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ORIGINAL ARTICLE

Impact of Bicuspid Aortic Valve Morphology on Aortic Valve Disease and Aortic Dilation in Pediatric Patients

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Abstract

Bicuspid aortic valve (BAV) is the most common congenital heart defect. BAV is associated with aortic stenosis and insufficiency, and aortic dilation in adult groups, but data in pediatric groups are limited. We sought to assess the impact of BAV morphology on aortic valve disease and aortic dilation in pediatric patients. We performed a retrospective review of all echocardiograms in patients with isolated BAV who were followed at our institution from July 2002 to July 2012. BAV morphology, aortic valve stenosis and/or insufficiency, and aortic dimensions were measured manually. Comparisons were made between right–left cusp fusion (RL) and right–noncoronary cusp fusion (RN) BAV morphologies. Generalized least square models were fit to analyze the impact of specific variables on aortic dilation. There were 1075 echocardiograms in 366 patients (72% male) with isolated BAV. Aortic valve insufficiency and stenosis were more common in RN ($p < 0.001$ for both). The median aortic sinus Z score was higher in the RL (0.47; IQR −0.31 to 1.44) than in the RN group (0.02; −0.83 to 0.82) ($p < 0.001$). There was no difference in median ascending aorta Z score between groups. Patients with the highest weights had larger aortas ($p < 0.001$), but the absolute difference between the highest and lowest weight groups was small (1.5 mm). The impact of BAV morphology on aortic valve disease and aortic dilation in pediatric patients presages that seen in adults. Patient body weight does not make significant clinical impacts on aortic diameters, suggesting that Z scores for aortic diameters should be based on ideal body weights.

Keywords Bicuspid aortic valve · Aortic stenosis · Aortic insufficiency · Aortic dilation · Pediatrics · Weight

Introduction

Bicuspid aortic valve (BAV, OMIM#109730) is the most common congenital cardiac malformation, affecting 1–2% of the general population with a 2:1 male predominance [1]. While it may occur sporadically, recent literature increasingly supports a genetic basis. The prevalence of BAV in first-degree relatives has been demonstrated to be 9–12%, suggesting an autosomal dominant pattern of inheritance with incomplete penetrance [2, 3]. BAV is associated with multiple cardiac complications. Progressive development of aortic stenosis and/or insufficiency (AS/AI), which are the leading indications for aortic valve replacement, is common in patients with BAV [1, 4]. Aortic dilation and aneurysm have been reported in 20–84% of patients, predisposing them to aortic dissection [5–8]. Additionally, some investigators have demonstrated gradual left ventricular dysfunction associated with BAV [9, 10]. Limited data exist on BAV and the progression of aortic dilation in pediatric patients, and there are no guidelines for clinical management of BAV in this patient population [11–15]. Data regarding the degree of aortic dilation and progression, as well as valvulopathy, are limited in pediatric populations. Better understanding of the breadth of BAV and its associated complications in pediatric patients is necessary to develop risk stratification and provide more accurate, cost-effective care. Hence, we sought to determine the prevalence and essential components of the progression of valvulopathy, aortopathy, and left ventricular dysfunction in the pediatric population with isolated BAV

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to better guide clinical judgment and practice. Secondarily, we sought to assess the impact of body weight on aortic size in pediatric patients.

Methods

The University of Arkansas for Medical Sciences Institutional Review Board approved the retrospective study and waived the need for individual patient consent. The study period was from July 2002 to July 2012. Patients were identified using the Syngo Dynamics echocardiography database at Arkansas Children's Hospital. Demographic, anthropometric, and cardiac anatomy and function data were culled from the echocardiography reports. Echocardiograms were included in the study for all patients from birth up to and including 20 years of age with a diagnosis of isolated BAV. Patients with any other cardiac abnormalities, excluding a small patent foramen ovale, were excluded. All echocardiograms performed during the study period were performed in accordance with published guidelines for pediatric echocardiograms [16].

Study data were collected and entered into the Research Electronic Data Capture (REDCap) system hosted at UAMS [17]. Data collected directly from the echocardiogram reports included demographic and anthropometric data, blood pressure, and left ventricular dimensions and shortening fraction. All study echocardiograms were manually reviewed to determine BAV morphology. If the valve morphology was definitively determined on one echocardiogram for a given patient, and there were other studies wherein it could not be clearly determined, the morphology was assigned based on the echocardiogram with definitive images. If all available echocardiograms did not clearly demonstrate the valve morphology, the patient was excluded from the study. The presence and severity of aortic valve stenosis (AS) and/or insufficiency (AI) were determined and measured by a single reviewer (R.A.W.) in accordance with published guidelines [18, 19]. The severity of the aortic valve stenosis was based on the mean Doppler gradient (mild <25 mmHg; moderate 25–50 mmHg; severe ≥ 50 mmHg). Systolic measurements of the aortic sinus of Valsalva, sinotubular junction, and ascending aorta were made by a single reviewer (J.M.) from inner-edge to inner-edge using parasternal long-axis images in accordance with published pediatric recommendations [20]. *Z* scores for the aortic sinus of Valsalva and sinotubular junction were computed using the regression equations of Pettersen et al. [21], and those for the ascending aorta were computed using the equation published by Gautier et al. [22].

