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ORIGINAL ARTICLE

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A Report From the MIBAVA Consortium

See Editorial by Simpson

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BACKGROUND: Bicuspid aortic valve (BAV) is the most prevalent congenital heart defect affecting 1% to 2% of the population. It is associated with ascending aorta dilatation. Valve morphology, aortic stenosis (AS), and aortic insufficiency (AI) have been proposed as potential risk factors; however, evaluating their role is difficult, as these factors are inherently related. The aim of this study was to determine whether BAV morphology and dysfunction are independent determinants for ascending aorta dilatation in pediatric patients.

METHODS: A multicenter, retrospective, cross-sectional study of pediatric BAV patients followed since 2004 was performed. Imaging data were assessed for BAV morphology, severity of AS and AI, history of coarctation, and aortic dimensions. Associations were determined using multivariable regression analysis. A subset of patients undergoing aortic interventions (balloon dilation or Ross) were assessed longitudinally.

RESULTS: Data were obtained from 2122 patients (68% male; median age 10.2 years). Fifty percent of patients had ascending aorta dilatation. Right and noncoronary cusp fusion, increasing AS and AI, and older age were independently associated with ascending aorta dilatation. A history of coarctation was associated with less ascending aorta dilatation. In patients with neither AS nor AI, 37% had ascending aorta dilatation (4% severe). No complications related to aortic dilatation occurred in this cohort. Aortic *Z* scores were determined, and a *Z*-score calculator was created for this population.

CONCLUSIONS: In this large pediatric cohort of patients with BAV, valve morphology, AS, and AI are independently associated with ascending aorta dilatation, suggesting that hemodynamic factors influence aortopathy. However, even in BAVs with no AS or AI, there is significant ascending aorta dilatation independent of valve morphology. Interventions that led to changes in degree of AI and AS did not seem to influence change in aortic dimensions. The current BAV cohort can be used as a reference group for expected changes in aortic dimensions during childhood.

Key Words: bicuspid aortic valve ■ dilatation ■ hemodynamics ■ phenotype ■ risk factors

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CLINICAL PERSPECTIVE

Bicuspid aortic valve is known to be associated with aortic valve dysfunction and ascending aorta dilatation. Although patients with bicuspid aortic valve are known to have an increased risk for aortic dissection, the precise mechanism and risk factors for this complication are not entirely clear. Thus, the implications of aortic dilatation, especially in younger patients with bicuspid aortic valve are not known. This article describes an association between aortic valve dysfunction (both stenosis and insufficiency) with ascending aorta dilatation. Although no causal relationships could be confirmed, this association will provide important information to young patients that may be at higher risk of progressive aortic dilatation depending on their valve function. The *Z* scores that were generated and *Z*-score calculator that was created will help practitioners determine the relative severity of aortic dilatation in their specific patients. Given the lack of aortic complications in this cohort, no strict cutoffs for surgical intervention can be recommended; however, providing a benchmark to compare patients against will remain helpful given the known association between aortic dilatation severity and dissection. Moreover, dedicated *Z* scores for patients with bicuspid aortic valve are more likely to pick up extreme phenotypes and outliers compared with existing *Z* scores for the general population.

Bicuspid aortic valve (BAV) is the most common congenital heart defect with a prevalence of ≈1.4%.[1,2] It is commonly associated with aortic valve dysfunction and coarctation of the aorta (CoA) and has been linked to ascending aorta dilatation.[3] Less commonly, BAV has been linked to dilatation of the more proximal aortic sinuses. Patients with BAV are at increased risk of complications due to ascending aorta dilatation including aortic dissection.[4]

The cause of ascending aorta dilatation in pediatric patients with BAV is not clear and may involve valve characteristics (morphology and dysfunction),[5] inherent abnormalities in the arterial vascular structure,[6] abnormal flow dynamics,[7] and genetic variations.[8] Evaluating the role of valve characteristics as potential risk factors for ascending aorta dilatation has been difficult, as BAV morphology and function are inherently related.[5,9,10] While some of these factors have been studied in adults with BAV, less information is available in the pediatric population.[11] Ascending aorta dilatation progresses with age and younger patients with significant dilatation can thus be considered as a more severe presentation of the same disease. Predisposing factors contributing to ascending aorta dilatation may also be different in this younger group.

In adults, both genetic and hemodynamic factors have been described to contribute to BAV aortopathy, with different factors contributing to different patterns of aortic dilatation.[2] In pediatric patients, the hemodynamic factors mainly relate to valve morphology and valve dysfunction, as additional comorbidities such as hypertension are less relevant. The primary objective of the current study was to determine whether BAV morphology, valve function, and a history of CoA are independently related to ascending aorta dilatation in a large cohort of pediatric patients. Our secondary objectives were to determine whether these factors are independently related to aortic sinus dilatation, to determine the relationships between valve morphology, valve function and the presence of CoA, and to determine the influence of aortic valve interventions (balloon dilation and Ross procedure) on the progression of aortic dilatation over time. We also sought to generate aortic nomograms for patients with BAV that can be used as a reference for patient follow-up. We hypothesized that aortic valve morphology (specifically right and noncoronary cusp [R-N] fusion) and valve dysfunction (both aortic stenosis [AS] and insufficiency) would be associated with ascending aorta dilatation and that a history of CoA would be associated with decreased ascending aorta dilatation.

