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Is A Shorter Atrioventricular Septal Length An Intermediate Phenotype In The Spectrum Of Non-Syndromic Atrioventricular Septal Defects?

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Abstract

Atrioventricular septal defects (AVSD) account for 7% of all congenital cardiovascular malformations. The atrioventricular septum (AVS) is the portion of the septal tissue that separates the right atrium from the left ventricle; deficiency of the AVS contributes to the AVSD phenotype. A study of case and control families was performed to identify whether an intermediate phenotype consisting of a shortened AVS existed in relatives of children with an AVSD.

The AVS length (AVSL) was measured in echocardiograms of clinically unaffected parents and siblings from families that were identified through a child with a non-syndromic AVSD and in families with no history of congenital heart disease.

No significant differences were seen between case and control family members in terms of gender, age, weight, or height. The AVSL was significantly shorter in case parents when compared to control parents. Similar findings were noted within the sibling groups. There was significant evidence for two component distributions in the case parent, case sibling, and control sibling groups after standardizing the AVSL for age and BSA (asAVSL). Heritability of asAVSL was 0.82 and 0.71 in non-syndromic case and control families, respectively.

Evidence for two component distributions from the analysis of asAVSL for case parents and case siblings suggests the presence of an intermediate phenotype for non-syndromic AVSD. The high heritability in the control families suggests that there may be polygenic involvement in the determination of AVSL. Broadening the definition of AVSD to include those with a shortened AVSL may increase the power of genetic association and mapping studies to identify susceptibility genes for AVSD.

Keywords

atrioventricular septal defect; defect; endocardial cushion; atrioventricular canal defects; heart defects; congenital; phenotype

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INTRODUCTION

Congenital heart defects (CHDs) constitute a major proportion of clinically significant birth defects and are an important component of pediatric cardiovascular disease, with an estimated prevalence of six to nine per 1000 live births.^{1–3} Atrioventricular septal defects (AVSDs), also known as atrioventricular canal defects or endocardial cushion defects, include a spectrum of anomalies characterized by involvement of the atrial and/or ventricular septa, and one or both of the atrioventricular (AV) valves; they account for approximately 7% of all CHDs.⁴

With normal cardiac development, the septal leaflet of the tricuspid valve inserts into the septum slightly more inferior than the septal leaflet of the mitral valve. A small portion of septal tissue superior to the tricuspid septal leaflet insertion separates the right atrium from the left ventricle; this is the atrioventricular septum (AVS).⁵(Figure 1)

There is a paucity of information regarding the AVS, and details regarding the normal development of the AVS are relatively unknown. Failure of fusion of the atrioventricular endocardial cushions has long been suggested as the mechanism for AVSD formation.⁶ However, more recent studies have demonstrated that the development of the atrioventricular septal area is highly complex involving multiple primordial structures, including the endocardial cushions.^{5, 7} Results from these investigations suggest a possible role of the endocardial cushions, mesenchyme from the primary atrial septum, and spina vestibuli in the development of the AVS.^{5, 8} The length of the AVS (AVSL) is not routinely measured in echocardiograms, unless there is concern for Ebstein's malformation. In prior investigations however, it was noted that all of the patients with normally structured tricuspid valves had a BSA-standardized AVSL (sAVSL) less than 8 mm/m², while those with Ebstein's malformation had a sAVSL greater than 8 mm/m², providing the basis for the displacement index which can assist in the diagnosis of Ebstein's malformation.^{9, 10} It has also been demonstrated that the absence of the AVS results in the AVSD phenotype, implying that those patients with a complete AVSD have an AVS that measures 0 mm.

Although AVSDs commonly occur in the setting of Down syndrome, they also occur in infants without a diagnosed syndrome. Numerous investigations have been performed in the attempt to identify causative genes in syndromic and non-syndromic AVSDs.¹¹ Although such causative genes have not yet been identified, it has been demonstrated that the developmental origins of syndromic and non-syndromic AVSDs differs.¹² Non-syndromic AVSDs are estimated to occur in approximately one per 10,000 live births.^{1, 13, 14} Most non-syndromic AVSDs are considered to be sporadic and/or the result of multifactorial inheritance.¹⁵ However, there are numerous reports of non-syndromic AVSDs transmitted within families, suggesting that the defect segregates with a Mendelian pattern.^{15–27} The pattern of recurrence has most often suggested an autosomal dominant model with monogenic or oligogenic inheritance.²⁸ Although AVSDs appear to be transmitted in an autosomal dominant fashion, there are parents in these pedigrees who do not demonstrate the phenotype of an AVSD or a defect along its spectrum, and yet they may have multiple affected offspring. These parents may have an intermediate phenotype, e.g., a shortened AVSL; however, no intermediate phenotype has yet been sought.

