PROTOCOL

Title: Atrioventricular Septal Defect – A Congenital Heart Surgeons' Society Inception Cohort Study

Cohort: Atrioventricular Septal Defect (AVSD)

Study: Atrioventricular Septal Defect (AVSD) Study

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1. Abstract

Context:
Atrioventricular Septal Defect (AVSD) is a rare congenital cardiac malformation of the atrioventricular septum. It results in a common atrio-ventricular valve orifice that connects both atria to both ventricles. Typically the connection is symmetrical thereby allowing equal balanced blood flow into each ventricle. But there is a spectrum of unequal atrio-ventricular connection associated with underdevelopment of either left or right ventricle. These neonates have an unbalanced flow and that in the extreme situation results in a heart that is functionally a single ventricle. The degree of unbalance affects both the type and risk of operative repair. The criteria that define the limits of operative repair and risk are unknown.

In our preliminary retrospective multi-center analysis we identified criteria that define the amount of unbalance. Our proposed prospective study of a multi-center inception cohort of neonates born with complete AVSD will define the limits of unbalanced flow and ventricle development to determine the optimal surgical treatment and outcomes.

Hypothesis:
Survival, morbidity and functional outcomes of newborns with AVSD can be optimized through improved matching of repair strategy to morphologic/physiologic substrate.

Study Design:
We will enroll a prospective cohort of infants with complete AVSD at participating Congenital Heart Surgeons' Society (CHSS) member institutions. The CHSS Data Center at The Hospital for Sick Children in Toronto, Ontario, Canada will collect and abstract clinical data and obtain copies of initial cardiac echocardiograms, follow-up echocardiograms & CT/MRI studies for independent review. An annual cross-sectional follow-up of the cohort, including details of future tests and interventions, including quality of life measurements, will be entered into the dataset. CHSS member institutions receiving Institutional Review Board (IRB)/Research Ethics Board (REB) approval for the study will be the participating sites. All study data will be stored securely and typically analyzed at the CHSS Data Center.

Study Measures:
Longitudinal multivariate analyses of demographic, cardiac morphology, function, and procedural variables will be used to search for risk factors that affect outcomes. These will include analyses of recurring events such as follow-up echocardiographic/CT/MRI measures of heart function and re-interventions.

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2. Specific Aims

2.a. Objective: To improve survival among patients with atrioventricular septal defects (AVSD) by further characterizing that portion of the disease spectrum customarily referred to as unbalanced atrioventricular septal defect (uAVSD) and evaluating the relationships between patient and procedural factors and outcomes.

The AVSD is a spectrum of disease that includes subcategories characterized by varying degrees of malalignment of the common atrioventricular (AV) junction, ventricular hypoplasia, and intrinsic valvar abnormalities. These morphologic features, in combination or in isolation, may result in disproportionate flow into right and left ventricles. This condition is commonly referred to as "unbalanced" atrioventricular septal defect.

Proper selection of treatment strategies for uAVSD is particularly difficult. Consensus regarding a standard definition of "unbalance" is lacking, and there are few evidence-based guidelines for selection of treatment strategies. The overall high degree of mortality observed in patients with uAVSD is likely to reflect suboptimal choices of treatment strategy. Thus, overall survival might be better if the relationships between morphologic and physiologic aspects of the disease and the outcomes of various surgical treatment strategies were more fully understood. Treatment choices are relatively clear at the extreme ends of the anatomic spectrum of disease. When the AVSD is severely unbalanced, the smaller ventricle is incapable of supporting adequate cardiac output and functionally univentricular repair is required. In contrast, a biventricular repair strategy is uniformly appropriate for balanced AVSD. Between these extremes, the choice of repair strategy is confounded by gaps in present knowledge of the relationship between patient factors, anatomy, repair strategy, and outcome.

2.b. Hypothesis: Survival and late outcomes of patients with uAVSD can be optimized through improved matching of repair strategy to morphologic/physiologic substrate.

Aim 1 (A_1): Define the anatomic features of uAVSD.

Sub-Aim 1a: Characterize the full anatomic and functional spectrum of complete AVSD.

Sub-Aim 1b: Identify anatomic relationships and develop novel indices to improve the ability to discriminate between unbalanced and balanced complete AVSD (CAVSD).

Aim 2 (A_2): Determine patient and morphologic/physiologic factors that are associated with selection of surgical strategy (single ventricle repair, biventricular repair, intermediate (pulmonary artery banding)) and survival.

Aim 3 (A_3): Determine relationships between patient and anatomic characteristics, selected surgical strategy, and outcome.

Aim 4 (A_4): Develop and evaluate a clinically applicable prediction model to facilitate clinical decision making.

