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The Presence of Bicuspid Aortic Valve Does Not Predict Ventricular Septal Defect Type

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Abstract

Previous studies have identified an increased incidence of bicuspid aortic valve (BAV) in patients with ventricular septal defect (VSD). Because endocardial cushion remodeling contributes to both the formation of semilunar valves and ventricular septation, we hypothesized that examination of humans with BAV and VSD would identify a specific VSD type. We evaluated VSD type in pediatric patients diagnosed with BAV and VSD (n=82) and compared findings to patients diagnosed with VSD and normal aortic valve morphology (n=429). VSD type was described as conoventricular, muscular, inlet or conoseptal using a clinical taxonomy. Based on the contribution of the outflow tract endocardial cushions to the membranous ventricular septum, we expected patients with BAV to have conoventricular VSD. In both patient groups, conoventricular VSD was most common; however, the prevalence was not significantly different when BAV patients were compared to those with normal aortic valve morphology (67% vs. 57%, p=0.11). The primary finding of this study is that despite a developmental link between semilunar valve formation and ventricular septation during cardiogenesis, there is no clear association between BAV and VSD type. This may be due to phenotypic and genetic heterogeneity of BAV and VSD, other modifying factors as manifested by differences in associated CVM, as well as limitations of the clinical taxonomy of VSD.

Keywords

valves; cardiac development; congenital heart disease

INTRODUCTION

Bicuspid aortic valve (BAV, OMIM 109730) is the most common congenital cardiovascular malformation (CVM) and occurs in 1–2% of the population [Ward, 2000; Hoffman and Kaplan, 2002]. BAV is heritable and has been shown to be genetically heterogeneous [Cripe et al., 2004; Martin et al., 2007]. Previous studies have identified an association between BAV and other CVMs, particularly ventricular septal defect (VSD) [Duran et al., 1995; Ciotti et al., 2006]. VSD type has been clinically classified as conoventricular, muscular, inlet or conoseptal based on morphologic characteristics [Van Praagh et al., 1989]. However, it remains unknown which type of VSD may be associated with BAV.

During cardiogenesis, outflow tract development includes valve formation as well as ventricular and aortopulmonary septation to produce the semilunar valves and two discrete ventricular outlets. Although cells from neural crest lineages are present in semilunar valves [Nakamura et al., 2006], the majority of cells that form the cusps of semilunar valves

originate from endothelial derived cells [de Lange et al., 2004, Lincoln et al., 2004]. Cell proliferation and expansion and remodeling of extracellular matrix to form the mature valves have been extensively studied [Lincoln et al., 2004, Hinton et al., 2006]. Less is known about ventricular septation, but the budding muscular septum divides the ventricular chambers and fuses with the proximal aspect of the outflow tract endocardial cushions and subsequently the membranous septum completes ventricular septation [Webb et al., 2003].

Based on these considerations, we hypothesized that individuals with BAV and VSD would have a particular type of VSD, namely conoventricular VSD. Thus, in this study we sought to determine the relationship between BAV and VSD type in humans.

MATERIALS AND METHODS

To identify patients with diagnoses of both BAV and VSD, a digital echocardiographic database in the Division of Cardiology at Cincinnati Children's Hospital was searched by diagnosis from January 2000 through December 2006. Among the total (BAV and VSD), we identified a subgroup having only BAV and VSD (BAV and VSD only). For control purposes, a group of patients with VSD and normal aortic valve morphology (VSD) was identified from January 2006 through December 2006 during the same clinical and echocardiographic study period; we identified a subgroup having only VSD (VSD only). Medical records of each subject were also reviewed to exclude patients with a known genetic syndrome, e.g. Down syndrome. The Institutional Review Board at Cincinnati Children's Hospital approved this study.

Aortic valve morphology was examined in both systole and diastole in the echocardiographic parasternal short-axis view. In all patients, BAV was classified according to a standardized decision tree that identifies two characteristic morphologies as either Anterior-Posterior (AP) or Right-Left (RL) [Cripe et al., 2004] (Fig 1A). VSD was classified as conoventricular, muscular, inlet or conoseptal according to Van Praagh's classification system [Van Praagh et al., 1989] (Fig 1B). Other CVMs were noted when present.

Statistical comparisons were made using Fisher's exact analysis performed with Stat View (SAS, Cary, North Carolina).

RESULTS

The study population included 511 individuals (257 males and 254 females). The ethnicity was 79% Caucasian, 14% African American, 3% Hispanic, 3% Asian and 1% other. The median age $\pm$ standard deviation (range) was 7 ± 540 (1–3690) days in the BAV and VSD group and 4 ± 720 (1–5760) days in the VSD group. There was a preponderance of males and Caucasians in the BAV and VSD cohort as previously described [Ferencz et al., 1997]. A total of 82 patients with BAV and VSD and 429 patients with VSD and normal aortic valve morphology were analyzed (Fig 2).

The proportion of conoventricular VSDs in patients with BAV and VSD (67%) was not significantly increased when compared to patients with VSD (57%) (Fisher's exact $p=0.11$) (Table I). In an effort to control for phenotypic heterogeneity, we examined the cohort having BAV and VSD only (30) and VSD only (322). The relative proportions of all VSD types were similar, and the proportion of conoventricular VSDs in patients with BAV and VSD only (60%) was not significantly increased when compared to patients with VSD only (45%) (Fisher's exact $p=0.18$). Interestingly, all 3 patients with inlet VSD had BAV. Conversely, we estimated 3.2% of patients with conoventricular VSD had BAV, an incidence of BAV approximately three times greater than found in the general population.

