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ORIGINAL ARTICLE

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Incidence, morphology, and progression of bicuspid aortic valve in pediatric and young adult subjects with coexisting congenital heart defects

Talha Niaz, MBBS[1] | Joseph T. Poterucha, DO[1] | Jonathan N. Johnson, MD[1,2] | Cecilia Craviari, MD[1] | Thomas Nienaber, MBBS[1] | Jared Palfreeman, DO[1] | Frank Cetta, MD[1,2] | Donald J. Hagler, MD[1,2]

[1]Department of Pediatrics/Division of Pediatric Cardiology, Mayo Clinic, Rochester, Minnesota, USA

[2]Department of Medicine/Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA

Correspondence
Donald J. Hagler MD, Professor of Pediatrics and Medicine, Divisions of Pediatric Cardiology and Cardiovascular Diseases, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA.
Email: hagler.donald@mayo.edu

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Abstract

Background: Bicuspid aortic valve (BAV) occurs both as an isolated cardiac lesion and in association with congenital heart defects (CHD). Their aim was to identify the incidence and morphology of BAV in patients with coexisting CHD and compare their disease progression to patients with isolated BAV.

Methods: The Mayo Clinic echocardiography database was retrospectively analyzed to identify pediatric and young adult patients (≤22 years) who were diagnosed with BAV from 1990 to 2015. The morphology of BAV was determined from the echocardiographic studies before any intervention.

Results: Overall, 1010 patients with BAV were identified, 619 (61%) with isolated BAV and 391 (39%) with BAV and coexisting CHD. The incidence of BAV was highest in patients with coarctation of the aorta (36%) and interrupted aortic arch (36%). In comparison to patients with isolated BAV, patients with BAV and left-sided obstructive lesions more frequently had right-left cusp fusion ($P = .0001$). BAV in patients with right-sided obstructive lesions was rare, but they more frequently had right-noncoronary or left-noncoronary cusp fusion ($P = .01$). No significant progression of aortic stenosis or regurgitation was observed in patients with BAV and coexisting CHD; however in patients with isolated BAV the severity of aortic regurgitation increased with age. In patients with isolated BAV, the ascending aorta diameter (z-score) increased with age, peaked around 8–9 years of age, and was larger in comparison to patients with BAV and coexisting CHD. The sinus of Valsalva diameter (z-score) in patients with BAV and ventricular septal defect was larger than isolated BAV patients after 18 years ($P < .04$).

Conclusions: The morphology of BAV, the pattern and progression of aortic dilatation, and the severity of aortic valve disease vary in pediatric and young adult patients with BAV and coexisting CHD. However, there was no significant BAV disease progression when associated with these CHD.

KEYWORDS
ascending aorta dilation, aortic valve stenosis, bicuspid aortic valve, congenital heart defects, sinus of Valsalva

1 | INTRODUCTION

Bicuspid aortic valve (BAV) has been vigorously studied and reviewed in literature, yet many features of clinical presentation and disease progression still remain undefined.[1,2] The morphology of cusp fusion in BAV is an important factor in determining progression of disease and may lead to different patterns of valvular and aortic complications.[3–7] Hemodynamic, molecular and

genetic mechanisms have been proposed to explain these differences.[8–10]

BAV occurs both as an isolated cardiac lesion and in association with other congenital heart defects (CHD). Even though the association of BAV with defects such as coarctation of aorta (CoA) is well recognized, the association with other cardiac lesions has not been well described.[11–14] The purpose of this study was to identify the incidence of BAV, define the cusp fusion morphology in association with various forms of CHD, and determine the differences in prognosis and progression of BAV disease in patients with CHD compared with patients with isolated BAV. This study ultimately attempts to describe the natural history of BAV in patients with associated CHD and to determine if coexisting CHD predispose to rapid or worse disease progression.

2 | METHODS

2.1 | Definitions

We defined BAV as a complete fusion of two aortic valve cusps, with or without the presence of a distinct raphe, resulting in two functional cusps.[15,16] We defined a unicuspid aortic valve as fusion of all three aortic valve cusps resulting in a single functional cusp, with a rudimentary single commissure. The types of BAV were defined by the specific cusps participating in the fusion (raphe) and confirmed morphologically by the origin of the coronary arteries arising from their respective cusps. The types were defined as right and left fusion (RL); right and noncoronary fusion (RN); and left and noncoronary fusion (LN) (Figure 1).

2.2 | Study population

This study was approved by the Mayo Clinic Institutional Review Board. Using the Mayo Clinic echocardiographic database, we retrospectively identified pediatric and young adult patients diagnosed with BAV ≤22 years of age from 1990 to 2015. We used an age limit of ≤22 years in order to study the transition of disease and various echocardiographic parameters from pediatric to young adult age. These patients were most commonly referred for echocardiography due to cardiac murmur, BAV screening or evaluation of other types of CHD. We included patients who had BAV with clearly identifiable valve morphology by echocardiography. Only the echocardiographic studies performed prior to any aortic valve intervention were included in the determination of BAV morphology. Patients were excluded from the study if they had a unicuspid aortic valve, or if they had difficult acoustic windows resulting in images inadequate for confirmation of morphology. In order to determine the incidence of BAV in various types of CHD, we identified the total number of patients with each CHD type diagnosed via echocardiogram at Mayo Clinic during the study time period.