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3. Background and Rationale

The AVSD is a spectrum of disease characterized by varying degrees of incomplete development of the septal tissue surrounding the atrioventricular valves along with varying degrees of abnormalities of the atrioventricular valves themselves. The essence of this cardiac malformation is a common atrioventricular junction [1]. The AVSD may be subcategorized into several groups of lesions (Appendix 1) [1-5]. A complete AVSD is defined as an AVSD with a common AV valve and both a large defect in the atrial septum just above the AV valve (ostium primum ASD [a usually crescent-shaped ASD located between the antero-inferior margin of the fossa ovalis and the atrioventricular valves]) and a nonrestrictive defect in the ventricular septum just below the AV valve (in the canal (posterior) portion of the ventricular septum). The AV valve is one valve that bridges both the right and left sides of the heart.

Identification and surgical treatment of balanced AVSD is straightforward with excellent outcomes in the majority of cases [6-9]. Unbalanced AVSD, however, encompasses a broad array of complex anatomies that present significant diagnostic and therapeutic challenges. These anatomic variations include right or left ventricular dominance, malalignment of the atrial and/or ventricular septa, variations in ventricular septal defect morphology, and abnormalities of the atrioventricular valve apparatus with potential abnormalities of atrioventricular valve function. The frequent incidence of comorbidities such as Trisomy 21 or heterotaxy syndrome, with its attendant pulmonary and systemic venous anomalies, further complicate the anatomic and therapeutic considerations coincident to uAVSD. Indeed, the very definition of what constitutes 'unbalanced' in AVSD is not well established. In addition, several surgical approaches are available to address the various anatomic substrates of uAVSD, including biventricular repair, single ventricle palliation, and "one and a half ventricle" repairs. Finally, there is scant literature documenting outcomes associated with these approaches. Historically, reported outcomes have been suboptimal with mortality approaching 25% in some series and low freedom from reintervention [10-13]. Still fewer reports directly address surgical decision-making [14]. To achieve significant improvement in the treatment of uAVSD, clearer understanding of the morphologic and physiologic aspect of the disease and diagnostic criteria is needed [15]. Once diagnostic clarity is achieved, then the relationships between morphology/physiology and treatment strategies can be explored with the expectation of arriving at inferences that can guide clinical decisions going forward.

As a precursor to a proposed prospective study, a multi-institutional retrospective study was undertaken. That study had three principle aims: to measure the incidence of uAVSD, to determine early mortality rates associated with surgical repair of uAVSD, and to validate a reliable echocardiographic measurement that could be utilized as an enrollment tool for a prospective study. The atrioventricular valve index (AVVI) was originally introduced by Cohen and colleagues [16] as an echocardiographic measure of unbalance in AVSD, but it remains underutilized as a diagnostic criterion.

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The original AVVI was calculated using the echocardiographic subcostal left anterior oblique (LAO view) to measure the area of common AVV apportioned over each ventricle and calculating the ratio of the smaller AV valve area over the larger AV valve area, so that left-dominant uAVSD was expressed as RAVV area/LAVV area and right dominant uAVSD the inverse [15, 16].

The modified AVVI also is calculated using the echocardiographic subcostal left anterior oblique (LAO view) to measure the area of common AVV apportioned over each ventricle but is calculated by determining the ratio of the left atrioventricular valve area divided by the total atrioventricular valve area (LAVV area/ Total AVV area) [15, 17].

We modified the expression of AVVI (mAVVI) to simplify its use and evaluated its utility as an enrollment tool.

The major findings of the retrospective study are:

a. Incidence of uAVSD amongst a cohort of complete AVSD who had a measurable AVVI and had surgery was 19% (58/305).

b. Early mortality amongst the uAVSD cohort was 22.4% [UVR 7/22 (32%), BVR 4/34 (12%), PA Band 1/1 (100%)]. Notably, early mortality amongst the balanced AVSD cohort was 6.9% (17/247). UVR=Univentricular Repair. BVR=Biventricular Repair.

c. Modified AVVI proved a reproducible and reliable method for identifying uAVSD from a cohort of all complete AVSDs. All patients with mAVVI <0.2 underwent UVR, and nearly all patients with mAVVI 0.4 – 0.6 underwent BVR. Heterogeneity of surgical strategy was found among patients with mAVVI 0.19 – 0.39. There was a notable clustering of mortality within this range of mAVVI. This was true whether patients were undergoing UVR or BVR within that range of AVVI. For an AVVI between 0.19 and 0.39 (N=38), 26 patients underwent BVR (7 deaths), and 12 patients underwent UVR (4 deaths).

It is important to understand that, for the retrospective study, the range of mAVVI chosen to define balanced AVSD was selected *a priori* by the investigators. That is, a mAVVI of 0.4 – 0.6 was called "balanced" (0.1 to either side of the middle – 0.5). This range of mAVVI was found to be reasonably concordant with outcome and surgical decision-making, as stated above. However, this construct was chosen as a starting point, and could conceivably change in light of new data obtained during the prospective study. In addition, there may be other echocardiographic measurements that are essential to proper assignation of "unbalance", such as ventricular volumetric surrogates or septal malalignment assessments, and mAVVI should therefore be considered an important *component* of the anatomic landscape of AVSD rather than a measure that defines unbalance. Therefore, the exact range of mAVVI that corresponds to "balanced" AVSD remains to be established and also to be determined is whether other factors that, when present, impact the breadth of this range.

