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Original Article

The registry of anomalous aortic origin of the coronary artery of The Congenital Heart Surgeons' Society

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Abstract The anomalous aortic origin of a coronary artery from the wrong sinus of Valsalva with interarterial, intramural, and/or intraconal course is a rare congenital anomaly that is associated with a high risk of sudden death in children. The Congenital Heart Surgeons' Society established the Registry of Anomalous Aortic Origin of the Coronary Artery to help determine the outcome of children and young adults managed with surgical intervention versus observation and to test the hypothesis that subsets of patients with anomalous aortic origin of a coronary artery can be identified in whom the risk of intervention is less than the risk of observation. All institutional members of the Congenital Heart Surgeons' Society were recruited for participation. The registry consists of a retrospective cohort of patients diagnosed between 1 January, 1998 and 20 January, 2009 and a prospective, population-based cohort of patients newly diagnosed from 21 January, 2009 onwards. Baseline demographics, diagnoses, and results of tests will be obtained through a review of the medical records. Annual follow-up data will be collected. Data will be analysed for different factors of risk at diagnosis, different strategies of treatment, and the impact of both on the outcomes of the patients. As of June 2010, 28 institutions had applied for approval from their institutional review board and 16 institutions had received approval from their institutional review board. Seventy-four patients have enrolled to date. We hope to use the established Pediatric Cardiomyopathy Registry as a guide to successful implementation, with a cooperative effort between institutions. The overall purpose of the Registry of Anomalous Aortic Origin of the Coronary Artery is to determine the outcome of surgical intervention versus observation in children and young adults with anomalous aortic origin of a coronary artery, and to describe the natural and "unnatural" history of these patients over the course of their lifetime. In this report, we describe the creation and design of the Registry of Anomalous Aortic Origin of the Coronary Artery. Data from the registry will be published at a later date.

Keywords: Congenital cardiac disease; paediatric cardiac disease; interarterial coronary artery; intramural coronary artery; intraconal coronary artery

ANOMALOUS AORTIC ORIGIN OF A CORONARY ARTERY from the wrong sinus of Valsalva with an interarterial, intramural, and/or intraconal course is a rare congenital anomaly in which the left main coronary artery, the left anterior descending coronary artery, or the circumflex coronary artery usually arises from the right sinus of Valsalva, or the right coronary artery usually arises from the left sinus of Valsalva. Rarely, these vessels may arise from the non-coronary sinus of Valsalva. Both the anomalous aortic origin of the left coronary artery

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and the anomalous aortic origin of the right coronary artery are associated with sudden cardiac death, but the former appears to carry a higher risk.[1–3] This risk is thought to be greatest during or just after exercise, notably among otherwise healthy children and young adults.[3,4] In fact, in the United States of America, the anomalous aortic origin of a coronary artery is the second leading cause of sudden cardiac death in young individuals, behind hypertrophic cardiomyopathy.[5] The true prevalence of the anomalous aortic origin of a coronary artery is unknown. One large angiographic study evaluated more than 100,000 adults with coronary angiography and found the incidence to be 0.3%.[6] The largest population-based study in children found the incidence of anomalous aortic origin of a coronary artery in children to be 0.17%, using echocardiography on approximately 3000 children with structurally normal hearts.[7]

The cause of ischaemia and sudden death in patients with anomalous aortic origin of a coronary artery is unclear. On the basis of autopsy studies of patients with anomalous aortic origin of a coronary artery, sudden cardiac death is hypothesised to occur from decreased flow of blood through the anomalous coronary artery, resulting in myocardial ischaemia and/or ventricular tachyarrhythmias.[2,8] This diminished flow of blood likely results from an anatomical malformation of the anomalous vessel, including:

- acute angulation of the take-off from the aorta creating a "slit-like" orifice that easily collapses;
- presence of an ostial ridge; and/or
- proximal interarterial, intramural, and/or intraconal course that gets compressed between the great arteries or within the aortic wall.[4,8,9]

On account of these malformations, the risk of cardiac ischaemia increases with vigorous exercise, when there is a significantly greater cardiac output and demand for oxygen placed on the heart.[1,10] Ischaemia is unlikely to occur every time the patient exercises; rather, it appears that the collective effect of several smaller ischaemic events may lead to a myocardium that is more prone to lethal tachyarrhythmias.[8,11]

