Is a Shorter Atrioventricular Septal Length an Intermediate Phenotype in the Spectrum of Nonsyndromic Atrioventricular Septal Defects?

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Background: Atrioventricular septal defects (AVSDs) 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 AVSDs.

Methods: AVS length (AVSL) was measured on the echocardiograms of clinically unaffected parents and siblings from families that were identified through children with nonsyndromic AVSDs and in families with no histories of congenital heart disease.

Results: No significant differences were seen between case and control family members in terms of gender, age, weight, and height. AVSLs were significantly shorter in case parents compared with 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 AVSL for age and body surface area. Heritability of AVSL standardized for age and body surface area was 0.82 and 0.71 in nonsyndromic case and control families, respectively.

Conclusions: Evidence for two-component distributions from the analysis of AVSL standardized for age and body surface area for case parents and case siblings suggests the presence of an intermediate phenotype for nonsyndromic 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 shortened AVSL may increase the power of genetic association and mapping studies to identify susceptibility genes for AVSD. (J Am Soc Echocardiogr 2012;25:782-9.)

Keywords: Atrioventricular septal defect, Defect, Endocardial cushion, Atrioventricular canal defects, Congenital heart defects, Phenotype

Congenital heart defects 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 1,000 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 valves; they account for approximately 7% of all congenital heart defects.[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) (Figure 1).[5]

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] Atrioventricular septal length (AVSL) is not routinely measured on echocardiography, 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 body surface area (BSA)–standardized AVSL (sAVSL)

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Abbreviations

asAVSL = Atrioventricular septal length standardized for age and body surface area

AVS = Atrioventricular septum

AVSD = Atrioventricular septal defect

AVSL = Atrioventricular septal length

BSA = Body surface area

sAVSL = Atrioventricular septal length standardized for body surface area

< 8 mm/m^2, whereas those with Ebstein's malformation had sAVSL > 8 mm/m^2, 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 complete AVSDs have AVS lengths that measure 0 mm.

Although AVSDs commonly occur in the setting of Down syndrome, they also occur in infants without diagnosed syndromes. Numerous investigations have been performed in the attempt to identify causative genes in syndromic and nonsyndromic AVSDs.[11] Although such causative genes have not yet been identified, it has been demonstrated that the developmental origins of syndromic and nonsyndromic AVSDs differs.[12] Nonsyndromic AVSDs are estimated to occur in approximately one per 10,000 live births.[1,13,14] Most nonsyndromic AVSDs are considered to be sporadic and/or the result of multifactorial inheritance.[15] However, there are numerous reports of nonsyndromic 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), but no intermediate phenotype has yet been sought.

The major goal of this investigation was to measure AVSLs in a study of case and control families to determine whether the parents and siblings of children with nonsyndromic AVSDs demonstrate shorter AVSLs, possibly indicating an intermediate phenotype. We hypothesized that a subset of the "unaffected" parents and siblings of case children would have shorter AVSLs than the remainder of the case parents and siblings, whose AVSLs, in turn, would not be different from 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 nonsyndromic 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 nonsyndromic AVSDs 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. Echocardiography was performed 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 AVSLs in an attempt to define and describe an intermediate phenotype of AVSDs. Because of the time frame of the conduct of the original study, echocardiograms were stored on VHS tapes and were not digitized. A Philips Sonos 5500 echocardiographic machine (Philips Medical Systems, Andover, MA) was used for detailed measurements.

AVSL was measured using the caliper tool as part of the installed software package on the machine. AVSL 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 (S.S.P.), for a total of nine measurements of AVSL.

For the purposes of assessing interrater reliability, repeat measurements (10%) were made by a blinded independent investigator (L.T.M.) with substantial echocardiographic experience. Two repeat measurements of 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, and frequencies were determined for categorical variables. Case and control subgroups were compared for differences using Student's t and χ^2 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. Because 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 percentage 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 univariate and multivariate linear regression analysis models to