Echocardiographic Definition and Surgical Decision-Making in Unbalanced Atrioventricular Septal Defect

A Congenital Heart Surgeons’ Society Multiinstitutional Study

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Background—Although identification of unbalanced atrioventricular septal defect (AVSD) is obvious when extreme, exact criteria to define the limits of unbalanced are not available. We sought to validate an atrioventricular valve index (AVVI) (left atrioventricular valve area/total atrioventricular valve area, centimeters squared) as a discriminator of balanced and unbalanced forms of complete AVSD and to characterize the association of AVVI with surgical strategies and outcomes.

Methods and Results—Diagnostic echocardiograms and hospital records of 356 infants with complete AVSD at 4 Congenital Heart Surgeons’ Society (CHSS) institutions (2000–2006) were reviewed and AVVI measured (n = 315). Patients were classified as unbalanced if AVVI ≤0.4 (right dominant) or ≥0.6 (left dominant). Surgical strategy and outcomes were examined across the range of AVVI. Competing risks analysis until the time of commitment to a surgical strategy examined 4 end states: biventricular repair (BVR), univentricular repair (UVR), pulmonary artery banding (PAB), and death before surgery. A prediction nomogram for surgical strategy based on AVVI was developed. The majority of patients had balanced AVSD (0.4 < AVVI < 0.6) and underwent BVR. Patients with AVVI < 0.19 uniformly underwent UVR. Heterogeneous repair strategies were found when 0.19 < AVVI < 0.39 (UVR and BVR), with a disproportionate number of deaths in this range. AVVI ≥ 0.6 (left dominant) was less common. The proportion of subjects predicted for the end states at 12 months after diagnosis are: BVR, 86%; UVR, 7%; PAB, 1%; death without surgery, 1%; alive without surgery, 5%.

Conclusions—AVVI effectively characterizes the transition between balanced and unbalanced AVSD with important correlation to anatomic substrate and selected surgical strategy. (Circulation. 2010;122[suppl 1]:S209–S215.)

Key Words: diagnosis ■ heart defects, congenital ■ heart septal defects ■ echocardiography ■ atrioventricular septal defect

Unbalanced atrioventricular (AV) septal defect (uAVSD) occurs in approximately 10% of patients with atrioventricular septal defect (AVSD).1 Although identification of severe forms of uAVSD is straightforward, criteria to identify milder forms are not well established. The main objectives of this study were to determine whether atrioventricular valve index (AVVI) is a reliable discriminator of uAVSD and balanced AVSD (bAVSD) and to determine the association of AVVI with surgical strategy and outcome in AVSD.

Anatomic features of uAVSD include varying amounts of ventricular hypoplasia, as well as malalignment of the atrioventricular junction. In complete AVSD, the common AV valve can be situated either equally over the right and left ventricles (balanced) or unequally over the ventricles (unbalanced). An important determinant of whether an AVSD can be repaired is the relative size of the right and left valve after division of the common AV valve, that is the degree of balance between the two valves. The AVVI was introduced by Cohen et al as an echocardiographic method of assessing the relative size of the right and left components of the divided common AV valve after repair.2 Described nearly 15 years ago, AVVI has not been widely applied as a tool in determining appropriate surgical strategy in the setting of unbalanced AVSD and has never been independently assessed as a reliable discriminator of uAVSD.
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Glenn, Fontan)1,8 or palliative procedures such as pulmonary
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clinical decisions are heavily influenced by the degree of
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of literature directly addresses surgical decision-making in
broad array of available treatment options, make informed
uAVSD and its attendant complexities, coupled with the
remain a surgical challenge.2,6,7 The low prevalence of
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the treatment of choice with excellent outcomes.3–5 Surgical
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the denominator. In so doing, all expressions of AVVI (and
is always the numerator and the total AV valve area is always
calculation, whereby the area of the left AV valve component
and denominator change simultaneously as the amount of
unbalance changes. To simplify the usage and understanding
of AVVI, as well as to improve its granularity across the
range of AVVI, we describe a modification of the AVVI
calculation, whereby the area of the left AV valve component
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Biventricular repair (BVR) of balanced AVSD (bAVSD) is
the treatment of choice with excellent outcomes.3–5 Surgical
outcomes for uAVSD, however, are poor in comparison and
remain a surgical challenge.2,6,7 The low prevalence of
uAVSD and its attendant complexities, coupled with the
broad array of available treatment options, make informed
clinical decision-making difficult. In addition, a scant amount
of literature directly addresses surgical decision-making in
patients with uAVSD. Perhaps more importantly, current
clinical decisions are heavily influenced by the degree of
ventricular hypoplasia. Single-stage BVR is undertaken if the
ventricles are deemed adequate, whereas in cases of severe
uAVSD, staged univentricular repair (UVR) (Norwood,
Glenn, Fontan)1,8 or palliative procedures such as pulmonary
artery banding (PAB)6 are chosen. The degree of malalign-
ment of the AV junction using AVVI, although not com-
monly assessed quantitatively, may be a critical determinant
of the feasibility of BVR. The present investigation was
undertaken to establish AVVI as a reliable tool to standardize
enrollment in a proposed prospective multicenter study of
uAVSD.