We divided the study population into two main cohorts; Cohort I consisted of isolated BAV patients and Cohort II consisted of patients with BAV + CHD. Shunt lesions (atrial septal defect, ASD; ventricular septal defect, VSD; and patent ductus arteriosus, PDA) were further categorized as Isolated or Combined shunt lesions based on the presence of other concurrent CHD. Because of the very low number of

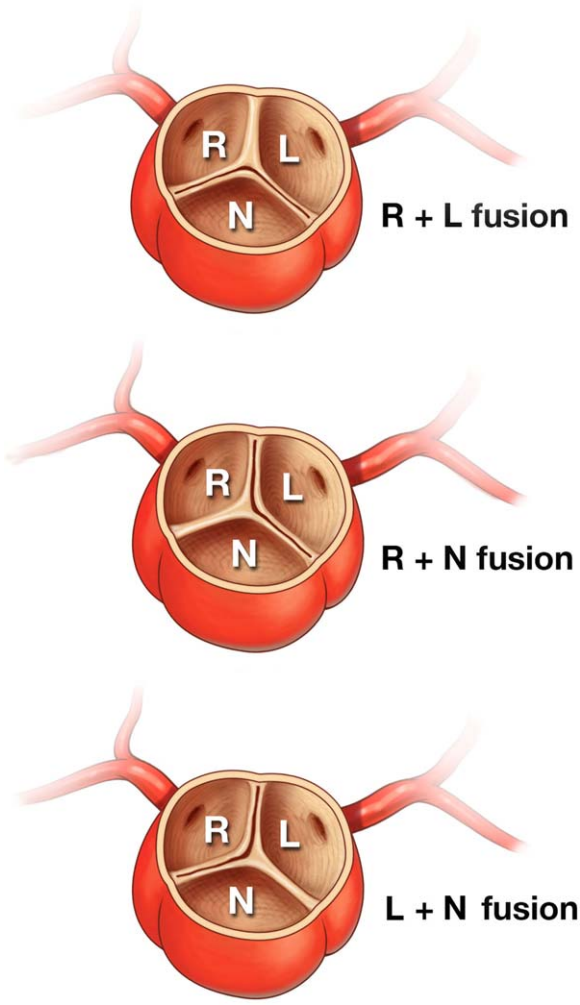

FIGURE 1 Cusp fusion morphology in bicuspid aortic valve. Top: R + L, right & left cusp fusion. Middle: R + N, right & noncoronary cusp fusion. Bottom: L + N, left & noncoronary cusp fusion.

BAV patients with right ventricular outflow tract obstructive lesions, we identified patients with BAV and concomitant tetralogy of Fallot (TOF) or pulmonary atresia (PA) from the entire Mayo Clinic database regardless of their age and performed a separate subgroup analysis to study the unique characteristics in this subset of patients. However, this group was not included in the overall analysis for incidence and progression of disease.

2.3 | Data collection

Demographic data including age, gender, date of birth, heart rate, blood pressure, and body surface area measured by Haycock's method were obtained from the echo reports. We recorded data from multiple serial echocardiographic studies performed on each patient prior to any intervention on the aortic valve in order to analyze the disease progression. The morphology of aortic valve cusp fusion was identified from echocardiograms performed prior to any intervention on the aortic valve. Two independent reviewers (TN, DJH) reviewed the images to confirm and validate the morphology. Patients with ambiguous morphology were excluded. All echocardiographic measurements including the mean