All data analyses were performed using SAS Version 9.4 (Cary, NC, USA) and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Summary statistics were expressed as mean ($\pm$ SD) or median with interquartile range, as appropriate, for continuous variables and count (%) for categorical variables. Comparisons between right–left coronary cusp fusion (RL) and right–noncoronary cusp fusion (RN) BAV morphology groups were made using Wilcoxon–Mann–Whitney for continuous variables and Pearson's Chi-square variables. Because left–noncoronary cusp fusion BAV morphology was exceedingly rare in the study cohort, those patients and echocardiograms were excluded from analysis. Descriptive age-based trends in aortic measurement *Z* scores were established using Lowess plots in those patients with at least 2 echocardiograms, with additional stratifications for BAV morphology, gender, body mass index (BMI), AS severity, and AI severity. Association between age and mean aortic measurement *Z* scores was analyzed using a generalized least squares model. Age was parameterized using a restricted cubic spline with 4 knots. A compound symmetry correlation structure was used to account for repeated measurements on a patient [23, 24]. A similar analysis was done to test for the association between the weight-for-age *Z* score on aortic *Z* scores. The distributions of weights within the study cohort were analyzed, and *Z* scores of weight-for-age were created based on the study cohort data. Those *Z* scores were then used to determine tertiles of weight-for-age for all patients, and the impact of weight-for-age on aortic dimensions was analyzed. We present estimated difference and 95% confidence intervals in mean aortic *Z* score measurements between different groups based on weight-for-age *Z* scores. All statistical tests carried out were two-sided and a p value <0.05 was considered to be statistically significant.

Results

There was a total of 1101 echocardiograms with isolated BAV, 26 of which with left–noncoronary cusp fusion (2.4% of echocardiograms) were excluded. The final study cohort included a total of 366 subjects (71.6% male) with isolated BAV who underwent a total of 1075 echocardiograms during the study period. The BAV morphology was RL in 228/366 (62.3%) patients, with RN occurring less commonly (138/366, 37.7%). Each patient underwent a median of 2 (IQR 1, 4) echocardiograms, with no difference between BAV morphology groups. Baseline patient demographic and clinical data are reported in Table 1. Demographic and clinical data from study echocardiograms are reported in Table 2.

Bicuspid aortic valve morphology had significant impacts on the aortic sinus and on the function of the aortic valve. For the entire cohort, the aortic sinus diameter remained stable across the age range. However, when subanalysis of BAV morphology was performed, the mean aortic sinus *Z* score was significantly higher in the RL group compared to

Table 1 Baseline demographic and clinical measurements at the time of first echocardiogram in patients with isolated bicuspid aortic valve

Variable	Number	Right–left ($N=228$)	Right–noncoronary ($N=138$)	Combined ($N=366$)	p value
Male	366	155 (69.7%)	103 (74.6%)	262 (71.6%)	0.31
Age (years)	366	6.2 (1.1, 13.0)	7.2 (1.7, 11.6)	6.6 (1.3, 12.6)	0.82
Body surface area (m^2)	356	0.87 (0.48, 1.49)	0.86 (0.49, 1.41)	0.87 (0.49, 1.47)	0.63
Body mass index (kg/m^2)	356	17 (14.9, 20.3)	17 (14.9, 20.3)	17 (14.9, 20.3)	0.82
Body mass index Z score	356	0.36 (−0.63, 1.13)	0.33 (−0.84, 1.41)	0.35 (−0.8, 1.2)	0.80
Body mass index group	356				0.39
< 25th percentile		55 (25.0%)	39 (28.7%)	94 (26.4%)	
25–75th percentile		80 (36.4%)	40 (29.4%)	120 (33.7%)	
> 75th percentile		85 (38.6%)	57 (41.9%)	142 (39.9%)	
Mass (kg)	362	22.8 (11, 48.6)	23.2 (11.6, 48)	22.8 (11.1, 48.5)	0.81
Weight-for-age Z score	362	0.21 (−1, 0.91)	0.12 (−0.92, 1.31)	0.17 (−0.97, 1.07)	0.51
Height (cm)	356	118 (81, 157)	118 (83, 149)	118 (81, 153)	0.51
Median number of echocardiograms	366	2 (1, 4)	2 (1, 4)	2 (1, 4)	0.16

Results are reported in either count with percentage or median with interquartile range

BMI percentiles were computed using WHO growth charts for patients aged 0–2 years and the CDC growth charts for patients 2 years and older

Right–left bicuspid aortic valve with fusion of the right and left coronary cusps, *Right–noncoronary* bicuspid aortic valve with fusion of the right and noncoronary cusps, m^2 square meters, *kg* kilograms, *cm* centimeters

the RN group ($p<0.001$), with a divergence between the two groups that began at 3 years of age (Fig. 1). Conversely, the RN group more commonly had AS ($p<0.001$) and AI ($p<0.001$) than the RL group.