The major goal of this investigation was to measure the AVSL in a study of case and control families in order to determine whether the parents and siblings of children with a non-syndromic AVSD demonstrate a shorter AVSL, possibly indicating an intermediate phenotype. We hypothesized that a subset of the “unaffected” parents and siblings of case children will have shorter AVSLs than the remainder of the case parents and siblings whose

AVSLs, in turn, will not be different than the AVSLs of parents and siblings in control families.

METHODS

Subject Population

Case families were those who participated in The Family Study of Endocardial Cushion Defects which was conducted between 1994 and 2004 at the University of Iowa. The non-syndromic AVSD cases were identified through cardiac catheterization, echocardiographic, and surgical records at The University of Iowa Hospitals and Clinics and recruited for the study. If the family agreed to participate, a three-generation pedigree was constructed and a health history questionnaire was administered over the phone. The families (parents and siblings) were then scheduled for echocardiographic examinations. Seventy-two families of children with a non-syndromic AVSD were recruited and examined.

Children free of congenital heart defects and their parents and siblings from Muscatine, Iowa were also recruited to serve as control families. Echocardiograms were obtained in a similar fashion for the families who agreed to participate. Seventy-four control families were recruited and examined. Case and control family members underwent echocardiographic examination by separate sonographers. The study was approved by the University of Iowa Institutional Review Board.

Echocardiographic Analysis

The 427 available echocardiograms from the case and control family members were reviewed to measure the AVSL in an attempt to define and describe an “intermediate phenotype” of AVSDs. Due to the timeframe of the conduct of the original study, echocardiograms were stored on VHS tapes and were not digitized. A Philips Sonos 5500 echocardiographic machine was utilized for detailed measurements.

The AVSL was measured using the caliper tool as part of the installed software package on the machine. The length of the AVS was defined as the length from the hinge point of the mitral valve to the hinge point of the tricuspid valve along the septum in an apical four-chamber view. The three sharpest apical four-chamber views during systole were chosen for measurements. Three repeat measurements were in each view made by the primary investigator (SSP) for a total of nine measurements of the AVSL.

For the purposes of assessing interrater reliability, repeat measurements (10%) were made by a blinded independent investigator (LTM) with substantial echocardiographic experience. Two repeat measurements of the AVSL were made in each of two views, chosen independently by the independent investigator, for a total of four measurements.

Statistical Analysis

Descriptive Analysis—Using the set of measurements obtained by the primary investigator, the mean of the three AVSL measurements from each of the three separate views, i.e., the mean of nine measurements, was determined. Descriptive statistics for gender, age, weight, height, BSA, and AVSL measurements were estimated for case and control parents and siblings. Means and standard deviations were estimated for continuous variables, while frequencies were determined for categorical variables. Case and control subgroups were compared for differences using Student’s t- and chi-square tests.

Reliability—An intraclass correlation coefficient was estimated using the mean of the three AVSL measurements from each of the three separate views to determine intrarater

reliability. Similarly, the intrarater reliability among the independent investigator's measurements was assessed using the mean of the two AVSL measurements from each of the two separate views. As two different sonographers obtained the echocardiograms for the case and control families, two separate intraclass correlation coefficients were calculated to account for sonographer differences. Interrater reliability was assessed by performing paired t-tests using the overall mean measurement (of nine and four measurements, respectively) from each investigator and calculating percent error and a coefficient of variation to estimate the degree of variability between the two investigators.

AVSL Standardization—Pediatric echocardiographic measurements of cardiovascular structures are routinely adjusted to account for the effects of body size. BSA appears to be a better parameter of growth than height or weight alone.²⁹

The AVSL measurements of the case parents were examined using univariable and multivariable linear regression analysis models to determine if there was an association with BSA, age, or gender. Similar analyses were performed for the case sibling, control parent, and control sibling groups. An evaluation of regression diagnostics was performed; influential points were identified by examination of scatterplots and were re-evaluated for measurement and/or data entry error. Measurements were standardized by age and BSA based on these results (asAVSL).

