



Aortic arch tortuosity, a novel biomarker for thoracic aortic disease, is increased in adults with bicuspid aortic valve☆

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ABSTRACT

Introduction: Arterial tortuosity has emerged as a predictor of adverse outcomes in congenital aortopathies using 3D reconstructed images. We validated a new method to estimate aortic arch tortuosity on 2D CT. We hypothesize that arch tortuosity may identify bicuspid aortic valve (BAV) patients at high risk to develop thoracic aortic aneurysms or aortic dissections (TAD).

Methods: BAV subjects with chest CT scans were retrospectively identified in our clinical records and matched to tricuspid aortic valve (TAV) controls by age, gender, and presentation with TAD. Subjects with prior ascending aortic intervention were excluded. Measurements included aortic arch tortuosity, length, angle, width and height. Total aortic tortuosity was estimated in subjects with available abdominal images.

Results: 120 BAV and 234 TAV subjects were included. Our 2D measurements were highly correlated with 3D midline arch measurements and had high inter- and intra-observer reliability. Compared to TAV, BAV subjects had increased arch tortuosity (median 1.76 [Q1–Q3: 1.62–1.95] vs. 1.63 [1.53–1.78], $P < 0.01$), length (149 [136–160] vs. 135 [122–152] mm, $P < 0.01$), height (46 [41–53] vs. 39 [34–47] mm, $P < 0.01$), and vertex acuity (70 [61–77] vs. 75 [68–81] degree, $P < 0.01$). In a multivariable analysis, arch tortuosity remained independently associated with BAV after adjusting for aortic diameter and other clinical characteristics.

Conclusions: We found that aortic arch tortuosity is significantly increased in BAV and may identify BAV patients who are at increased risk for TAD. Further studies to evaluate the association between tortuosity and clinical outcomes are in progress.

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⁵ This author assisted with study design, subject ascertainment and statistical analysis.

⁶ This author contributed subjects to the primary study cohort.

⁷ This author contributed the validation cohort and assisted with manuscript revision.

⁸ This author assisted with the measurement validation and assisted with manuscript revision.

1. Introduction

In a 2016 statement, the guidelines for the diagnosis and management of patients with thoracic aortic disease was amended to recommend prophylactic repair of the ascending aorta in asymptomatic patients with bicuspid aortic valves (BAV) when the maximum aortic diameter is >5 cm and patients have other risk factors for aortic dissection, such as hypertension, a family history of aortic dissection or rapid aortic enlargement [1,2]. These recommendations were largely extrapolated from observations in patients with Marfan syndrome and heritable thoracic aortic disease (TAD) when, in fact, the risk for dissection in most BAV patients may be significantly lower [3–8]. Cohort studies consistently show that aortic diameter is not an accurate predictor of acute dissections, because almost half of acute dissections occur when the diameter is <5 cm [9]. Currently all BAV patients are screened as if they are likely to develop TAD, when only 25% may develop significant aortic dilation or aortic dissections [10]. There is an urgent clinical need for alternative features that may identify patients who could benefit from intensive surveillance and early interventions to prevent aortic dissections. Image-guided analysis of aortic root and valve morphology [11–16], as well as turbulent flow in the ascending aorta [17–21], are correlated with aortic dilation in BAV cohorts but the independent predictive value of these observations has not been determined. More recently, arterial tortuosity has emerged as a reproducible predictor of aortic events in many heritable aortopathies [22–25]. Tortuosity is calculated as the ratio of the midline and straight-line distances between two points. Tortuosity of the vertebral arteries is significantly increased in pediatric patients with early onset aortic dissections and provides incremental information about risk that is independent of aortic diameter and other clinical risk factors [22]. Tortuosity of the descending thoracic aorta is increased in Type B dissection patients who develop enlarging thoracoabdominal aneurysms or ruptures [24]. Tortuosity may reflect pathologic remodeling in response to progressive structural compromise of the vascular media due to genetic mutations, atherosclerosis or hemodynamic stress. The extent and distribution of tortuosity are therefore promising indicators of disease burden.

