Title: Determining the Natural and “Unnatural” History of Anomalous Aortic Origin of a Coronary Artery with Interarterial or Intraconal or Intramural course (AAOCA): Establishing a Multi-Institutional Registry

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Study Principal Investigator

Julie A. Brothers, M.D.
The Children’s Hospital of Philadelphia
Division of Cardiology, 8NW75
Philadelphia, PA, 19104
Phone 267-426-7517
Fax 215-590-4978
Email: brothersj@email.chop.edu

Site Principal Investigator

Christopher A. Caldarone MD
The Hospital for Sick Children
Division of Cardiovascular Surgery
Toronto, ON, M5G 1X8
Phone 416-813-6420
Fax 416-813-8776
Email: christopher.caldarone@sickkids.ca
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### ABBREVIATIONS AND DEFINITIONS OF TERMS

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<td>AAOCA</td>
<td>Anomalous aortic origin of a coronary artery with interarterial or intraconal or intramural course</td>
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<td>ALCA</td>
<td>Anomalous left coronary artery</td>
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<td>ARCA</td>
<td>Anomalous right coronary artery</td>
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<td>SCD</td>
<td>Sudden cardiac death</td>
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<td>CHSS</td>
<td>Congenital Heart Surgeons Society</td>
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ABSTRACT

Context: Anomalous aortic origin of a coronary artery with interarterial or intraconal or intramural course (AAOCA) is a rare heart anomaly associated with a high risk of sudden death in children. There is debate among cardiologists and cardiac surgeons regarding how to treat a child with AAOCA, especially those who do not have symptoms.

Objectives: The purpose of the study is to determine the outcome of surgical intervention versus observation in children and young adults with AAOCA. To do this we will create a registry of AAOCA subjects that will enable us to develop a risk stratification model utilizing a large multi-institutional registry under the auspices of the Congenital Heart Surgeon Society (CHSS). We will then test the hypothesis that subsets of subjects with AACOA can be identified in whom the risk of intervention is less than the risk of observation.

Study Design/Setting/Participants: This is a retrospective and prospective study. Subjects will be enrolled either when identified retrospectively from medical records or prospectively when diagnosed with AAOCA. Baseline demographics, diagnoses, and test results will be obtained through retrospective chart review. Follow-up health-related information will be obtained through annual questionnaires. The project will be carried out at several participating CHSS member institutions, with the data stored and analyzed at the CHSS Data Center.

Study Measures: Data will be analyzed for different risk factors at diagnosis, different treatment strategies and the impact of both on subject outcome.
1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Anomalous aortic origin of a coronary artery with interarterial or intraconal or intramural course (AAOCA) is a rare congenital anomaly that consists of either the left main coronary arising from the right sinus of Valsalva (ALCA) or the right coronary arising from the left (ARCA). Both carry an increased risk of myocardial ischemia and sudden death in children and young adults, especially during or just after exercise. The treatment and management of asymptomatic children is controversial because the true risk of sudden death is unknown. We are currently unable to risk-stratify which children are at increased risk from those who are not. While most physicians would agree that surgical intervention is indicated if a subject presents with signs or symptoms of myocardial ischemia, what remains unclear is the treatment of asymptomatic subjects, especially those with ARCA, which may carry a lower risk of sudden death. This dilemma is even greater in young (< 30 years) subjects who have a higher risk of sudden death than those asymptomatic individuals identified in later adulthood.

Our lack of established evidence-based treatment and management guidelines is largely because this is a rare anomaly with inadequate subject numbers in any one institution to power studies aimed at assessing risk of myocardial ischemia and sudden death over the long-term. Because these lesions are associated with a risk of sudden death, the clinician faces pressure to “do something” although there are no evidence-based guidelines on which to base a therapeutic plan. The center of the critical knowledge gap is the lack of risk stratification data on which to balance the risk and preventive efficacy of intervention against the risk of observation.

The Congenital Heart Surgeons Society (CHSS) Data Center

The CHSS is a consortium of approximately 100 surgeons from 60 university-based hospitals in the United States, Canada, and South America. They all share an interest in the management and outcomes of surgery for congenital heart lesions. The CHSS Data Center was established in 1985 and has several studies ongoing, with over 4,000 neonates and children being followed. The CHSS extracts subject information and contacts families for follow-up information on a regular basis. The analyses from these data have enabled pediatric cardiovascular surgeons and cardiologists to utilize the best treatment options for a variety of congenital heart defects; they have also allowed for better counseling of subjects and their families regarding prognostic outcomes. The collaboration of these institutions has led to improved treatment and management strategies in this population. Further, the CHSS has published many studies in several peer-reviewed journals.