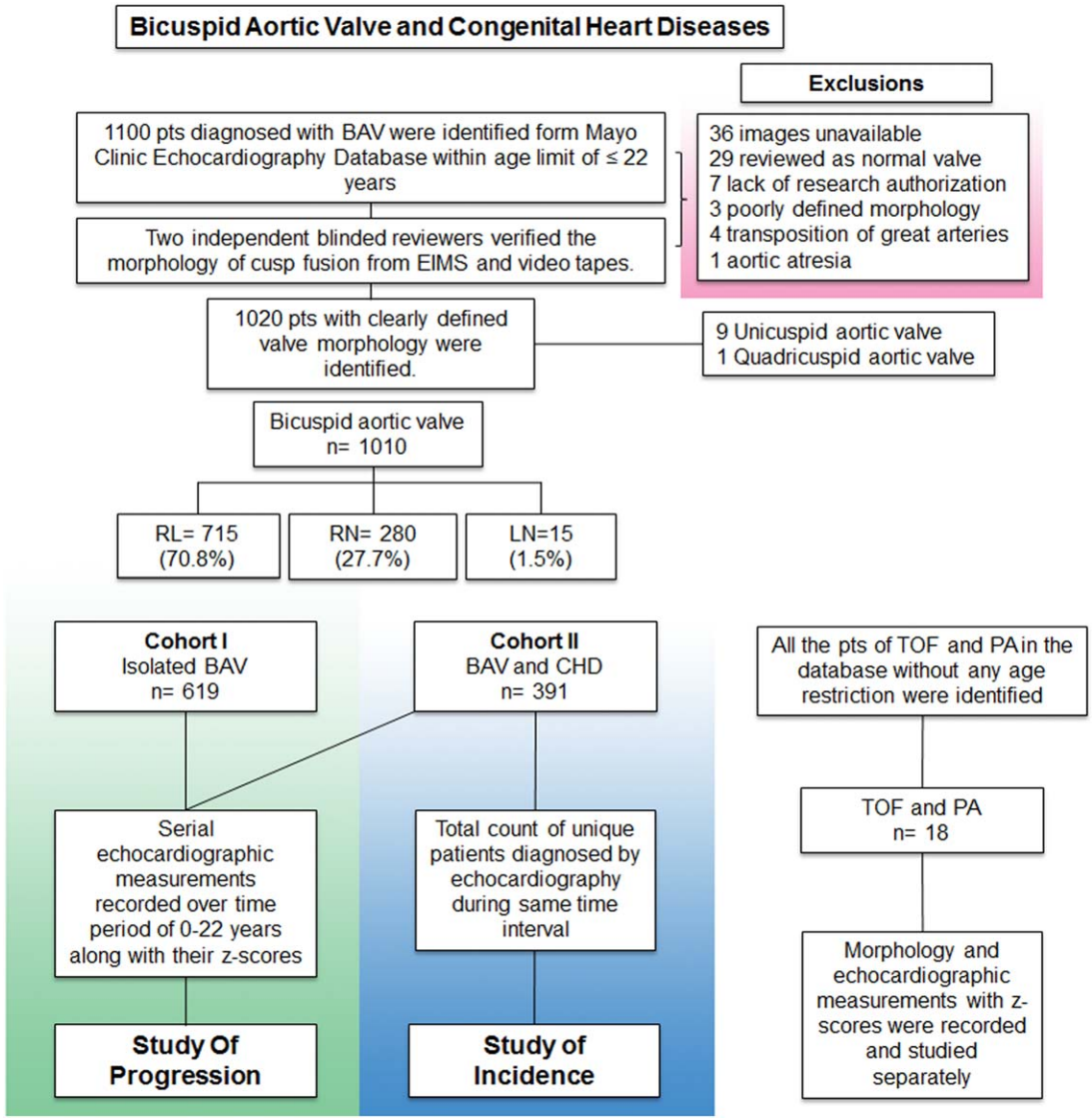

FIGURE 2 Flow chart of the study design. The figure explains the study design in the form of flow chart. BAV bicuspid aortic valve, CHD congenital heart defect, EIMS echo information management system (Mayo Clinic), Abbreviations: PA, pulmonary atresia; TOF, tetralogy of Fallot.

systolic gradient across aortic valve, grade of aortic regurgitation (AR), linear measurements of left ventricular internal dimension (LVIDD), left ventricular posterior wall thickness (LVPWT), and aortic measurements at the sinus of Valsalva and mid-ascending aorta (AscAo) were obtained according to the American Society of Echocardiography guidelines.[17] Measurements were converted to z-scores as reported by Colan.[18,19]

2.4 | Statistical analysis

All statistical calculations were performed with JMP version 10.0 software (SAS Institute Inc., Cary, NC, USA). Categorical variables were compared by using z-test. Continuous variables were compared by using a two-sided unpaired Student's *t*-test and nonparametric Wilcoxon test, as appropriate. In order to study the progression of disease by age using echocardiographic parameters, we plotted smooth-line graphs with age in years on the x-axis and echocardiographic data in the form of z-scores on the y-axis. We compared the mean echocardiographic values between patients with isolated BAV versus patients with BAV + CHD at each year to assess age-specific differences. *P* values $<.05$ were considered significant.

3 | RESULTS

A total of 1100 patients with BAV were identified from Mayo Clinic echocardiography database from 1990 to 2015. A total of 3697 studies were analyzed, with an average of 4 studies per patient. There were 619 (61%) patients with isolated BAV and 391 (39%) patients with BAV + CHD.

The study design is shown in Figure 2. The median age of patients at the first echocardiographic evaluation was 12 years (range 0–22 years). The male to female ratio was 2:1, with 674 (67%) males and 336 (33%) females (Table 1).

TABLE 1 Incidence and morphology of bicuspid aortic valve in patients with co-existing congenital heart defects

Congenital cardiac defects	Total no. of pts with lesions	No. of pts with BAV	% of pts with BAV	RL	RN	LN
Total BAV pts		1010		715 (70.8%)	280 (27.7%)	15 (1.5%)
Male		674		477 (70.8%)	184 (27.3%)	13 (1.9%)
Female		336		238 (70.8%)	96 (28.6%)	2 (0.6%)
Isolated BAV		619		419 (67.7%)	197 (31.8%)	3 (0.5%)
BAV + CHDs		391		296 (75.7%)	83 (21.2%)	13 (3.3%)
Left-sided obstructive lesions						
Coarctation of aorta	682	247	36.2%	*209	33	5
Interrupted aortic arch	33	13	36.4%	8 (67%)	3 (25%)	1 (8%)
Subaortic stenosis	285	30	10.5%	24 (80%)	6 (20%)	0
Supravalvar mitral ring	20	4	20.0%	4 (100%)	0	0
Hypertrophic cardiomyopathy	484	5	1.0%	5 (100%)	0	0
Right sided obstructive lesions						
Pulmonary atresia	270	5	1.8%	1 (20%)	3 (60%)	1 (20%)
Tetralogy of Fallot	408	3	1.0%	1 (33%)	0	†2 (67%)
Mixing lesions						
Atrial septal defect	3890	76	2.0%	54 (71%)	20 (26%)	2 (2%)
Ventricular septal defect	2624	100	3.8%	66 (66%)	31 (31%)	3 (3%)
Patent ductus arteriosus	3560	75	2.1%	48 (64%)	26 (35%)	1 (1%)
Complex cardiac lesions						
Double outlet right ventricle	75	5	6.7%	3 (60%)	2 (40%)	0
Ebstein's anomaly	417	9	2.2%	8 (89%)	1 (11%)	0
Hypoplastic left heart syndrome	94	23	24.5%	17 (74%)	4 (17%)	2 (9%)
TAPVR	87	2	2.3%	1 (50%)	1 (50%)	0
PAPVR	124	4	3.2%	2 (50%)	2 (50%)	0
AV canal defect	406	8	2.0%	5 (62%)	3 (38%)	0
Left persistent SVC	226	10	4.4%	7 (70%)	2 (20%)	1 (10%)

*$P < .0001$.
†$P < .01$ when compared with isolated BAV.
Abbreviations: BAV, bicuspid aortic valve; PAPVR, partial anomalous pulmonary venous return; SVC, superior vena cava; TAPVR, total anomalous pulmonary venous return.