Aortic dimension Z scores were affected by some factors such as valve morphology, but not by other factors. The aortic sinus and sinotubular junction Z scores were not affected by age. Similarly, none of the aortic Z scores were affected by gender or the presence or severity of AS or AI. Conversely, age and body size did affect the ascending aorta size (Fig. 2). The Z scores of the ascending aorta increased significantly with age. Additionally, the ascending aorta Z scores were higher in those with BMI < 25% than in those with BMI > 75%. However, when tertiles of weight-for-age were analyzed, the absolute aortic dimensions increased as weight-for-age increased. While the absolute diameters were higher in those in the highest tertile (weight-for-age Z score > 1.5), the absolute differences between the lowest tertile (weight-for-age Z score < −0.5) and the highest tertile were small (1.9 mm at 5-years-old, 2.1 mm at 10-years-old, and 2.1 mm at 15-years-old, $p<0.001$ for all) and of no meaningful clinical significance.

Surgical interventions were rare in the study cohort. Table 3 demonstrates the details of those patients who underwent surgical interventions. There were 4 patients who underwent 5 interventions. Two patients underwent interventions before 1.5 years of age, one of whom subsequently underwent a Ross procedure at 13.4 years. The remaining 2 patients underwent surgical intervention at 18.2 and 20.2 years.

Discussion

Mild dilation of the aortic sinus of Valsalva in the setting of BAV has been reported in a number of studies [25–27]. In most studies, dilation is considered to be present when the mean Z score in the BAV group is statistically greater than the expected Z score of 0. Therefore, while dilation may be statistically present in the cohort, it is not likely clinically present, which would be indicated by a Z score ≥ 2. In a smaller cohort, Spaziani et al. have previously reported dilation of the aortic sinus in 11% of pediatric patients with isolated BAV [14]. The present data in our study are in keeping with the findings of these aforementioned prior studies.

The degree of dilation of the aortic sinus was directly affected by BAV morphology. There was no evidence of aortic sinus dilation in those with RN fusion morphology. However, the median aortic sinus Z score in those with RL fusion morphology was significantly higher. This finding is in keeping with some studies in adult populations [28–30]. The definitive etiology of the greater degree of aortic dilation in RL fusion is uncertain at present. Some investigators have used 4-dimensional cardiac MRI to evaluate flow dynamics in patients with BAV and found differences in blood flow profiles between BAV morphologies [31, 32]. The differences in the blood flow profiles were associated with differences in aortic dilation. Other investigators have evaluated the biochemical profiles of matrix metalloproteinases and inhibitors in BAV and have shown that patients with RL have a biochemical profile that predisposes them to a more aggressive aortic dilation

Table 2 Demographic and clinical measurements for all echocardiograms in patients with isolated bicuspid aortic valve

Variable	Number	Right–left ($n=648$)	Right–noncoronary ($n=427$)	Combined ($n=1075$)	p value
Male	1075	425 (66%)	299 (70%)	724 (67%)	0.13
Age (years)	1075	9.1 (3.7, 14.1)	9.9 (4.1, 14.6)	9.5 (4, 14.3)	0.08
Body surface area (m^2)	1054	1.04 (0.65, 1.58)	1.17 (0.64, 1.64)	1.07 (0.65, 1.62)	0.17
Body mass index (kg/m^2)	1054	18 (15, 22)	18 (16, 23)	18 (16, 23)	0.22
Body mass index *Z* score	1054	0.44 (−0.65, 1.38)	0.44 (−0.71, 1.48)	0.44 (−0.66, 1.45)	0.81
Body mass index percentile group	1054				0.54
< 25%		154 (24%)	107 (25%)	261 (25%)	
25–75%		210 (33%)	127 (30%)	337 (32%)	
> 75%		267 (42%)	189 (45%)	456 (43%)	
Mass (kg)	1068	29 (16, 57)	34 (16, 60)	31 (16, 59)	0.1
Weight-for-age *Z* score	1068	0.30 (−1.01, 1.18)	0.24 (−0.90, 1.33)	0.27 (−0.97, 1.22)	0.34
Height (cm)	1054	132 (100, 162)	137 (98, 164)	133 (100, 162)	0.22
Systolic blood pressure (mmHg)	919	109 (97, 121)	109 (96, 120)	109 (96, 120)	0.54
Diastolic blood pressure (mmHg)	900	64 (57, 70)	63 (58, 69)	64 (57, 70)	0.78
Left ventricular end-diastolic dimension (cm)	949	4 (3.2, 4.6)	4 (3.4, 4.8)	4 (3.3, 4.7)	0.18
Left ventricular end-systolic dimension (cm)	949	2.5 (2, 2.9)	2.5 (2.1, 3)	2.5 (2, 3)	0.14
Left ventricular shortening fraction	949	37 (33, 41)	36 (33, 41)	37 (33, 41)	0.32
Aortic valve parameters					
Peak aortic valve gradient (mmHg)	1070	13.7 (8.4, 22)	17.1 (10.3, 28.2)	14.8 (9.2, 24.3)	*< 0.001*
Mean aortic valve gradient (mmHg)	1070	6.4 (4.1, 10.6)	8.3 (5, 14)	7 (4.4, 11.9)	*< 0.001*
Aortic stenosis	1070				*0.012*
Trivial/mild		631 (97.7%)	402 (94.8%)	1,033 (96.5%)	
Moderate		15 (2.3%)	22 (5.2%)	37 (3.5%)	
Aortic insufficiency	1070				*< 0.001*
None/trivial		437 (67.8%)	219 (51.5%)	656 (61.3%)	
Mild		149 (23.1%)	151 (35.5%)	300 (28.0%)	
Moderate/severe		59 (9.1%)	55 (12.9%)	114 (10.7%)	
Aortic parameters					
Aortic sinus diameter (cm)	1031	2.3 (1.8, 2.8)	2.2 (1.8, 2.6)	2.2 (1.8, 2.7)	0.14
Aortic sinus *Z* score	1010	0.47 (−0.31, 1.44)	0.02 (−0.83, 0.82)	0.29 (−0.55, 1.17)	*< 0.001*
Aortic sinotubular junction diameter (cm)	1023	1.9 (1.4, 2.3)	1.9 (1.5, 2.3)	1.9 (1.4, 2.3)	0.21
Aortic sinotubular junction *Z* score	1002	0.59 (−0.33, 1.31)	0.49 (−0.19, 1.28)	0.54 (−0.23, 1.3)	0.91
Ascending aorta diameter (cm)	1009	2.2 (1.6, 2.8)	2.3 (1.8, 2.8)	2.2 (1.7, 2.8)	0.099
Ascending aorta *Z* score	989	1.53 (0.43, 2.48)	1.44 (0.49, 2.79)	1.51 (0.45, 2.6)	0.34