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This prospective study aims to establish the echocardiographic indices, as well as patient anatomic and physiologic factors that favor BVR and those that favor UVR. These elements will be used to create a prediction model that facilitates optimal patient and procedure matching, thereby maximizing clinical outcomes. A hypothetical construct of the elements relevant to such a prediction model follows.

FAVORING BVR	FAVORING UVR
Favorable mAVVI	Unfavorable mAVVI
Favorable AV valve color inflow quantification	Unfavorable AV valve color inflow quantification
Favorable Ventricular volume measurement	Unfavorable ventricular volume measurement
Favorable septal alignment	Unfavorable septal alignment
Favorable leaflet geometry	Unfavorable leaflet geometry
Significant common AV valve regurgitation	Competent common AV valve
Poor ventricular function	Better ventricular function
Elevated PA pressures	Normal PA pressures
Echo measures of elevated EDP	Echo measures of normal EDP
Larger RV/LV inflow angle	Smaller RV/LV inflow angle

4. Study Design

4.a. Enrollment: All subjects diagnosed with complete AVSD at participating CHSS institutions will be considered for enrollment in the study. Patients who have undergone prior cardiac surgery at a non-CHSS institution will not be included. Potential cases will be identified at each participating institution in accordance with the IRB/REB approved screening methods, and enrolled in accordance with the IRB/REB approved consent and enrollment processes. Informed consent (and authorization, as applicable), enrollment form completion, and data collection will be carried out by the participating center. The Patient Enrollment Form for the study will be used to enroll new subjects. The CHSS Data Center Registration Form for the study will be used to register new subjects. A copy of the signed consent (and authorization, as applicable) will be securely sent to The CHSS Data Center along with a copy of the patient charts and imaging records. Data collection will be ongoing from enrollment forward, with submission of data annually and after any surgical intervention. Data submitted will include clinical records, echocardiograms, and procedural records. Data will be de-identified and securely stored at the

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CHSS Data Center at The Hospital for Sick Children, Toronto, Ontario, Canada. The data will be abstracted by the Data Center staff. In addition to data submission from the participating center, annual follow-up will be performed by CHSS Data Center staff. The patients will be followed for their life. The study will be considered completed when the last enrolled patient is known to have died.

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Patients who meet the eligibility criteria but are known to have passed away before being consented will be enrolled in the study. However their families will not be contacted for consent, follow-up or for any other study related purpose.

4.b. Follow-Up: Upon consent (and authorization, as applicable) at the submitting institution and registration at the CHSS Data Center, Data Center staff will contact the parent/guardian of the subject to welcome them into the study and remind them of the annual contacts throughout their study participation. Similarly, when the subject is eligible to and provides consent (and authorization, as applicable) to participate in the study him/herself, and the CHSS Data Center is provided with this information, the CHSS Data Center staff will contact the subject to welcome him/her into the study (study continuation) and remind him/her of the annual contacts throughout his/her study participation.

Life-long annual cross-sectional follow-up will be conducted on this cohort. This phase is an essential component of establishing the cohort and is unique to this type of observational study. This is also important in understanding the progression of the patients being treated and managed with different approaches. Using this cohort of surviving subjects, the Data Center will utilize a study Follow-up Form and Questionnaires to collect information on the health status and quality of life of the subject. The CHSS Data Center non-standardized questionnaires and the PedsQL™ standardized questionnaires [18-25] cover several aspects of quality of life issues for subjects such as health status, activity level, and medical care. Demographics/contact information and medical/surgical updates are collected on the CHSS Data Center Follow-up Form. At yearly intervals, specially trained personnel from the CHSS Data Center will contact each subject or the parent/guardian of each subject, as applicable, for such follow-up (e.g., by telephone, mail, fax or electronically, as appropriate).

Throughout the course of the study the subject's clinical and surgical cardiac-related reports will be obtained as well. Typically this information will be sent to the Data Center from the participating sites. In cases where the subject is followed at a non-CHSS institution or a non-participating CHSS institution, with the permission of the subject (parents/guardians, as applicable), the CHSS Data Center may send the subject (parents/guardians, as applicable) a Consent for Release of Medical Information form, which the subject (parents/guardians, as applicable) can then sign and take to their health care provider requesting that the specified information be released to the CHSS Data Center. Alternatively, the subject (parents/guardians, as applicable) may themselves request through the institution that holds the information, that the information be forwarded to the CHSS Data Center.

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4.c. Subject Completion/Withdrawal: Subjects may withdraw (or be withdrawn by their parents/guardians, as applicable) from the study at any time without any impact on their care. Subjects 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 re-contact the subject/subject's parents/guardians and verify outcome, in which case the subject 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. If a subject withdraws or is withdrawn or discontinued from the study at any stage, no further information about him/her will be collected for use in the analysis. However information already collected will continue to be used as needed to maintain the integrity of the research.

