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Research paper

The association between cardiac magnetic resonance-derived aortic stiffness parameters and aortic dilation in young adults with bicuspid aortic valve: With and without coarctation of aorta

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ABSTRACT

Background: Bicuspid aortic valve (BAV) is associated with progressive aortic dilation. Studies in aortopathies have shown a correlation between increased aortic stiffness and aortic dilation. We aimed to evaluate aortic stiffness measures as predictors of progressive aortic dilation by cardiac magnetic resonance (CMR) in BAV patients.

Methods: This is a retrospective study of 49 patients with BAV (median age 21.1 years at first CMR visit) with ≥2 CMR at the Wisconsin Adult Congenital Heart Disease Program (WAtCH). Circumferential aortic strain, distensibility, and β-stiffness index were obtained from CMR-derived aortic root cine imaging, and aortic dimensions were measured at aortic root and ascending aorta. A linear mixed-model and logistic regression were used to identify important predictors of progressive aortic dilation.

Results: Over a median of 3.8 years follow-up, the annual growth rates of aortic root and ascending aorta dimensions were 0.25 and 0.16 mm/year, respectively. Aortic strain and distensibility decreased while β-stiffness index increased with age. Aortic root strain and distensibility were associated with progressive dilation of the ascending aorta. Baseline aortic root diameter was an independent predictor of >1 mm/year growth rate of the aortic root (adjusted OR 1.34, 95 % CI 1.03–1.74, $p = 0.028$). Most patients (61 %) had coexisting coarctation of aorta. Despite the higher prevalence of hypertension in patients with aortic coarctation, hypertension or coarctation had no effect on baseline aorta dimensions, stiffness, or progressive aortic dilation.

Conclusion: Some CMR-derived aortic stiffness parameters correlated with progressive aortic dilation in BAV and should be further investigated in larger and older BAV cohorts.

1. Introduction

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly with a prevalence of 0.5–2 % in the general population [1]. Bicuspid aortopathy is the most commonly associated pathology found in 20–84 % of patients with BAV and poses a greater risk of aortic dissection and death [2,3]. However, risk stratification for subsequent aortic events in BAV patients remains challenging, partly because BAV patients are commonly diagnosed at a younger age and the cutoffs used to define aortic dilation differ between pediatric and adult guidelines. In adult patients, for prevention of acute aortic events, surgical repair of the aorta in the context of BAV is therefore recommended once the maximal aortic dimension reaches a certain criteria depending on the presence of other risk factors [4]. Aortic wall stiffness (or reduced aortic elasticity) is defined as decreased aortic vascular compliance and considered an early manifestation of vascular aging [5]. Vascular

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stiffness can be reliably obtained using noninvasive imaging techniques such as echocardiography or cardiac magnetic resonance (CMR) and was initially used for the detection of atherosclerotic vascular changes, which in turns reflect adverse cardiovascular outcomes [6]. The concept of aortic stiffness was later applied to studies on patients with elevated risk for aortic dilation. Several previous studies have demonstrated that these biomechanical parameters, particularly the aortic strain, distensibility, and β-stiffness index, are abnormal in a number of aortopathies [7–10]. CMR-derived aortic stiffness is increased in patients with connective tissue disease including Marfan syndrome, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome, and is associated with a higher rate of aortic root dilation and surgical root replacement during follow-up. Abnormal aortic elastic properties were also observed in complex congenital heart disease patients such as repaired tetralogy of Fallot and repaired coarctation of aorta [11,12]. In BAV patients, a relationship between certain valve phenotypes, degree of valvular dysfunction, and varying patterns of aortopathy was reported in the past [13,14]. However, a correlation between aortic stiffness measures and progressive aortic dilation leading to subsequent aortic event has not yet been well established in BAV patients. By determining changes in serial measurements of aortic stiffness in our study, we may be able to detect early signs of aortic dilation and therefore identify high-risk individuals in this population.