Treatment of patients with anomalous aortic origin of a coronary artery remains controversial and varies among clinicians. Recommendations may include observation alone, exercise restriction, medical therapy (such as beta-blockers), and/or surgical repair.[12] Most agree that surgical intervention is indicated if a patient of any age presents with signs and/or symptoms of myocardial ischaemia. What remains unclear is the treatment of asymptomatic patients who are diagnosed with anomalous aortic origin of a coronary artery serendipitously. This therapeutic dilemma is greatest in those with anomalous aortic origin of the right coronary artery, whose risk of sudden cardiac death is thought to be significantly lower than those with anomalous aortic origin of the left coronary artery, and in young patients (that is, those less than 30 years of age) whose risk of sudden cardiac death is probably greater than those identified in later adulthood. We are currently unable to adequately stratify risk to predict which patient is at higher risk for sudden cardiac death than a different one, given the same basic anatomy.

Indeed, there is a critical gap in knowledge in how to treat patients, mainly due to the lack of data about stratification of risk on which to balance the risk of intervention against that of observation. This gap in knowledge persists because the lesion is relatively uncommon and no single institution has large enough experience to accomplish the necessary steps to develop a model to stratify risk. To the best of our knowledge, no large, population-based studies have been carried out to evaluate patients with anomalous aortic origin of a coronary artery over time.

Therefore, the Registry of Anomalous Aortic Origin of the Coronary Artery was designed to describe the presentation, clinical course, and clinical outcomes of patients, aged 30 years or younger at the time of diagnosis, undergoing different treatment modalities, with the ultimate goal of developing evidence-based guidelines for treatment and management. In this report, we describe the creation and design of the Registry of Anomalous Aortic Origin of the Coronary Artery. Data from the registry will be published at a later date.

Methods

Anomalous Coronary Artery Working Group

In 2006, before the implementation of the Registry of Anomalous Aortic Origin of the Coronary Artery, the Anomalous Coronary Artery Working Group was formed. This Working Group is an interdisciplinary collaboration between cardiologists and cardiothoracic surgeons from institutions whose surgeons are members of the Congenital Heart Surgeons' Society. The Congenital Heart Surgeons' Society is an association of approximately 90 congenital and paediatric cardiac surgeons, predominantly from 60 university-based hospitals in the United States of America, Canada, and South America, who share an interest in the management and outcomes of surgery for congenital cardiac lesions. The Congenital Heart Surgeons' Society Data Center was established in 1985 and has several studies ongoing, with more than 4000 patients being followed up. The collaboration of these institutions has led to improved

treatment and strategies of management for patients with paediatric and congenital cardiac disease.[13,14]

The Working Group felt it was important to understand current opinions of physicians regarding the management of patients with anomalous aortic origin of a coronary artery. In 2007, we sent a questionnaire to all participating members of the Congenital Heart Surgeons' Society to distribute to paediatric cardiologists, cardiothoracic surgeons, and nurse practitioners at their institutions.[12] This voluntary survey-based study was designed to report current attitudes and beliefs regarding treatment and strategies of management of children and adolescents with anomalous aortic origin of a coronary artery, from practitioners at several different institutions.

The results from this study emphasised the heterogeneity regarding current recommendations for the management and treatment of patients with anomalous aortic origin of a coronary artery among practitioners in North and South America. The survey yielded reports of post-operative complications and deaths that had not been described in previous publications.[12] The findings of our Working Group underscored the need to develop a database with a goal of eventually developing more cohesive and evidence-based guidelines for treatment and management. Thus, the next step for our Working Group was to establish the Registry of Anomalous Aortic Origin of the Coronary Artery.