1.2 Compliance Statement

This study will be conducted in full accordance with each CHSS member institutions’ Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the HIPAA Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with CHSS member institutions’ IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.
Relevant Literature and Data

Anomalous aortic origin of a coronary artery with interarterial or intracoronary or intramural course (AAOCA) is a rare congenital anomaly in which the left main coronary artery arises from the right sinus of Valsalva (ALCA) or the right arises from the left sinus (ARCA). Both ALCA and ARCA are associated with sudden cardiac death (SCD) but the former appears to carry a higher risk (1-9). This risk is greatest during or just after exercise, notably among young, otherwise healthy children and young adults (3,7-9). The true prevalence of AAOCA is unknown; however, studies have reported anywhere from 0.1-0.3% of subjects (10-14).

The clinical challenge for physicians is diagnosing AAOCA prior to SCD, because these individuals often are asymptomatic (10,15). When symptomatic, the most common cardiovascular presenting complaints are those that occur during or just after exertion, including: chest pain, dizziness, or syncope (3,16-18). The initial diagnosis is usually made by transthoracic echocardiography but confirmatory tests often include CT scan, cardiac magnetic resonance imaging, or cardiac catheterization with coronary angiography.

Once the diagnosis is made, treatment and management remains controversial, with some cardiologists recommending exercise restrictions and others advocating surgical repair (20). While most cardiologists and cardiac surgeons would agree that surgical intervention is indicated if a subject of any age with AAOCA presents with signs or symptoms of myocardial ischemia, what remains unclear is the treatment of asymptomatic subjects who are identified with this anomaly by chance. This dilemma is even greater in the young (<30 years) subjects who have a higher risk of SCD than those asymptomatic individuals identified in later adulthood (1,9). There are certainly many subjects who remain asymptomatic, survive childhood, and are diagnosed in late adulthood when they undergo routine angiography to evaluate for coronary artery disease (13,14).

The critical knowledge gap is mainly due to the lack of risk stratification data on which to balance the risk and preventive efficacy of intervention against the risk of observation. This knowledge gap persists because the lesion is relatively uncommon and no single institution has the capability to accomplish the necessary steps to develop a risk stratification model because there are inadequate subject numbers in any one institution. This proposal will address the steps required to create a risk stratification model using the infrastructure of the CHSS to rapidly develop the only registry of children and young adults with AAOCA ever assembled and thereby accomplish our study objectives as outlined below.

2 STUDY OBJECTIVES

Our overall purpose is to develop and maintain an ongoing comprehensive multi-institutional registry comprised of clinical information about subjects who have been evaluated and/or followed at any of the participating CHSS institutions. The database will provide:

1) clinical data warehousing,
2) interfacing with data analysis for critical program review, and
3) future access to clinical data for investigational purposes (with IRB approval).

2.1 Clinical Objectives

A. To determine the natural history of AAOCA through examination of a large multi-center registry.
1. Relate the natural history of AAOCA to initial diagnostic and prospectively acquired diagnostic and anatomic data.

B. To determine the “unnatural” history of AAOCA (e.g., after surgical or catheter-based intervention) through examination of a large multi-center registry.
   1. Relate the “unnatural” history to anatomic risk factors and surgical/interventional techniques

C. To develop clinically applicable predictive models of these natural and “unnatural” histories

D. Obtain follow-up data to assess long-term clinical outcome over time

2.2 Quantitative Objectives

A. To obtain information on demographic data, diagnoses, and tests and procedures performed

B. To obtain trends in relative frequency of AAOCA

3 REGISTRY DESIGN

3.1 General Schema of Study Design

All subjects evaluated and/or followed at CHSS member institutions for AAOCA will qualify to be included in the database. The database will be ongoing. Expired subjects followed by CHSS member institutions prior to their demise and those unable to be located will be included in the retrospective aspect of the database. Data collection will be ongoing for a patient’s lifetime to assess for long-term outcomes of AAOCA. We will establish the registry by initially retrospectively identifying subjects with AAOCA who have been cared for by physicians in the CHSS participating institutions. We will simultaneously prospectively enroll newly identified subjects into the registry upon diagnosis from January 21, 2009 forward. Following receipt of informed consent, a subject enrollment form will be completed at each CHSS member institution for enrollment into the study (see Subject Enrollment Form). Information gathered will be obtained from existing data and records, diagnostic tests, and surgical and/or catheter interventions. Annually, specially trained personnel from the CHSS will call the family, checking on the child’s clinical progress and obtaining additional follow-up information and records (See attached Questionnaire Forms).