Methods
Between January 2000 and December 2006, all 356 infants
with complete AVSD were enrolled at each of 4 Congenital
Heart Surgeons’ Society (CHSS) member institutions1
were identified and enrolled. Between January 2000 and
December 2006, all 356 infants with complete AVSD
seen at each of 4 Congenital Heart Surgeons’ Society
(CHSS) member institutions1 could be included for
inclusion. Exclusion criteria included those with primary inter-
vention at an outside institution, major systemic or pulmonary
venous anomalies (except left superior vena cava draining to
the coronary sinus), heterotaxy syndrome, aortic or pulmonar
atresia, and severe/fatal chromosomal abnormalities.

Table 1. Patient Demographic Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire Cohort (n=356)</th>
<th>Deaths (n=41)</th>
<th>Balanced by AVI and Underwent Surgery (n=247)</th>
<th>Unbalanced by AVI and Underwent Surgery (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (d, mean±SD,</td>
<td>Missing: 15; 71.0±89.4</td>
<td>Missing: 4; 36.1±48.5</td>
<td>Missing: 0; 72.1±65.6</td>
<td>Missing: 0; 73.9±162.2</td>
</tr>
<tr>
<td>median and range)</td>
<td>45 (0–1071)</td>
<td>13 (0–170)</td>
<td>60 (0–342)</td>
<td>15 (0–1071)</td>
</tr>
<tr>
<td>Weight at diagnosis (kg, mean±SD, median and range)</td>
<td>Missing: 61; 3.9±1.4</td>
<td>Missing: 8; 3.1±1.1</td>
<td>Missing: 40; 4.0±1.2</td>
<td>Missing: 8; 3.7±1.6</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>Missing: 1; 198/157</td>
<td>0; 23/18</td>
<td>Missing: 0; 136/111</td>
<td>Missing: 0; 34/24</td>
</tr>
<tr>
<td>Genetic abnormalities</td>
<td>Missing: 58; 192</td>
<td>12; 18</td>
<td>Missing: 31; 158</td>
<td>Missing: 9; 17</td>
</tr>
<tr>
<td>Noncardiac abnormalities</td>
<td>Missing: 197; 33</td>
<td>8; 25</td>
<td>Missing: 137; 19</td>
<td>Missing: 22; 11</td>
</tr>
</tbody>
</table>

As described in the article by Cohen et al,2 the AVVI is
expressed as the ratio of the area of the smaller AV valve
component to the divided common AV valve component over
the larger component. Thus, the numerator and denominator may be either left or right AV valve area, depending on dominance, and the calculated AVVI must be clarified as being either right or left dominant. In addition, the values of the numerator and denominator change simultaneously as the amount of unbalance changes. To simplify the usage and understanding of AVVI, as well as to improve its granularity across the range of AVVI, we describe a modification of the AVVI calculation, whereby the area of the left AV valve component is always the numerator and the total AV valve area is always the denominator. In so doing, all expressions of AVVI (and therefore dominance) are numeric, without the need to clarify right or left dominance.