4.d. Echo Core Lab: All echocardiograms will be securely sent to The Hospital for Sick Children in Toronto, Ontario, Canada. Echocardiograms will be reviewed by a dedicated echo sonographer at The Hospital for Sick Children. The echo sonographer will confirm the diagnosis, independently measure a mAVVI, and perform additional echo analysis as required for the study on all baseline and follow-up echos, under the supervision of the lead echocardiographer (M.D.) of the echo core lab.

5. Participation Criteria

Participation in this cohort is voluntary for member institutions and surgeons. In an effort to encourage consistent enrollment of study patients by member institutions, foster active surgeon involvement, and ensure imaging studies of sufficient quality for analysis, each participating center will be expected to support the following initiatives:

5.a. Echocardiography Training: Echocardiograms must be of sufficient quality and completeness that all study measurements may be performed by the echo sonographer. To ensure quality and completeness, each participating center will identify one lead sonographer and one echocardiographer (M.D.) who will review the echo powerpoint presentation that is available online (www.chssdc.org/content/avsd-atrioventricular-septal-defect) and participate in the webinar training offered by the Data Center. These webinars will be recurring to facilitate accrual of additional participating sites.

In addition, the CHSS Data Center may provide feedback, in a secure manner, to the participating center with respect to the quality and completeness of the echocardiograms received, as a communication tool and aid to improving the quality and completeness of the echocardiograms, as needed.

5.b. Member Participation: It is expected that a surgeon representative of the participating center will attend a minimum of one project related working session, either at a CHSS "work weekend" or at a national meeting where work on the study is being conducted.

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Deleted: Echocardiograms must be of sufficient quality and completeness that all study measurements may be performed by the echo core lab personnel. To ensure this quality and completeness, each participating center will send at least one lead sonographer and one echocardiographer (M.D.) to a one day educational seminar hosted by the echo core lab team. The number and location of these seminars is to be determined, but will most likely be held at the Data Center or in conjunction with national pediatric cardiology meetings. These seminars will be recurring to facilitate accrual of additional participating sites, and their cost to the participating site covered under the study budget.¶

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6. Study Population

6.a. Inclusion Criteria

1. Diagnosis of or referral with complete AVSD at a CHSS member institution within first year of life
2. Admitted to CHSS institution for surgery after January 1, 2012
3. Age ≤ 365 days at admission for surgery
4. Atrioventricular and Ventriculoarterial concordance (includes Tetralogy of Fallot and Double Outlet Right Ventricle)
5. Informed written consent, as applicable

6.b. Exclusion Criteria

1. Partial or Transitional AVSD (separate AV valve orifices, restrictive VSD or intact ventricular septum)
2. Total or Partial Anomalous Pulmonary Venous Drainage (TAPVC or PAPVC)
3. Aortic atresia
4. Heterotaxy
5. First Intervention at a non-CHSS institution

6.c. Number of Subjects Projected: The retrospective study accrued approximately 350 patients over six years from four member institutions, roughly 60 of whom were considered to have uAVSD. Thus, each participating center may be expected to enroll an average of 10-15 patients per year. As such, between 300-450 subjects would be accrued within one year if one third to one half of CHSS members participated. We estimate a total of 1500 patients will be enrolled.

7. Study Endpoints and Evaluation

7.a. Primary Endpoints: The primary endpoints to be analyzed are surgical strategy, and early and late survival.

7.b. Secondary Endpoints: Secondary endpoints to be analyzed are:

a. Echocardiographic measures of function including AV valve regurgitation or stenosis, ventricular function, and the presence or absence of left ventricular outflow tract obstruction.
b. Unplanned reintervention after primary surgical repair
c. Residual pulmonary hypertension (pulmonary artery pressure ≥ 2/3 systemic pressures).

7.c. Statistical Methods: Descriptive statistics will be calculated, including means with standard deviations, medians with ranges, 95% confidence intervals, and minimum, 25th percentile and 75th percentile (interquartile range), median, and maximum values for all continuous variables. Frequency counts and percentages will be used for categorical variables.

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Cluster analysis using selected variables will be used to determine the appropriate number of differentiated groups of patients, followed by discriminant function analysis to determine which variables define the various groups of patients.

Competing risks methodology will be used to examine 4 end states until commitment: biventricular repair, univentricular repair, what we have termed "intermediate repairs", and death prior to surgery. The bootstrap bagging method and risk analysis will be performed on each end state to determine associated factors. In addition, survival and hazard modeling will be performed from the time of commitment. A prediction nomogram will be developed based on the AVVI or other echocardiographic measures (as determined by cluster and discriminant factor analysis), and utilized to predict given end states. 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.