Italics in the table highlight the comparisons that are statistically significantly different

Results are reported in either count with percentage or median with interquartile range

Right–left bicuspid aortic valve with fusion of the right and left coronary cusps, *Right–noncoronary* bicuspid aortic valve with fusion of the right and noncoronary cusps, m^2 square meters, *kg* kilograms, *cm* centimeters, *mmHg* millimeters of mercury

pattern [33]. Additionally, it has been shown that the development of different BAV morphologies results from different embryologic mechanisms [34], and this may well have implications for the development of aortic dilation. Compounding the complexity of the picture is the fact that there are cohorts with familial BAV and ascending aorta dilation with many family members having aortic dilation whether or not BAV is present, thus indicating an intrinsic abnormality in the aortic wall [35]. Ultimately, it is likely that the differences in aortic dilation seen between the different BAV morphologies arise from a complex interaction of factors.

Multiple investigators have reported dilation of the mid-ascending aorta in the setting of BAV [25, 26, 36]. Those studies, performed in smaller cohorts, showed progressive dilation of the ascending aorta throughout childhood. More recently, Niaz et al. have reported on a larger cohort of patients and showed that significant ascending aortic dilation is not present in isolated BAV prior to 3 years of age [37]. Moreover, in that study, the ascending aorta *Z* score

