Title: Vancouver Pediatric Palpitation Score

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Background:
Palpitations are the sensation of irregular, rapid or forceful pulsations in the chest. A 2015 study from the United States which looked into national representative data for emergency room (ER) visits showed palpitations to be the chief complaint in 1.5% of all ER visits in the 0-9 year age group; this number rose to 5.5% in the 10-19 year age group (1). Similar data can be seen from Canada where Caddell et al. showed that palpitations are amongst the common reasons for referral to a pediatric cardiologist at a tertiary level clinic (2).

Palpitations can be caused by a variety of conditions and are broadly divided into those which are accompanied by a normal heart rhythm and those which are accompanied by an abnormal heart rhythm, or arrhythmia. A study by Premkumar et al. showed that 41% of children who presented with arrhythmia had a history of palpitation (3). An ER study from the UK showed that palpitations were the main complaint (61%) in children who were diagnosed with cardiac arrhythmias (4). As the management of an arrhythmia is quite different from the management of palpitations accompanied by a normal rhythm, it is crucial to differentiate between the two. This can be difficult as palpitations are almost never present when the patient is at the clinic. The key to diagnosing a palpitation as a cardiac event is to obtain an electrocardiogram during the event.

The patient's clinical history and physical evaluation are important in guiding further investigations to determine the cause for the palpitations. Palpitations in children with a normal heart rhythm can be caused by a variety of factors including fever, exercise, anemia and anxiety. Children with arrhythmia can present with chest pain, syncope and shortness of breath in addition to palpitations; if prolonged,

they can develop signs of congestive heart failure (3) (4). Symptoms such as rapid regular pounding in the neck, abrupt onset and offsets and sensation of skipped beats have shown to be able to predict rhythm disturbances in adults (8), however, there are no pediatric studies correlating the history with likelihood of underlying arrhythmia. Rarely arrhythmias can lead to sudden death (6). Children with previous history of heart disease or heart surgery carry a higher risk of arrhythmia (7). There are some familial inherited arrhythmia conditions and therefore a thorough family history must be taken. Family history of cardiac arrest, pacemaker or defibrillator implant in first degree relatives might also increase the risk of arrhythmia.

Baseline investigations usually include an echocardiogram and electrocardiogram (ECG). These tests are typically normal. Children with a history of heart disease may have abnormal testing and further investigations may be required. Children with pre-excitation on ECG are more likely to have palpitations due to atrioventricular re-entry (11). If symptoms occur primarily with exertion, an exercise test may be useful. However, the diagnostic yield of exercise testing is poor. Draper et al. showed graded exercise testing in children with arrhythmias to have an overall sensitivity of only 5.7% (9). Ambulatory monitoring (or Holter) may not always capture an episode in the 24-48 hours of monitoring. Since conventional methods may not suffice for capturing the rhythm during symptoms, a number of technologies have been developed to capture the rhythm during episodes of palpitation including invasive strategies like implantable loop recorders (5) (12). If an arrhythmia is detected then the child may be put on medications or may have electrophysiology study (EPS) with catheter ablation done to remedy the arrhythmia (13). Given the number of investigations available and their cost, it would be beneficial to have a predictor of which patients are likely to have an arrhythmia detected as a cause of their palpitations.

Predictive scores, which incorporate clinical history and physical evaluation data, can be a useful tool in helping diagnose the clinical risk a symptom poses to a child. The Canadian syncope risk score (CSRS) was developed to predict the risk of a serious adverse event within 30 days after visit to the emergency department with syncope. In a multicentre validation study the CSRS was able to successfully identify high-risk patients with syncope and has been used to triage and prioritise inpatient care to adults who need early cardiac assessment (10). Similar scores have been developed in other fields of clinical cardiology to help with risk stratification and patient management. There are no scores for palpitations in children. Our goal is to develop a score which has a high predictive value in foretelling arrhythmia as the cause for palpitations. As history is something that can be performed by any physician, we are seeking to develop a tool which has a high sensitivity and specificity to predict arrhythmias, prior to undertaking further investigations. A risk score for palpitations would add to the armamentarium of the physician in targeting referrals and investigations for speedy management. This can be a simple clinical tool which can be applied by all clinician's not just cardiologists and will reduce inappropriate referrals.

Hypothesis:
Symptom based score can predict paroxysmal arrhythmias within 12 months in a child presenting with palpitations.

Objective:
Develop a clinical score to predict arrhythmia as a cause for palpitations in children.

Study design:
Prospective observational cohort study.

Population, enrollment and data collection:
All children (6-18 years inclusive) presenting with a primary complaint of palpitations to a participating institution will be eligible for the study. Children with a complaint of palpitations identified during clinical assessment will also be eligible.