2. Methods

2.1. Study design

This was a retrospective cohort study approved by the institutional review board at the Children's Wisconsin. A total of 1070 adult patients between the age of 17 and 59 years old with a BAV ICD-9 code who followed at the Wisconsin Adult Congenital Heart Disease (WAtCH) Program at the Herma Heart Institute, Children's Wisconsin, from January 2008 to June 2019 were reviewed. Of these patients, 49 patients with BAV who had $\geq$2 serial CMR for the evaluation of their valve function and/or aortic dimensions were included in the study. Patients with known genetic aortopathy syndromes or congenital heart disease of great complexity according to the 2018 AHA/ACC Adult Congenital Heart Disease Guideline were excluded [15]. CMR performed in patients who underwent aorta replacement surgery following their surgery were excluded from the analysis.

2.2. CMR protocol and data collection

CMR was performed with institutional standard protocols using the commercially available whole body scanner (Siemens Skyra 3 Tesla, Siemens Avanto 1.5 Tesla, or Philips Ingenia 1.5 Tesla). ECG-gated 2-dimensional cine steady-state free precession (SSFP) imaging was performed in standard 4-chamber, 2-chamber, and short axis views. Additional aortic root stacks were obtained with cine SSFP or cine gradient echo (GRE) imaging. Contrast-enhanced magnetic resonance angiography image acquisition was performed after the administration of 0.2 ml/kg of gadobutrol (Gadovist®, Bayer HealthCare, Whippany, NJ) or 0.4 ml/kg of gadodiamide contrast agent (Omniscan®, GE Healthcare, Waukesha, WI) and 3-dimensional images were reconstructed for visualization of the entire thoracic aorta. Typically, angiograms were performed with ECG-gating in diastole during breath-hold. All data and images were processed using cvi42 software (Circle Cardiovascular Imaging Inc., Calgary, AB, Canada).

All measurements and calculations were done by a single investigator (V.C.) for each CMR to ensure reliability, reproducibility, and accuracy. Independent quality checks were performed by a second CMR reader, who was blinded to patient demographics and clinic data. The CMR imaging acquisition sequences and aortic measurements were performed according to the current guidelines [16]. The aortic dimensions were measured at two levels as illustrated in Fig. 1. The sinus of Valsalva (aortic root) maximal dimensions were measured from cusp to commissure in mid-systole on the thin-sliced (4–6 mm) aortic root stack cine imaging. This technique for aortic root measurement has been validated in prior literature [17]. The maximal dimensions of the ascending aorta were obtained from the 3-dimensional reconstructed magnetic resonance angiography images where the ascending aorta had the greatest dimension. Magnetic resonance angiography remains the sequence of choice for aorta measurements [16]. For determination of aortic stiffness parameters, aortic root cross-sectional areas in systole and diastole were measured by means of manual planimetry on the thin-