METHODS

Study Design

The MIBAVA (Mechanistic Interrogation of BAV-associated Aortopathy) Leducq consortium is an international research collaborative with the goal of determining the cause of ascending aorta dilatation in patients with BAV. Within this consortium, we created a registry of patients with BAV followed at the participating centers. This registry was used to conduct a multicenter, retrospective, cross-sectional study of all pediatric patients followed with BAV at the Mechanistic Interrogation of BAV-associated Aortopathy centers, further expanded to include patients followed at the Ann & Robert H. Lurie Children's Hospital, Chicago, IL. Children 0 to 17.9 years of age diagnosed with BAV who underwent at least one echocardiogram between July 1, 2004, and January 31, 2016, were included. Exclusion criteria for registry inclusion were (1) BAV associated with interrupted aortic arch or complex congenital heart disease requiring single ventricle palliation and (2) patients with BAV who underwent aortic valve replacement or aortic root/ascending aorta repair or replacement before the first available echocardiogram. Exclusion criteria for detailed analysis and *Z*-score creation also included patients with known genetic syndromes, those with associated congenital heart disease requiring surgery (with the exception of coarctation), and those with significant congenital heart disease affecting the left heart (mitral valve disease, sub-AS). A subset of patients who underwent

aortic valve intervention (balloon dilation or Ross procedure) at a single center (Hospital for Sick Children) were analyzed longitudinally for changes in aortic dimensions over time. Patients were included in longitudinal analysis if they underwent aortic valve balloon dilation or Ross procedure and had at least 3 echocardiograms available for analysis post-procedure. Mean duration of follow-up for patients in both groups was 4.7±2.8 years.

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study was approved by the institutional review committees of each participating institution. No informed consent was required.

Measurements

Investigators at each center analyzed echocardiograms to determine BAV morphology, aortic dimensions (annulus, sinus, sinotubular junction, and ascending aorta), and the presence and severity of AS, AI, and CoA. Echocardiograms before any aortic valve intervention were used to determine valve morphology. Aortic dimensions and *Z* scores were determined from the last echocardiogram before any aortic valve or root intervention. A subset of patients (n=119) was included that underwent surgical aortic valve repair (but not replacement) or balloon dilation before 2004. In these patients, the last echocardiogram before any additional intervention was analyzed. In patients undergoing longitudinal analysis, every echocardiogram post-balloon dilation or Ross procedure was analyzed. No further analysis was performed after a patient underwent a subsequent aortic valve replacement or aortic root repair.

Valve morphology was classified according to presumed leaflet fusion: right and left coronary cusp (R-L) fusion, R-N fusion, or left and noncoronary cusp fusion (Figure 1A). If the valve was unicuspid or the morphology was unclear, it was excluded from further analysis.

Measurements of the maximal (mid-systolic) aortic dimensions were acquired from the parasternal long-axis view at the level of the valve annulus, aortic sinuses, sinotubular junction, and ascending aorta at the level of the right pulmonary artery (Figure 1B). Measurements were converted into *Z*-scores based on the hospital for sick children *Z*-scores (Table I in the Data Supplement). One of the study sites (site 2) used the leading-edge technique, while all other sites used the inner-edge technique. Due to this discrepancy, 50 patient echocardiograms from site 2 were randomly chosen to have their measurements repeated using the inner-edge technique. Using Bland-Altman analysis, there were no significant differences between measurement techniques (*P* value 0.48 for the aortic sinus and 0.58 for the ascending aorta), and there was minimal bias (Figure I in the Data Supplement), thus, the entire cohort was included for analysis. *Z* scores are standard in pediatric echocardiographic interpretation given the significant differences in patient size. Aortic dilatation was defined as a *Z* score ≥2, while significant dilatation was defined as a *Z* score ≥4. The specific pattern of dilatation was described according to involvement of both the aortic sinuses and ascending aorta (type 1), ascending aorta alone (type 2), or aortic sinuses alone (type 3).[2] Severity of AS was quantified from the highest reported mean instantaneous pressure gradient obtained using continuous wave Doppler. Gradients were stratified according to severity based on previously published guidelines (none <10 mm Hg; mild, 10–25 mm Hg; moderate, 25–40 mm Hg; and severe, >40 mm Hg).[12] AI severity was determined from the echocardiography report, with readers quantifying AI severity based on previously published guidelines.[13] The presence of CoA on echocardiogram was determined from the echocardiography report, based on isthmus dimension, peak instantaneous gradient across the isthmus and the abdominal aorta Doppler flow pattern.

Clinical Profile

Patient charts were reviewed to determine the cardiac history including associated congenital heart disease, prior surgical or interventional procedures, complications, and the presence of genetic syndromes known to affect the aorta.