3.1 | Incidence

Patients with left sided obstructive lesions had higher incidence of BAV compared with isolated BAV: CoA 36.2%, interrupted aortic arch 36.4%, hypoplastic left heart syndrome (HLHS) 24.5%, supravalvular mitral ring 20%, and subaortic stenosis (SAS) 10.5% (Table 1). Right sided obstructive lesions had an overall incidence of concomitant BAV similar to that of the general population.[20,21] For patients with shunt lesions, incidence of BAV was 3.8% in patients with VSD while patients with ASD or PDA had a 2% incidence of concomitant BAV (Table 1). Complex cardiac lesions including Ebstein's anomaly, total anomalous pulmonary venous return, partial anomalous pulmonary venous return and atrioventricular canal defect had incidence similar to the general population (Table 1).

3.2 | Morphology

There was no gender difference in the type of cusp fusion morphology. Patients with left sided obstructive lesions and concomitant BAV had a greater frequency of RL cusp fusion ($P = .0001$) as compared with patients with isolated BAV (Table 1). Whereas right sided obstructive lesions with concomitant BAV more commonly demonstrated noncoronary cusp involvement, RN or LN cusp fusion ($P = .01$). Shunt lesions with concomitant BAV that were present with other types of CHD ("combined") were not associated with any particular cusp morphology. However in subgroup analysis of purely "isolated" shunt lesions and BAV, patients with isolated VSD and BAV more commonly had RN cusp fusion ($P = .03$). Similarly patients with isolated PDA and BAV also more commonly had RN cusp fusion ($P = .04$) (Figure 3 and Table 1).

Noncoronary cusp fusion valve morphology was more commonly found in patients with BAV and coexisting TOF or PA. Though only 3 patients were present with BAV and concomitant TOF or PA, 2 of them had LN cusp fusion. To examine this further and considering the small number of patients in this cohort, we performed a separate subgroup analysis of all the patients with BAV and coexisting TOF ($n = 11$) and PA ($n = 7$) regardless of their age. A statistically significant association of LN cusp fusion ($P = .001$) in patients with BAV + TOF and both RN cusp fusion ($P = .004$) and LN cusp fusion ($P = .0001$) was found in patients with BAV + PA.