Finally, surgical strategies will be analyzed and a prediction model generated which will predict the most appropriate surgical strategy for a given set of patient and anatomic factors. Initial procedure strategy indicated will assess the number of intended univentricular repair or biventricular repairs. Parametric risk-hazard analysis will be used to identify predictors of death for univentricular and for biventricular repair, which will allow prediction of the 5-year univentricular survival advantage for every infant. Survival will be scrutinized for children managed discordantly to univentricular survival advantage predictions.

7.d. Demographic Data Points: Subject name, parent name, date of birth, social security number, contact details of the family, "in-house" cardiologist name and address, referring cardiologist name and address, referring institution name and address, primary care physician name and address, name and address of clinical setting where records (including late follow-up studies) are obtained from member institutions. The Personal Health Information which we are collecting will be stored at The Hospital for Sick Children in Toronto, Ontario, Canada. These records will be stored in a locked storage area accessible only to the CHSS Data Center research team. They will be stored in locked cabinets and access to these cabinets will also be restricted to Data Center research team only. Each patient will be assigned a unique study number. Any electronic abstraction will be done in a separate secure database which will be linked by study number. These databases will be stored on password protected computers and secure access server managed by The Hospital for Sick Children Information Services department. The data need to be collected for purposes of late follow-up and annual receipt of clinical documents. This information will help in checking vital status of patients from electronic databases. Should a patient or family elect to withdraw their consent, we will not contact them again nor will we request further medical records from their institutions.

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7.e. Clinical Documents and Studies: The participating center will forward any and all of the following clinical documents pertaining to the subject:

- diagnostic history and physical examination
- hospital admission notes
- hospital discharge notes
- all cardiac operative notes
- cardiac catheterization reports
- outpatient clinic visit notes
- death notes/autopsy report
- CT cardiac imaging and interpretation
- MRI cardiac imaging and interpretation
- All echo reports (pre and post op)
- *Echo images (along with echo report) at the following time points:

1) Complete, diagnostic echo (pre-intervention)
2) Pre-discharge echo (post initial repair)
3) Late post op echo (1 year post op to 4 years post op)

***All echo images should be transthoracic and in DICOM (or DICOM compatible) format**

7.f. Clinical Data Points: The administrative, echo/imaging, catheterization, surgical, clinical and autopsy data collection forms will contain the clinical data points.

8. Study Administration

8.a. Data Collection and Management

i. Privacy: Each CHSS member institution associated with this study will have IRB/REB approval from their IRB/REB, and will utilize a Data Transfer Agreement with the CHSS Data Center to maintain the highest level of confidentiality for all study participants. After applicable written informed consent (and authorization, as applicable) is obtained, each subject's medical record will be reviewed for baseline and surgical data. This information, including demographic information, will be collected, and along with the consent form (and authorization, as applicable) and completed Patient Enrollment Form, will be securely transferred to the Data Center. Likewise, when the subject provides assent, and when the subject is eligible to and provides consent (and authorization, as applicable) to participate in the study him/herself, the signed forms and any updates in contact information will be securely transferred to the Data Center as well. Similarly, subsequent follow up information and questionnaires will be securely transferred to and obtained by the Data Center. Upon enrollment by the participating institutions, each subject is assigned a unique screening number. Upon registration at the Data Center, each subject is assigned a unique study number that is used for all data entry and analysis purposes, and the CHSS Data Center Registration Form is completed. Trained dedicated personnel at the Data Center will perform all data extraction and entry of specific variables, in a de-identified manner, into secure, password protected computerized databases. A master list

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(key) will be kept separate from the study data. Only appointed personnel at the Data Center will be able to connect the individual subject to the data. The Data Center will be responsible for maintaining a log of IRB/REB approvals and checking to ensure that participating sites are not submitting records or data without the appropriate IRB/REB approval documentation on file.

ii. Security: Appropriate patient identity protection safeguards will be observed by the participating CHSS member institutions, as well as the CHSS Data Center, for the transmission of the patient information (e.g., baseline and follow-up patient care charts or compact discs (CDs) or echo tapes). Secure file transfer or secure courier service will be used as appropriate. The Follow-up Form and Questionnaires will be securely provided to the subjects or parents/guardians (as applicable), and returned to the Data Center by the subjects (or parents/guardians), in a secure manner acceptable to the subjects (parents/guardians, as applicable) (e.g., mail, fax, electronically). The master list (key) and the study data will all be securely stored (using a double lock system) at the Data Center, and kept separate from each other. Likewise, the patient information sent to the Data Center, including CDs of echocardiograms, magnetic resonance images (MRIs), CT scans and cardiac catheterizations, will be securely stored separately at the Data Center. The CDs will be sent to the Data Center securely with the subject name on the outside; once at the Data Center, 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 Data Center. 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.

iii. De-identification: Each subject is assigned a unique study number at the CHSS Data Center that is used for all data entry and analysis purposes. All data analysis, review, and published results will be performed in a de-identified manner.

8.b. Confidentiality

All data and records generated for this study will be kept confidential in accordance with applicable institutional policies, laws and regulations. The investigators and site personnel and the coordinating site will use the study data and records only for these study purposes. Safeguards are described under Data Collection and Management. The information collected as part of this study will be securely retained for 7 years after all study publications are completed. The research information will be securely destroyed according to the applicable institutional policy effective at that time.