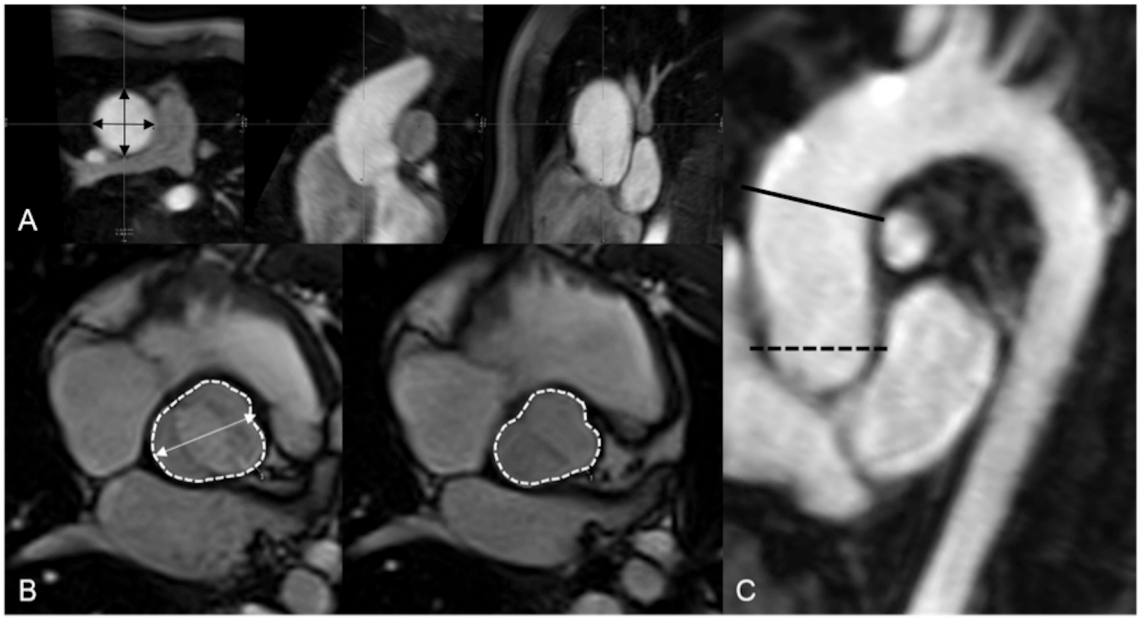

Fig. 1. Measurement of aortic stiffness and aortic diameters by CMR. A. Maximal diameter of ascending aorta was measured using MRA (black double arrows). B. Systolic and diastolic phases of thin-sliced aortic root cine SSFP images used to determine aortic root stiffness (white dashed lines). Maximal aortic root diameter was measured in mid systole (white double arrow). C. Levels of aorta used for measurements (black solid line for ascending aorta and black dashed line for aortic root). CMR = cardiac magnetic resonance; MRA = magnetic resonance angiography; SSFP = steady-state free precession.

sliced aortic root stack cine images (Fig. 1). Brachial blood pressures including systolic and diastolic blood pressures obtained at the time of the CMR or at contemporary office visit within 3 months of CMR were used in calculations of distensibility and β-stiffness index. Aortic stiffness parameters were calculated from the aortic root areas and brachial blood pressures as previously described using the following equations [6–8,18,19]. For the different aortic stiffness parameters, a lower aortic strain and distensibility score indicated a stiffer aorta while the inverse was true for the β-stiffness index, with a higher score indicating a stiffer aorta.

$$Aortic\ Strain = \frac{Systolic\ Area - Diastolic\ Area}{Diastolic\ Area}$$

$$Aortic\ Distensibility = \frac{Strain}{Brachial\ Pulse\ Pressure}$$

$$\beta - Stiffness\ Index = \frac{ln(Systolic\ Blood\ Pressure/Diastolic\ Blood\ Pressure)}{Strain}$$

2.3. Statistical analysis

Data were summarized using median (interquartile range) or count (%). Continuous variables were compared using Mann-Whitney-Wilcoxon test between groups while Chi-square or Fisher's exact test was used to compare categorical variables. The correlation coefficients between aortic stiffness parameters and age were estimated using a mixed model approach. A normal approximation procedure was used to calculate the confidence intervals for the Fisher's z-transformed correlation coefficients. A linear mixed model was used to investigate the relationship between each demographic variable or aortic stiffness parameter and the aortic root and ascending aorta diameter changes over time. Moreover, patients were categorized into rapid growth (aortic root growth of $\geq$1 mm/year) and slow growth (<1 mm/year). In order to assess the impact of the aortic stiffness measures on the growth of the aorta, a logistic regression analysis was performed. A stepwise backward logistic regression with elimination method was used to determine the important predictors for aortic dilation. SAS version 9.4 (SAS Institute, Cary, NC) and R were used for the analyses.

3. Results

3.1. Demographics and clinical characteristics

The baseline demographic and imaging data of the 49 BAV patients in the study cohort are shown in Table 1. The median age at the time of first CMR was 21.1 years old. All patients had at least two CMR during follow-up, ranging between 2 and 5 CMR per patient, over a median of 3.8 years follow-up. In our series, 30 patients (61 %) had coexisting coarctation of aorta; of this number, 27 patients (55 %) required one or more interventions to correct significant coarctation. Of the 27 patients who had intervention for coarctation of aorta, 9 underwent end-to-end anastomosis, 9 had subclavian flap repair, 6 had patch aortoplasty, and 3 had reconstruction with interposition grafting. The median age of initial repair was 1 month. For this subset of patients, throughout the follow-up period, no patient had significant residual coarctation of aorta defined by arm-to-leg blood pressure gradient of $\geq$20 mm Hg. Other previous surgical interventions in these 27 patients included repair of sinus venosus defect and partial anomalous pulmonary venous return in 2 patients and subaortic membrane resection in 1 patient.