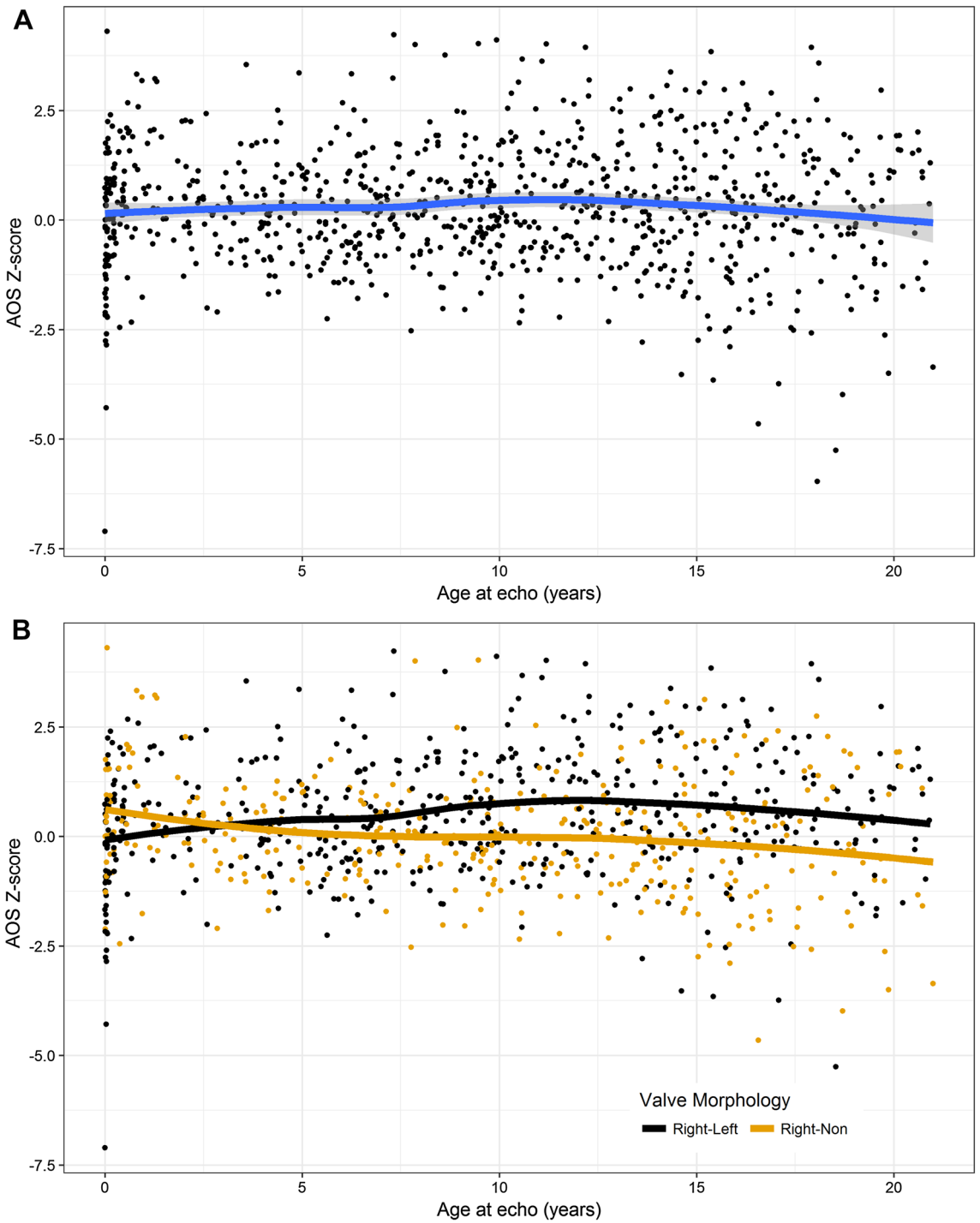

Fig. 1 Impact of age and bicuspid aortic valve morphology on aortic sinus (AOS) *Z* score. **a** A normal median AOS diameter *Z* score with no increase in *Z* score with increasing age. **b** The impact of aortic valve morphology on the mean AOS *Z* score, with larger diameters in the right–left group ($p < 0.001$). Right–left indicates bicuspid aortic valve with fusion of the right and left coronary cusps; right–non, bicuspid aortic valve with fusion of the right and noncoronary cusps

did not progress out to age 22 years. In the present study, while the mean ascending aorta *Z* score was > 0 across all age groups, indicating dilation, the *Z* score did not reach 2 until approximately 10 years of age, and remained there until age 16 when there was the beginning of a slight increase in the *Z* score out to age 21 years. These data indicate that concern regarding aortic dilation in BAV during childhood should be limited, as significant dilation is quite rare. This