8.c. Regulatory and Ethical Considerations

i. Compliance Statement: This study will be conducted in compliance with each participating CHSS member institutions' research policies and procedures and all applicable laws and regulations. The participating sites will perform the study in accordance with this protocol, will obtain consent (and authorization, as applicable) and assent (as appropriate), and will report unexpected problems in accordance with CHSS member institutions' IRB/REB policies and

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procedures and applicable laws and regulations. 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.

ii. Data and Safety Monitoring Plan: The study investigators will be responsible for safety monitoring. This is an observational study which involves only data collection from the hospital/institutional sources (e.g., operative notes, echocardiogram, cardiac catheterization, etc.) as well as from the annual follow-up form and questionnaires sent to the subjects or parents/guardians. This study does not dictate any specific surgical treatment or medications. All procedures performed on the patients are standard of care and the study does not involve any additional hospital visits for the subjects or parents/guardians. There is minimal safety risk with this study, mainly from the potential for breach of privacy and loss of confidentiality. The investigators and site personnel and the CHSS Data Center personnel will ensure that confidential information, including PHI/identifying personal information, will be secured as described above and will not be revealed to unauthorized parties.

iii. 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 and the CHSS Data Center personnel. Safeguards are described under Data Collection and Management. We believe this study overall is minimal risk.

iv. Potential Benefits of Study 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 these patients. There may be no direct benefit to the subject from participation in this study.

v. Risk-Benefit Assessment: The study as a whole represents minimal risk to the subjects. The potential benefit of identifying children with Atrioventricular Septal Defect and enrolling them into this study outweighs the risk of participation.

vi. Recruitment Strategy: Subjects will be identified from surgeons or cardiologists caring for these subjects at the individual CHSS member institutions. Subjects at each of the participating CHSS member institutions will be identified using their own IRB/REB approved methods for screening, consenting and enrolling subjects.

vii. Informed Consent/Assent: Applicable written informed consent/assent (and authorization, as applicable) will be obtained at the time of the patient's routine clinical assessment at the CHSS member institution. The consent (and authorization, as applicable) will be discussed at length and ample time will be allowed for the parent/guardian and subject (as applicable) to discuss it amongst themselves and decide whether they would like to participate. The principal investigator at each participating CHSS member institution, his or her designees/study coordinator will have responsibility for subject recruitment and obtaining applicable written informed consent/assent (and authorization, as applicable) for study participation. As part of

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the study, written consent will include a combined or separate authorization (as appropriate) to have the subject's medical information securely sent to the CHSS Data Center for data abstraction and entry into the study database. Site investigators and personnel will not allow information from the subjects' charts to be sent to the CHSS Data Center unless applicable written consent and such authorization have been obtained. Once the parent/guardian or subject (as applicable) has provided applicable written informed consent, and authorization (as applicable), the data can be securely sent to the CHSS Data Center. The site investigator's phone number will be on the consent form and the original will be maintained in the subject's confidential study records at the respective participating site. The CHSS Data Center will not register any living patient until a copy of the signed consent form and authorization (as applicable) is received.

viii. Inclusion of Deceased Patients: Inclusion in the study is requested for patients identified prospectively at the participating CHSS member institutions, but who die before written informed consent is obtained, and will be conducted in compliance with all applicable laws and regulations, including approval for waiver/alteration of the consent process (as applicable). Families of these patients will not be contacted for research purposes. Only the information already in the medical record will be used and only aggregated data will be reported in publications, precluding families from identifying themselves in any publication. When a participating CHSS institution sends information on a deceased patient, the CHSS Data Center will follow the same procedures to include them in the study that are used for those enrolled while living patient participants.

ix. Publications: We anticipate the results of this study will be presented at national meetings and/or published in academic journals. We will not disclose any subject PHI or identifying personal information in any presentation or publication about the study.

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9. Appendices

9.a. Appendix 1: Definitions

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The following definitions are used by the STS Congenital Heart Surgery Database and the EACTS Congenital Heart Surgery Database and are published in the STS Congenital Heart Surgery Database Data Specifications version 3.0, which became the active version of definitions for these databases on January 1, 2010 [1, 2, 3]:

