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Bicuspid Aortic Valve Morphology and Interventions in the Young

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Objectives The aim of this study was to determine whether the morphologic subtype of bicuspid aortic valve (BAV) is associated with valve intervention in the young.

Background Analysis of BAV morphology is of prognostic relevance, as the fusion of right- and noncoronary leaflets (R-N) is associated with a greater degree of valve dysfunction compared with other subtypes. However, it is currently unknown whether morphologic differences translate into clinically relevant outcomes such as valve intervention.

Methods A nested cohort study was conducted on 310 patients with right- and left-coronary leaflet (R-L) and R-N fusion who were selected randomly from an inception cohort of 1,192 patients with BAV who were identified between 1986 and 1999. Supplementary information on clinical parameters was collected retrospectively from medical charts and databases.

Results Median age at follow-up was 16.1 years (range 5.6 to 34.4 years), and 71% were male. The R-N fusion (n = 108) was strongly predictive of valve intervention when compared with The R-L fusion (n = 202; hazard ratio 4.5, 95% confidence interval [CI] 2.5 to 8.1; p < 0.0001). In a longitudinal analysis of 799 echocardiograms, R-N fusion also was associated with a greater progression of valve dysfunction. This was true for both increasing aortic valve gradient (generalized estimating equations [GEE] risk ratio 27.2, 95% CI 1.2 to 619.6, p = 0.0386) and aortic regurgitation (GEE risk ratio 2.4, 95% CI 1.3 to 4.3, p = 0.0029).

Conclusion The morphology of BAV is predictive of clinically important end points. The R-N fusion is associated with a more rapid progression of aortic stenosis and regurgitation and a shorter time to valve intervention. (J Am Coll Cardiol 2007;49:2211–4) © 2007 by the American College of Cardiology Foundation

The progression of aortic stenosis and/or regurgitation in patients with bicuspid or bicommissural aortic valve (BAV) is a common indication for valve intervention in the young (1,2). There are currently no published data to suggest which patients with BAV are more likely to require intervention during childhood. In 2004, we reported our observations on morphologic subtypes of BAV in 1,192 children and adolescents. Fusion of the right- and noncoronary leaflets (R-N) was associated with at least a 2-fold greater odds of having moderate or severe aortic stenosis (odds ratio 2.3, 95% confidence interval (CI) 1.5 to 3.6, p ≤ 0.001) and aortic regurgitation (odds ratio 2.0, 95% CI 1.4 to 2.8, p = 0.0002), compared with other forms of BAV (3). In light of these results, we sought to determine whether aortic stenosis and regurgitation continue to progress more rapidly during childhood and adolescence in this group of patients and whether morphological differences translate into clinically important outcomes such as valve intervention.

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Methods

From our inception cohort of 1,192 patients with BAV identified between 1986 and 1999, a total of 864 patients had either isolated BAV or BAV and aortic coarctation, 853 of whom had fusion of right- and left-coronary leaflets (R-L) or R-N. From this base population, patients were selected randomly to form the nested cohort study population. Characteristics of the inception cohort have been previously published (3). Patients up to 18 years of age with BAV diagnosed by echocardiography were identified by searching the Cardiovascular Program database at Children's Hospital Boston, and BAV was defined as partial or complete fusion of 2 of the aortic valve leaflets, with or without the presence of a central raphe (4). Patients with complete or partial fusion of more than 2 leaflets (unicommissural) or other forms of complex congenital heart diseases such as truncus arteriosus were excluded. All echocardiograms performed before any surgical or catheter

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Abbreviations and Acronyms

BAV = bicuspid aortic valve

CI = confidence interval

GEE = generalized estimating equation

R-L = right-left coronary leaflet

R-N = right-noncoronary coronary leaflet

intervention or diagnosis of endocarditis was reviewed for severity of aortic stenosis and regurgitation. Echocardiographic assessment of aortic stenosis was expressed in terms of the maximum instantaneous Doppler gradient (mm Hg). Classification of the severity of aortic regurgitation was based on composite evaluation of proximal jet width, abdominal aortic Doppler, and left ventricular end-diastolic dimension. Patients were classified as having none, trivial, mild, moderate, or severe aortic regurgitation. The classification of moderate or severe regurgitation required pan-diastolic retrograde flow in the descending aorta and a left ventricular end-diastolic dimension adjusted for body surface area >2 standard deviations above the mean. Additional clinical data regarding diagnosis of endocarditis and catheter and surgical interventions were obtained from electronic and paper medical records and hospital databases.