Statistics

Continuous variables were reported as mean and SD except for age, which was not normally distributed and was reported as median and interquartile range. Dichotomous and polytomous variables were summarized using frequencies. Between-group differences in continuous variables were assessed using 1-way ANOVA with F tests or Wilcoxon rank-sum tests. Between-group differences in categorical variables were assessed using Fisher exact tests. Outcome variables (aortic sinus, sinotubular junction, and ascending aorta *Z* scores) were assessed both as continuous variables and as

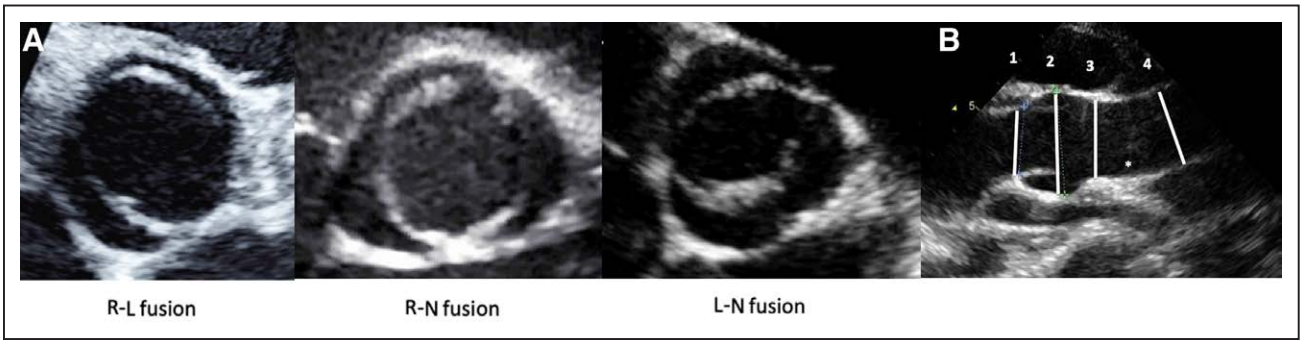

Figure 1. Bicuspid aortic valve (BAV) morphology and aortic measurements.
A, BAV fusion patterns. **B**, Measurement locations of the aortic sinuses and ascending aorta. 1, aortic annulus; 2, aortic sinus; 3, sinotubular junction; and 4, ascending aorta. A separate high parasternal view was often used to visualize the ascending aorta. L-N indicates left and noncoronary cusp; R-L, right and left coronary cusp; and R-N, right and noncoronary cusp. *Right pulmonary artery.

dichotomous variables using +2 and +4 as the threshold values (ie, dilated *Z* score >2 or dilated *Z* score >4 versus nondilated *Z* score <2).

Multivariable linear regression was applied to quantify the adjusted associations of independent variables, including BAV morphology, severity of AS and insufficiency, a history of CoA, and age, with each *Z*-score outcome variable. Both 95% CIs and *P* values were evaluated based on *t* statistics.

Next, we developed *Z*-score models using the LMS method (Lambda, Mu, Sigma)[14] for the maximal aortic valve annulus, sinus of Valsalva, and ascending aorta dimensions in relation to body surface area. For a given distribution, the LMS method assesses and quantifies the changes in a distribution by parametrizing the location (Median, mu), coefficient of variation (sigma), and skewness (lambda) using generalized additive models. The (possibly nonlinear) associations with the independent variable (ie, body surface area) were separately modeled and quantified for each of the parameters using cubic splines, which were estimated using a penalized likelihood method. Given the nonnegative nature of the dimensions, we considered 3 distributions, namely Box-Cox Cole and Green, Box-Cox power exponential,[15] and t-distributions[16] and selected the one with the optimal Akaike information criteria. To extend the applicability of this method, a web app was developed for BAV *Z*-score calculation (https://sickkidscvdmc.shinyapps.io/MIBAVA_normogram/).

For the longitudinal analysis, we separately analyzed the post-balloon and post-Ross longitudinal echo data in patients with moderate-to-severe versus no or mild aortic insufficiency. We used the independent estimating equation models to assess and quantify the association of aortic insuffciency with aortic annulus, aortic sinus, sinotubular junction, and ascending aorta dimensions. We assessed the time trend using natural cubic spline, but the nonlinear time trends were not significant for any of the outcome variables. Hence, we presented the results of the models with a linear trend. The standard errors were estimated using robust sandwich estimators.

Significance level of 5% was applied to all analyses. Data analysis was conducted using SAS v9.4 (SAS Statistical Software, Cary, NC) and R v3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Data were obtained from 2122 pediatric patients (0–17.9 years) followed at 5 institutions. Patient demographics and clinical characteristics are shown in Table 1. One hundred seventy-one patients were excluded due to the presence of genetic syndromes, and 388 patients were excluded due to the presence of significant congenital heart disease leaving a total of 1564 patients for cross-sectional analysis. For the longitudinal analysis, 309 echocardiograms from 53 patients were included in the balloon dilation group, and 116 echocardiograms from 21 patients were included in the Ross procedure group. Balloon dilation was performed at a median age of 0.6 years (range, 0–16.0 years), and Ross procedure was performed at a medium age of 10.6 years (range, 0.6–17.2 years). Of note, no complications related to aortic dilation occurred in this cohort.

Valve Morphology and Function

The most common BAV morphology was R-L fusion (65.7%) followed by R-N fusion (32.9%). There were no significant differences in the frequency of different valve morphology between males and females. One hundred forty-nine patients had indeterminate or unicuspid valve morphology and were excluded from further analysis. Overall, 308 (14.4%) patients had at least moderate AS and 122 (5.6%) had at least moderate AI. R-L fusion was associated with CoA, while R-N fusion was associated with AS and AI (Table II in the Data Supplement).