Admixture Analysis—Admixture analysis was used to test the hypothesis that the overall observed distribution of asAVSL measurements actually reflected the sum of two or more separate component distributions, each of which might represent a different etiology, e.g., a gender effect or a major genetic effect, or a smaller versus a larger number of AVSL shortening alleles.

The distribution of the asAVSL measurements was formally tested for evidence of admixture using the program NOCOM.^{30–32} Case parents, case siblings, control parents, and control siblings were separately analyzed.

Heritability Analysis—For a quantitative trait, familial aggregation (the tendency for a trait to cluster in families) can be examined by estimating correlation coefficients between pairs of relatives, e.g., between parents and children. Significant evidence for familial aggregation suggests that shared genetic and/or shared environmental factors are likely to be involved in the etiology of the trait.

The heritability of the asAVSL was estimated based on measurements from unaffected siblings and parents of cases using the Polygenic and QTL Mapping option in MENDEL³³. The heritability of asAVSL was also estimated for the control families.

RESULTS

Participants

Four hundred twenty-seven echocardiograms were reviewed using the measurement protocol. Eighteen family members were excluded due to insufficient information – either the echocardiogram windows were inadequate for reliable measurements of the AVS or height and/or weight data were not available for calculation of BSA. Of the remaining participants, 212 were members of a non-syndromic case family and 199 were member of a control family.

Descriptive Analysis

Table 1 describes group characteristics (% male, mean age, height, weight, and AVSL) for each study group. There were no significant differences between the case and control parent groups in terms of gender distribution, age, weight, height, or BSA. However, the mean AVSL was significantly different between the two groups of parents. More specifically, the mean AVSL measurement in the case parent group was significantly shorter than in the control parent group.

No significant differences in gender distribution were noted among the sibling groups. Significant differences were noted, however, in terms of age, weight, and BSA. As case families were ascertained using historical records, many siblings were adults when they were echoed. Due to their significantly older age, the case siblings also had a higher mean weight and BSA. However, the case sibling mean AVSL was significantly shorter than the control sibling group.

Reliability

Interrater reliability of these AVSL measurements was first assessed using a paired t-test which tested the hypothesis of no difference. The t-statistic was not significant ($p=0.57$), suggesting that the measurements made by the two investigators were similar. The coefficient of variation between the two investigators was 13.7%. In addition, the percent error was 10.9%. These two measures suggest that the variation of the measurements was small. Intrarater reliability for each investigator was also evaluated by estimation of an intraclass correlation coefficient. The overall intraclass correlation coefficient of the three means for the primary investigator (SSP) was 0.979 and the intraclass correlation coefficient of the two means for the independent investigator (LTM) was 0.983. When the sonographer who obtained the echocardiogram was taken into account, the intraclass correlation coefficient for the case group for the primary and independent investigators were 0.968 and 0.992, respectively. Similarly, the respective intraclass correlation coefficients were 0.955 and 0.993 for the control group.

Standardization

Figure 2 is a scatterplot of unadjusted AVSL measurements versus BSA by relationship. The regression line is also plotted for each relationship group. Univariable analysis was performed to evaluate the association between AVSL and BSA ($p<0.0001$). Based on the two regression lines, it appears that the AVSL increases as BSA increases during childhood and once adult size is reached, growth of the AVSL plateaus. Given the significant association, the AVSL was standardized using the BSA estimate to account for body growth differences.

A scatterplot was constructed depicting the relationship between unadjusted AVSL measurements and age by gender (data not shown). Males and females appeared to be distributed equally within the plot. A Student's t-test was conducted to evaluate for differences in unadjusted AVSL by gender, which was not significant, suggesting the AVSL measurements were similar with respect to gender ($p=0.26$). Univariable analysis did not identify a significant relationship between BSA-standardized AVSL measurements and gender ($p=0.14$).

The unadjusted AVSL measurements were examined for association with age for all siblings and parents (Figure 3). Similar to the relationship with BSA, this figure suggests that there is rapid growth of the atrioventricular septum throughout childhood and adolescence, which plateaus in adulthood. Univariable analysis revealed a significant association between BSA-

standardized AVSL measurements and age ($p < 0.0001$). For the remainder of the analyses, measurements were adjusted to account for both age and BSA differences (asAVSL).