Study Population
All patients with complete AVSD and atrioventricular and ventriculo-arterial concordance diagnosed at <1 year of age were eligible for inclusion. Exclusion criteria included those with primary intervention at an outside institution, major systemic or pulmonary venous anomalies (except left superior vena cava draining to the coronary sinus), heterotaxy syndrome, aortic or pulmonary atresia, and severe/fatal chromosomal abnormalities.

Patient Characteristics and Groups
A total of 356 patients met inclusion criteria and their clinical records were reviewed (see Table 1 for patient characteristics). Of these, 330 underwent surgical repair (303 biventricular repair, 24 univentricular repair, 3 “intermediate repair” [PAB]). Fifteen of the 356 patients had echocardiograms that were not evaluable. Thus, 341 patients had their primary diagnostic echocardiogram reviewed. Of those, 315 had echo views that allowed measurement of an AVVI. Determination of balanced or unbalanced was made in the remaining 26 by simple inspection (all these cases were clearly balanced or unbalanced).

To evaluate AVVI as a discriminator of uAVSD and to examine the association of AVVI and surgical strategy, the 327 patients who had BVR or UVR were analyzed. To determine the time to commitment to a repair strategy and produce the prediction nomogram the group of 341 patients who had an AVVI measured were analyzed. Finally, to look at survival and hazard based on repair strategy, the 327 patients who had BVR or UVR were analyzed. (Patients undergoing intermediate repair were excluded because of the inability to accurately model only 3 subjects.)

Data Collection
Clinical data were abstracted from submitted copies of medical records (diagnostic echocardiogram report, operative note, discharge summary). Echocardiograms were converted to digital format if necessary and were evaluated by 1 of 4 echocardiographers blinded to treatment strategy. AVVI was calculated for all patients, and an extensive echocardiographic evaluation was performed in those patients who had an AVVI of 0.4 or ≥0.6. Borderline AVVIs were adjudicated by 2 echocardiographers, and consensus was reached. All data were entered into a database by the Data Center staff or participating surgeons.

Measurement of AVVI
AVVIs were obtained using the method described by Cohen et al.2 From an en face image of the AV valve in the subcostal left anterior oblique view, the relationship between the AV valve and the ventricular septum can be well visualized.9,10 The orifice of the common AV valve is traced in diastole. The traced common AV valve is then subtended along a line corresponding to the plane of the interventricular septum, creating left and right components. AVVI is then calculated by dividing the left AV valve area by the total AV valve area, producing an index ranging from 0.0 to 1.0. We defined right dominant hearts as having an AVVI of ≥0.4 and left dominant...
variable models. Missing value indicator variables were entered to assess the reliability of variables for inclusion into the final multivariable model. Bootstrap bagging was used with cluster analysis to guide final variable selection and to prevent the risk of model overdetermination. Various mathematical transformations of the AVVI variable were tested to determine the optimal calibration of the relationship to risk, and the significance of interaction terms were explored. The hazard function was parametrically modeled, examining the data for multiple phases of risk, as described previously. This technique was used to estimate the number of patients reaching these events or states at any given time after the initial diagnosis. The frequency and range of AVVI, surgical strategy, and status at last follow-up are represented in Figure 1. As shown, the frequency of AVVI values within the patient cohort. This frequency plot was then overlaid with selected surgical strategy. Finally, the range of AVVI values with corresponding selected surgical strategy was populated with patient mortality data points. Figure 1 is the resulting histogram.

Data Analysis
All data analyses and graphs were produced with SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC). Data are given as frequency, median with range, or means±SD as appropriate, with the number of missing values indicated.

Assessment of AVVI as Discriminator
The reliability of AVVI as a measurement tool to discriminate and granulate unbalance, and its severity was assessed by first observing the frequency of AVVI values within the patient cohort. This frequency plot was then overlaid with selected surgical strategy. Finally, the range of AVVI values with corresponding selected surgical strategy was populated with patient mortality data points. Figure 1 is the resulting histogram.