Aortic Sinus and Ascending Aorta Dilatation

Fifty percent of patients had aortic sinus or ascending aorta dilatation, or both with the majority having isolated ascending aorta dilatation. Nine percent of patients had significant aortic sinus or ascending aorta dilatation, or both (*Z* score ≥4; Table 1). There were no differences in the number of males and females with ascending aorta dilatation (48.9% versus 46.7%), but there were slightly more males with aortic sinus dilatation compared with females (12.4% versus 7.7%, *P*=0.001). There were no differences in *Z* scores when comparing site 2 to the other study sites.

In univariable analysis, R-L fusion was associated with a larger aortic sinus, while R-N fusion was associated with a larger ascending aorta (Table III in the Data Supplement). Increasing AS severity was associated with a smaller aortic sinus and a larger ascending aorta, while increasing AI severity was associated with a larger aortic sinus and ascending aorta (Table IV in the Data Supplement). A history of CoA was inversely associated with aortic sinus and ascending aorta dilatation (Table V in the Data Supplement). Valve morphology (R-N fusion), severity of AS, severity of AI, and absence of CoA were positively associated with type 1 or 2 dilatation, while valve morphology (R-L fusion) was positively associated with type 3 dilatation (Tables III through V in the Data Supplement).

Among the 496 patients with neither AS nor AI, the mean ascending aorta *Z* score was 1.6±1.3, with 36.5% of patients having ascending aorta dilatation and 3.6% having an ascending aorta *Z* score ≥4. There were no differences in the ascending aorta *Z* score based on valve morphology within this group (Figure 2; R-L fusion mean 1.51, R-N fusion mean 1.77, *P* value 0.17).

The results of the multivariable regression analysis for aortic sinus dimension are shown in Table 2 and

Table 1. Baseline Clinical Characteristics of the Study Population Were Summarized

	N	Mean (SD)
Age at echo, y (median, IQR)	2122	10.2 (3.9–15.2)
Sex	2122	
Male		1445 (68.1%)
Female		677 (31.9%)
Medical history		
Known cardiac genetic disorder	2122	171 (8.1%)
Turner		48
Marfan		7
Loeys Dietz/Ehlers Danlos		2
Other		114
Aortic valve fusion type	1974*	
R-L		1294 (65.6%)
R-N		652 (33.0%)
L-N		28 (1.4%)
History of AS	2113	
Any AS		743 (35.2%)
Mild		375 (17.7%)
Moderate		141 (6.7%)
Severe		222 (10.5%)
History of AI	2113	
Any AI		1129 (53.4%)
Mild		965 (45.7%)
Moderate		112 (5.3%)
Severe		51 (2.4%)
Aortic dilatation (*Z* score >2.0)		
Any dilatation	2122	1058 (49.9%)
Aortic sinus	2107	229 (10.9%)
Sinotubular junction	1278	125 (9.8%)
Ascending aorta	2081	998 (48%)
Severe aortic dilatation (*Z* score >4.0)		
Any dilatation	2122	194 (9.1%)
Aortic sinus	2107	18 (0.9%)
Sinotubular junction	1278	9 (0.7%)
Ascending aorta	2081	184 (8.8%)
Aortic dilatation type	2074	
Type 1		172 (8.1%)
Type 2		822 (38.9%)
Type 3		53 (2.5%)
Associated cardiac disease	2122	
Any cardiac disease		757 (35.7%)
Coarctation of aorta		544 (25.6%)
Sub-aortic stenosis		58 (2.7%)
Atrial septal defect		207 (9.8%)
Ventricular septal defect		239 (11.2%)
Mitral valve disease		142 (6.7%)
Other		85 (4.0%)

AI indicates aortic insufficiency; AS, aortic stenosis; IQR, interquartile range; L-N, left and noncoronary cusp fusion; R-L, right and left coronary cusp fusion; R-N, right and noncoronary cusp fusion; Type 1, aortic sinus and ascending aorta dilatation; Type 2, isolated ascending aorta dilatation; and Type 3 isolated aortic sinus dilatation.

*One hundred forty-eight patients had unknown, indeterminate, or possibly unicuspid valve morphology.

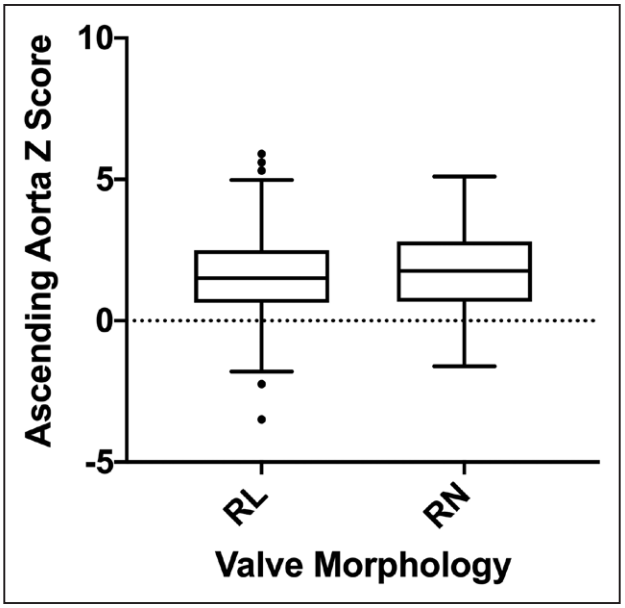

Figure 2. Ascending aorta Z score in patients with no aortic stenosis (AS) or aortic insufficiency (AI).
R-L indicates right and left coronary cusp fusion; and R-N, right and noncoronary cusp fusion.

