.
3. Lipshultz SE, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003;348:1647-55.
4. Nugent AW, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 2003;348:1639-46.
5. Colan SD, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. Circulation 2007;115:773-81.
6. Lipshultz SE, et al. Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry. Lancet 2013;382:1889-97.
7. Maron BJ, et al. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. Circulation 2009;119:1085-92.
8. McKenna WJ, Goodwin JF. The natural history of hypertrophic cardiomyopathy. Curr Probl Cardiol 1981;6:1-26.
9. Nugent AW, et al. Clinical features and outcomes of childhood hypertrophic cardiomyopathy: results from a national population-based study. Circulation 2005;112:1332-8.
10. Ostman-Smith I, et al. Age- and gender-specific mortality rates in childhood hypertrophic cardiomyopathy. Eur Heart J 2008;29:1160-7.
11. Kaski JP, et al. Outcomes after implantable cardioverter-defibrillator

treatment in children with hypertrophic cardiomyopathy. Heart 2007;93:372-4.
12. Gersh BJ, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg 2011;142:e153-203.
13. O'Mahony C, et al. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. Heart 2013;99:534-41.
14. Elliott PM, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.
15. O'Mahony C, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35: 2010-20.
16. Vriesendorp PA, et al. Validation of the 2014 European Society of Cardiology guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Circ Arrhythm Electrophysiol 2015;8:829-35.
17. Norrish G, et al. Risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy: A systematic review and meta-analysis. Eur J Prev Cardiol 2017 [Epub ahead of print].
18. Maron BJ, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol 2013; 61:1527-35.