Competing Risks Analysis
Competing risks analysis was used to examine rates of transition from the time of diagnosis to the mutually exclusive time-related events of various commitment states and death without any procedure, in addition to determining the incremental risk factors associated with each outcome, as described previously. This technique was used to estimate the number of patients reaching these events or states at any given time after the initial diagnosis. Noninformative imputation based on available patient data were used to calculate and place the mean for missing values. Missing value indicator variables were created and used in multivariable analyses to adjust for any bias introduced by missing data. The hazard function was parametrically modeled, examining the data for multiple phases of risk, as described previously. Demographic, morphological, and procedural factors associated with each outcome were identified through multivariable analysis of these parametric models. Multivariable analysis was performed both with and without institutions included as factors. Only those variables associated with 5 or more events were included, to prevent the risk of model overestimation. Various mathematical transformations of the AVVI variable were tested to determine the optimal calibration of the relationship to risk, and the significance of interaction terms were explored. Bootstrap bagging was used with cluster analysis to guide final variable selection and to assess the reliability of variables for inclusion into the final multivariable models. Missing value indicator variables were entered into final multivariable models as appropriate.

Prediction Nomogram
The competing risks analysis was then used to produce a prediction nomogram, by solving across the range of AVVIs at 12 months for surgical strategy. This nomogram predicts the surgical strategy patients underwent at 12 months after diagnosis based on their AVVI at the time of diagnosis. Twelve months was chosen because the majority of patients are committed to a repair strategy by this time.

Survival and Hazard Analysis
Multiphase parametric modeling of the survival and hazard function was performed to determine the overall survival of patients from the time of commitment to either UVR or BVR strategies.

Results

AVVI as a Discriminator of uAVSD
The frequency and range of AVVI, surgical strategy, and status at last follow-up are represented in Figure 1. As shown, the frequency of patients over the spectrum of AVVIs approximated a normal distribution, and the median AVVI was 0.47. A total of 247 of 305 (81%) of patients had balanced AVSD and 58 of 305 (19%) patients had uAVSD as defined by AVVI (see Table 2). The histogram clearly demonstrates that AVVI values of 0.4 and 0.6 correlate with changes in clinical decision-making, whereby virtually all patients with balanced AVSD (0.4<AVVI<0.6) underwent BVR (245/247), and all patients with severely uAVSD (AVVI<0.19) underwent UVR (10/11). Between an AVVI of 0.19 to 0.39 clinical decision-making was heterogeneous, because 26 of 38 patients underwent BVR and 12 of 38 underwent UVR. The histogram also demonstrates a notable clustering of mortality within this range of AVVI. The number of patients with AVVI of >0.6 was small (n=8), and surgical strategy varied among this group. These data, therefore, seem to support our a priori AVVI-based definition of bAVSD and uAVSD.

Association of AVVI With Surgical Strategy
Table 2 summarizes surgical strategy among patients defined as balanced or unbalanced by AVVI. As stated above,
virtually all bAVSD patients underwent BVR (245/247), with only 1 patient undergoing UVR and the other PAB. Within the unbalanced cohort, 34 of 58 underwent BVR and 22 of 58 underwent UVR. All of these UVRs were performed on patients with right dominant uAVSD (22/50). There were very few intermediate repairs (n/H11005 2).

To examine the relationship between AVVI and surgical strategy, a competing risks analysis for transition to surgical commitment with all patients beginning at the time of diagnosis was performed (Figure 2). Among the 341 patients who underwent echocardiographic review, the competing risks demonstrated that 24 months after diagnosis, 90% (303 patients) were committed to a BVR and 7% (24 patients) to a UVR. Of the remaining 3% of these children, 3 patients had PAB, 4 patients died without surgery, and 7 patients remained alive without surgery or commitment to a surgical strategy. The time-related hazard function for commitment to a BVR strategy demonstrated 2 phases, an early phase accounting for 52 events and a larger late phase accounting for 247 events, whereas the function for UVR had an early phase accounting for 19 events and a late phase accounting for 4 events. The time related hazard function for death before surgery and PAB surgery was characterized by a constant phase only of 4 and 3 events respectively. Incremental risk factors from multivariable hazard modeling of each outcome, both inclusive and exclusive of institutions, are given in Table 3.