Figure II in the Data Supplement. Similar to univariable analysis, valve morphology (R-L fusion) and severity of AI were independently associated with aortic sinus dilatation. Severity of AS and a history of CoA were each inversely associated with aortic sinus dimension.

The results of the multivariable regression analysis for ascending aorta dimension are shown in Table 2 and Figure III in the Data Supplement. Similar to univariable analysis, valve morphology (R-N fusion), AI, and AS were independently associated with ascending aorta dilatation. A history of CoA was inversely associated with ascending aorta dimension. The severity of ascending aorta dilatation increased with age.

The dimension of the sinotubular junction correlated with the dimension of the aortic sinus, while there was less correlation between the dimension of the sinotubular junction and ascending aorta (Figure IV in the Data Supplement). The relationship between BAV morphology and valve function with sinotubular junction dimension was similar to that of the aortic sinus (data not shown).

The results of the longitudinal analysis following balloon dilation are shown in Table 3. Independent of AI severity, there was no significant progression in the aortic valve annulus, sinus of Valsalva, sinotubular junction, or ascending aorta *Z* scores over time. Patients with moderate-to-severe AI were more likely to have a larger aortic annulus, aortic sinus, and sinotubular junction. The results of the longitudinal analysis following Ross procedure are shown in Figure 3. In the first 5 years following the Ross procedure, there was a mild increase in aortic annulus and sinotubular junction *Z* scores (P=0.008 and P<0.001, respectively). The aortic sinus and ascending aorta *Z* scores remained stable

Table 2. Multivariable Linear Regression Analysis for Aortic Sinus and Ascending Aorta Dilatation

	Aortic Sinus* Coef (95% CI)	*P* Value	Ascending Aorta* Coef (95% CI)	*P* Value
BAV fusion type (ref: R-L)				
R-N	−0.446 (−0.589 to −0.303)	<0.001	0.174 (0.019 to 0.329)	0.028
L-N	−0.090 (−0.671 to 0.490)	0.76	0.123 (−0.488 to 0.733)	0.69
AS severity (ref: no AS)				
Mild	−0.547 (−0.780 to −0.314)	<0.001	0.280 (0.027 to 0.532)	0.030
Moderate	−0.493 (−0.802 to −0.184)	0.002	0.758 (0.422 to 1.094)	<0.001
Severe	−0.702 (−0.957 to −0.447)	<0.001	0.862 (0.585 to 1.138)	<0.001
AI severity (ref: no AI)				
Mild	0.260 (0.091 to 0.430)	0.003	0.121 (−0.062 to 0.304)	0.194
Moderate	1.080 (0.680 to 1.479)	<0.001	0.837 (0.406 to 1.268)	<0.001
Severe	1.921 (1.480 to 2.363)	<0.001	0.934 (0.449 to 1.418)	<0.001
Coarctation	−0.262 (−0.429 to −0.095)	0.002	−0.751 (−0.932 to −0.569)	<0.001
Age, y	0.032 (0.020 to 0.043)	<0.001	0.018 (0.006 to 0.031)	0.004

AI indicates aortic insufficiency; AS, aortic stenosis; BAV, bicuspid aortic valve; L-N, left and noncoronary cusp fusion; R-L, right and left coronary cusp fusion; and R-N, right and noncoronary cusp fusion.

*Analyses are based on *Z* scores.

(Figure 3A through 3D). Patients post-balloon dilation and post-Ross procedure had similar rates of change in absolute aortic dimensions and aortic *Z* scores.

Nomograms for the aortic valve annulus, sinus of Valsalva, and ascending aorta dimensions versus body surface area are shown in Figure 4. The parameter functions were estimated nonparametrically, thus there is no simple equation to calculate aortic *Z* scores. We have developed a web application which will allow the user to calculate the *Z* score based on the patient's height, weight, and aortic dimension (https://sickkidscvdmc.shinyapps.io/MIBAVA_normogram/).

DISCUSSION

In this study, we examined the relationship between BAV morphology, valve function, and CoA with ascending aorta and aortic sinus dimensions in a large cohort of pediatric patients. We found a high incidence of ascending aorta dilatation with about 50% of all patients having ascending aorta *Z* scores ≥2 and 9% having ascending aorta *Z* scores ≥4. AI and AS severity are independently associated with significant ascending aorta dilatation. AI severity is independently associated with aortic sinus dilatation, while AS severity is independently associated with a smaller aortic sinus. R-N fusion is associated with increased valve dysfunction (AI and AS) but also independently associated with ascending aorta dilatation. R-L fusion is associated with CoA and aortic sinus dilatation, while CoA is independently associated with less dilatation of the aortic sinus and ascending aorta. Patients with significant AI post-balloon dilation had more aortic dilatation at baseline; however, there was little progression over time and the rate of dilatation was similar to patients without significant AI post-balloon dilation. Patients post-Ross procedure had an initial period of progressive dilatation followed by stabilization of aortic *Z* scores.