Statistical analyses. Continuous variables are presented as mean ± standard deviation or median and range depending on the normality of their distribution. Ordinal and nominal variables are summarized as frequency and percentage. Patient characteristics according to the morphologic subtype of BAV were compared using chi-square tests, independent Student *t* tests, or Mann-Whitney *U* tests where appropriate. Freedom from valve intervention was plotted and compared using the Kaplan-Meier method and log-rank statistic. To assess the predictive value of the morphologic subtype of BAV on time to first valve intervention and time to first subacute bacterial endocarditis, Cox proportional hazard models accounted for duration of follow-up and adjusted for covariates. The proportional-hazards assumption was verified by time-dependent interactions and goodness-of-fit statistics.

Given that echocardiograms were performed serially and at variable time intervals, all analyses of progressive valve dysfunction took into consideration the nonindependent nature of the data structure. Generalized estimating equations (GEEs) were used to produce regression models for cluster sampling data by specifying distribution and link functions (i.e., IDENTITY for aortic valve gradient and LOGIT for progression of aortic regurgitation). Two-tailed p values <0.05 were considered statistically significant. The sample size provided >90% power to detect a 20% difference in progressive aortic regurgitation and a risk ratio of 2.0 for increasing aortic valve stenosis between the 2 morphologic subtypes of BAV. Data analysis was performed with SAS software Version 9.1 (SAS Institute, Cary, North Carolina).

Results

We identified 310 patients who met study criteria of whom 202 (65%) had fusion of the R-L, and 108 (35%) had fusion of the R-N. The mean event-free follow-up duration was 14.4 ± 7.0 years, with a median age at end of follow-up of 16.1 years (range 5.6 to 34.4 years). There were 222 (71%) males and 88 (29%) females.

Aortic stenosis/aortic regurgitation. Of the 310 patients, 164 had serial echocardiographic studies before any valve intervention or subacute bacterial endocarditis, permitting ascertainment of the rate of progression of valve disease in this subset. Characteristics of this subgroup of patients are provided in Table 1.

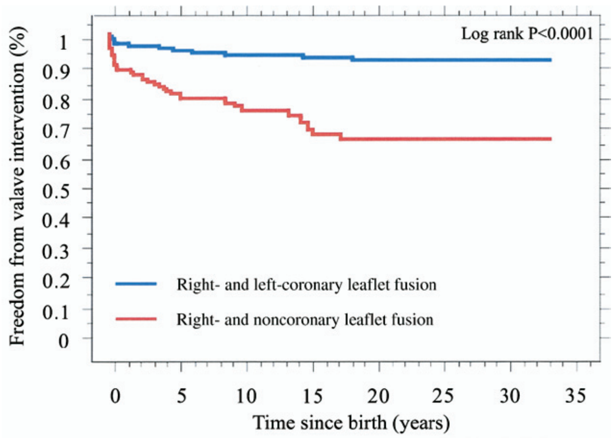
In a longitudinal analysis of 799 echocardiograms, aortic stenosis was more progressive in patients with fusion of the R-N compared with patients with fusion of the R-L (GEE risk ratio 27.2, 95% CI 1.2 to 619.6, p = 0.0386). Similarly, aortic regurgitation also was more progressive in patients with R-N fusion compared with those with fusion of the R-L. During follow-up, aortic regurgitation worsened by at least 1 category in 55 patients (33.5%): 28 patients (27.2%) with R-L fusion and 27 patients (44.3%) with R-N fusion. Aortic regurgitation was more than twice as likely to progress in patients with R-N fusion (GEE risk ratio 2.4, 95% CI 1.3 to 4.3, p = 0.0029).