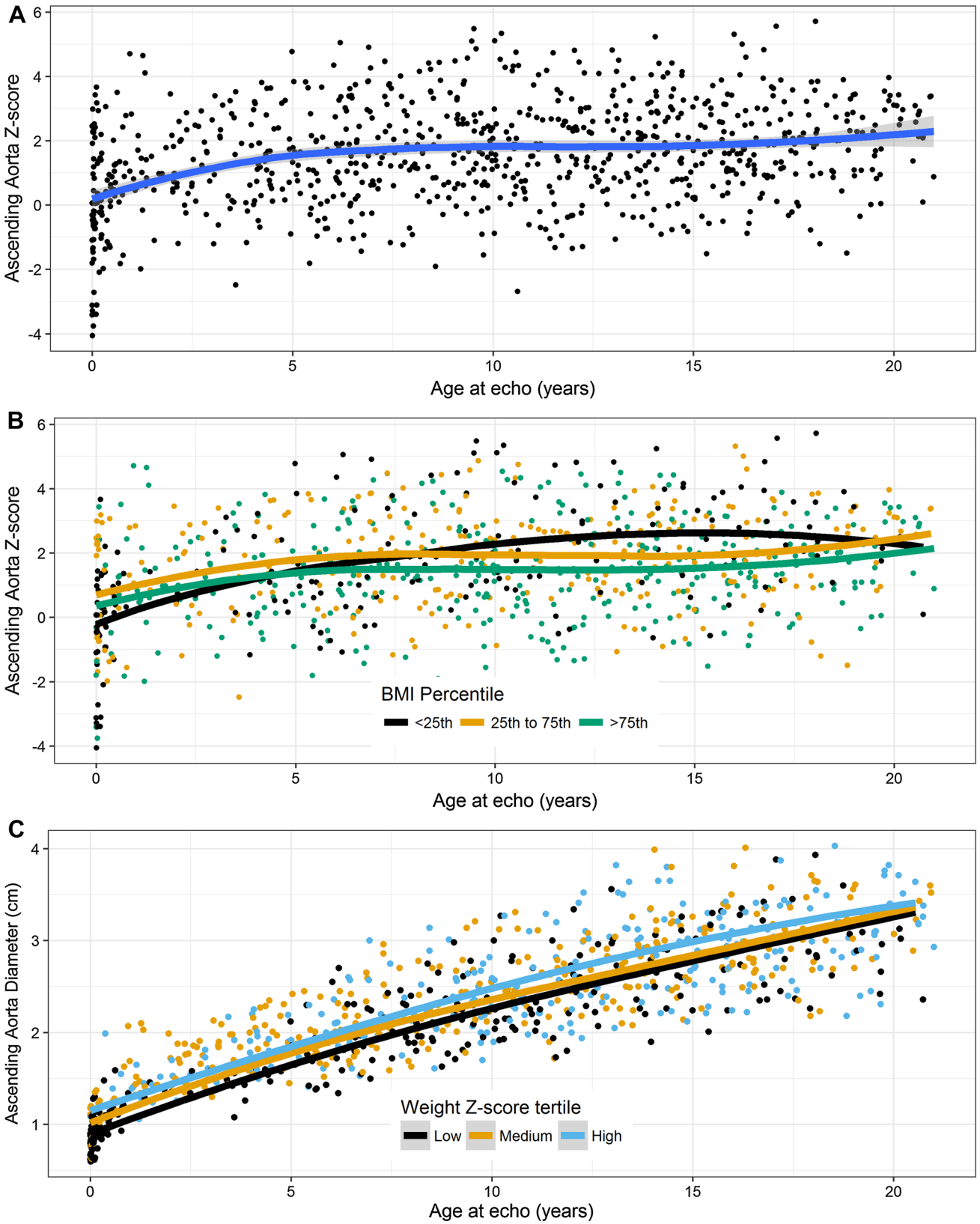

Fig. 2 Impact of age and body size on the ascending aorta in isolated bicuspid aortic valve. **a** An increase in the mean ascending aorta *Z* score during the first 8 years of life with a subsequent plateau in the ascending aorta *Z* score out to 21 years of age. **b** The impact of body mass index on the mean ascending aorta *Z* score, with those with lower body mass index having a higher ascending aorta *Z* score. **c** The ascending aorta is consistently larger across the entire age range in those with higher body weight-for-age *Z* scores. *Echo* echocardiogram, *BMI* body mass index

Table 3 Surgical interventions in isolated bicuspid aortic valve patients from birth to 21 years of age

Patient	Age (years)	Gender	Reason for intervention	Surgical intervention
Patient 1	0.45	Male	Hypoplastic ascending aorta	Patch enlargement of ascending aorta
Patient 2	1.32	Male	Aortic stenosis	Aortic valvuloplasty
	13.3		Aortic stenosis and insufficiency	Ross procedure
Patient 3	18.2	Female	Ascending aorta aneurysm	Ascending aorta plication
Patient 4	20.2	Male	Aortic stenosis and insufficiency	Mechanical aortic valve replacement

is consistent with the findings of Mahle et al. that ascending aorta intervention in pediatric patients with isolated BAV is exceedingly rare [13]. These findings suggest that aggressive follow-up of aortic dilation in pediatric patients with BAV may not be warranted, especially among those patients with RN fusion morphology.

The morphology of the aortic valve was associated with differences in aortic valve disease. Specifically, those patients with RN fusion morphology were found to have greater prevalence and worse degrees of both aortic valve stenosis and aortic insufficiency. Similarly, in a cohort of patients with congenital heart disease of various types, Fernandes et al. have previously shown that RN fusion morphology is associated with a greater degree of aortic valve disease [38]. Further, those investigators have also shown that progression of aortic valve disease is more aggressive in patients with RN fusion morphology [39]. These findings suggest that, in contradistinction to the follow-up of the ascending aorta, follow-up of aortic valve disease is more important in patients with RN fusion morphology.

In the present study, body weight had a minimal impact on the absolute diameter of the aorta. While patients who were obese were found to have lower *Z* scores for aortic dimensions, their absolute aortic dimensions were only minimally increased compared to the lowest weight-for-age *Z* score tertile group. This finding is of considerable significance given the methodology by which cardiac dimensions are determined to be either large or small in pediatric populations. Specifically, body surface area indexed *Z* scores are used to quantify the size of various cardiovascular structures [20]. As a result, when patients are obese, a given aortic diameter would be expected to have a lower *Z* score than if the same patient with the same aortic diameter were of normal weight. Conversely, this assumes that an obese patient will have an aortic diameter that is significantly greater than that of a normal weight patient. The present data indicate that while the true difference in aortic diameter is clinically insignificant, there is a much larger difference in aortic *Z* score. These findings suggest that when the patient weight is significantly different from ideal, the use of body weight-dependent *Z* scores is unsound, a finding in keeping with multiple prior, though dated, studies [40–44]. Our group has recently shown that an increase from an ideal body weight to an obese body weight can result in a decrease in the aortic *Z* score by nearly 1 standard deviation [45]. As a result of this error at extremes of weight, it is our institutional practice to use ideal body weight to determine the degree of aortic enlargement in those patients who are either over or underweight.

The study was retrospective in nature and is therefore subject to the limitations of such a design. The possibility of referral bias is present, as the study only included those patients who were referred for an echocardiogram. A blood pressure was not recorded with all echocardiograms, likely owing to patient incooperativity. The impact of missing blood pressure measurements on the findings of the study is likely to be negligible.