There are 2 main hypotheses on the pathophysiology of BAV aortopathy. The first is that hemodynamic and rheological factors are responsible for progressive aortic dilatation. The concept of post-stenotic dilatation is based on the presence of elevated mechanical wall stress caused by an upstream flow disturbance. Several MRI flow studies have suggested that flow disturbances related to valve dysfunction but also valve morphology alone cause abnormal localized aortic wall stress resulting in eccentric aortic wall remodeling.[17–20] The second hypothesis suggests a genetic cause resulting in intrinsic aortic wall abnormalities, although identifying specific genes has proven challenging.[21,22] Obviously both hypotheses are not mutually exclusive as there may be interactions between genetic and hemodynamic factors. Moreover, patients with BAV may prove to be diverse with a subgroup of patients in whom genetic factors may be more important. From this perspective, it is interesting to study bicuspid aortopathy in a pediatric age group as it may help to better understand the different factors contributing to aortic dilatation.

A first interesting observation from our study was the independent association between valve morphology (R-N fusion) and ascending aorta dilatation. R-N fusion is known to be associated with valve dysfunction, with increased rates of AI and AS,[23] a finding confirmed in our pediatric cohort. Previous pediatric studies have failed to show any independent association between valve morphology and ascending aortic dilatation, with associations observed on univariable analysis likely secondary to the effect of valve morphology on valve dysfunction.[5,10] However, the smaller size of these studies may have limited their ability to detect subtle associations. Recent 4-dimensional MRI flow data suggest that even in the absence of AS, R-N fusion results in significant flow disturbance in the ascending aorta.[7] The independent association that we observed between R-N fusion and ascending aorta dilatation may be related to low-velocity flow disturbances. This requires further study in pediatric patients where comorbidities are less important.

Our data support that valve dysfunction is an important determinant of aortopathy in the pediatric popula-

Table 3. Independent Estimating Equation Models for Aortic Dimensions Following Balloon Dilation

Variable	Aortic Valve Annulus *Z* Score, Coef (95% CI)	*P* Value	Aortic Sinus *Z* Score, Coef (95% CI)	*P* Value	Sinotubular Junction *Z* Score, Coef (95% CI)	*P* Value	Ascending Aorta *Z* Score, Coef (95% CI)	*P* Value
Moderate or severe AI	2.172 (1.000 to 3.344)	<0.001	1.099 (0.167 to 2.030)	0.021	1.552 (0.398 to 2.707)	0.008	0.603 (–0.560 to 1.765)	0.31
Linear yearly progression	–0.033 (–0.096 to 0.030)	0.31	0.005 (–0.039 to 0.048)	0.82	0.051 (–0.068 to 0.171)	0.40	–0.006 (–0.127 to 0.115)	0.93
Interaction between AI	–0.050 (–0.186 to 0.085)	0.47	0.004 (–0.086 to 0.094)	0.93	–0.042 (–0.179 to 0.095)	0.55	0.030 (–0.135 to 0.195)	0.72

AI indicates aortic insufficiency.

tion. Previous pediatric studies have consistently shown a relationship between AI severity and ascending aorta dilatation.[5,9,10] However, there are conflicting results regarding the impact of AS, with most groups failing to show an independent relationship using multivariable analysis.[5,10] Our data confirm the relationship between AI and ascending aorta dilatation. We also found an independent relationship between AS and ascending aorta dilatation. AI and AS are often present together, making their individual assessment difficult. Our large