The prediction nomogram was created to further elucidate association between surgical strategy and AVVI. This demonstrates that the proportion of subjects in each of the end states at 12 months after diagnosis are: BVR, 86%; UVR, 7%; PAB, 1%; death without surgery, 1%; alive without surgery, 5% (Figure 3). It is important to note that surgical decisions were not made based on AVVI. Nonetheless, AVVI appears to accurately reflect the transition in surgical decision making from UVR to BVR strategies through the 0.2 to 0.4 range of AVVI. It should also be noted that there are only 8 patients in this analysis with an AVVI of >0.6. As such, the prediction nomogram appears to suggest that patients with AVVI of ≥0.6 would undergo BVR, even as AVVI approaches 1.0 (a non sequitur). In a larger dataset, it is likely that the frequency of UVR would increase again as the AVVI moved toward 1.0. In fact, when these 8 patients are closely examined, heterogeneous surgical strategies are indeed used (3 had a true BVR, 2 had PAB, and 3 were so-called “one-and-a-half ventricle” repairs).

Overall Mortality, Survival, and Hazard
Of the 356 patients who met inclusion criteria, 41 died. Eleven of these deaths were in patients who either did not have an AVVI measured or did not undergo surgery. Four patients underwent a Norwood procedure without progressing further through staged palliation, and 1 patient underwent an SVC to pulmonary artery anastomosis after a coarctation operation.
repair with atrial septectomy and PAB. Of the patients who died who did not undergo surgical repair, 2 were unbalanced, 2 were balanced, and 2 did not have a determination of their balancedness.

Within the cohort of those patients who had an AVVI measured and underwent surgery, 17 of 247 (6.9%) balanced patients died (16 BVR, 1 PAB), whereas 13 of 58 (22.4%) unbalanced patients died (7 UVR, 5 BVR, 1 PAB). When survival was stratified by repair strategy (n = 330), in the BVR group, survival was 97% at 1 month, 92% at 5 months, and 89% at 30 months. Survival in the UVR group was 88%, 75%, and 66%, respectively (Figures 4 and 5). The hazard function for time-related survival was characterized by a short early hazard phase (20 events) and a longer late phase (12 events).

**Discussion**

**Measurement of Unbalance Using AVVI**

Historically, ventricular size has been the dominant measure of unbalance.13,14 Assessment of ventricular size, whether by catheterization or echocardiography, however, is prone to inaccuracy, and other noninvasive means of such assessment are not firmly established. Comparing ventricular size to distinguish bAVSD from uAVSD may be confounded by the fact that right ventricular volumes are normally larger than left ventricular volumes in patients with bAVSD.14-16 More importantly, derangements in alignment of the common AV junction may play an important, even preeminent role, in the pathophysiology of uAVSD. This malalignment of the AV junction can be quantified using the AVVI. This large multicenter cohort study demonstrates that AVVI is a simple, reliable discriminator of unbalance in AVSD. Our study also introduces a modification of the AVVI calculation, as first described by Cohen et al, in order to simplify its use and understanding as well as to improve its granulation across the range of AVVI (left AV valve area/total AV valve area).2 We chose AVVI values of 0.4 and 0.6 a priori as the transition from balanced to unbalanced AVSD (right dominant and left dominant, respectively). These values were selected with a view toward capturing milder, and perhaps clinically underappreciated, forms of uAVSD for detailed echocardiographic analysis. A notably high frequency of uAVSD (nearly 20%) in this series reflects that intent. Most importantly, AVVI not only distinguishes balanced and severely unbalanced forms of AVSD. This study demonstrates that AVVI, over a relatively narrow range, brings into focus a subset of uAVSD patients for whom there is uneven application of surgical strategy and, it would appear, elevated risk of mortality. As such, AVVI may be used as a simple, yet relatively sensitive, method not only to identify patients with uAVSD but also to granulate the entire spectrum of uAVSD, bringing into focus subsets of patients at elevated risk. In this way, AVVI appears an ideal tool for enrollment of patients in a larger, multicenter, prospective study of uAVSD. AVVI values of 0.4 and 0.6 seem to accurately reflect points of transition in anatomic substrate and associated surgical strategies.