3.2 Study Duration, Enrollment and Number of Sites

3.2.1 Duration of Study for Subject

Study duration will be for a patient’s lifetime from study initiation or subject enrollment.

3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at potentially 55 investigative sites in the United States and 5 sites in Canada and South America.

It is expected that approximately 10,000 subjects will be enrolled to produce 10,000 evaluable subjects
3.3 Study Population

3.3.1 Inclusion Criteria

1) Diagnosis and/or management of AAOCA at a CHSS member institution from January 1, 1998 forward

2) Male or female age 0-30 years at time of diagnosis

3) If surgical repair:
   a) Performed from January 1, 1998 to study initiation for retrospective subjects
   b) Performed from January 21, 2009 forward for prospectively identified subjects
   c) Completed operative note

4) Structurally normal heart or with small, hemodynamically insignificant lesion, including: patent ductus arteriosus, atrial septal defect, ventricular septal defect, mild pulmonic valvar stenosis, or bicuspid aortic valve without aortic stenosis.

5) Parental/guardian permission (informed consent), subject consent if > 18 years of age and if appropriate, child assent for the observational/questionnaire portion of the study.

3.3.2 Exclusion Criteria

1) Anomalous coronary from the pulmonary artery, coronary artery atresia, or other coronary artery anomalies (e.g., coronary-cameral fistula, coronary aneurysms, myocardial bridging)

2) Hemodynamically significant structural heart disease, except as outlined above.

3.3.3 Case ascertainment

Potential retrospective subjects will be identified by a query of all subjects identified with AAOCA from January 1, 1998 until January 20, 2009 through each participating hospital’s cardiology and cardiothoracic surgery databases and medical records. Subjects will also be enrolled from surgeons or cardiologists caring for these subjects at the individual institutions and upon new diagnosis from January 21, 2009 forward at the member institutions. The Subject Enrollment Form contains a box with inclusion criteria, which the chart abstractor will verify before continuing with the abstraction. This form will also be used to enroll new subjects once diagnosed.

3.3.4 Data sources (for existing records)

To identify all subjects with AAOCA who meet the criteria as detailed below, the contact person at each hospital (or their designee) will query their hospital’s cardiology and cardiothoracic surgery databases as described above from January 1, 1998 until January 20, 2009. Subjects will also be identified from surgeons or cardiologists caring for these subjects at the individual institutions and upon new diagnosis.

3.4 Bias and Blinding

To avoid an over-represented sample in those children who have moved and/or have been seen at multiple institutions (i.e., surgery at one place but followed clinically at another), when all the information is input at the CHSS Data Center, the extractor will note children with the same birthdate and diagnosis and ensure they are only entered into the registry only once.

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4 STUDY PROCEDURES

4.1 Subject Identification and Data Collection

The first phase will be to retrospectively identify subjects with AAOCA who have been cared for by physicians in the CHSS participating institutions. We will collect baseline demographic, tests/evaluation, and perioperative data. We will compile these data into a single AAOCA registry. To identify all subjects with AAOCA who meet the criteria as detailed below, the contact person at each hospital (or their designee) will query their hospital’s cardiology and cardiothoracic surgery databases (e.g., catheterization, echocardiography, exercise laboratory, surgical, and autopsy) and medical records from January 1, 1998 until January 20, 2009. Subjects will also be identified from surgeons or cardiologists caring for these subjects at the individual institutions and upon new diagnosis from January 21, 2009 forward at the member institutions. Once the subject population is identified, families and/or patients will be contacted by phone by the PI or the study coordinator at each participating institution. A verbal consent and authorization for telephone questionnaire and chart review will be obtained during this telephone contact. It is during this telephone conversation that permission will be asked to mail a written consent for authorization to allow data to be sent to the CHSS for enrollment in the registry. For those subjects who are prospectively after the study has begun, written consent will be obtained at the time of the clinic visit at the individual CHSS member institutions. Once the families have sent back the written informed consent and authorization to participate in CHSS data registry, then the CHSS can proceed with ongoing annual follow-up and medical record data can be sent to the CHSS. Waiver of consent and authorization for retrospective chart review will be maintained for descendents and subjects who cannot be located.