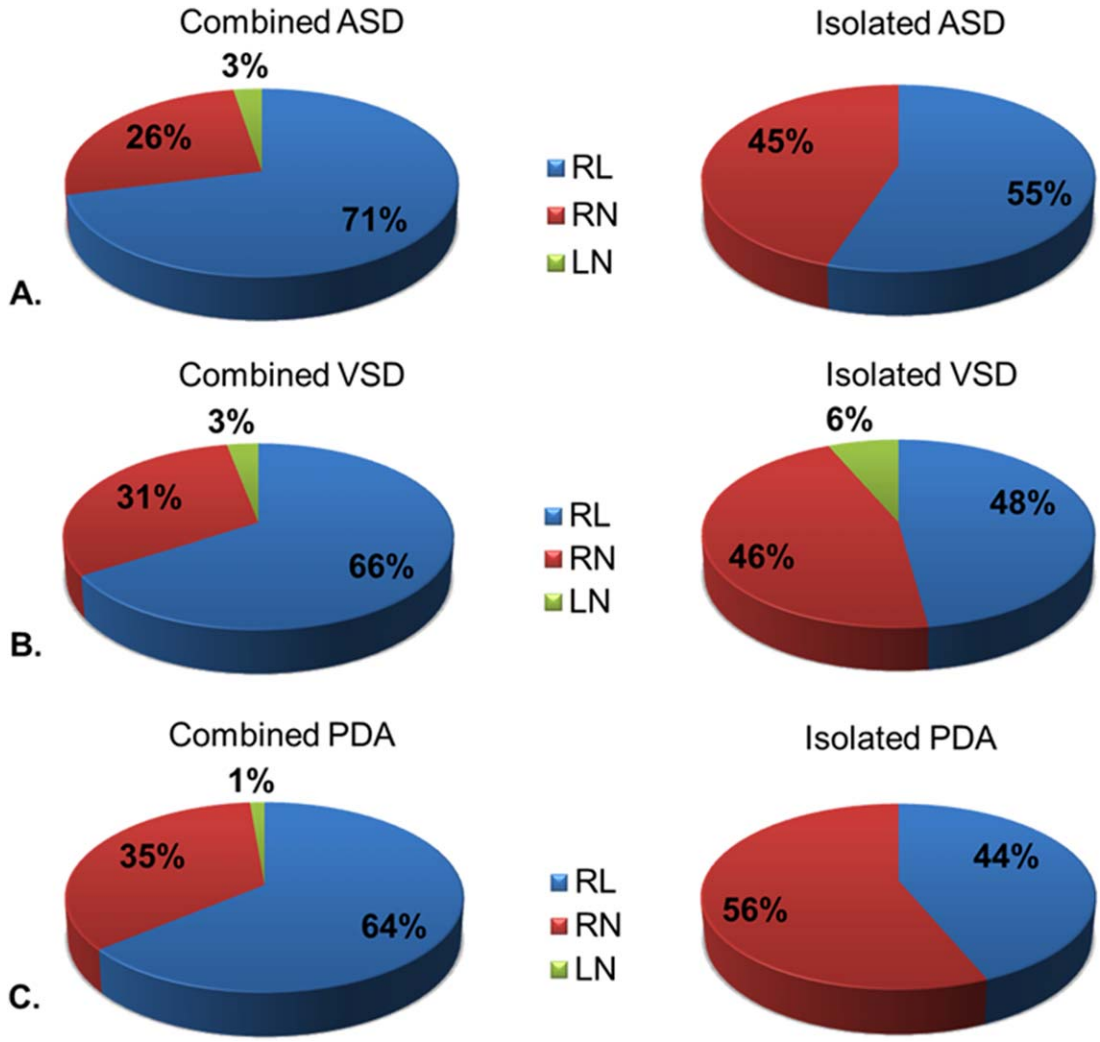

FIGURE 3 Comparison of bicuspid aortic valve morphology in combined and isolated shunt lesions. Combined shunt lesions group contains patients with bicuspid aortic valve and shunt lesions irrespective to presence of any other congenital heart defect while isolated shunt lesions group only includes patients with bicuspid aortic valve and the particular shunt lesion. (A) Higher number of patients with right-noncoronary fusion in isolated atrial septal defect in comparison to combined atrial septal defect group. (B) Higher number of patients with right-noncoronary fusion in isolated ventricular septal defect in comparison to combined ventricular septal defect group. (C) Higher number of patients with right-noncoronary fusion in isolated patent ductus arteriosus versus combined patent ductus arteriosus group. Abbreviations: ASD, atrial septal defect; BAV, bicuspid aortic valve; PDA, patent ductus arteriosus; RN, right-noncoronary; VSD, ventricular septal defect

3.3 | Disease progression

3.3.1 | Valvular measurements

In patients with BAV + CHD there was no progression of aortic valve stenosis as measured by mean systolic gradient (Figure 4). In the first year of life, the aortic valve mean systolic gradient was higher in patients with isolated BAV as compared with BAV + CHD ($P < .001$). No significant difference in aortic valve stenosis was observed in older patients except patients with subaortic stenosis (SAS) who had higher gradients. Patients with isolated BAV had higher grades of AR as compared with patients with BAV + CHD; this became statistically significant at the age of 20 years in comparison to BAV patients with concomitant CoA ($P = .0003$), VSD ($P = .03$), or PDA ($P = .03$).

3.3.2 | Left ventricular measurements

There was no significant increase in the LVPWT or LVIDD z-scores with age. However in younger patients from age of 0 to 3 years, greater LVPWT measurements were observed in patients with BAV + CHD as compared with isolated BAV patients ($P < .05$) (Figure 5).

3.3.3 | Aorta measurements

Progressive increase in AscAo diameter (z-score) by age was observed in all groups (Figure 6). AscAo diameter (z-score) was significantly larger in patients with isolated BAV compared with BAV + CHD ($P = .0001$). A period of peak growth in mid-AscAo (z-score) was observed in isolated BAV patients around age of 8-9

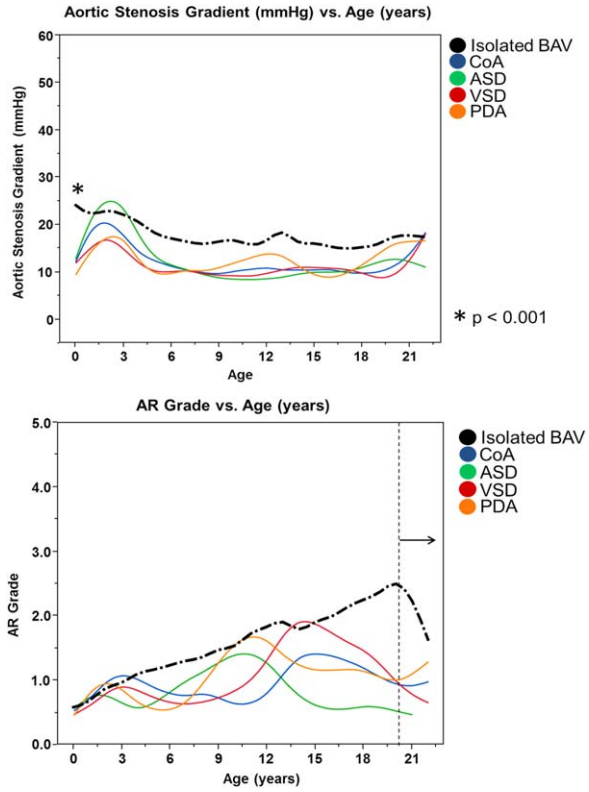

FIGURE 4 Progression of aortic stenosis and aortic regurgitation in patients with bicuspid aortic valve and congenital heart defects. Age in years is plotted along x-axis. Aortic stenosis mean gradient and aortic regurgitation grade are plotted along y-axis. Dotted line represents isolated bicuspid aortic valve. Colored lines represent congenital heart defects according to the color coding. (A) Aortic stenosis gradient is higher at birth in patients with isolated BAV as compared with other groups ($P < .001$), due to presence of congenital aortic stenosis in some patients. There is no progression of gradient of aortic stenosis in any group. (B) Aortic regurgitation grade is higher in isolated bicuspid aortic valve patients as compared with other lesions from age 20 onwards ($P < .04$) as shown by the arrow. Abbreviations: AR, aortic regurgitation; ASD, aortic septal defect; BAV, bicuspid aortic valve; CoA, coarctation of aorta; PDA, patent ductus arteriosus; VSD, ventricular septal defect