**Surgical Strategy and Outcomes in uAVSD**

Surgical therapy for uAVSD remains a significant challenge for several reasons. It is a rare lesion with widely varying anatomic features. Anatomic criteria to define uAVSD are lacking, and there are several surgical strategies used in its treatment. The optimal management strategy for a given anatomic substrate is unknown, and guidelines to assist this decision are nonexistent. BVR is almost uniformly applied for patients with bAVSD, and selection of an appropriate repair strategy (UVR) is straightforward when uAVSD is severe. However, patients with milder forms of uAVSD are not as easily assigned and may or may not be appropriate candidates for BVR. As a result, surgical outcomes in patients with uAVSD are suboptimal, with early mortality rates ranging between 10% to 25% and late event-free survival of merely 50%.17-20 In contrast to patients with bAVSD. It should be noted that mortality for repair of bAVSD was higher in this series than is commonly reported.21-23 These data should be interpreted with caution, however, as we are reporting overall mortality for an inception cohort rather than operative mortality in a surgical series. In addition, this type of divergence in outcome data is commonly seen when registry data are com-
pared with single center retrospective reports and most likely reflects the elimination of reporting bias.

Unbalanced AVSD possesses several distinct features that may impact surgical decision-making apart from simple left or right sided hypoplasia. Malalignment of the common AV junction may preclude division into right and left components that can sustain biventricular physiology, irrespective of the degree of ventricular hypoplasia. The high prevalence of trisomy 21, with its attendant poor outcomes in UVR, places a premium on achieving successful BVR, if at all possible. Specific patient morphological and other variables are needed to make this decision on a case by case basis. There are undoubtedly other anatomic features such valvar leaflet dimension, papillary muscle abnormalities, as well functional echo indices such as color inflow that could improve our understanding of optimal surgical strategies for uAVSD. We performed a detailed echocardiographic survey of all uAVSD patients, and many of these echo parameters were evaluated. Correlation of these variables with outcome and AVVI would require expansive analysis and discussion, which we considered beyond the scope of this study, and is the subject of a separate, ongoing investigation. As is the case with other anatomic substrates, forcing borderline anatomies into biventricular pathways may result in excess early mortality. An index such as AVVI, complemented by additional, as yet undetermined, echocardiographic indices may be useful in predicting optimal repair strategy, thereby improving early and late outcomes.

Factors Predicting the Choice of Surgical Strategy
Risk analysis reinforced the correlation of AVVI and selected surgical strategy. When risk analysis was performed to determine incremental risk factors for time-related transition from diagnosis (Table 3) to BVR, 2 variables were of importance whether the analysis was performed without or with institutions as additional risk factors. We found that in the early phase the chance of BVR was decreased if patients were more unbalanced (AVVI farther from the midpoint of 0.5) but increased if patients had increased height at the time of diagnosis. We hypothesize that being larger at the time of diagnosis is a marker for a less severe (ie, more balanced) lesion. In the case of UVR, we found that the squared transformation of AVVI was the sole predictor when institution was represented, and it may be that these centers do not perform a detailed echocardiographic survey of all uAVSD patients, and many of these echo parameters were evaluated. Correlation of these variables with outcome and AVVI would require expansive analysis and discussion, which we considered beyond the scope of this study, and is the subject of a separate, ongoing investigation. As is the case with other anatomic substrates, forcing borderline anatomies into biventricular pathways may result in excess early mortality. An index such as AVVI, complemented by additional, as yet undetermined, echocardiographic indices may be useful in predicting optimal repair strategy, thereby improving early and late outcomes.

AVVI As Discriminatory Echo Tool
In the present study, we examined the ability of AVVI as an echocardiographic tool to identify unbalance among a cohort of complete AVSD. We explored the relationship between AVVI and observed surgical decision-making. We found that AVVI correlated with distinct patterns of clinical decision-making. AVVI As Discriminatory Echo Tool

Conclusions
AVVI distinguishes between balanced and unbalanced forms of complete AVSD. A narrow range of AVVI (0.19 to 0.39) is associated with heterogeneity of surgical strategy as well as increased surgical risk. Proper selection of surgical strategy within this range of AVVI, as well as delineation of other
important anatomic factors, is required to optimize outcomes in uAVSD. Clarification of the interaction between patient factors, selected surgical strategy, and outcomes will require a larger, prospective, multi-institutional inception cohort trial.

Acknowledgments

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Disclosures

None.

References


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