Admixture Analysis

Histograms of the asAVSL measurements were plotted and examined for evidence of admixture (i.e., multiple components) in each group: non-syndromic AVSD case parents and siblings and control parents and siblings (Figure 4). By examination, it appears that there are two underlying distributions for asAVSL in the case parents and siblings.

To formally test the hypothesis that there is more than one distribution within the subgroup distributions, likelihood ratio tests were conducted in the each case and control subgroup (Table 2). Significant evidence was found for two component distributions in the case parent and case sibling groups. The control parent group did not yield evidence for admixture. The control sibling group demonstrated evidence for two component distributions; however, the second component only contained two percent of the measurements in the extreme upper tail.

Heritability Analysis

The heritability of the asAVSL was estimated based on the parents and siblings in case and control families. The heritability in case families was estimated to be 0.815 (standard error 0.098); the heritability in control families was 0.712 (standard error 0.077). It is interesting to note that although the heritability was higher in the case families than in the control families, the estimate was fairly high in the control families, suggesting that shared genetic and/or environmental factors are involved in determining the length of the AVS.

DISCUSSION

This study evaluated AVSL measurements in parents and siblings of non-syndromic AVSD cases as well as parents and siblings in families without a history of congenital heart defects. The unadjusted AVSL ranged from 1.8 to 13.0 mm in the family members of non-syndromic AVSD cases and from 2.9 to 17.4 mm in control family members. The magnitude of the unadjusted AVSL measurements in control family members was consistent with previous findings.¹⁰ The sAVSL of the control family members, however, ranged from 1.8 to 13.1 mm/m², demonstrating a wider range than has been previously reported.^{9, 10, 34} In addition, it appears that there is growth of this structure throughout childhood which slows during young adulthood. Although there were sAVSL measurements greater than 8 mm/m² (i.e., the historical upper limit of normal value), the majority of the measurements were less than 8 mm/m² (90.5% in control families). There was a significant association between the unadjusted AVSL measurements and age and BSA suggesting the need for adjustment to account for growth.

The major objective of this study was to measure the AVSL in a study of case and control families in order to determine whether the parents and siblings of a child with a non-syndromic AVSD demonstrate a shorter AVSL, possibly indicating an intermediate phenotype. In comparison to control family members, both case parents and siblings had significantly shorter mean AVSL (and sAVSL), suggesting the possibility of an intermediate phenotype in the relatives of non-syndromic AVSD cases.

There are a few potential mechanisms for a shortened AVS in the parents and siblings of non-syndromic AVSD cases. The most logical is demonstrated by Falconer's polygenic threshold model for discontinuous traits. Every individual is assumed to have an underlying liability (vulnerability, susceptibility, or predisposition) for a trait. The liability is assumed

to be normally distributed and represents the sum of all the multifactorial effects, both genetic and environmental, that are relevant to the trait for that individual.

The liability is impossible to directly measure as most of the causal components are still unknown and therefore cannot be measured. The threshold model states that as the number of polygenes (i.e., any of a group of genes, each having a small quantitative effect, that together produce a wide range of phenotypic variation) and environmental exposures for a trait increases, the liability increases. When the liability reaches a threshold, a recognizable phenotype occurs. In this case, the spectrum of AVSD represents the phenotype. An individual with a liability to the left of the threshold, e.g., a parents or sibling of a case, may have a shortened AVSL which is not currently recognized as being part of the AVSD spectrum. As the number of AVSL shortening alleles an individual inherits increases, their liability increases and at higher liability values they are likely to manifest the clinically recognizable disease of non-syndromic AVSD.

Admixture analysis of asAVSL provided significant evidence for two component distributions in the parents and siblings of cases. In addition, there was evidence for two component distributions in the siblings of controls. After further examination of the distribution of the control sibling asAVSL measurements (Figure 4B), it appears that the second component follows the natural breakpoint in the observed distribution. The proportion of the measurements in the second group was approximately 2%, suggesting that if a second distribution exists, it represents a very small proportion of individuals with very long AVSLs. There was no evidence for admixture in the parents of controls.

It is important to note that a large proportion of the measurements in the case parents and siblings are estimated to be in the lower distribution (i.e., a large proportion of the data demonstrate a shorter AVSL which is consistent with a downward shift in comparison to the control distribution). Based on the distribution of asAVSL measurements in the control families, possible thresholds for a shortened asAVSL measurement can be suggested. Possible cut-off points based on the asAVSL measurement distributions within the control adults and children would be 1.82 mm/m² for adults and 2.37 mm/m² for children (2 standard deviations below the mean). Applying these cut-offs to the entire study population, this would include 5.7% of parents and 4.5% of siblings, all of whom were from case families.