BAV morphology did not correlate with a particular VSD type. AP BAV morphology was present in 66/82 (80%) while RL BAV was present in 16/82 (20%) patients with BAV and VSD, consistent with previous findings [Fernandes et al., 2004]. AP BAV was seen in 45/55 (82%) conoventricular and 17/22 (77%) muscular VSDs. In patients with BAV and VSD only, the relative frequencies of BAV morphology in general and by VSD type were the same. These findings confirm that there does not appear to be a specific relationship between BAV morphology and VSD or VSD type.

Additional CVMs were identified in both groups and included aortic arch anomalies (46), atrial septal defects (18), mitral valve abnormalities (8) and conotruncal defects (6). In patients with BAV and VSD vs VSD only, aortic coarctation (40% vs 4%) and atrial septal defect (7% vs 2%) occurred more commonly, however, complex CVM (23% vs 21%) occurred with the same frequency. The prevalence of malalignment conoventricular VSDs in patients with BAV and VSD (14%) was not different when compared to patients with VSD (15%), but the type of associated CVM was different. In patients with BAV and malalignment VSD, there was a preponderance of aortic arch abnormalities (interrupted aortic arch 5, conotruncal defect 3) whereas patients with malalignment VSD and normal aortic valve morphology had a preponderance of conotruncal abnormalities (interrupted aortic arch 3, conotruncal defect 34).

DISCUSSION

The primary finding of this study is that the presence of BAV does not predict VSD type. In particular, conoventricular VSD occurs at nearly the same frequency in patients with BAV than in patients with a normal aortic valve. The lack of a clear association indicates that factors other than VSD morphology account for the co-occurrence of BAV and VSD. This may be due to phenotypic and genetic heterogeneity of BAV and VSD, other modifying factors as manifested by differences in associated CVM, as well as limitations of the clinical taxonomy of VSD.

The co-occurrence of BAV and VSD, previously noted in humans [Duran et al., 1995] and mice [Sierro et al., 2007], is not surprising given developmental studies that indicate that valvulogenesis and some aspects of ventricular septation are regulated by shared mechanisms within a common developmental pathway [Webb et al., 2003]. A recent study reported findings of semilunar valve anomalies and septal defects, including a majority with either BAV (70%) or VSD (50%), in *Cxcr7* deficient mice [Sierro et al., 2007]. Endothelial specific inactivation of *Cxcr7* using Tie2-Cre mice recapitulated the phenotype of *Cxcr7* knock out mice supporting a major role for CXCR7 in outflow tract morphogenesis via its role in endothelial cell signaling. The relevance of these findings to the clinical taxonomy of VSD and BAV, which is based on anatomical distinctions and distinguishes valve malformations from septation defects, remains to be determined, but as the genetic basis of pediatric heart disease is elucidated and genotype-phenotype relationships are appreciated, these clinical observations will be increasingly important.

If the ultimate goal is to understand the origins of pediatric heart disease, then a strategy involving human genetic studies and developmental studies in animal models will be required. Therefore, it may be informative to expand phenotype analysis in mouse models such as the *Cxcr7* knock out to establish the developmental associations. In humans with BAV and VSD, phenotypic and genetic heterogeneity may partially mask the general anatomy-based clinical association underscoring the idea that phenotype may not be specific to the underlying etiology. Associated CVM such as malalignment of the VSD and interruption of the aortic arch may help elucidate subtle clinical distinctions and ultimately complex developmental differences. Since both BAV and VSD can be subclinical and “late”

diagnoses further limited by selective use of echocardiography, family based human genetics research studies with meticulous phenotyping may be required to demonstrate the nature of this relationship. As the genetic basis of nonsyndromic pediatric heart disease is elucidated, phenotypic precision will become increasingly important to establishing a molecular taxonomy.

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Figure 1. BAV morphology and VSD type

BAV morphology (A) has been classified as anterior Posterior (AP) or Right-Left (RL) (modified from Cripe et al with permission [Cripe et al., 2004]). VSD type (B) has been classified as conoventricular, muscular, inlet or conoseptal (modified from van Praagh et al. with permission [Van Praagh et al., 1989]).

Figure 2. Study population

Pediatric patients with BAV and VSD (A) were analyzed as two groups: the whole group consisted of all patients with BAV and VSD and a subgroup consisted of patients with BAV and VSD only. BAV morphology and VSD type were described for both groups. Patients with VSD and normal aortic valve morphology (B) were analyzed similarly.

TABLE I

VSD Type Frequency in Patients with BAV and VSD

	CV	MU	IN	CS	TOTAL
All BAV and VSD	55 (67%)	22 (27%)	3 (4%)	2 (2%)	82
BAV and VSD only	18 (60%)	11 (37%)	1 (3%)	0 (0%)	30
All VSD	246 (57%)	173 (41%)	0 (0%)	10 (2%)	429
VSD only	147 (45%)	166 (52%)	0 (0%)	9 (3%)	322

BAV bicuspid aortic valve; CS conoseptal; CV conoventricular; IN inlet; MU muscular; VSD ventricular septal defect