AVC (AVSD), Complete (CAVSD): ''Indicate if the patient has the diagnosis of 'AVC (AVSD), Complete (CAVSD).' An 'AVC (AVSD), Complete (CAVSD)' is a 'complete atrioventricular canal' or a 'complete atrioventricular septal defect' and occurs in a heart with the phenotypic feature of a common atrioventricular junction. An 'AVC (AVSD), Complete (CAVSD)' is defined as an AVC with a common AV valve and both a defect in the atrial septum just above the AV valve (ostium primum ASD [a usually crescent-shaped ASD in the inferior (posterior) portion of the atrial septum just above the AV valve]) and a defect in the ventricular septum just below the AV valve (inlet VSD). The AV valve is one valve that bridges both the right and left sides of the heart. Balanced AVC is an AVC with two essentially appropriately sized ventricles. Unbalanced AVC is an AVC defect with two ventricles in which one ventricle is inappropriately small. Such a patient may be thought to be a candidate for biventricular repair or, alternatively, may be managed as having a functionally univentricular heart. AVC lesions with unbalanced ventricles so severe as to preclude biventricular repair should be classified as single ventricles. Rastelli type A: The common superior (anterior) bridging leaflet is effectively split in two at the septum. The left superior (anterior) leaflet is entirely over the left ventricle and the right superior (anterior) leaflet is similarly entirely over the right ventricle. The division of the common superior (anterior) bridging leaflet into left and right components is caused by extensive attachment of the superior (anterior) bridging leaflet to the crest of the ventricular septum by chordae tendineae. Rastelli type B: Rare, involves anomalous papillary muscle attachment from the right side of the ventricular septum to the left side of the common superior (anterior) bridging leaflet. Rastelli type C: Marked bridging of the ventricular septum by the superior (anterior) bridging leaflet, which floats freely (often termed a 'free-floater') over the ventricular septum without chordal attachment to the crest of the ventricular septum.''

AVC (AVSD), Intermediate (transitional): ''An AVC with 2 distinct left and right AV valve orifices but also with both an ASD just above and a VSD just below the AV valves. While these AV valves in the intermediate form do form 2 separate orifices they remain abnormal valves. The VSD is often restrictive.''

AVC (AVSD), Partial (incomplete) (PAVSD) (ASD, primum): ''An AVC with an ostium primum ASD (a usually crescent-shaped ASD in the inferior (posterior) portion of the atrial septum just above the AV valve) and varying degrees of malformation of the left AV valve leading to varying degrees of left AV valve regurgitation. No VSD is present.''

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TOF, AVC (AVSD): ‘‘TOF with complete common atrioventricular canal defect is a rare variant of common atrioventricular canal defect with the associated conotruncal abnormality of TOF. The anatomy of the endocardial cushion defect is that of Rastelli type C in almost all cases.’’ (“TOF” is “Tetralogy of Fallot” and is defined as a group of malformations with biventricular atrioventricular alignments or connections characterized by anterosuperior deviation of the conal or outlet septum or its fibrous remnant, narrowing or atresia of the pulmonary outflow, a ventricular septal defect of the malalignment type, and biventricular origin of the aorta. Hearts with tetralogy of Fallot will always have a ventricular septal defect, narrowing or atresia of the pulmonary outflow, and aortic override; hearts with tetralogy of Fallot will most often have right ventricular hypertrophy.)

Single ventricle, Unbalanced AV canal: ‘‘Single ventricle anomalies with a common atrioventricular (AV) valve and only one completely well developed ventricle. If the common AV valve opens predominantly into the morphologic left ventricle, the defect is termed a left ventricular (LV)–type or LV-dominant AV septal defect. If the common AV valve opens predominantly into the morphologic right ventricle, the defect is termed a right ventricular (RV)–type or RV-dominant AV septal defect.’’

VSD, Type 3 (Inlet) (AV canal type): A VSD that involves the inlet of the right ventricular septum immediately inferior to the AV valve apparatus.