At time of the initial study, a total of 43 % of patients had a history of hypertension and 47 % were on medical therapy for treatment of hypertension or prevention of aortic dilation. In this cohort at the time of initial evaluation, 18 % were on β-blocker alone, 16 % were on angiotensin-converting enzyme inhibitor or angiotensin receptor blocker alone, and 12 % were on both. The majority of patients had no hemodynamically significant stenosis or regurgitation of their BAV. There were 14 % with mild stenosis, 4 % with moderate stenosis, and none with severe stenosis, defined by peak velocity and mean gradient by Doppler echocardiographic interrogation of transaortic flows. Similarly, 37 % had mild aortic regurgitation, 10 % had moderate regurgitation, and none had severe regurgitation at the time of the initial CMR study.

Table 1
Baseline demographic, clinical, and CMR characteristics in the study population.

Characteristic[a]	Estimate (n = 49)
Demographics	
Age, years	21.1 (15.7, 29.8)
Male gender	25 (51)
BSA, m^2	1.9 (1.5, 2.1)
Aortic coarctation	30 (61)
Previous intervention	27 (55)
No previous intervention	3 (6)
Hypertension	21 (43)
Medication use	23 (47)
β-Blocker alone	9 (18)
ACEI/ARB alone	8 (16)
β-Blocker and ACEI/ARB	6 (12)
SBP, mm Hg	120 (110, 128)
DBP, mm Hg	68 (62, 76)
Aortic stenosis	
Mild	7 (14)
Moderate	2 (4)
Severe	0 (0)
Aortic regurgitation	
Mild	18 (37)
Moderate	5 (10)
Severe	0 (0)
Baseline aortic measurements, mm	
Aortic root (sinus of Valsalva) diameter	34.4 (29.8, 37.2)
Sinotubular junction diameter	25.5 (22.1, 29.6)
Ascending aorta diameter	30.7 (27.1, 36.6)
Baseline CMR-derived aortic stiffness parameters	
Aortic strain, %	21 (15, 34)
Aortic distensibility, 10^{-3} mm Hg^{-1}	4.5 (3.0, 6.9)
Aortic β-stiffness index	2.5 (1.6, 3.6)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BSA, body surface area; CMR, cardiac magnetic resonance; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a] Data are expressed as median (interquartile range) or count (%).

3.2. CMR-derived aortic stiffness and aortic dimensions

Baseline aortic dimensions and aortic stiffness measures assessed by CMR are summarized in Table 1. The majority of patients in our study had normal aortic root and ascending aorta size at their first CMR. Over a median follow-up period of 3.8 years, the annual growth rates of aortic root and ascending aorta were 0.25 and 0.16 mm/year, respectively. None of the patients developed aortic dissection or rupture. Only 3 patients (6 %) met the criteria for surgery and underwent valve-sparing replacement of the aortic root or ascending aorta during the study period. Table 2 compares patient demographic data and baseline aorta dimensions and stiffness parameters between patients with isolated BAV and those with concomitant coarctation of aorta. Although individuals with prior aortic coarctation were significantly older, had higher prevalence of hypertension, and higher blood pressures at baseline, there was no significant difference of the baseline aortic root and ascending aorta size, or baseline stiffness parameters between the two groups.

Fig. 2 depicts the scatter plots demonstrating relationships between each CMR-derived stiffness parameters and the patients' age at the time of the CMR. Aortic strain and distensibility decreased with age. Inverse correlations between age and aortic strain (r = −0.39, 95 % CI [−0.59, −0.19], $p < 0.001$), and age and aortic distensibility (r = −0.42, 95 % CI [−0.63, −0.21], $p < 0.0001$) were detected. Similarly, aortic β-stiffness index increased with age with a positive correlation (r = 0.45, 95 % CI

Table 2
The effect of coarctation of aorta on baseline aortic stiffness and aortic dimensions in BAV patients.