After consent is obtained, each subject’s record will be retrospectively reviewed for baseline (i.e., at time of diagnosis and/or initial evaluation by the participation institution) and surgical (if applicable) data. This information will be collected and sent confidentially to the CHSS Data Center that is located at the Hospital for Sick Children in Toronto. Malik Baxi, MD, MPH, the CHSS Research Program Manager, will not be an investigator in this study and will be responsible for the data at the CHSS and for supplying only de-identified data to the investigators for future analysis. Data will be abstracted from these confidential medical records submitted to the Data Center. For those subjects identified after study initiation (i.e., on or after January 20, 2009), compact discs of any echocardiograms, MRIs, CT scans, and cardiac catheterizations will also be sent, when possible, to the CHSS data center. Trained dedicated personnel at the CHSS will perform all data extraction and entry into a secure computerized database. Records will be kept in a locked, secure location with restricted access. Each study participant will be assigned a corresponding study number that is used for all further analysis, and specific variables will be entered into a secure, password protected computer at the Data Center. These data files are restricted to the study data center. Each member institution utilizes a HIPAA data use agreement with the CHSS and the study data center to maintain the highest level of confidentiality for all participants.

4.2 Follow-Up Questionnaire

The second phase will be a unique opportunity to obtain follow-up data on subjects from multiple institutions. Using this cohort of surviving subjects, we will utilize a Questionnaire (see appendix) regarding the current health status of the subject. This non-standardized questionnaire covers several broad aspects of quality of life issues for patients and their families such as demographics, health status, activity level, and medical care. In yearly intervals, specially trained personnel from the CHSS will contact the subject by phone utilizing a phone script to standardize the calls (see
attached). If subjects cannot be contacted after 3 attempts, then the subject will be considered “lost to follow-up.”

4.3 Unscheduled Visits

N/A

4.4 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Principal Investigator at the participating CHSS institution if there is an inability to recontact the subject and verify outcome, in which case the data would be considered as “lost to follow-up.” The Investigator may also withdraw subjects to protect the subject for reasons of safety or for administrative reasons.

5 STUDY ENDPOINTS AND EVALUATIONS

5.1 Primary Endpoints

After we have collected the data for our registry, we will utilize statistical analyses to ascertain the following. Our primary study endpoints will be: signs of myocardial ischemia, subject symptoms of myocardial ischemia, or sudden death between date of surgical repair or diagnosis (if observation alone) and any time in the follow-up period.

5.2 Secondary Endpoints

Secondary endpoints will include the following:

a. The relationship between anatomic risk factors and surgical/interventional techniques to evidence of myocardial ischemia or sudden death after surgery.

b. The relationship between initial and follow-up diagnostic tests and anatomic data to evidence of myocardial ischemia or sudden death in the follow-up period since diagnosis.

6 MEASUREMENTS AND EVALUATIONS

6.1 Subject Identification and Data Collection

Data collection will include the following areas of interest: subject and parent name; date of birth; medical record number; home address; telephone numbers; referring physician information; hospital where records obtained; date of first visit; diagnosis; gender, ethnicity and race; echocardiographic data, electrocardiogram data, cardiac catheterization data; CT scan and MRI data; holter monitor results; exercise test results; nuclear medicine results; medications; hospitalizations for surgery, including date of admission and discharge, date of surgery, height and weight at surgery, surgical procedure, and complications, if applicable. The questionnaire will collect data regarding frequency of cardiology visits, medications, activity restrictions, exercise-related symptoms, and procedures since initial diagnosis.

Please see CRFs in appendix for more details.

6.2 Efficacy Evaluations

N/A
6.3 Pharmacokinetic Evaluation (only if applicable)

N/A

6.4 Safety Evaluation

There are no safety evaluations except to ensure subject confidentiality.