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10. References

1. Jacobs JP, Jacobs ML, Mavroudis C, Chai PJ, Tchervenkov CI, Lacour-Gayet FG, Walters III H, Quintessenza JA. Atrioventricular Septal Defects: Lessons Learned About Patterns of Practice and Outcomes From the Congenital Heart Surgery Database of the Society of Thoracic Surgeons. World Journal for Pediatric and Congenital Heart Surgery 2010 1: 68-77, April 2010.
2. STS Congenital Heart Surgery Database Version 3.0 Data Collection Form Annotated - dated 9.16.2009. [http://www.sts.org/sites/default/files/documents/pdf/ndb/CongenitalDataCollectionForm3_0_Annotated_20090916.pdf]. Accessed March 26, 2011.
3. STS Congenital Heart Surgery Database Version 3.0 Data Specifications - dated 9.4.2009. [http://www.sts.org/sites/default/files/documents/pdf/CongenitalDataSpecificationsV3_0_20090904.pdf]. Accessed March 26, 2011.
4. Jacobs JP, Burke RP, Quintessenza JA, Mavroudis C. Congenital Heart Surgery Nomenclature and Database Project: Atrioventricular Canal Defect. The Annals of Thoracic Surgery April 2000 Supplement, The Annals of Thoracic Surgery, 69(4 Suppl):S36-43, April 2000.
5. Bharati S, Lev M. The spectrum of common atrioventricular orifice (canal). Am Heart J 1973;86:553-61.
6. Suzuki T, Bove EL, Devaney EJ, et al. Results of definitive repair of complete atrioventricular septal defect in neonates and infants. Ann Thor Surg 2008;86:596-603.
7. Nunn GR. Atrioventricular canal: Modified single patch technique. Semin Thorac Cardiovasc Surg 2007;10:28-31.
8. Crawford FA, Stroud MR. Surgical repair of complete atrioventricular septal defect. Ann Thorac Surg 2001;72:1621-9.
9. Bando K, Turrentine MW, Sun K, et al. Surgical management of complete atrioventricular septal defects: A twenty-year experience. J Thorac Cardiovasc Surg 1995;110:1543-54.
10. Corno A, Marino B, Catena G, Marcelletti C. Atrioventricular septal defects with severe left ventricular hypoplasia. Staged palliation. J Thorac Cardiovasc Surg. 1988;96(2):249-52.
11. Owens GE, Gomez-Fifer C, Gelehrter S, Owens ST. Outcomes for patients with unbalanced atrioventricular septal defects. Pediatr Cardiol 2009;30:431-5.
12. Walter EMD, Ewert P, Hetzer R, et al. Biventricular repair in children with complete atrioventricular septal defect and a small left ventricle. Eur J Cardiothorac Surg 2008;33:40-7.
13. Lim HG, Bacha EA, Marx GR, et al. Biventricular repair in patients with heterotaxy syndrome. J Thorac Cardiovasc Surg 2009;137:371-7.
14. De Oliveira NC, Sittiwangkul R, McCrindle BW, et al. Biventricular repair in children with atrioventricular septal defect and a small right ventricle: anatomic and surgical considerations. J Thorac Cardiovasc Surg 2005;130:250-7.
15. Overman DM, Baffa JM, Cohen MS, Mertens L, Gremmels DB, Jegatheeswaran A, McCrindle BW, Blackstone EH, Morell VO, Caldarone C, Williams WG, and Pizarro C. Unbalanced Atrioventricular Septal Defect: Definition and Decision Making. World Journal for Pediatric and Congenital Heart Surgery April 2010 1: 91-96, doi:10.1177/2150135110363024

Deleted: 9

Deleted: <#>Ferencz C, Loffredo CA, Correa-Villasenor A, Wilson PD. Genetic and environmental risk factors of major cardiovascular malformations: The Baltimore-Washington infant study 1981-1989. Futura Publishing Co., Armonk, NY, pp 103-122.¶ <#>Freedom RM, Bini M, Rowe RD. Endocardial cushion defect and significant hypoplasia of the left ventricle: A distinct clinical and pathological entity. Eur J Cardiol. 1977;7(4):263-281.¶

Deleted: ¶
Corno A, Marino B, Catena G, Marcelletti C. Atrioventricular septal defects with severe left ventricular hypoplasia. Staged palliation. J Thorac Cardiovasc Surg. 1988;96(2):249-52.

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Deleted: 3

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16. Cohen MS, Jacobs ML, Weinberg PM, Rychik J. Morphometric analysis of unbalanced common atrioventricular canal using two-dimensional echocardiography. J Am Coll Cardiol. 1996;28:1017-23.
17. Jegatheeswaran A, Pizarro C, Caldarone CA, et al. Echocardiographic Definition and Surgical Decision Making in Unbalanced Atrioventricular Septal Defect: A Congenital Heart Surgeons' Society Multiinstitutional Study. Circulation 2010;122,Suppl 1;S209-S215.
18. Varni JW, et al. The PedsQL™: Measurement Model for the Pediatric Quality of Life Inventory. Medical Care 1999;37(2):126-139.
19. Varni JW, et al. The PedsQL™ 4.0: Reliability and validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in healthy and patient populations. Medical Care 2001;39(8):800-812.
20. Varni JW, et al. The PedsQL™ 4.0 Generic Core Scales: Sensitivity, responsiveness, and impact on clinical decision-making. Journal of Behavioral Medicine 2002;25:175-193.
21. Varni JW, et al. The PedsQL™ 4.0 as a pediatric population health measure: Feasibility, reliability, and validity. Ambulatory Pediatrics 2003;3:329-341.
22. Varni JW & Limbers CA. The PedsQL™ 4.0 Generic Core Scales Young Adult Version: Feasibility, reliability and validity in a university student population. Journal of Health Psychology 2009;14:611-622.
23. Varni JW, Limbers CA, Neighbors K, Schulz K, Lieu JEC, Heffer RW, Tuzinkiewicz K, Mangione-Smith R, Zimmerman JJ & Alonso EM. The PedsQL™ Infant Scales: Feasibility, internal consistency reliability and validity in healthy and ill infants. Quality of Life Research 2011;20:45-55.
24. Uzark K, Jones K, Burwinkle TM & Varni JW. The Pediatric Quality of Life Inventory™ in children with heart disease. Progress in Pediatric Cardiology 2003;18:141-148
25. Uzark K, Jones K, Slusher J, Limbers CA, Burwinkle TM & Varni JW. Quality of life in children with heart disease as perceived by children and parents. Pediatrics 2008;121:e1060-e1067

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