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Compliance with Ethical Standards

Conflict of interest The authors have no competing interests to disclose. All authors have approved the final version of the manuscript.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

Informed Consent As a result of the retrospective design of the study, the need for informed consent was waived by the Institutional Review Board.

References

1. Braverman AC, Güven H, Beardslee MA, Makan M, Kates AM, Moon MR (2005) The bicuspid aortic valve. Curr Probl Cardiol 30:470–522
2. Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW (2004) Bicuspid aortic valve is heritable. J Am Coll Cardiol 44:138–143
3. Huntington K, Hunter AG, Chan KL (1997) A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. J Am Coll Cardiol 30:1809–1812
4. Braverman AC (2011) Aortic involvement in patients with a bicuspid aortic valve. Heart 97:506–513
5. Verma S, Siu SC (2014) Aortic dilatation in patients with bicuspid aortic valve. N Engl J Med 370:1920–1929
6. Siu SC, Silversides CK (2010) Bicuspid aortic valve disease. J Am Coll Cardiol 55:2789–2800
7. Michelena HI, Khanna AD, Mahoney D, Margaryan E, Topilsky Y, Suri RM, Eidem B, Edwards WD, Sundt TM, Enriquez-Sarano

M (2011) Incidence of aortic complications in patients with bicuspid aortic valves. JAMA 306:1104–1112
8. Wojnarski CM, Svensson LG, Roselli EE, Idrees JJ, Lowry AM, Ehrlinger J, Pettersson GB, Gillinov AM, Johnston DR, Soltesz EG, Navia JL, Hammer DF, Griffin B, Thamilarasan M, Kalahasti V, Sabik JF, Blackstone EH, Lytle BW (2015) Aortic dissection in patients with bicuspid aortic valve-associated aneurysms. Ann Thorac Surg 100:1666–1673 (**discussion 1673**)
9. Tzemos N, Therrien J, Yip J, Thanassoulis G, Tremblay S, Jamorski MT, Webb GD, Siu SC (2008) Outcomes in adults with bicuspid aortic valves. JAMA 300:1317–1325
10. Grotenhuis HB, Ottenkamp J, Westenberg JJ, Bax JJ, Kroft LJ, de Roos A (2007) Reduced aortic elasticity and dilatation are associated with aortic regurgitation and left ventricular hypertrophy in nonstenotic bicuspid aortic valve patients. J Am Coll Cardiol 49:1660–1665
11. Svensson LG, Adams DH, Bonow RO, Kouchoukos NT, Miller DC, O'Gara PT, Shahian DM, Schaff HV, Akins CW, Bavaria JE, Blackstone EH, David TE, Desai ND, Dewey TM, D'Agostino RS, Gleason TG, Harrington KB, Kodali S, Kapadia S, Leon MB, Lima B, Lytle BW, Mack MJ, Reardon M, Reece TB, Reiss GR, Roselli EE, Smith CR, Thourani VH, Tuzcu EM, Webb J, Williams MR (2013) Aortic valve and ascending aorta guidelines for management and quality measures. Ann Thorac Surg 95:S1–S66
12. Bonow RO, Carabello BA, Kanu C, de Leon AC, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B (2006) ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation 114:e84–e231
13. Mahle WT, Sutherland JL, Frias PA (2010) Outcome of isolated bicuspid aortic valve in childhood. J Pediatr 157:445–449
14. Spaziani G, Ballo P, Favilli S, Fibbi V, Buonincontri L, Pollini I, Zuppiroli A, Chiappa E (2014) Clinical outcome, valve dysfunction, and progressive aortic dilation in a pediatric population with isolated bicuspid aortic valve. Pediatr Cardiol 35:803–809
15. Mart CR, McNerny BE (2013) Shape of the dilated aorta in children with bicuspid aortic valve. Ann Pediatr Cardiol 6:126–131
16. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, Pignatelli RH, Rychik J, Echocardiography TFOTP-COTASO, Echocardiography PCOTASO (2006) Guidelines and standards for performance of a pediatric echocardiogram: a report from the Task Force of the Pediatric Council of the American Society of Echocardiography. J Am Soc Echocardiogr 19:1413–1430
17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG (2009) Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377–381
18. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA, Doppler QTFOTNASCOTASOE (2002) Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 15:167–184
19. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ, Echocardiography ASO (2003) Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 16:777–802
20. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, Lai WW, Geva T (2010) 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 23:465–495 (**quiz 576**)
21. Pettersen MD, Du W, Skeens ME, Humes RA (2008) 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 21:922–934
22. Gautier M, Detaint D, Fermanian C, Aegerter P, Delorme G, Arnoult F, Milleron O, Raoux F, Stheneur C, Boileau C, Vahanian A, Jondeau G (2010) Nomograms for aortic root diameters in children using two-dimensional echocardiography. Am J Cardiol 105:888–894
23. Pinheiro J, Bates D, DebRoy S et al (2017) Linear and nonlinear mixed effects models. http://CRAN.R-project.org/packages/nlme/index.html. Accessed 20 Feb 2017
24. Harrell FE Jr (2017) Regression modeling strategies. http://CRAN.R-project.org/web/packages/rms/index.html. Accessed 20 Feb 2017
25. Beroukhim RS, Kruzick TL, Taylor AL, Gao D, Yetman AT (2006) Progression of aortic dilation in children with a functionally normal bicuspid aortic valve. Am J Cardiol 98:828–830
26. Gurvitz M, Chang RK, Drant S, Allada V (2004) Frequency of aortic root dilation in children with a bicuspid aortic valve. Am J Cardiol 94:1337–1340
27. Ciotti GR, Vlahos AP, Silverman NH (2006) Morphology and function of the bicuspid aortic valve with and without coarctation of the aorta in the young. Am J Cardiol 98:1096–1102
28. Schaefer B, Lewin M, Stout K, Gill E, Prueitt A, Byers P, Otto C (2008) The bicuspid aortic valve: an integrated phenotypic classification of leaflet morphology and aortic root shape. Heart 94:1634–1638
29. Jassal D, Bhagirath K, Tam J, Sochowski R, Dumesnil J, Giannoccaro P, Jue J, Pandey AS, Joyner C, Teo K, Chan K (2010) Association of bicuspid aortic valve morphology and aortic root dimensions: a substudy of the aortic stenosis progression observation measuring effects of rosuvastatin (ASTRONOMER) study. Echocardiography 27:174–179
30. Khoo C, Cheung C, Jue J (2013) Patterns of aortic dilatation in bicuspid aortic valve-associated aortopathy. J Am Soc Echocardiogr 26:600–605
31. Hope MD, Hope TA, Meadows AK, Ordovas KG, Urbania TH, Alley MT, Higgins CB (2010) Bicuspid aortic valve: four-dimensional MR evaluation of ascending aortic systolic flow patterns. Radiology 255:53–61
32. Barker AJ, Markl M, Burk J, Lorenz R, Bock J, Bauer S, Schulz-Menger J, von Knobelsdorff-Brenkenhoff F (2012) Bicuspid aortic valve is associated with altered wall shear stress in the ascending aorta. Circ Cardiovasc Imaging 5:457–466
33. Ikonomidis J, Ruddy J, Benton S, Arroyo J, Brinsa T, Stroud R, Zeeshan A, Bavaria J, Gorman J, Gorman R, Spinale F, Jones J (2012) Aortic dilatation with bicuspid aortic valves: cusp fusion correlates to matrix metalloproteinases and inhibitors. Ann Thorac Surg 93:457–463
34. Fernandez B, Duran A, Fernandez-Gallego T, Fernandez MC, Such M, Arque J, Sans-Coma V (2009) Bicuspid aortic valves with different spatial orientations of the leaflets are distinct etiological entities. J Am Coll Cardiol 54:2312–2318