7 STATISTICAL CONSIDERATIONS

7.1 Primary and Secondary Endpoints

1. Our main objective is to establish a registry of AAOCA subjects. In so doing, we then aim to clarify the natural and unnatural history of AAOCA that will allow us to develop clinically predictive models to identify subsets of subjects in whom intervention is warranted. To do this, we will assess the following endpoints: signs of myocardial ischemia, subject symptoms of myocardial ischemia, or sudden death between date of surgical repair/intervention (if applicable) and any time in the follow-up period.

2. Secondary endpoints will include the following:
   
   a. The relationship between anatomic risk factors and surgical/interventional techniques to evidence of myocardial ischemia or sudden death after surgery.
   
   b. The relationship between initial and follow-up diagnostic tests and anatomic data to evidence of myocardial ischemia or sudden death in the follow-up period since diagnosis.

7.2 Statistical Methods

Descriptive statistics will be calculated, including means, standard deviations, 95% confidence intervals, medians, and minimum and maximum values for all continuous variables. Frequency counts and percentages will be used for categorical variables. Different modes of presentation will be described and chi-square tests used to compare symptoms with diagnosis and coronary anatomy. Different evaluation and treatment strategies of the various institutions will be described. Chi-square tests will be performed to determine whether differences exist between different surgical options and post-operative morbidity and mortality, including signs/symptoms of myocardial ischemia. Similarly, chi-square tests will be performed to determine whether differences exist between different non-surgical treatment options (observation, exercise restriction, beta-blockade) and morbidity and mortality, including signs/symptoms of myocardial ischemia since date of diagnosis. A multivariate analysis of parametric models will be established using demographic, institutional, anatomical, and surgical factors (when appropriate) and their association with outcome (death, re-operation, exercise restriction, cardiac medication, no limitations). These models will be used to assess different combinations of risk factors and determine the extent of the risk factors to help predict whether certain subject or management characteristics predict outcome. In addition, it is anticipated that this will be the first time that the statistical methodology of Competing Risks Analysis will be applied to this subject population.

7.3 Sample Size and Power

As this is a study of a rare disease with an unknown number of subjects, our sample size will be estimated based on numbers of known children with this at several hospitals. We estimate the sample size to be in the range of 10000 evaluable children and young adults.
For the power calculation, we will use a comparison of two proportions using a two sided test, with an alpha of 0.05, and a power of 0.80.

We will define the reference population as those that did not have an intervention and had a sudden cardiac death rate of 30%. Utilizing a clinically significant difference of 20%, we would need 93 subjects in each group (i.e., those that had an intervention and those that did not).

8 SAFETY MANAGEMENT

This is a minimal risk study. The only intervention will be a follow-up questionnaire. The only risk is release of PHI and loss of confidentiality. Every effort will be made to keep PHI from disclosure. Any breach will be reported.

9 STUDY ADMINISTRATION

9.1 Data Collection and Management

1. Privacy. Each study participant is assigned a corresponding study number that is used for all analysis purposes. A master list will be kept separate from our case report forms. Each CHSS member institution associated with this study will have IRB approval from their institution using this IRB as a template. There will be a Data Center Research Assistant at the CHSS who will be responsible for maintaining the database of IRB approvals and assuring that no site submits data without a current IRB approval letter on file.

2. Security. The data will be stored at the CHSS. The Key database and the study data will be stored separately and have different password protection. The investigators will only have access to de-identified data and only Dr Maulik Baxi at the CHSS will be able to connect the individual subject to the data. The compact discs will be stored at the CHSS in a locked, secured file cabinet. The compact discs will be sent to the CHSS confidentially and securely with the subject name on the outside; once at the CHSS, the name will be removed and the study number will replace the name. When possible, the scans will only contain de-identified data prior to being sent to the CHSS. However, it may not always be possible to remove identifiers from the scans. If this is the case, all attempts at keeping the subject information confidential will be made as described above.

3. Anonymization, de-identification or destruction. Each study participant is assigned a corresponding study number that is used for all analysis purposes. All data analysis, review, and published results will be performed in a de-identified manner.