Organisation

The Registry of Anomalous Aortic Origin of the Coronary Artery was funded by a grant from the Children's Heart Foundation during the period from 1 January, 2009 to 31 December, 2010, and through the Cardiac Center Development Grant at the Children's Hospital of Philadelphia from 1 April, 2009 to 31 March, 2010. These funds were directed to the primary awardee of the grant, the University of Pennsylvania and the Children's Hospital of Philadelphia, and then subcontracted to the Congenital Heart Surgeons' Society Data Center at the Hospital for Sick Children in Toronto, Ontario, Canada. The Children's Hospital of Philadelphia serves as the site for the study. The principal investigator of the study (J. A. Brothers), who initiated the registry, oversees the direction of the registry, and is responsible for finding funding for the registry. The Anomalous Coronary Artery Working Group was responsible for determining the data that were to be extracted from charts of patients and forming the "case report forms". Members of the Working Group communicate regularly by teleconference and have an annual meeting regarding the Registry of Anomalous Aortic Origin of the Coronary Artery. The Congenital Heart Surgeons' Society Data Center has a core team who are responsible for helping with:

- obtaining approval from the institutional review boards at the various participating sites,
- obtaining legal agreements to share data from the various participating sites,
- extraction of data,
- entry of data,
- housing of data, and
- statistical analyses.

The Congenital Heart Surgeons' Society Data Center also has specially trained personnel who will make annual follow-up phone calls to patients and their families.

Study design

The Registry of Anomalous Aortic Origin of the Coronary Artery was implemented to address the specific aims as detailed in Table 1. The overall purpose of the study is to determine the outcome of surgical intervention versus observation in children and young adults with anomalous aortic origin of a coronary artery, and to describe the natural and "unnatural" history of these patients over the course of their lifetime. The term "unnatural" history is used to describe the history of patients treated with surgical or transcatheter intervention.

To achieve our goals, we established the Registry of Anomalous Aortic Origin of the Coronary Artery by

Table 1. Objectives of the Registry of Anomalous Aortic Origin of the Coronary Artery.

1. To determine the natural history, including morbidity, and mortality of children and young adults with anomalous aortic origin of a coronary artery, through examination of a large multi-centre registry.
2. To determine the "unnatural" history, including morbidity and mortality, of children and young adults with anomalous aortic origin of a coronary artery after surgical or transcatheter intervention, through examination of a large multi-centre registry.
3. To monitor trends in the incidence of anomalous aortic origin of a coronary artery with respect to selected sociodemographic characteristics and presentation of the patient at diagnosis.
4. To relate the natural history of anomalous aortic origin of a coronary artery to initial diagnostic and prospectively acquired diagnostic and anatomic data.
5. To relate the "unnatural" history to anatomic risk factors and techniques of surgical or transcatheter intervention.
6. To determine the outcome of surgical or transcatheter intervention versus observation in children and young adults with anomalous aortic origin of a coronary artery.
7. To develop clinically applicable models that stratify risk associated with these natural and "unnatural" histories.
8. To establish evidence-based guidelines for the treatment and management of children and young adults with anomalous aortic origin of a coronary artery.

initially retrospectively identifying patients with anomalous aortic origin of a coronary artery who had been cared for by physicians at the participating institutions of the Congenital Heart Surgeons' Society. We also prospectively enrol newly identified patients into the registry upon diagnosis from the start date of the registry, 21 January, 2009. Patients in the retrospective cohort were identified through query of the medical records at each institution, and were eligible if identified with anomalous aortic origin of a coronary artery from 1 January, 1998 until 20 January, 2009. This date of starting the retrospective analysis was chosen because the Working Group felt that before that date, echocardiographic imaging was not adequate to evaluate the origin of a coronary artery accurately. Further, it gave us 10 years in which to establish an estimate of prevalence. All patients who were enrolled will be followed prospectively from the date of enrolment. We estimated that we would need 100 patients in the natural and "unnatural" groups to provide enough power for initial statistical analyses.

Each participating institution obtained approval for "human subjects research" from its own institutional review board. "Data sharing agreements" were established between each participating institution and the Congenital Heart Surgeons' Society Data Center.

