Development of a Risk Calculator to Predict Sudden Cardiac Death in Children with Hypertrophic Cardiomyopathy

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1. STUDY OVERVIEW

1.1 GOAL

A retrospective cohort study to discriminate risk for sudden cardiac death (SCD) in patients with Hypertrophic cardiomyopathy (HCM).

1.2 BACKGROUND

Hypertrophic cardiomyopathy (HCM) is a commonly inherited heart muscle disease, which can present in childhood, adolescence or adulthood. It accounts for 42% of childhood cardiomyopathy and has an incidence of 0.47/100,000 children[1]. It is a frequent cause of sudden cardiac death (SCD) with those aged between 8-16 years at highest risk[2,3].

For adults with HCM, identified risk factors for SCD include non-sustained ventricular tachycardia (VT)[4,5], left ventricular (LV) hypertrophy (>3cm)[6] presence of LV outflow tract obstruction[7], family history of sudden death[2], and hypotensive response of blood pressure on exercise testing[8].

However, the risk factors are less clear in the pediatric population. Historically along with the risk factors listed above, myocardial bridging was thought to be associated with a poor outcome in children with HCM[9].Other screening tools have included the use of ECG measurements of R and S wave height on ECG along with septal hypertrophy by echocardiogram to predict those at risk for SCD[10]. HCM is inherited in an autosomal dominant pattern, the most frequently encountered HCM-associated mutations occur in MYH7 and MYBPC3 genes. To date no correlation has been found between specific genotype and outcome in patients with HCM[11]. Loar *et al* reported a significant increase in ventricular hypertrophy in genotype positive patients[12]. As LV wall thickness remains one of the SCD risk factors in adults, one could postulate therefore that being genotype positive may increase the risk of SCD. Analysis of data from SickKids Hospital (Toronto, ON) in pediatric HCM revealed that mutations in MYH7 gene and a higher number of pathogenic mutations in one or more genes were associated with a higher incidence of major adverse cardiac events[13]. Emerging imaging tools such as Cardiac MRI to determine the presence of Late Gadolinium enhancement may also predict those who have developed myocardial fibrosis and are at risk for SCD[14,15].

The European Society of Cardiology (ESC) recently published guidelines on the diagnosis and management of HCM in adults[16] which led to the development of a clinical risk calculator to predict the risk of SCD at 5 years in adults >16 years old[17]. This model uses age, maximum LV

wall thickness (mm), left atrial size (mm), maximum LVOT gradient (mmHg), family history of sudden cardiac death, non-sustained VT, unexplained syncope. No such tool exists for children where findings such as being genotyped may have additional risk.

Exercise restriction and β Blocker therapy remains the mainstay of treatment to reduce the risk of SCD in children with HCM[18]. Implantation of an implantable cardioverter defibrillator (ICD) is a potentially life-saving therapy for children with HCM, therefore the ability to predict which children are at risk from SCD and who would benefit from an ICD may change the current state of practice. The ESC currently recommends implantation of an ICD after a life-threatening ventricular arrhythmia in children or in those who have two or more major risk factors; however these risk factors have not been clearly defined[16].

1.3 OBJECTIVES

1. To develop and validate a SCD risk calculator that is age-appropriate for children with HCM that includes clinical and genetic factors

2. RESEARCH PLAN

2.1 STUDY DESIGN

This is a retrospective cohort study of pediatric HCM patients using chart and registry review methodology.

2.2 SUBJECT SELECTION

2.2.1 Inclusion Criteria

HCM patients ≤18 years of age at first presentation will be included. This includes phenotype positive patients, and phenotype negative gene positive patients considered at risk. Phenotype positive patients are patients with a clinical diagnosis of HCM based on signs, symptoms, family history, EKG and/or echocardiographic features (septal or LV posterior wall thickness z-score (PWd) > +2.0 or ratio of hypertrophied region to PWd > 1.3 in the absence of anatomic LVOT obstruction) of HCM.