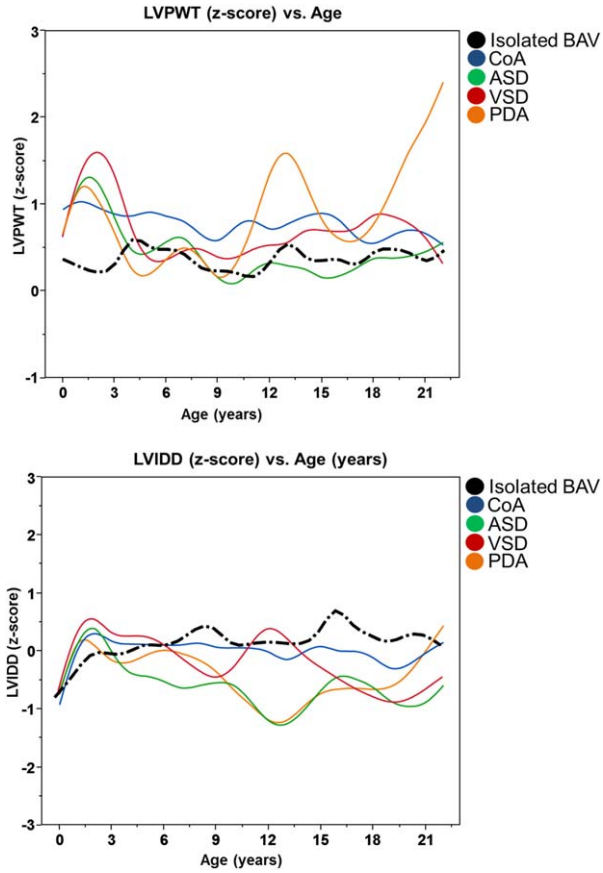

FIGURE 5 Age wise progression of left ventricular measurements in patients with bicuspid aortic valve and congenital heart defects. Age in years is plotted along x-axis. Left ventricular posterior wall thickness and left ventricular internal dimension diastolic are plotted along y-axis. Dotted black line represents isolated bicuspid aortic valve. Colored lines represent congenital heart defects according to the color coding. (A) Patients with isolated BAV have lower LVPWT in earlier age group. (B) No significant differences were present between isolated BAV and patients with coexisting congenital heart defects. Abbreviations: ASD, aortic septal defect; BAV, bicuspid aortic valve; CoA, coarctation of aorta; LVIDD, left ventricular internal diastolic dimension; LVPWT, left ventricular posteriors wall thickness; PDA, patent ductus arteriosus; VSD, ventricular septal defect

years, while other lesions did not show any period of peak growth during the respective time interval.

An increase in the sinus of Valsalva diameter (z-score) with age was also observed in all groups (Figure 6). During earlier age intervals there was no significant difference in the sinus of Valsalva diameter (z-score) between patients with BAV + CHD and isolated BAV. However, from the age of 18 years and onwards, patients with BAV + VSD had significantly greater sinus of Valsalva diameter (z-score) compared with isolated BAV patients ($P < .04$) (Figure 6). In patients with isolated BAV there was a sharp rise in sinus of Valsalva diameter (z-score) around 8-9 years of age followed by a decrease as shown in Figure 6.

3.4 | Additional analysis of right-sided obstructive lesions

3.4.1 | Tetralogy of Fallot

We found 11 patients with TOF and BAV including older age patients (Table 2). The median age was 33 years (range 0–63 years). LN cusp fusion was present in 2/11 patients (18%) with BAV and TOF compared with 0.3% patients in the isolated BAV cohort ($P = .001$). In addition, noncoronary cusp involvement, LN (18%) + RN (45%), was very high in TOF patients; 64% in TOF versus 33% in isolated BAV cohort ($P = .03$). There were no patients with AS while

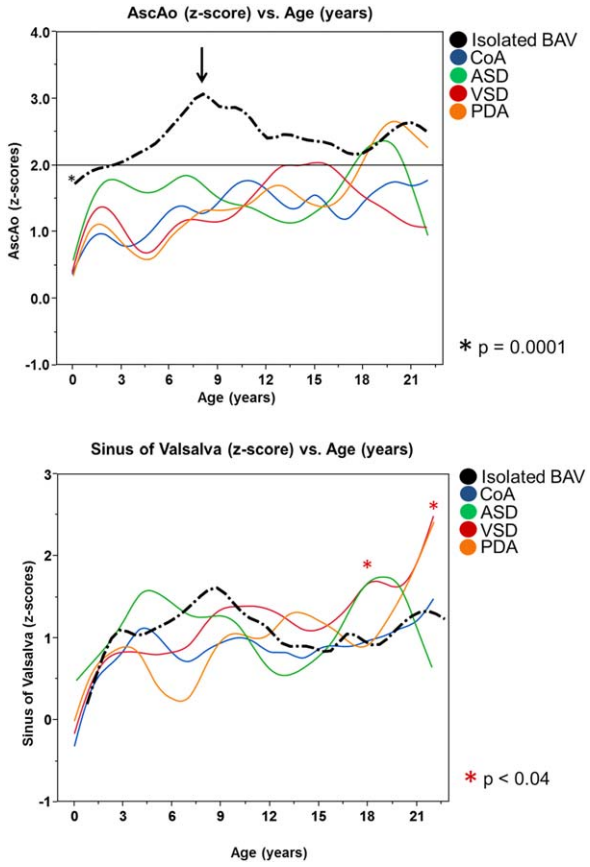

FIGURE 6 Age wise progression of aortic dimensions in patients with bicuspid aortic valve and congenital heart defects. Age in years is plotted along x-axis. Mid-Ascending aorta diameter and sinus of Valsalva diameter are plotted along y axis. Dotted line represents isolated bicuspid aortic valve. Colored lines represent congenital heart defects according to the color coding. *P* values are calculated at every age interval by difference between isolated bicuspid aortic valve and every congenital heart defect. (A) Ascending aorta diameter is significantly higher in patients with isolated BAV in comparison to BAV and other congenital heart defects. Arrow represents the period of peak growth of diameter in isolated BAV patients at age of 8–9 years. (B) Sinus of Valsalva diameter in BAV+VSD is higher in comparison to isolated BAV from age of 18 years and onwards. Abbreviations: AscAo, mid-ascending aorta; ASD, aortic septal defect; BAV, bicuspid aortic valve; CoA, coarctation of aorta; PDA, patent ductus arteriosus; VSD, ventricular septal defect

only mild AR was present in 3/11 (27%) patients. Mid-AscAo dilation was found in 9/10 (90%) patients while the sinus of Valsalva dilation was present in 6/9 (67%) patients with echocardiographic data available for measurement.