Patients

Patients aged 30 years or younger at time of diagnosis who underwent evaluation and/or treatment at a participating institution were eligible for inclusion in the study. Patients whose first presentation was sudden death were also included in the study if the death occurred at a participating centre or the patient was transported to a participating centre. Data from the pathological examination at the participating institutions are included, but coroners, medical examiners, and pathologists were not officially queried for this project. We wanted to capture as many different coronary anomalies that are at high risk for sudden death as possible, but we did not want to include children with significant structural cardiac disease. Our focus was on children who were otherwise healthy, who were found to have anomalous aortic origin of a coronary artery. However, we chose to allow some minor structural cardiac defects if the patient had anomalous aortic origin of a coronary artery and a small, haemodynamically insignificant lesion, such as:

- patent arterial duct,
- atrial septal defect,
- ventricular septal defect,
- mild pulmonary valvar stenosis, or
- bileaflet aortic valve without aortic stenosis.

Further, we wanted to ensure inclusion of only those coronary anomalies that fit the definition of anomalous aortic origin of a coronary artery. We excluded any patients who had

- anomalous origin of the coronary artery from the pulmonary artery,
- coronary artery atresia,
- coronary arterial fistula,
- coronary aneurysms,
- myocardial bridging,
- other coronary artery anomalies, and
- as well as any patient with haemodynamically significant structural cardiac disease unrelated to the coronary anomaly.

There was significant discussion among the members of the Working Group regarding how best to define anomalous aortic origin of a coronary artery. Ultimately, we chose to include those patients with forms of anomalous aortic origin of a coronary artery that have previously been linked to sudden cardiac death. We wanted to ensure inclusion of even very rare types of anomalous aortic origin of coronary arteries, as it may be possible with a registry to collect enough patients to evaluate adequately the outcome of these very rare anomalies. We chose to use the nomenclature for anomalous aortic origin of a coronary artery from the version of the International Paediatric and Congenital Cardiac Code derived from the nomenclature of the International Congenital Heart Surgery Nomenclature and Database Project of the European Association for Cardio-Thoracic Surgery and the Society of Thoracic Surgeons (Table 2).

Collection of data

Currently, submission of data to the Registry of Anomalous Aortic Origin of the Coronary Artery is voluntary through each institution. In January, 2009, a "blast" email was sent out to all the members of the Congenital Heart Surgeons' Society with details of the Registry of Anomalous Aortic Origin of the Coronary Artery. Simultaneously, a link was posted on the website of the Congenital Heart Surgeons' Society to the registry with details about participation. These initiatives resulted in responses from 38 interested institutional members of the Congenital Heart Surgeons' Society. Each participating institutional member of the Congenital Heart Surgeons' Society designated a physician contact, either a cardiologist or cardiothoracic surgeon, and a study coordinator, for the Registry of Anomalous Aortic Origin of the Coronary Artery. The study coordinator is the person responsible for

- coordinating submission to the institutional review board,
- identifying patients,
- obtaining consent from patients and/or families, and
- collecting data.

Table 2. The nomenclature for Anomalous Aortic Origin of a Coronary Artery from the version of The International Paediatric and Congenital Cardiac Code (IPCCC) derived from the nomenclature of the International Congenital Heart Surgery Nomenclature and Database Project of The European Association for Cardio-Thoracic Surgery (EACTS) and The Society of Thoracic Surgeons (STS)