35. Loscalzo M, Goh DL, Loeys B, Kent K, Spevak PJ, Dietz H (2007) Familial thoracic aortic dilation and bicommissural aortic valve: a prospective analysis of natural history and inheritance. Am J Med Genet 143A:1960–1967
36. Holmes KW, Lehmann CU, Dalal D, Nasir K, Dietz H, Ravekes WJ, Thompson WR, Spevak PJ (2007) Progressive dilation of the ascending aorta in children with isolated bicuspid aortic valve. Am J Cardiol 99:978–983
37. Niaz T, Poterucha JT, Johnson J, Craviari C, Nienaber T, Palfreeman J, Cetta F, Hagler DJ (2016) Incidence, morphology, and progression of bicuspid aortic valve in pediatric and young adult subjects with coexisting congenital heart defects. Cong Heart Dis 12:261–269
38. Fernandes SM, Sanders SP, Khairy P, Jenkins KJ, Gauvreau K, Lang P, Simonds H, Colan SD (2004) Morphology of bicuspid aortic valve in children and adolescents. J Am Coll Cardiol 44:1648–1651
39. Fernandes SM, Khairy P, Sanders SP, Colan SD (2007) Bicuspid aortic valve morphology and interventions in the young. J Am Coll Cardiol 49:2211–2214
40. Tanner JM (1949) Fallacy of per-weight and per-surface area standards, and their relation to spurious correlation. J Appl Physiol 2:1–15
41. Henry WL, Gardin JM, Ware JH (1980) Echocardiographic measurements in normal subjects from infancy to old age. Circulation 62:1054–1061
42. Gutgesell HP, Rembold CM (1990) Growth of the human heart relative to body surface area. Am J Cardiol 65:662–668
43. Dallaire F, Bigras JL, Prsa M, Dahdah N (2015) Bias related to body mass index in pediatric echocardiographic Z scores. Pediatr Cardiol 36:667–676
44. Reed CM, Richey PA, Pulliam DA, Somes GW, Alpert BS (1993) Aortic dimensions in tall men and women. Am J Cardiol 71:608–610
45. Braley KT, Tang X, Makil ES et al (2017) The impact of body weight on the diagnosis of aortic dilation: misdiagnosis in overweight and underweight groups. Echocardiography 34(7):1029–1034