3.4.2 | Pulmonary atresia with ventricular septal defect

There were 8 patients with pulmonary atresia and BAV Table 3. 1 patient was excluded due to lack of images for determination of valve morphology. The median age was 6 years (range 0–59 years). The predominant cusp fusion morphology was RN (71%) and LN (29%); no patient had RL cusp morphology. Mid-AscAo dilation was present in 4/6 (67%) patients and the sinus of Valsalva dilation was present in 2/7 (29%) patients with echocardiographic data available for measurement.

4 | DISCUSSION

In our study, BAV morphology was found to vary with types of CHD associated with BAV. RL cusp fusion was frequently present in left sided obstructive lesions, while RN or LN cusp fusion was more frequently present in the small number of patients with right sided obstructive lesions. Significant differences were present in the progression of various echocardiographic parameters. The grade of AR was higher in patients with isolated BAV compared with those with concomitant CHD. LVPWT (z-score) was higher in patients with BAV + CHD compared with those with isolated BAV. AscAo diameter (z-score) was significantly larger in isolated BAV patients, while the sinus of Valsalva diameter (z-score) was larger in the BAV patients with VSD after the age of 18. Overall, there was no additional worsening of valvular obstruction, left ventricular dilation or hypertrophy, or aortic dilation in patients with BAV + CHD compared with patients with isolated BAV during childhood.

4.1 | Left-sided obstructive lesions

Similar to observations by Fernandes et al., the incidence of BAV in left sided obstructive lesions was very high with RL cusp fusion as the most common morphology.[16] In various studies, the incidence of BAV in patients with CoA has varied from 25% to 85%.[22–25] The incidence of BAV in patients with CoA was 36% in our study and we observed RL cusp fusion in 84% of these patients. Interestingly, patients with BAV and CoA had smaller aortic dimensions (z-scores) as compared with patients with isolated BAV, similar to findings of Beaton et al.[22] Similarly, the incidence of BAV in interrupted aortic arch was also very high (36%), with 75% of patients having RL cusp fusion.

4.2 | Shunt lesions

BAV was present in 3.8% of all patients with VSD, and only 2% of patients with ASD and PDA. When looking only at patients with BAV and coexisting isolated VSD or PDA (in absence of other CHD findings such as CoA), RN cusp fusion emerged as the predominant morphology. We also found that sinus of Valsalva diameter in patients with VSD and BAV was significantly larger than patients with isolated BAV from the age of 18 years and onwards. In the literature, aneurysm of the sinus of Valsalva has been reported in 3 patients with BAV and VSD.[23–25]

4.3 | Right-sided obstructive lesions

Patients with right sided obstructive lesions such as TOF and PA had a very low incidence of BAV. However, RN and LN cusp fusion were uniquely associated with these lesions. To further analyze this finding, we selectively identified all the patients with BAV and TOF or PA, regardless of their age which provided further evidence for our initial

TABLE 2 Patients with bicuspid aortic valve and tetralogy of fallot

Morphology	AscAo (mm)	AscAo (z-score)	Ao Sinus (mm)	Ao Sinus (z-score)
LN	8	4.8	43	4.9
LN	35	4.2	33	2.5
RL	–	–	–	–
RL	24	0.4	38	4.7
RN	53	12.9	31	2.3
RL	33	4.2	34	3.3
RN	38	3.4	32	0.6
RL	37	2.2	40	1.9
RN	35	3.5	33	1.5
RN	38	3.7	48	5.5
RN	35	3.4	–	–

Abbreviations: AscAo, ascending aorta; Ao-sinus, sinus of Valsalva; F, female; LN, left-noncoronary fusion; M, male; RL, right-left fusion; RN, right-noncoronary fusion.
– represent data not available due to limited echo images.

observation. AscAo and sinus of Valsalva dilation were present in most of these patients. However, we are unable to speculate due to low numbers whether these patients are at any greater risk for aortic dilation related to both the conotruncal lesion and the BAV aortopathy.

5 | STUDY LIMITATIONS

Patients were obtained using the echocardiography database at Mayo Clinic, which is a large referral center. Patients were referred for echocardiography for many reasons, including physical findings, screening based on first degree relatives or symptoms. Thus, some referral bias is likely. Due to these potential biases, this study may not represent general population incidences.

TABLE 3 Patients with bicuspid aortic valve and pulmonary atresia

Morphology		AscAo (mm)	AscAo (z-score)	Ao Sinus (mm)	Ao Sinus (z-score)
RN	M	30	1.35	32	0.9
LN	M	–	–	43	5.82
LN	F	35	5.7	28	1.9
RN	M	20	1.9	23	2.6
RN	M	22	2.7	19	0.2
RN	M	21	3.4	17	0.3
RN	F	10	2.1	9	0.3

Abbreviations: AscAo, ascending aorta; Ao-sinus, sinus of Valsalva; F, female; LN, left-noncoronary fusion; M, male; RL, right-left fusion; RN, right-noncoronary fusion.
– represent data not available due to limited echo images.

6 | CONCLUSION

We conclude that the incidence and morphology of cusp fusion in BAV varies with different coexisting types of CHD. However, in childhood no significant difference in valvular dysfunction, left ventricular growth or aortic dilation was noted in patients with BAV and coexisting CHD compared with patients with isolated BAV. Aortic valve regurgitation and AscAo dilation is noted more commonly in patients with isolated BAV than those with BAV and CHD.