1	Coronary anomaly, AAOC (Anomalous aortic origin of coronary)
2	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery
3	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Interarterial course of left main from right aortic sinus of Valsalva (interarterial course = the epicardial course of a coronary artery between the great arteries)
4	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Interarterial course of right coronary from left aortic sinus of Valsalva (interarterial course = the epicardial course of a coronary artery between the great arteries)
5	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Interarterial course of the Circumflex from right aortic sinus of Valsalva (interarterial course = the epicardial course of a coronary artery between the great arteries)
6	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Interarterial course of the LAD from right aortic sinus of Valsalva (interarterial course = the epicardial course of a coronary artery between the great arteries)
7	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Intraconal or intraseptal course of LAD from RCA (LAD coursing within ventricular septum beneath RVOT before coursing epicardially to anterior interventricular groove)
8	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Intraconal or intraseptal course of left main from RCA (LMCA coursing within the ventricular septum beneath the RVOT before branching above the septum into LAD and Cx)
9	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Intraconal or intraseptal course of the circumflex coronary artery from the right coronary artery
10	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Intramural course without interarterial course and without intraconal (intraseptal) course of the circumflex coronary artery (Cx)
11	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Intramural course without interarterial course and without intraconal (intraseptal) course of the left anterior descending coronary artery (LAD)
12	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Intramural course without interarterial course and without intraconal (intraseptal) course of the left main coronary artery (LMCA)
13	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery, Intramural course without interarterial course and without intraconal (intraseptal) course of the right coronary artery (RCA)
14	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier
15	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier for dominance of coronary system, Left dominant
16	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier for dominance of coronary system, Right dominant
17	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier for orifice morphology, With 1 orifice within sinus (the intima of the "carina" of the coronary is deep to the plane of the aortic intima)
18	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier for orifice morphology, With 2 orifices within sinus
19	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier for orifice morphology, With 2 orifices within sinus, Two orifices close to each other (double barrel orifice)
20	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier for orifice morphology, With 2 orifices within sinus, Two orifices widely spaced orifices within same sinus
21	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier for orifice morphology, With slit-like orifice
22	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, With acute angulation (less than 45 degrees)
23	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, With coronary compression between great arteries
24	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, With high ostial takeoff (ostial takeoff is above sinotubular junction)
25	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, With interarterial course (interarterial course = the epicardial course of a coronary artery between the great arteries)

Table 2. *Continued*

26	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, With intraconal or intraseptal course (Septal course through conal septum = infundibular septum)
27	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, With intramural course
28	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, Without acute angulation (greater than 45 degrees)
29	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, Without coronary compression between great arteries
30	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, Without high ostial takeoff (ostial takeoff is not above sinotubular junction)
31	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, Without interarterial course (interarterial course = the epicardial course of a coronary artery between the great arteries)
32	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, Without intraconal or intraseptal course (Without course through conal septum = infundibular septum)
33	Coronary anomaly, AAOC (Anomalous aortic origin of coronary), Aberrant coronary artery-modifier, Without intramural course

Legend: RVOT = Right Ventricular Outflow Tract

Information from the medical record of the patient will be sent confidentially to the Congenital Heart Surgeons' Society Data Center for entry of data into the Registry of Anomalous Aortic Origin of the Coronary Artery. For those patients prospectively identified, compact discs of multiple diagnostic studies will also be sent, whenever possible, to the Congenital Heart Surgeons' Society Data Center, to be stored in a locked, secured location. Compact discs will be collected for the as many as possible of the following studies:

- echocardiograms,
- magnetic resonance imaging,
- computerised axial tomographic scans, and
- cardiac catheterisations.

However, we acknowledge the problems that may arise with the voluntary collection and submission of data. For example, early in its experience, the Pediatric Cardiomyopathy Registry had initially depended on voluntary submission of data as well.[15] They found that the advantage of this strategy was its low cost, but the disadvantages were potential underreporting of cases and delay of submission and collection of data. In the paper describing the Pediatric Cardiomyopathy Registry, Greiner et al described that after 1 year of voluntary submission of data, they changed to an active approach. They hired full-time personnel to

- travel to participating centres,
- collect data,
- complete enrolment of new cases, and
- perform abstraction of data at regular intervals.

They found that this active strategy significantly improved their enrolment and provided more complete data for the registry.[15] The use of the example of the Pediatric Cardiomyopathy Registry has allowed us to seek funding to ultimately utilise this active approach to help ensure more complete and accurate collection, submission, and abstraction of data.

Procedures of collection of data

Once the patient is identified, the patient and/or the parent, if applicable, are contacted by phone by the study coordinator at each participating institution. Verbal consent and authorisation for the questionnaire by the telephone and review of the chart will be obtained during this contact on the telephone. Permission will also be obtained to mail a written consent for authorisation to allow data to be sent to the Congenital Heart Surgeons' Society. Once written informed consent is obtained, data from the medical record can be sent to the Congenital Heart Surgeons' Society and ongoing annual follow-up

can proceed. Waiver of consent will be maintained for decedents and patients who cannot be located.