2.2.2 Exclusion Criteria

(i) Neuromuscular, metabolic, syndromic (other than Noonan Syndrome and related RAS-opathies) or endocrine (including infants of diabetic mothers) causes of HCM

(ii) Other treatable causes of LVH (systemic hypertension, anatomic defect causing LVOT obstruction e.g. aortic stenosis, subAS, subaortic membrane)

2.2.3 Subject screening

Eligible subjects who were seen since 1990 will be identified through review of the following data sources:

(i) Electronic Medical Records (and paper charts where needed)

(ii) Other relevant cardiac databases (ie. echocardiography, heart failure)

Patients will be screened for eligibility from participating sites. This is a multi-centre study led by SickKids Hospital (Toronto), participating institutions include Stollery Children's Hospital (Edmonton), BC Children's Hospital (Vancouver), Stanford Children's Health (Palo Alto), Children's Hospital of Philadelphia, Texas Children's Hospital (Houston), Morgan Stanley Children's Hospital (New York), Children's Medical Center of Dallas, University of Michigan Medical Center (Ann Arbor), Cincinnati Children's Hospital, Children's Hospital of Eastern Ontario (Ottawa), The Royal Children's Hospital (Melbourne). REB/IRB approval and service & data transfer agreements will be put in place at each participating centre above as well as new centres that get added.

3. DATA COLLECTION

3.1 Specific data fields for the initial retrospective review

We will be collecting information on:

- *Screening and demographics*: Variables include eligibility screening and basic demographics such as month/year of birth and gender.

- *Medical history, family history, cardiac work-up*: This information will be captured at the time of first evaluation of HCM (+/-12 months), last reported evaluation and event driven. Events include death, transplant, SCD, aborted SCD, mechanical circulatory support, cardiac surgery, device implantation (e.g. ICD). Data variables to be collected include family history of HCM and sudden cardiac death, history of syncope & history of aborted SCD. Cardiac imaging (echo, cMRI) & other cardiac tests (Holter, exercise) measurements will be captured along with date of test. Management recommendations including exercise restrictions and prescribed medications will also be collected.

- *Genetic testing*: Results of clinical genetic testing will be captured including test used, gene affected and familial inheritance.

Please refer to appendices for detailed case report forms.

4. DATA STORAGE AND CONFIDENTIALITY

All efforts will be made to protect the privacy of individuals in the study. All subjects will be given de-identified study IDs. The link between study ID and the patient identifiers will be maintained locally in a separate, password protected spreadsheet with access limited to study coordinators. De-identified data will be stored using an external REDCap study database that is a web-based program that runs on a dedicated server located within SickKids Hospital. The server, back-up client software, and back-up tapes are supported through SickKids Center for Computational Medicine. The database protects privacy by allowing only site-specific access to research staff from any site to only view the information captured at their sites with the exception of the central repository located at SickKids which will manage all de-identified data.

5. STATISTICAL ANALYSIS

5-year SCD risk score will be calculated, and discrimination and accuracy assessments will be performed. Three risk groups (low, medium, high) will be constructed using the calculated risk score. Kaplan-Meier methods with log-rank tests will be used to compare freedom from SCD; competing risk models will be applied to analyze aborted SCD events. C-statistic will be used to quantify the discriminatory ability of the risk scoring, the discrepancy between predicted and observed risk will be also assessed. A revised calculator will be generated from the test cohort using additional variables if needed. This calculator will then be tested in a validation cohort to determine its ability to predict SCD events. We anticipate screening 3,000 HCM patients across all sites of which 70-80% are anticipated to be eligible for inclusion in this analysis. We anticipate that this number will provide enough power based on anticipated SCD event rate of 6% (n=100-150) to develop a new calculator.

6. CLINICAL RELEVANCE

Children with HCM remain at high risk for SCD. Current clinical risk factors are largely extrapolated from the adult population where a model has been developed to predict those who are at risk of SCD at 5 years[16,17.] The ability to predict those at risk for SCD in the pediatric population using a prediction model may guide frequency of patient surveillance in those who are at higher risk and may inform indications for ICD insertion for primary prevention. Ultimately this may improve long term outcomes in this population.

7. TIMELINE

We anticipate 12 months for data collection after REB approval and approval of MTAs, 12 months for data analysis and write-up of risk calculator.

8. BUDGET

Funding for data collection and analysis is supported through the Ted Rogers Centre for Heart Research Cardiac Precision Medicine Program at the Hospital for Sick Children.

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