Bacterial endocarditis. In the nested study cohort of 310 patients, there were 4 (0.1%) documented cases of endocar-

Table 1 Characteristics of Patients With Serial Echocardiographic Studies Before Valve Intervention or Subacute Bacterial Endocarditis

	Right-Left Fusion n = 103	Right-Non Fusion n = 61	p Value
Age (yrs)			
At first echocardiogram	5.2 ± 4.9	5.0 ± 4.3	0.840
At last echocardiogram	11.8 ± 5.9	10.5 ± 5.5	0.156
Weight (kg)			
At first echocardiogram	21.1 ± 19.2	20.9 ± 16.5	0.942
At last echocardiogram	45.5 ± 24.9	42.7 ± 25.3	0.490
Height (cm)			
At first echocardiogram	101.7 ± 39.2	106.0 ± 35.9	0.491
At last echocardiogram	142.2 ± 34.1	139.2 ± 34.5	0.588
Male gender, n (%)	73 (70.8)	45 (73.8)	0.689
Aortic coarctation, n (%)	41 (39.8)	5 (8.2)	<0.001
Aortic stenosis (mm Hg)			
At first echocardiogram	0 (0, 65)*	20 (0, 70)*	<0.001
At last echocardiogram	0 (0, 100)*	25 (0, 100)*	<0.001
Aortic regurgitation, n (%)			
At first echocardiogram			
None	76 (73.8)	29 (47.5)	
Trivial	16 (15.6)	12 (19.7)	
Mild	10 (9.7)	13 (21.3)	0.004
Moderate	0 (0)	7 (11.5)	
Severe	1 (1.0)	0 (0)	
At last echocardiogram			
None	55 (53.4)	18 (29.5)	
Trivial	21 (20.4)	4 (6.6)	
Mild	23 (22.3)	28 (45.9)	<0.001
Moderate	3 (2.9)	8 (13.1)	
Severe	1 (1.0)	3 (4.9)	

*Non-normally distributed continuous variables are summarized as median (range).



Number at risk								
	R-L	202	190	162	111	50	3	2
	R-N	108	85	72	40	19	8	3
	Total	310	275	234	151	69	11	5

Figure 1 **Bicuspid Aortic Valve: Freedom From Intervention**

R-L = right- and left-coronary leaflet fusion;
R-N = right- and noncoronary leaflet fusion.

ditis. Given the limited number of endocarditis cases, statistical analysis could not be performed.

Valve intervention. The BAV with fusion of the R-N (n = 108) was strongly predictive of valve intervention when compared with fusion of the R-L (n = 202; hazard ratio 4.5, 95% CI 2.5 to 8.1, $p < 0.0001$). As depicted in Figure 1, the actuarial freedom from valve intervention for R-N fusion versus R-L fusion was 79.4% versus 94.5% at 1 year, 75.5% versus 93.0% at 5 years, 68.1% versus 92.2% at 15 years, and 64.1% versus 90.9% at 20 years ($p < 0.0001$). As summarized in Table 2, 49 of the 310 patients underwent valve intervention with 16 of 202 (8%) patients with fusion of the R-L compared with 33 of 108 (31%) patients with fusion of the R-N.

The majority of initial interventions (38 of 49) were balloon angioplasty. Additional interventions were performed in 11 patients, with 2 patients undergoing 3 interventions. Additional interventions included 5 repeat balloon aortic valvuloplasties (1 R-L fusion and 4 R-N fusion), 3 surgical aortic valvuloplasties (1 R-L fusion and 2 R-N fusion), 1 aortic valve replacement (R-L fusion), and 4 Ross procedures (1 R-L fusion and 3 R-N fusion).