The heritability of the echocardiographic measurements of selected cardiac structures has been previously examined.^{35–44} For example, the heritability has been estimated to be 0.96 for aortic root measurements, 0.72 for sinotubular junction measurements, and 0.57 for aortic valve annulus measurements in first-degree relatives of children with a left ventricular outflow tract obstructive malformation.⁴⁴ The closer the estimated heritability is to 1, the greater the role of genes influencing inter-individual variation in the trait. The estimated heritability of asAVSL was high in the control group, suggesting genetic variants or quantitative trait loci shared by relatives likely explain a substantial portion of the familial aggregation. It is interesting to note that the heritability in the non-syndromic families was slightly higher, suggesting that there may be more genetic evidence to explain the inheritance of the length of the AVS in families with an AVSD member. In addition, the non-syndromic case family heritability may be different than the control families due to other major genetic effects in addition to polygenic effects. As mentioned previously, two different sonographers obtained the echocardiograms for case and control families. The images of the control families were subjectively sharper, likely due to sonographer experience. These images may have been more accurately measured than the images obtained from the case families possibly leading to less valid heritability estimates for the case families.

The major strength of this study is innovation. No other study has examined the parents and siblings of AVSD cases with the goal of identifying an intermediate phenotype. The heritability of the AVS has never been examined in families of AVSD cases or controls before.

A major limitation of this study was the echocardiograms. Since the examinations were conducted when echocardiograms were stored on videotape, they precluded more accurate computerized measurements. As the cardiac structure of interest is small, using the caliper tool obscured the hinge points in some cases, likely leading to inaccurate measurements of the AVS. However, the intrarater and interrater reliabilities demonstrated close agreement within each investigator as well as between the two investigators. Due to this significant perceived limitation, a validation study was performed comparing the echocardiograms from the control sample within this study and digitized echocardiograms obtained from healthy subjects from a pediatric cardiology clinic. One hundred digitized echocardiograms were reviewed and the AVSL was measured (Table 3). The echocardiograms were separated into two groups by age (child – less than 18 years of age and adult – 18 years of age or older). The digitized child group demonstrated no significant differences in terms of age, BSA, AVSL, or sAVSL compared to the control siblings from the videotape study. In terms of age, the adult group from the digitized population was found to be significantly younger than the parents of controls from the videotape study, although, this was likely due to the fact that these adults were undergoing echocardiograms for clinical purposes and not for a research study as the videotape echocardiogram adults were. However, no significant differences were seen in BSA, AVSL, or sAVSL within the adult group. These results suggest that the measurements made using the videotapes are reliable.

A second limitation was that there were two sonographers who performed the studies, and that could influence quality of the imaging in the different study groups. A final limitation involves the control sample. The families were chosen among those participating in a research study conducted during the same time period who were recruited from a single city in Iowa. Although the control family members were similar to case family members in terms of age, gender, weight, and height, the control families may not represent the population from which the case families were obtained, as case families were recruited from the entire catchment area of the University of Iowa, not just from one city.

This represents the first study to investigate the possible existence of a shortened AVS in parents and siblings of children with a non-syndromic AVSD. The length of the AVS was shorter in both the case parents and siblings in comparison to control parents and siblings. Evidence for two component distributions from the analysis of case parents and siblings suggests the presence of an intermediate phenotype for non-syndromic AVSD. Measurement criteria for a shortened AVSL were determined based on the distribution of asAVSL measurements in control families. The heritability of AVSL was estimated to be 0.71 in the control families, suggesting the possibility of substantial genetic involvement. Broadening the definition of AVSD to include those with a shortened AVSL may increase the power of genetic association and mapping studies to identify susceptibility genes. In addition, this approach may allow high and low-risk subgroups of unaffected family members to be distinguished, improving the ability to tailor recurrence risk estimates for specific individuals.

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Figure 1. Four-chamber View Demonstrating Measurement of Atrioventricular Septum. Panel A is an illustrated four-chamber view depicting the atrioventricular septum for comparison purposes. Panel B is a still image of an apical four-chamber view from a study participant. The line within the image depicts the measurement of the atrioventricular septum.

Figure 2.