Characteristics[a]	No aortic coarctation ($n = 19$)	Aortic coarctation ($n = 30$)	p-Value[b]
Age, years	15.7 (14.3, 22.0)	24.1 (18.5, 31.6)	0.007
Male gender	11 (58)	14 (47)	0.444
BSA, m^2	1.6 (1.4, 2.0)	2.0 (1.6, 2.1)	0.094
SBP, mm Hg	115 (94, 118)	125 (112, 134)	0.0002
DBP, mm Hg	64 (62, 68)	70 (64, 80)	0.009
Hypertension	2 (11)	19 (63)	0.0003
Medication use	7 (37)	16 (53)	0.260
Baseline aortic root diameter, mm	33.8 (32.5, 35.2)	35.2 (29.4, 37.9)	0.448
Baseline ascending aorta diameter, mm	32.2 (26.4, 38.0)	29.1 (27.1, 35.0)	0.129
Aortic strain, %	21 (16, 44)	21 (14, 28)	0.429
Aortic distensibility, 10^{-3} mm Hg^{-1}	4.7 (3.0, 10.7)	4.3 (2.9, 6.3)	0.189
Aortic β-stiffness index	2.6 (1.1, 3.6)	2.5 (1.7, 3.8)	0.395

BAV, bicuspid aortic valve; BSA, body surface area; CMR, cardiac magnetic resonance; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a] Data are expressed as median (interquartile range) or count (%).
[b] $p < 0.05$ was considered statistically significant.

[0.27, 0.63], $p < 0.0001$). To determine the important predictors of progressive ascending aortic dilation over time in patients with BAV, a linear mixed model was conducted separately for the growth of the aortic root and ascending aorta (Table 3). Older age, large body surface area (BSA), and decreased aortic strain and aortic distensibility on serial CMR were predictive of progressive dilation of the ascending aorta over time. However, the effect of serial changes of aortic strain and distensibility on aortic dilation was not statistically significant after adjusting for age, gender, BSA, systolic and diastolic blood pressures. For the aortic root, similar results were observed with older age and large BSA being the predictive factors for progressive growth of the aortic root. Male gender was predictive, but changes in the aortic wall stiffness markers were not. The effect of aortic coarctation, hypertension, and medication use on aortic dilation were also assessed in the model, none of these factors was associated with progressive enlargement of the aorta over time. On the contrary, prior coexisting aortic coarctation was associated with smaller ascending aorta size in BAV patients. In our study, medication use was defined as treatment with any β-receptor antagonist and/or angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist at the time of the initial study.

To further evaluate the characteristic features between those with different growth rates of the aorta, the study subjects were classified into slow growth group in which the progression of the aortic root dimension was <1 mm/year, and the rapid growth group in which the aortic root dilated ≥1 mm/year. As shown in Table 4, in a logistic regression analysis with backward elimination, baseline aortic root diameter at the time of first CMR was the only predictive factor for aortic root growth rate of ≥1 mm/year (OR 1.22, 95 % CI 1.03–1.43, $p = 0.019$). It remained the significant predictive factor after adjusting for age, gender, BSA and blood pressure (adjusted OR 1.34, 95 % CI 1.03–1.74, $p = 0.028$). Age, BSA, systolic and diastolic blood pressure as well as baseline aortic stiffness did not predict the faster rate of aortic root dilation. Parallel analysis for the ascending aorta was not performed given the growth rate of the ascending aorta in our cohort was much smaller than that of the aortic root and most patients were categorized into the slow growth group.