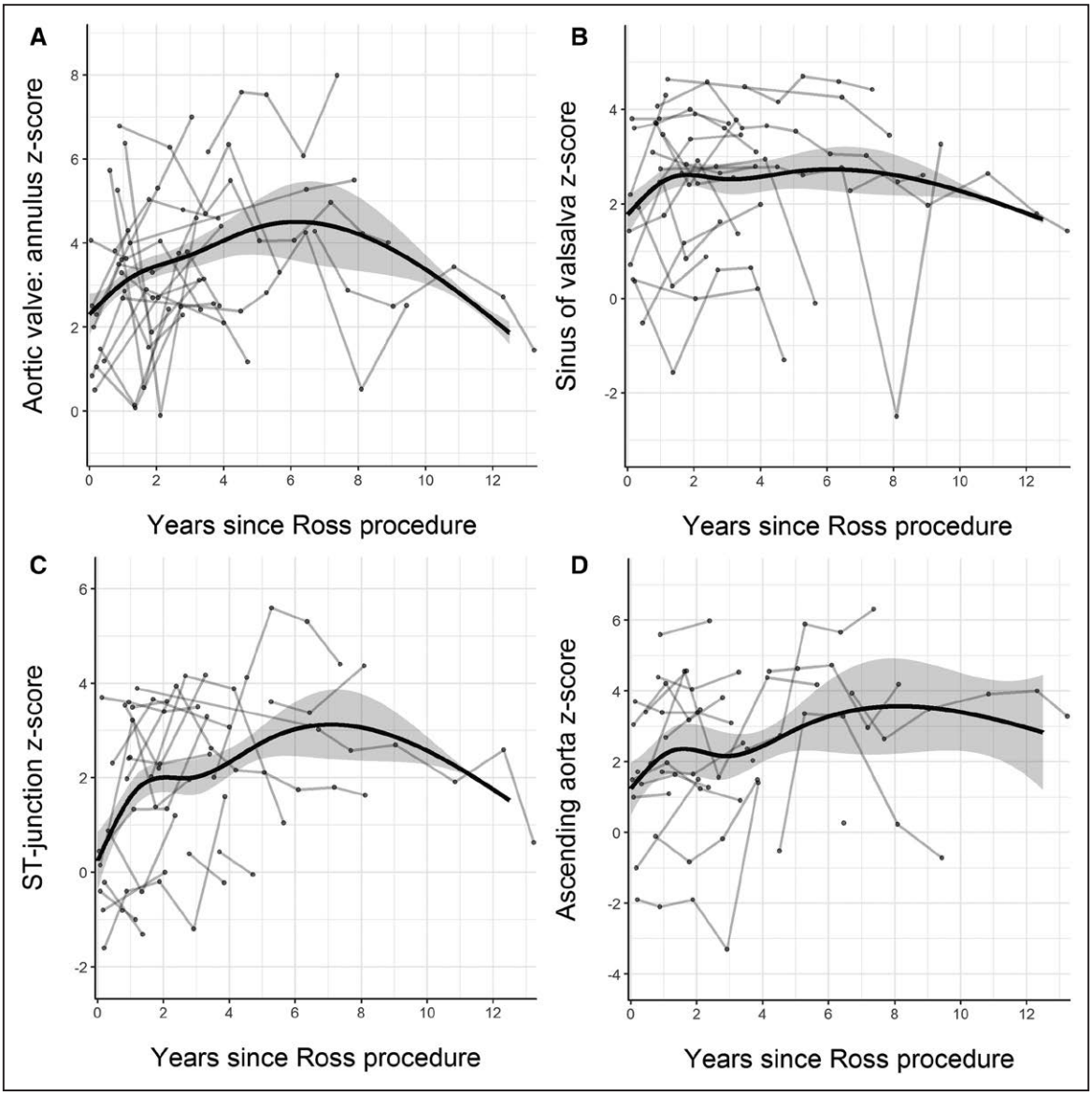

Figure 3. The progression of aortic Z scores over time in patients post-Ross procedure.
A, Aortic valve annulus *Z* score; **B**, sinus of Valsalva *Z* score; **C**, sinotubular (ST) junction *Z* score; and **D**, ascending aorta *Z* score. Thick line indicates independent equation estimate; shaded region, 95% CI; and thin dotted lines, individual patient-specific data.

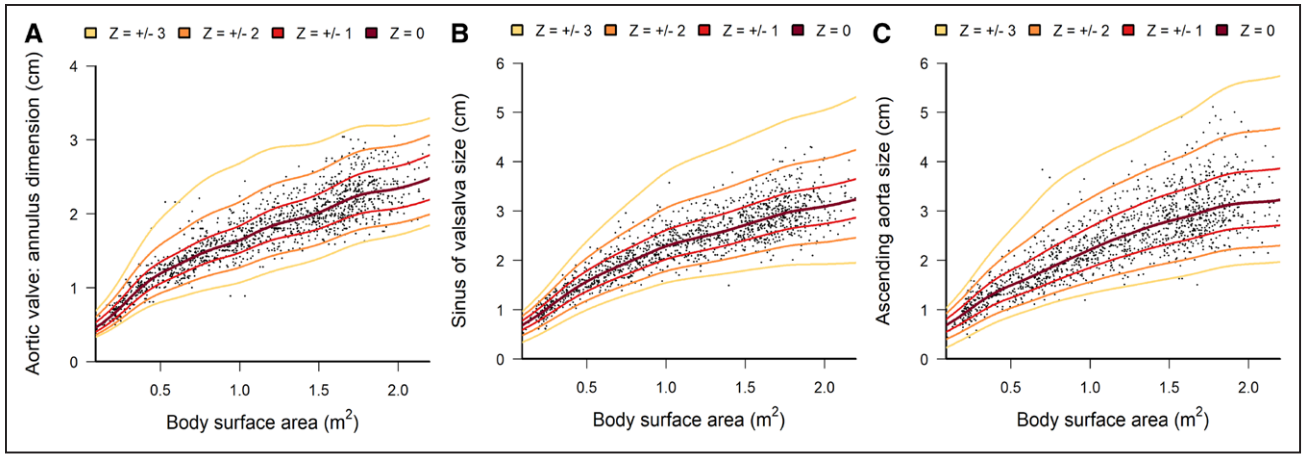

Figure 4. Nomograms showing the relationship between body surface area and aortic dimensions.
A, aortic valve annulus dimension; **B**, sinus of Valsalva dimension; and **C**, ascending aorta dimension, along with proposed *Z*-score distribution.

sample size may have allowed us to more accurately identify the independent associations of AS and AI with ascending aorta dimension.

Despite the association between valve dysfunction and aortopathy, we also demonstrated that children with normally functioning BAVs had increased mean ascending aorta *Z* scores, unrelated to valve morphology. Moreover, in patients post-aortic balloon dilation, there were no significant differences in the subsequent rate of aortic enlargement based on the presence of significant AI. These observations suggest that there is an underlying abnormality increasing the likelihood of ascending aorta dilatation that is further exacerbated by valve morphology and dysfunction. Studies in patients with normal BAV function suggest the presence of flow abnormalities in the ascending aorta in patients with aortic dilatation. These abnormalities may be related to inherent vascular dysfunction,[6] abnormal flow dynamics[7] or an underlying genetic predisposition,[8] and are subject to ongoing investigation.