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CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTIONS

Data analysis/interpretation: Niaz, Poterucha, Hagler
Drafting article: Niaz
Statistics: Niaz
Data collection: Niaz, Craviari, Nienaber, Palfreeman
Concept/Design: Poterucha, Hagler
Critical revision of article: Poterucha, Johnson, Cetta, Hagler
Approval of article: Hagler

REFERENCES

[1] Michelena HI, Prakash SK, Della Corte A, et al. Bicuspid aortic valve: identifying knowledge gaps and rising to the challenge from the International Bicuspid Aortic Valve Consortium (BAVCon). *Circulation*. 2014;129(25):2691–2704.

[2] Della Corte A. Phenotypic heterogeneity of bicuspid aortopathy: a potential key to decode the prognosis?. *Heart*. [Editorial]. 2014;100(2):96–97.

[3] Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. *N Engl J Med*. [Review]. 2014;370(20):1920–1929.

[4] Holmes KW, Lehmann CU, Dalal D, et al. Progressive dilation of the ascending aorta in children with isolated bicuspid aortic valve. *Am J Cardiol*. 2007;99(7):978–983.

[5] Girdauskas E, Disha K, Borger MA, Kuntze T. Relation of bicuspid aortic valve morphology to the dilatation pattern of the proximal aorta: focus on the transvalvular flow. *Cardiol Res Pract*. 2012;2012:478259.

[6] Pees C, Michel-Behnke I. Morphology of the bicuspid aortic valve and elasticity of the adjacent aorta in children. *Am J Cardiol*. [Comparative Study]. 2012;110(9):1354–1360.

[7] Jackson V, Petrini J, Caidahl K, et al. Bicuspid aortic valve leaflet morphology in relation to aortic root morphology: a study of 300 patients undergoing open-heart surgery. *Eur J Cardiothorac Surg*. 2011;3:e118–e124.

[8] Fernandez B, Duran AC, Fernandez MC, Arque JM, Such M, Sans-Coma V. Genetic contribution of bicuspid aortic valve morphology. *Am J Med Genet a*. 2011;155A(11):2897–2898.

[9] Alegret JM, Masana L, Martinez-Micaelo N, Heras M, Beltran-Debon R. LDL cholesterol and apolipoprotein B are associated with

ascending aortic dilatation in bicuspid aortic valve patients. *QJM*. 2015;108:795–801.

[10] Ikonomidis JS, Ruddy JM, Benton SM, Jr, et al. Aortic dilatation with bicuspid aortic valves: cusp fusion correlates to matrix metalloproteinases and inhibitors. *Ann Thorac Surg*. 2012;93(2):457–463.

[11] Keshavarz-Motamed Z, Garcia J, Kadem L. Fluid dynamics of coarctation of the aorta and effect of bicuspid aortic valve. *PLoS ONE*. 2013;8(8):e72394.

[12] Folger GM, Jr, Stein PD. Bicuspid aortic valve morphology when associated with coarctation of the aorta. *Cathet Cardiovasc Diagn*. 1984;10(1):17–25.

[13] Gelb BD, Zhang J, Sommer RJ, Wasserman JM, Reitman MJ, Willner JP. Familial patent ductus arteriosus and bicuspid aortic valve with hand anomalies: a novel heart-hand syndrome. *Am J Med Genet*. 1999;87(2):175–179.

[14] Quintero-Rivera F, Xi QJ, Keppler-Noreuil KM, et al. MATR3 disruption in human and mouse associated with bicuspid aortic valve, aortic coarctation and patent ductus arteriosus. *Hum Mol Genet*. 2015; 24:2375–2389.

[15] Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg*. 2007;133(5):1226–1233.

[16] Fernandes SM, Sanders SP, Khairy P, et al. Morphology of bicuspid aortic valve in children and adolescents. *J Am Coll Cardiol*. 2004;44 (8):1648–1651.

[17] Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr*. 2010;23(5):465–495.

[18] Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. *J Am Soc Echocardiogr*. 2008;21(8):922–934.

[19] Colan SD. Structural measurements and adjustment for growth. In: Lai WW, Mertens LL, Geva T, Cohen MS, eds. Echocardiography in Pediatric and Congenital Heart Disease. West Sussex: Wiley-Blackwell; 2009:765–785.

[20] Basso C, Boschello M, Perrone C, et al. An echocardiographic survey of primary school children for bicuspid aortic valve. *Am J Cardiol*. 2004;93(5):661–663.

[21] Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol*. 2010;55(25):2789–2800.

[22] Beaton AZ, Nguyen T, Lai WW, et al. Relation of coarctation of the aorta to the occurrence of ascending aortic dilation in children and young adults with bicuspid aortic valves. *Am J Cardiol*. 2009;103(2): 266–270.

[23] Lee SH, Kim JB, Park NH, Kim HS, Keum DY. Asymptomatic ruptured sinus of valsalva aneurysm combined with perimembranous ventricular septal defect, and bicuspid aortic valve in adult patient. *Thorac Cardiovasc Surg*. 2013;61(4):327–329.

[24] Anastassiades CP, Chee CE, Petsas AA. Infundibular ventricular septal defect, aneurysm of the sinus of Valsalva, and bicuspid aortic valve in a caucasian male. *J Am Soc Echocardiogr*. 2005;18(3): 268–271.

[25] Taguchi K, Kai T, Ogawa S, et al. Ruptured aneurysm of the sinus of Valsalva into the right ventricle combined with double coarctation of the aorta, bicuspid aortic valve and ventricular septal defect. *Kyobu Geka*. 1962;15:111–122.

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