Unadjusted Atrioventricular Septal Length versus Body Surface Area by Relationship. Scatterplot demonstrating the linear relationship between atrioventricular septal length and body surface area in siblings with a plateau in adults. Black line represents the regression line for siblings. Red line represents the regression line for parents. AVSL, atrioventricular septal length.

Figure 3.

Unadjusted Atrioventricular Septal Length versus Age by Relationship. Scatterplot demonstrating the linear relationship between atrioventricular septal length and age in siblings with a plateau in adults. Black line represents the regression line for siblings. Red line represents the regression line for parents. AVSL, atrioventricular septal length.

Figure 4.

Observed Distributions of Age- and BSA-standardized Atrioventricular Septal Length by Relationship. Panel A demonstrates the distributions in the non-syndromic atrioventricular septal defect case families, while panel B displays the distributions in the control families. The case families appear to have more than one underlying distribution, while the control families appear to have one distribution. asAVSL, age- and BSA-standardized atrioventricular septal length.

Table 1

Group Characteristics of Non-Syndromic AVSD Case and Control Parents

	NSAVSD parents (N=118)	Control parents (N=109)	p-value	NSAVSD siblings (N=92)	Control siblings (N=90)	p-value
% Male *	45.76%	46.79%	0.88	52.17%	52.22%	0.99
Age (yrs) ^	38.36 ± 9.32	37.83 ± 6.24	0.61	15.28 ± 10.26	10.81 ± 4.69	0.0002
Weight (kg) ^	80.20 ± 18.54	77.55 ± 16.92	0.26	56.08 ± 32.63	43.00 ± 22.14	0.0018
Height (cm) ^	171.05 ± 10.17	170.82 ± 9.13	0.86	149.60 ± 33.66	144.55 ± 25.18	0.25
BSA (m ²) ^	1.96 ± 0.27	1.92 ± 0.24	0.30	1.50 ± 0.61	1.29 ± 0.44	0.0089
AVSL (mm) ^	6.42 ± 1.98 (2.8–13.0)	8.90 ± 2.75 (3.1–17.4)	<0.0001	5.88 ± 2.12 (1.8–10.5)	7.82 ± 2.34 (2.9–15.2)	<0.0001
sAVSL (mm/m ²) ^	3.36 ± 1.25	4.67 ± 1.44	<0.0001	4.41 ± 1.84	6.43 ± 2.08	<0.0001

* = χ^2 test performed to test for differences among groups;

^ = Student's t-test performed to test for differences among groups; AVSD, atrioventricular septal defect; BSA, body surface area; NSAVSD, non-syndromic atrioventricular septal defect; AVSL, atrioventricular septal length; sAVSL, standardized atrioventricular septal length.

Table 2
Admixture Analysis of Age-and BSA-Standardized Atrioventricular Septal Length

	Case		Control	
	Parents	Siblings	Parents	Siblings
# of components	2	2	1	2
Mean 1	-0.022	-0.089	0.066	0.053
Mean 2	0.185	0.096		0.655
Common Standard Deviation	0.091	0.134	0.141	0.026
Proportion 1	0.941	0.907	1	0.974
Proportion 2	0.059	0.094		0.026
Test Statistic	9.044	9.664	3.346	13.608
p-value	0.011	0.008	0.19	0.001

Significant p-values are displayed in bold.

Table 3

Group Characteristics of Validation Study

	Child			Adult		
	Tape (N=82)	Digital (N=63)	p-value	Tape (N=117)	Digital (N=37)	p-value
Age (yrs) [^]	10.00 ± 4.07	9.81 ± 5.04	0.80	36.55 ± 7.67	24.70 ± 9.28	<0.0001
BSA (m ²) [^]	1.24 ± 0.41	1.25 ± 0.55	0.85	1.92 ± 0.25	1.90 ± 0.28	0.68
AVSL (mm) [^]	7.63 ± 2.18 (2.9–15.2)	7.42 ± 2.37 (3.1–14.3)	0.59	8.96 ± 2.79 (3.1–17.4)	9.28 ± 3.91 (4.5–25.8)	0.65
sAVSL (mm/m ²) [^]	6.55 ± 2.09	7.01 ± 3.24	0.33	4.70 ± 1.44	4.92 ± 1.84	0.46

[^] = Student's t-test performed to test for differences among groups: BSA, body surface area; AVSL, atrioventricular septal length; sAVSL, standardized atrioventricular septal length.