After consent is obtained, the medical record of each patient is initially reviewed for data at the baseline, that is, at the time of diagnosis and/or initial evaluation by a physician at the participating institution, and also for data about surgical or transcatheter intervention, if applicable. Collection of data will include the following areas of interest:

- name of the patient and parents;
- date of birth;
- medical record number;
- home address;
- telephone numbers;
- information about the referring physician;
- hospital where records are obtained;
- date of first visit;
- diagnosis;
- gender;
- ethnicity and race;
- echocardiographic data;
- data from electrocardiograms;
- data from cardiac catheterisations;
- data from computerised axial tomographic scans;
- data from magnetic resonance imaging studies;
- data from Holter monitors;
- data from exercise tests;
- data from nuclear medicine tests;
- medications; and
- data from hospitalisations for surgery or transcatheter intervention, including date of admission and discharge, date of surgery, height and weight at surgery, surgical procedure, and complications, if applicable.

Information about the follow-up of the patient will be retrieved annually thereafter.

The non-standardised questionnaire covers several broad aspects of quality-of-life issues for patients and their families. Data will be collected regarding current demographics, frequency of visits to the cardiologist, medications, restrictions of activity, exercise-related symptoms, and procedures since initial diagnosis. At yearly intervals, specially trained personnel from the Congenital Heart Surgeons' Society Data Center will contact the patient and/or family by phone utilising a scripted tool to facilitate the interview and standardise the calls. If the patient and/or family cannot be contacted after three attempts, then the patient will be considered "lost to follow-up".

Once patient information is sent to the Congenital Heart Surgeons' Society Data Center, trained dedicated personnel will perform all data extraction and data entry into a secure computerised database. Records will be kept in a locked, secure location with restricted access to maintain the highest level of confidentiality for all participants, and each member institution will utilise a data-sharing agreement with the Data Center that is compliant with The Health Insurance Portability and Accountability Act of the federal government of the United States of America (HIPAA).

All identifiers of the patient will be removed and a unique "study number" will be assigned to each patient participating in the study. These corresponding study numbers will be used for all further analyses. Instead of having each participating institution abstract information about the patient onto forms designed to collect the data, we decided to have all information about the patient sent to the Data Center to then be extracted by personnel at the Data Center. Potential advantages of this process include:

- decreasing the amount of work that each centre has to do, especially while this study is voluntary, and
- helping to standardise how information is abstracted.

Annually, personnel at the Data Center will contact families, as detailed above, during a specified month every year, as per their protocol for several other multicentre trials with annual follow-up.

Protocols are in place to avoid the possibility of counting patients more than once, such as those who have had surgery at one institution but are managed clinically at another institution. To avoid an over-represented sample in those children who have moved and/or have been seen at multiple institutions, when all the information is input at the Congenital Heart Surgeons' Society Data Center, the extractor will note children with the same date of birth and diagnosis and ensure that they are only entered into the registry once if they are indeed the same patient.

Recruitment and enrolment of patients to date

Thirty-eight institutional members of the Congenital Heart Surgeons' Society have expressed interest in participating in the Registry of Anomalous Aortic Origin of the Coronary Artery. As of June, 2010, the time at which this paper was written, 28 institutions had applied for approval from their institutional review board and 16 institutions had received approval from their institutional review board. Twelve institutions have a data-sharing agreement in place and can start submitting data about patients to the Data Center. To date, 74 patients are enrolled from five institutions.

Statistical considerations

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 of the patients will be described, and chi-square tests will be used to compare symptoms with diagnosis and anatomy of the coronary arteries. Different strategies of evaluation and treatment at the various institutions will be described. Chi-square tests will be performed to determine whether different surgical options are associated with differences in post-operative morbidity and mortality, including signs and/or symptoms of myocardial ischaemia. Similarly, chi-square tests will be performed to determine whether differences exist between different non-surgical treatment options, such as observation, restriction of exercise, implementation of beta-blocker, and morbidity and mortality, including signs and/or symptoms of myocardial ischaemia since the 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 several possible outcomes:

- death,
- re-operation,
- restriction of exercise,
- cardiac medication, and
- no limitations.

These models will be used to assess different combinations of factors and their association with risk, to help determine whether outcome can be predicted by certain factors, such as characteristics of patients or strategies of management. In addition, it is anticipated that this project will be the first time that the statistical methodology of Competing Risks Analysis will be applied to this cohort of patients.