The inclusion criteria are:

1. Normal cardiac physical exam
2. Normal ECG.
3. Age: 6-18 years
4. Recent and ongoing palpitations in the last 6 months.
5. Able to describe symptoms on the questionnaire

The exclusion criteria are:

1. Those with any cardiac diagnosis (including history of cardiac disease or surgery, abnormal echo or ECG) prior to completing the questionnaire.
2. An abnormal echocardiogram if performed (except for small atrial communications, small ventricular septal defects, small patent ductus arteriosus, bicuspid aortic valve with no hemodynamic significance, or other hemodynamically insignificant findings) at the time of questionnaire.
3. Those with family history of sudden unexpected death and/or inherited arrhythmia.

The study questionnaire will be completed by a clinician. Children 6 years and over are expected to be able to describe the features of their symptoms required to complete the questionnaire. These questions are part of any routine targeted history for a child with palpitations and therefore, no additional intervention will be required. The methods used in this study do not deviate from standard clinical care for palpitations.

After the history and physical and routine clinical assessment, documentation of the rhythm during symptoms will be facilitated using non-invasive monitoring strategies, as part of routine investigations. This will be a Holter monitor for daily or frequent symptoms, or an event recorder for weekly/monthly symptoms. Rarely a loop recorder may be used in children with symptoms which are not captured by a Holter or event recorder. During this time, participants are asked to record their activities and symptoms (if any) in a brief diary which we can use to correlate with the monitoring times. If an electrophysiology study was performed during the period of our study, we will record this data to define the specific type of rhythm disturbance and the pathways involved. As investigations are completed the 'diagnosis sheet' will be filled in by one of the investigators until a diagnosis is reached. We will follow up the children until a diagnosis is reached or up to a year after presentation to cardiology.

The information from all centres will be stored online on the secure data sharing platform Research Electronic Data Capture (REDCap) for later statistical analysis.

Ethical considerations

This study is a prospective observational study and no deviation of the routine clinical care is needed.

For the prospective observational study design, eligible participants will receive a study invitation letter with a copy of the consent/assent forms either prior to or at the time of their scheduled clinic visit, the eligible patient will be introduced to the study by their attending physician. Consenting will be undertaken by the research coordinator, who will be available in person during the clinic visit, or via email or telephone, to answer any questions regarding the study that participants should have. Potential participants will have at least 24 hours to consider participating in the study from the time they receive their consent forms.

Data Analysis:
Once there is documentation of the rhythm during a typical palpitation as described in the questionnaire, patients will be divided into one of two primary outcomes: 1. Detected arrhythmia and 2. No arrhythmia detected after one year of enrollment (including sinus tachycardia and sinus bradycardia). Assignment to a group will be based on a definitive tracing which the patient confirms to be representative of the clinical complaint, determined by a cardiologist. Patients with no definite diagnosis at 12 months will be placed under the "No arrhythmia detected" outcome. The scoring system will be developed after all data has been collected in consultation with a statistician. The groups will be analyzed and compared for demographics and questionnaire score. Using regression analysis, we aim to determine factors from the questionnaire that have a high predictive value for arrhythmia. Weightage will be given for these factors and a score which will give us a strong predictive value that the palpitations are due to an arrhythmia will be formulated.

Sample Size:
The difficulty with identifying a sample size is the lack of epidemiological data with regards to palpitations in children. However adult studies have shown about 40% of patients with palpitations to have a cardiac etiology (14). Assuming 50% of children with palpitations to have a cardiac arrhythmia and with 8 questions to be tested, we will need a sample size of 80-160 to use linear regression to produce reliable predictive values. We aim to produce this number by applying the study over the next 2-3 years to all children visiting the British Columbia Children's Hospital Heart Centre. With the participation of more centres, we will be able to achieve higher numbers.

Expected benefit and harm:
The protocol does not deviate from standard care for these patients. There are no additional harms for participating in the study. The patients in the study themselves will not benefit from this study. However if we are successful in developing a tool that predicts the likelihood of certain clinical features being predictive that arrhythmia is the cause of palpitations, then we will validate it in another cohort, likely at another institution. It is possible that one day, we will be able to diagnose arrhythmia in children with palpitations early, hence expediting interventions. There is a risk of a breach of confidentiality but, as described below, every effort will be made to protect patient confidentiality.

Data storage/protection
Every effort will be made to protect patient confidentiality. Patients will be assigned a confidential study ID. The information linking the study ID to the patient's name will be kept in an encrypted file on a password-protected computer in an office of site investigator research team.. The electronic de-identified data will be stored in REDCap with only password access by appropriate research staff. Data from other sites will also be entered into REDCap by members of their study teams. Hard copies of the

data or of the patient's information will be destroyed 5 years after the completion of the study, in accordance with UBC guidelines.

References

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Annex 1

Participating centres

We have invited multiple centres across North America to participate in the study. The following investigators have agreed to participate and will join us once we have cleared our ethics commitments.

1. Dr. Seshadri Balaji. Oregon state health university, Portland.
2. Dr. Andrew Blaufox. Cohen's children's medical centre, New York.
3. Dr. Susan Etheridge. University of Utah health hospital, Salt Lake City.