The presence of CoA was associated with significantly less aortic sinus, sinotubular junction, and ascending aorta dilatation. The relationship between CoA and aortic dilatation in patients with BAV has not been well defined. Fernandes et.al[5] found a similar relationship with ascending aorta dimension but no relationship to aortic sinus dimension. R-L fusion is known to be associated with a higher incidence of CoA.[23] This fusion pattern is also independently associated with larger aortic sinus dimensions, possibly confounding prior investigations with smaller sample sizes. CoA is known to be associated with hypoplasia of the aortic arch and ascending aorta,[24] and recent studies suggest that even after early repair, precoarctation arteries are thicker and stiffer compared with controls.[25] Abnormalities in vascular function have been detected in neonates before surgery, suggesting the possibility of an underlying primary vasculopathy.[26] These differences may restrict vessel growth and aneurysm formation. Patients with BAV and CoA may represent a different disease population. The findings in children seem to contrast with 2 recent adult studies suggesting that CoA is a risk factor for ascending aortic complications in patients with BAV.[27,28] This requires further study but confounding factors may include residual arch obstruction and chronic hypertension.

BAV is also associated with aortic sinus dilatation, although at a much lower rate than ascending aorta dilatation. R-L fusion and AI severity are independently associated with aortic sinus dilatation, while AS severity is independently associated with a smaller aortic sinus dimension.[5,9,29] Our results show a similar relationship, although we suspect that the influence of BAV morphology on aortic sinus dimension may be overestimated. Standard echocardiographic measurements from the parasternal long-axis view do not visualize the entire sinus enface,[30] and the elliptical aortic sinus shape specifically observed with R-L fusion may lead to overestimation of the sinus dimension when standard measurement techniques are applied.[31] Regarding valve function, it remains unclear whether aortic sinus dilatation is secondary to AI or whether AI is secondary to a dilated aortic sinus.[5,32] Larger longitudinal studies with cross-sectional (CT or MR) imaging are needed to further examine this relationship.

The majority of patients exhibited type 2 dilatation, involving dilatation of the ascending aorta alone. In contrast, adults most commonly exhibit type 1 dilatation involving both the ascending aorta and aortic sinuses.[2] Type 1 dilatation has been found to be most common in older adults and in those with R-L fusion.[2] However, we found that both type 1 and type 2 dilatation were associated with R-N fusion. As discussed above, the influence of R-L fusion on aortic sinus dimension needs further clarification. The increased incidence of type 1 dilatation in adults may be secondary to abnormal aortic flow or a genetic predisposition that makes the aortic sinuses more susceptible to progressive dila-

tation over time.[33] There may be distinct differences in the cause of BAV-associated aortopathy in pediatric and adult patient populations.

The clinical significance of these findings is important regarding prediction of further dilatation and possible thresholds for valve and ascending aorta interventions. If flow disturbance is the main contributing factor to progressive aortopathy this may influence timing of valve interventions but may also necessitate surgical strategies that aim to normalize flow patterns in the aorta. The addition of aortic *Z* scores for patients with BAV may contribute to this decision-making process. Although no patients in our cohort had an aortic complication, these *Z* scores will help practitioners determine the relative significance of aortic dilatation in this complex population.

Limitations

This study has limitations. Patients were identified in tertiary care centers, leading to possible referral bias for more severe aortic valve disease, and a higher incidence of CoA. Although our large sample size allowed us to investigate progression of disease and we followed a subset of the population longitudinally, we did not follow all patients longitudinally to determine their specific rates of aortic growth. Aortic sinus measurements obtained as per published echocardiographic guidelines may underestimate or overestimate dimensions compared with cross-sectional imaging due to sinus asymmetry. Two different measurement techniques for the aortic dimensions were used. However, we did not observe that measurement technique significantly altered the measured aortic dimensions in a random subset of 50 patients. The classification of aortic regurgitation severity is not quantitative may be subjective, especially when multiple institutions are making measurements. Lastly, this study did not evaluate the specific mechanisms for ascending aortic dilatation in patients with and without valve dysfunction.

Conclusions

Patients with BAV have a high incidence of significant ascending aorta dilatation. More severe AI and AS are independently associated with ascending aorta dilatation, although even patients with normal valve function have increased ascending aorta *Z* scores. After controlling for valve dysfunction, R-N fusion remains independently associated with ascending aorta dilatation. The presence of CoA in patients with BAV is inversely associated with aortic sinus and ascending aorta dimensions. Following aortic valve balloon dilation aortic *Z* scores remain stable in patients with and without significant AI. Immediately after Ross procedure, aortic *Z* scores increase slightly but then stabilize within 5 years. We propose that pediatric patients with BAV have an underlying abnormality increasing their susceptibility to ascending aorta dilatation that is further exacerbated by valve dysfunction. Ongoing study is required to determine the precise mechanisms of ascending aorta dilatation in patients with and without valve dysfunction.

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