Unbalanced Atrioventricular Septal Defect – A Congenital Heart Surgeons’ Society Inception Cohort 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 CHSS member institutions. The CHSS Data Center at The Hospital for Sick Children in Toronto will collect and abstract clinical data and obtain copies of initial cardiac Echocardiograms & CT/MRI studies for blinded review. An annual cross-sectional follow-up of the cohort, including details of future tests and intervention will be entered into the dataset.

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.

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 (A1): Define the anatomic features of uAVSD.
   SubAim 1a: To characterize the full anatomic and functional spectrum of complete AVSD.
   SubAim 1b: Identify anatomic relationships and develop novel indices to improve the ability to discriminate between unbalanced and balanced CAVSD.

Aim 2(A2): 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.

Aim3 (A3): Determine relationships between patient and anatomic characteristics, selected surgical strategy, and outcome.

Aim$ (A4): Develop and evaluate a clinically applicable prediction model to facilitate clinical decision making.

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, 2, 3, 4]. 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 [9, 10, 11, 12]. 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 [8, 13, 14, 15]. Still fewer reports directly address surgical decision-making [16]. 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 [17]. 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. This 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 [18] as an echocardiographic measure of unbalance in AVSD, but it remains underutilized as a diagnostic criteria.

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 [17, 18,].

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) [17, 20].

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 AVSD’s. 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 \textit{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 \textit{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.

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

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. Informed consent, enrollment form completion, and data collection will be carried out by the participating center. A copy of the signed consent and data release form will be sent to The CHSS Data Center along with 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 CHSS Data Center at The Hospital for Sick Children, Toronto, Canada. The data will be abstracted by the Data Center staff. In addition to data submission from the participating center, annual phone follow-up will be performed by 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. 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. Echo Core Lab: All echocardiograms will be reviewed by a dedicated team of echocardiographers who will constitute the echo core lab. This will be a “virtual” core lab which is structured using a password protected encrypted software platform. Echocardiograms will be loaded into the web-based system. Use of a web-based system will enable expedited echocardiographic interpretation and review by multiple echocardiographers without the
logistical issues and cost attendant to shipping of echos or travel for echo personnel. The echo core lab team will confirm the diagnosis, independently measure a mAVVI, and perform additional echo analyses as required for the study. A separate echocardiographic cohort of subjects undergoing three dimensional echo studies will also be accrued from participating centers performing such studies.

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 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 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.

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.

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. (Includes Tetralogy of Fallot or Double Outlet Right Ventricle with complete AVSD)
   2. Atrioventricular and Ventriculoarterial concordance (with the exception of DORV).
   3. Informed written consent.

6.b. Exclusion Criteria
   1. Partial or Transitional AVSD.
   2. Separate AV valve orifices
   3. Non-existent ventricular septal defect
   4. Aortic atresia
   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, 25\(^{th}\) percentile and 75\(^{th}\) percentile (interquartile range), median, and maximum values for all continuous variables. Frequency counts and percentages will be used for categorical variables. 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, Canada. Each patient will be assigned a unique identifying number and all subsequent records for that patient will be identified by that number. These records will be stored in a locked storage area accessible only to 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. 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, Toronto 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.

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, diagnostic echocardiogram and interpretation, hospital admission and discharge notes, operative notes, post-operative inpatient echocardiograms and interpretations, three dimensional echocardiograms and interpretations, cardiac catheterizations and interpretations, outpatient clinic visit notes, CT cardiac imaging and interpretation, MRI cardiac imaging and interpretation, and outpatient echocardiograms. Please see the attached data collection forms (administrative, surgical, echocardiographic/CT/MRI)

7.f. Clinical Data Points:

Please see attached administrative, imaging (echo, CT, MRI), catheter based, and surgical data forms.

8. Appendices

8.a. Appendix 1: Definitions

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.”

**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.

9. References