9.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with institutional policies and HIPAA on subject privacy and the investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Safeguards are described under Data Collection and Management. The information collected as part of this study will be retained for 3 years after the study is completed. At that time, the research information will either be destroyed or all the information that identifies the subject will be removed from the study results and the key destroyed.
9.3 Regulatory and Ethical Considerations

9.3.1 Data and Safety Monitoring Plan
The study investigators will be responsible for safety monitoring. There is minimal safety risk with this study, mainly from the potential breach of privacy and loss of confidentiality. The PI will ensure that confidential information will be secured as described above and that PHI will not be revealed. Access to subject information will be limited to the study personnel and PHI will be kept in a separate secure location in the PI’s office.

9.3.2 Risk Assessment
The main risk in this study is the potential breach of privacy and loss of confidentiality. There is a minimal risk of likelihood of harm. All reasonable safeguards to secure the confidentiality of information will be taken by the investigators and their research personnel. Access to subject information will be restricted to the investigators and their designees and passwords will be limited to such personnel. All identifying information will be kept separately in a secure location in the Principal Investigator’s office and case report forms and questionnaires will not have identifying information. At the CHSS, all information will be maintained in a secure, confidentially manner. Information will be maintained in a locked file cabinet in a locked room with restricted access to CHSS Data Center appointed personnel. Data will be stored within secure password protected computer files. We believe this study overall is minimal risk.

9.3.4 Potential Benefits of Trial Participation
Information collected may contribute to the care of children in the future who have the same heart condition as those that participate in this study. The information may also improve the future management of study participants. There may be no direct benefit to the subject from participation in our study.

9.3.5 Risk-Benefit Assessment
We feel that the study as a whole represents minimal risk to the subjects. We feel that the potential benefit of identifying children who may be at increased risk of ischemia and sudden death outweighs the risk of participation.

9.4 Recruitment Strategy (or Case Ascertainment)
Subjects will be identified through retrospective review of each participating hospital’s cardiology and cardiothoracic surgery databases (e.g., catheterization, echocardiography, exercise laboratory, surgical, and autopsy) and medical records from January 1, 1998 until present. Subjects will also be identified from surgeons or cardiologists caring for these subjects at the individual institutions.

9.5 Informed Consent/Assent
The phone questionnaire and chart review will be subject to verbal consent obtained by the PI or study coordinator at the individual CHSS member institutions upon initiating a telephone conversation with the parents and/or guardians. Please see attached verbal consent script. If a subject declines participation in the study, information from their charts will not be used in the study. Once verbal consent is obtained, a written informed consent form will be mailed to the parent(s) or legal guardian of any minor child or to subjects > 18 years of age. Informed assent will also be obtained from the minor child prior to participation. For those subjects who are identified after the study has begun (i.e., prospective subjects), written consent/assent will be obtained at the time of the clinic visit at the CHSS member institution. The written consent will be to obtain authorization to have their medical information securely and confidentially sent to the CHSS for data abstraction and
entry into the registry. We will not allow information from the subjects' charts to be sent to the CHSS unless written consent and HIPAA authorization have been obtained. Once the families have sent back the written informed consent, then the CHSS can proceed with ongoing annual follow-up and medical record data can be sent to the CHSS. Waiver of consent and authorization for retrospective chart review will be maintained for descendents and subjects who cannot be located. The local and overall Principal Investigator’s phone number will be on the consent form if the family has any questions. The family will keep a copy of the signed and dated consent form and the original will be maintained in the subject’s confidential study records.

For those subjects who turn 18 during the study, verbal consent (see attached) will be obtained at the next phone interview where the subject will answer the questions (using the Adult Questionnaire) instead of the parents.

9.5.1 Waiver of Consent

We are requesting a waiver of consent to collect data on deceased subjects or subjects that are lost to follow up.

9.6 Payment to Subjects/Families

There will be no monetary payment for participation in this study.

10 PUBLICATION

We anticipate the results of this study will be presented at national meetings and/or published in academic journals. We will not disclose PHI in any presentation or publication about the study.
11 REFERENCES

3.3.3 and 9.4: Case Ascertainment

At The Hospital for Sick Children, potential cases will be identified through queries of the Health Records, Cardiac Surgical Database, Exercise Laboratory Database, Echocardiography Database and Cardiac Catheterization Database.
Appendix
Case Report Forms
Written Consent Cover Letter (Adult and Child)
Written Consent Form
Verbal Consent Form
Verbal Consent Form for Subjects who turn 18 during the study
Phone Script for Follow-up Questionnaire