Sample size and power

As this project is a study of a rare disease with an unknown number of patients, our sample size was estimated based on numbers of known children with anomalous aortic origin of a coronary artery at multiple institutions. We estimate the sample size to be in the range of 1000 evaluable children and young adults.

For the calculation of power, we used a comparison of two proportions using a two-sided test, with an alpha of 0.05, and a power of 0.80. We defined the reference population as those that did not have a surgical or transcatheter intervention and used an estimated rate of sudden cardiac death of 30%. Utilising a clinically significant difference of 20%, we need 93 patients in each group, that is, those that had a surgical or transcatheter intervention and those that did not. We are on target for an initial analysis of data in Spring of 2011.

Discussion

The Registry of Anomalous Aortic Origin of the Coronary Artery is in the process of creating the largest clinical database of children and young adults with anomalous aortic origin of a coronary artery from medical institutions across North America. Significant interest exists in the development of this registry because many questions remain about the management and treatment of these patients. On account of the large number of patients, as well as the data from long-term follow-up, we should be able to answer some of the clinical questions pertaining to the various strategies of treatment. We will better understand the natural history of patients with anomalous aortic origin of a coronary artery, as well as the post-interventional history. Comparison of long-term morbidity and mortality between these two approaches should begin to clarify how best to manage children and young adults with anomalous aortic origin of a coronary artery. Furthermore, the registry may elucidate future directions regarding which modality of imaging should be considered the "gold standard" when diagnosing anomalous aortic origin of a coronary artery. Current possibilities include echocardiography, computerised axial tomographic scans, magnetic resonance imaging studies, and cardiac catheterisation. It may also help determine which imaging modality should be used for testing at follow-up. Future studies from the registry may include genetic analyses of those patients with more than one family member with anomalous aortic origin of a coronary artery and the use of magnetic resonance imaging to evaluate myocardial flow of blood and reserve of flow in the coronary arteries pre- and post-operatively.

To date, we have used a voluntary approach to the identification of patients and collection of data. Using the Pediatric Cardiomyopathy Registry as an example, the change to an active approach to collection of data would be advantageous for the long-term success of the registry.[15] Although the protocol for institutional review boards and the forms for entry of data are available on the website of the Congenital Heart Surgeons' Society (www.chssdc.com), our registry is still a voluntary one. To help with voluntary enrolment, it may be beneficial to have forms for enrolment of patients, which allow for the entry of information over the Internet for those participating institutions with approval from their institutional review board. Further, as we plan on following patients for their lifetime, the loss of patients to follow-up may be significant. We have tried to ameliorate this potential

loss of patients to follow-up with annual questionnaires that ask for not only contact information of the patient and parents, but also for contact information of a friend or relative of adult age, in case the patient moves. We hope this strategy will help to track the patient in the future.

The Registry of Anomalous Aortic Origin of the Coronary Artery has several potential limitations. First, while we will have a better understanding of the incidence and prevalence of patients with anomalous aortic origin of a coronary artery, we will still not be able to know completely the true numbers as we do not have the participation of 100% of the institutional members of the Congenital Heart Surgeons' Society. However, we do have participation from the majority of the major centres in the United States of America and Canada. Second, this analysis may exclude patients with anomalous aortic origin of a coronary artery that are seen in institutions that are not members of the Congenital Heart Surgeons' Society, but the latter should be a small minority of the total population of patients with this anomaly. Third, a database with national participation of coroners and medical examiners would improve our number of patients, since those who present with sudden death may never reach a centre participating in the study. Certainly, a database of reports from coroners, pathologists, and medical examiners would be beneficial in the future.

Indeed, with the establishment of this multi-centre Registry of Anomalous Aortic Origin of the Coronary Artery, we are one step closer to our overall goal of assessing the natural history of anomalous aortic origin of a coronary artery, as well as the long-term outcome of surgical repair. We will then be able to establish evidence-based guidelines for the treatment and management of children and young adults with anomalous aortic origin of a coronary artery, and therefore prevent the devastation of sudden cardiac death in the young.

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