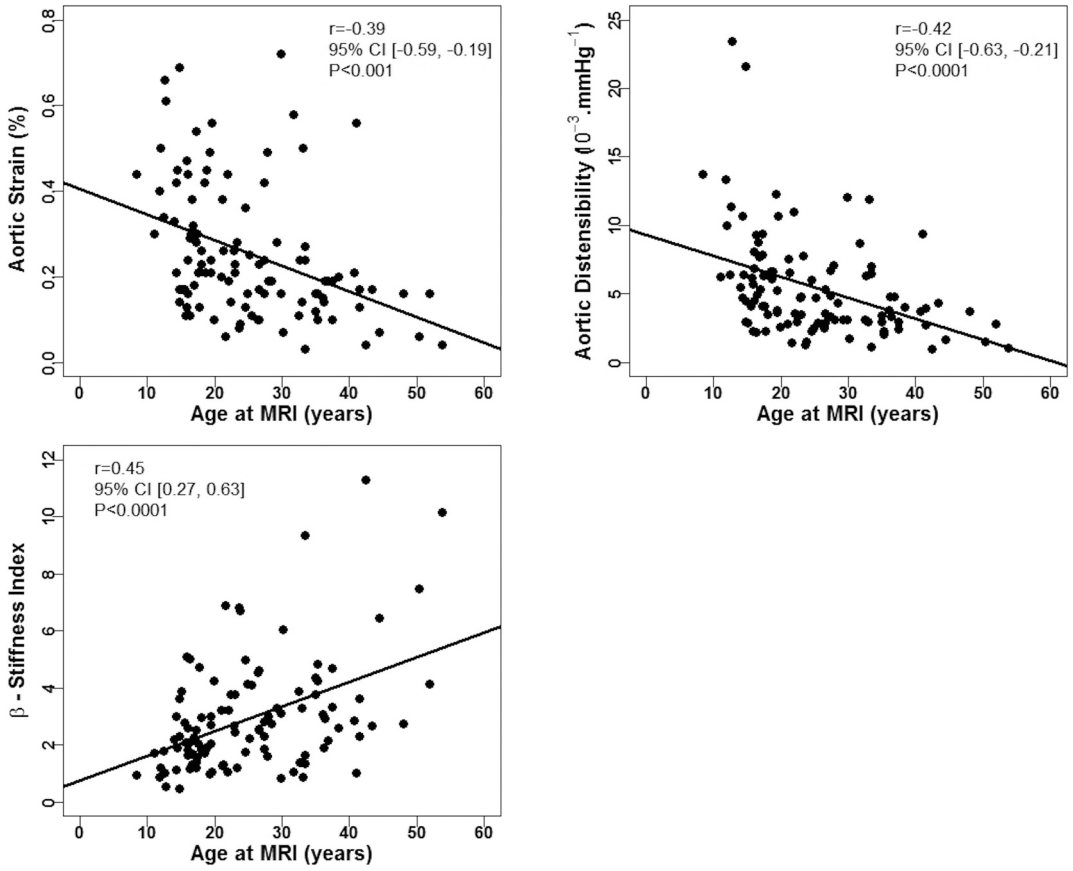

Fig. 2. Scatter plots for correlations between aortic stiffness with age. Lines were generated treating each sample as independent data. Correlation coefficients with 95 % confidence intervals were calculated using a mixed model approach to account for the repeated measurements. CMR = cardiac magnetic resonance.

Table 3
Univariate analysis using a linear mixed model for predicting aortic dilation at the aortic root and ascending aorta levels.

	Aortic root		Ascending aorta	
	Estimate, mm	*p*-Value[a]	Estimate, mm	*p*-Value[a]
Linear trajectory (per year)	0.30	<0.001	0.24	<0.0001
Intercept	34.67	<0.0001	31.91	<0.0001
Variables				
Age	0.29	0.0048	0.28	0.0017
Male gender	4.36	0.023	2.22	0.23
BSA	6.94	<0.001	5.33	<0.001
SBP	0.01	0.65	−0.01	0.69
DBP	−0.04	0.12	0.01	0.82
Hypertension	0.35	0.84	−1.04	0.59
Medication use	3.45	0.06	2.37	0.22
Coarctation of aorta	0.14	0.94	−4.54	0.03
Aortic strain	−1.14	0.48	−3.04	0.046
Aortic distensibility	−0.19	0.07	−0.22	0.016
Aortic β-stiffness index	0.10	0.40	0.09	0.42

BSA, body surface area; CMR, cardiac magnetic resonance; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a] $p < 0.05$ was considered statistically significant.

Table 4
Univariate logistic regression analysis for predicting aortic root growth between rapid growth (≥1 mm/year) and slow growth (<1 mm/year).