The primary indication for valve intervention was aortic stenosis in 41 patients (13 R-L fusion and 28 with R-N fusion), mixed aortic valve disease in 5 patients (1 R-L fusion and 4 R-N fusion), and pure aortic regurgitation in 2 patients, 1 of each morphology.

In regression analyses controlling for duration of follow-up, R-N fusion was associated with a >4-fold risk of valve intervention, when compared with R-L fusion (hazard ratio 4.5, 95% CI 2.5 to 8.1, $p < 0.0001$). Controlling for age, gender, and presence of aortic coarctation, R-N fusion remained an independent predictor for valve intervention (hazard ratio 2.9, 95% CI 1.6 to 5.4, p = 0.0005).

Discussion

The BAV is the most common congenital cardiac malformation in adults, identified in 1% to 2% of the general population (5). It is associated with significant morbidity and mortality, especially after the fourth decade of life when progression of stenosis and regurgitation due to calcific changes and sequela of infective endocarditis often require intervention (6–8). In childhood, age and severity at presentation and longer duration of follow-up have been identified as predictors of valve intervention (9,10). To date, no studies have examined whether valve morphology is a risk factor for valve intervention during childhood.

In the Second Natural History Study, Keane et al. (11) suggested that the freedom from aortic valve intervention was estimated to be 67% at 20-year follow up for patients presenting after 2 years of age (11). Consistent with these figures, we demonstrated a 64% freedom from intervention in patients with fusion of the R-N. However, in patients with fusion of the R-L, 91% freedom from intervention was noted. The overall greater freedom from valve intervention observed in our study may reflect increased rates of diagnosis

Table 2 **Bicuspid Aortic Valve Progression**

	Right-Left Fusion n = 202	Right-Non Fusion n = 108	p Value
Age at last follow-up (yrs)	16.0 ± 5.3	16.4 ± 6.4	0.611
Male gender, n (%)	143 (70.8)	79 (73.1)	0.661
Aortic coarctation, n (%)	89 (44.1)	13 (12.0)	<0.001
At least one valve intervention during follow-up (n, %)	16 (7.9)	33 (30.6)	<0.001
Type of valve intervention (n, %)			0.463
Balloon angioplasty	12	26	
Surgical valvuloplasty	3	6	
Aortic valve replacement	0	1	
Ross procedure	1	0	
Subacute bacterial endocarditis during follow-up (n, %)	1 (0.5)	3 (2.9)	0.085

Shown are patient characteristics according to morphology of bicuspid aortic valve.

of milder forms of disease resulting from improvements and availability of noninvasive imaging (12).

In 315 patients with an identified morphologic subtype of BAV undergoing valve replacement, Sabet et al. (1) found that the majority of aortic valve replacements in adult patients with a BAV had fusion of the R-L. In contrast, we demonstrate that fusion of the R-N is associated with a greater progression of valve dysfunction and a 4-fold risk of time-related valve intervention during childhood compared with BAVs with fusion of the R-L. This apparent discrepancy may be partly explained by the much greater overall prevalence of R-L fusion, identified in 70% of the 1,185 patients in our inception cohort and in 89% of patients with associated aortic coarctation (3). Moreover, we hypothesize that the proportion of adults with R-L fusion requiring intervention may be greater than in children, because many younger patients with fusion of R-N will have already undergone aortic valve intervention before adulthood. Longer-term follow-up of our cohort of patients is required to verify this speculation.

Study limitations. This study represents the population of children with BAV referred for echocardiography. Patients with BAV without significant aortic stenosis or regurgitation may not be referred for evaluation or echocardiography because of a lack of physical findings.

Conclusions

Our study demonstrates that children with BAVs and fusion of the R-N are much more likely to have progression of valve dysfunction and require intervention during childhood compared with other types of BAVs. As morphologic differences are determinants of clinical outcomes, these finding also may have implications regarding the follow-up of patients according to their subtype of BAV.

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