Aortic root[a]	Univariate analysis		
	<1 mm/year (*n* = 44)	≥1 mm/year (*n* = 5)	*p*-Value[b]
Age, years	21.1 (15.6, 30.0)	21.6 (16.0, 26.6)	0.55
Male gender	21 (48)	4 (80)	0.20
BSA, m^2	1.9 (1.5, 2.1)	2.0 (1.6, 2.0)	0.83
SBP, mm Hg	120 (110, 131)	118 (104, 120)	0.28
DBP, mm Hg	69 (63, 75)	64 (62, 80)	0.92
Aortic root diameter, mm	34.3 (29.4, 35.9)	41.2 (35.5, 46.4)	0.019
Ascending aorta diameter, mm	30.5 (26.4, 36.4)	34.4 (32.2, 39.0)	0.09
Aortic strain, %	22 (15, 40)	16 (16, 17)	0.26
Aortic distensibility, 10^{-3} mm Hg^{-1}	4.5 (3.0, 7.6)	5.3 (2.8, 6.4)	0.53
Aortic β-stiffness index	2.5 (1.3, 3.5)	2.5 (1.8, 4.1)	0.62

BSA, body surface area; CMR, cardiac magnetic resonance; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a] Data are expressed as median (interquartile range) or count (%).
[b] *p*-Value represents results from logistic regression analysis; $p < 0.05$ was considered statistically significant.

4. Discussion

To our knowledge, this is the first study to evaluate whether sequential changes in aortic elasticity detected on serial CMR would be predictive of progression of BAV-associated aortopathy. Previous studies have demonstrated a positive correlation between aortic stiffness and dilated aorta [20,21], and that stiffness is determinant of progressive dilation of ascending aorta in BAV patients [22,23]. This is likely related to abnormal wall architecture seen with BAV [24,25], similar to other forms of aortopathies. Aside from the abnormal molecular wall components, it has been shown that aortic flow patterns directed across the BAV in the setting of significant aortic valve disease can contribute to regional aortic stiffness and concomitant aortic dilation as observed using 4-dimensional flow CMR [26–29]. The variation in regions of aortic dilation in BAV aortopathy has been attributed to the different patterns of the abnormal aortic flow across the abnormal aortic valve, making BAV aortopathy unique compared to other aortopathies.

Our data were obtained from a cohort of adults with BAV that included adolescents and young adults. Negative changes of aortic root stiffness on serial CMR measurements, particularly the aortic strain and distensibility, were found to be predictive of progressive dilation of the ascending aorta over time in our study. As expected, older age at time of initial CMR was predictive of progression of aortopathy. This correlates and supports the data from previous studies in the general population that with age the aorta becomes stiffer over time [19]. Our data indicate that BAV patients, despite the younger age compared to the other studies, have stiffer aortic root when compared to general population when the same methods to assess stiffness were used [18,19,30], though direct comparison between BAV and control was not performed in our study. In the setting of BAV, this process is likely more advanced and progresses at a more rapid rate; however, further studies are needed to evaluate this.

We also verified, similar to previous studies [31,32], that the larger the aorta dimension, the faster the rate of dilation and higher risk of aortic events. We found that the baseline aortic root dimension at the time of initial study was the only significant predictor for rapid growth rate of the aortic root ≥1 mm/year, while baseline aortic root stiffness and other patient characteristics had no effect on this growth rate. This is very important because unlike other studies, our study was comprised mainly of younger adults with normal or only mildly dilated aorta at baseline. Moreover, aortic dissection in BAV can have a distinctive entry tear pattern in the aortic root in addition to ascending aorta, emphasizing the need to monitor aortic root growth in this population [33]. In line with the current practice guidelines [34], our findings support close monitoring with serial imaging surveillance and follow-up for BAV patients with baseline enlarged aortic root, especially if ≥4.5 cm, regardless of their measured biomechanical status.

BAV is a frequent association of coarctation of the aorta, occurring in up 80 % of cases. Several studies reported increased incidence of aortic dilation and subsequent aortic events in BAV patients with concomitant aortic coarctation compared to patients with isolated BAV or isolated coarctation [35,36]; however, the mechanism behind this process is not entirely understood. Many have theorized that increased aortic stiffness may play a role in this setting. Recent studies have demonstrated mixed findings with one study indicating no further augmentation in arterial stiffness in the setting of both BAV and coarctation, while another study demonstrated presence of BAV and coarctation was predictive [12,37]. It is important to note that in our series, the presence of both BAV and coarctation of the aorta was not associated with worsening stiffness parameters, nor it was predictive of progressive aortic dilation over time. In fact, our data suggested that patients with prior coarctation had smaller aorta when compared to those without. Given the limited sample size in our study, additional studies with larger sample size are needed to further explore the impact of coarctation on aortic mechanics. Similarly, we found that the presence of hypertension or medical therapy had no effect on the rate of dilation. Both the presence of hypertension and concurrent medical therapy can drastically impact aortic stiffness and in turn, aortic dimensions and aortic dilation [38]. While this is interesting, we believe this finding should be interpreted cautiously given the small sample size and incomplete data on duration of medical use, duration of hypertension diagnosis, and adequacy of blood pressure control.

Due to younger age, most of our subjects had modest aortic valve disease at the time of the study, which likely eliminated the hemodynamic effects from flow-mediated wall shear stress, and potentially allowed an assessment of vascular compliance exclusively driven by abnormal intrinsic elastic properties in BAV aortopathy. Unfortunately, there is currently no consensus on the stiffness measures that would best correlate with aortic outcomes. Measuring with aortic outcomes is extremely important given the aortic dimensions and aortic stiffness parameters may only represent a causal relationship. It is possible that the two could simply coexist according to the Laplace law where increased aortic dimensions, decreased wall thickness, and the overall increased wall tension reflect the changes in stiffness as a part of vascular remodeling process. Guala and colleagues [39] have supported

this concept by demonstrating that BAV patients with normal size aorta showed comparable aortic stiffness to healthy controls, while the BAV patients with dilated aorta had similar stiffness compared to dilated aorta in tricuspid aortic valve patients. Further studies validating aortic stiffness parameters with aortic outcomes will be crucial moving forward. Our findings suggest that negative changes in wall stiffness particularly the aortic strain and distensibility that are out of proportion of their corresponding aortic size are predictive of progressive aortic dilation. Based on our experience, of the 3 stiffness parameters obtained using CMR, aortic strain may be the most reliable measure, as it does not rely on other hemodynamic factors such as systolic and diastolic blood pressures.

4.1. Study limitations

The study had several limitations. First, this is a retrospective study with relatively small numbers of patients with varying ages and intervals between CMR. From a technical standpoint, our ability to obtain aortic stiffness was limited to the aortic root using the cross-sectional area difference. This technique has been previously validated in other studies [7,8,19,40]; however, other techniques such as the pulse wave velocity method, the gold standard for vascular stiffness assessment [6,41], may be needed to confirm our findings. Other segments of the aorta should also be further examined, especially the ascending aorta, which is generally the most affected region in the context of BAV unlike other types of aortopathy. Due to the small cohort, adequate power may not have been achieved to determine independent predictors in a multivariable analysis, and a larger study is needed to corroborate our findings as other factors may also play a role in driving the progression of aortopathy. Lastly, the use of 4-dimensional flow CMR and computational modeling of wall shear stress may be beneficial in providing additional information to the mechanisms of BAV aortopathy and localizing certain aortic segments with higher degree of wall shear stress and stiffness that predispose these areas to progressive dilation.

5. Conclusions

As described earlier, BAV patients are a very heterogeneous population. A substantial proportion of patients have stable aorta dimensions throughout their lifetime while another significant proportion of patients develop rapid progression of aortopathy leading to detrimental outcomes. There are currently no reliable prognostic factors to clinically predict such rapid progression or subsequent aortic outcomes in these patients. The findings from our study are appealing as they can guide further investigations to explore the role of aortic biochemical parameters as potential predictive factors in BAV aortopathy. Serial CMR may be an essential tool in identifying patients at risk in the future by monitoring the changes of CMR-derived aortic stiffness parameters, in addition to the increased aorta size, as in our study.

CRediT authorship contribution statement

Vasutakarn Chongthammakun: Conceptualization, Methodology, Investigation, Writing - Original draft.
Amy Pan: Formal analysis.
Michael Earing: Supervision, Writing - Reviewing and editing.
Abdulla Damluji: Formal analysis.
Benjamin Goot: Validation, Writing - Reviewing and editing.
Joseph Cava: Validation, Writing - Reviewing and editing.
Jennifer Gerardin: Supervision, Writing - Reviewing and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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