Until now, tortuosity studies uniformly relied on specialized software and workstations to reconstruct three-dimensional images that facilitate midline measurements. We sought to develop a new method to derive equivalent tortuosity measurements using two-dimensional (2D) images that are acquired for routine clinical use. We anticipate that our approach will greatly expand the number of images that are accessible to tortuosity measurements, accelerating the adoption of tortuosity in research and clinical applications.

We hypothesize that aortic arch tortuosity is increased in BAV and may be useful to identify the subgroup of patients who will develop aortic complications. In this study, we applied our 2D method to analyze aortic tortuosity in a large BAV cohort with a focus on potential associations between tortuosity measurements, clinical parameters and valve configuration.

2. Methods

2.1. Study design

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Committee for the Protection of Human Subjects at UTHealth and the research committee at Memorial Hermann Hospital-Texas Medical Center (MHH), which authorized waiver of informed consent for retrospective chart review. Potential subjects were selected from patients who received routine clinical care at MHH by querying customized databases in the Department of Radiology at MHH (Primordial Design, Inc., San Mateo, CA) and the Department of Cardiothoracic and Vascular Surgery at UTHealth. We also selected eligible cases from the UTHealth Bicuspid Aortic Valve Research Registry (www.clinicaltrials.gov/ct2/show/NCT01823432). The diagnosis of BAV was verified after review of images or operative reports. We defined TAD as aortic dilation (maximum diameter >4.0 cm or Z-score >2) [26] or a history of aortic dissection or elective aortic repair. Subjects with verified BAV who had at least one contrast-enhanced chest computed tomography (CT) scan as part of routine clinical care were eligible for inclusion. Subjects who underwent ascending aortic intervention (AAI) prior to

the first available images, or subjects with incomplete or technically difficult images, were excluded. BAV and tricuspid aortic valve (TAV) subjects were matched by age, gender, and the presence of TAD.

2.2. Aortic arch tortuosity measurements

CT images were analyzed using Aquarius iNtuition software (v4.4.12. TerraRecon, Foster City, CA), except for 12 subjects with external scans that were analyzed using Sante DICOM Editor software (v 5.2.1. SanteSoft, Nicosia, Cyprus). Aortic arch parameters were measured in the candy cane view in 2D multiplanar reconstructions (MPR, Fig. 1A). A triangle was drawn between the arch apex and the midline of the thoracic ascending (TAA) and thoracic descending aorta (TDA) at the level of the right pulmonary artery (PA). Arch length was calculated as the sum of these two segments. Arch angle is the vertex angle of the triangle, and arch width is the length of the base. Arch height is the vertical distance between the PA and the arch vertex. Arch tortuosity was defined as arch length divided by width.

In a subgroup of subjects with simultaneous chest and abdominal images, we also estimated total aortic tortuosity by drawing a line from the TDA at the PA level to the iliac bifurcation (Fig. 1B). Aortic diameters were measured at the sinuses of Valsalva, the sinotubular junction, and the mid-ascending aorta.

2.3. Echocardiographic measurements

Transthoracic and transesophageal images were directly reviewed to record valve orientation and phenotypic characteristics, including Sievers classification [27], the number and location of raphe, and Valve Degeneration (VD) score (a composite of valve calcification, thickness, and immobility) [10]. We abstracted additional echocardiographic parameters from imaging reports to evaluate the severity of aortic stenosis (AS) or aortic regurgitation (AR), and left ventricular ejection fraction (LVEF).

2.4. Validation of tortuosity calculations

Correlation between 2D and 3D measurements was estimated in two independent groups of 10 subjects at UTHealth and Vall d'Hebron Hospital. We also generated Bland-Altman plots to illustrate the mean difference between 2D and 3D measurements using STATA (v14. StataCorp LLC. College Station, TX) [28]. To assess reliability, two independent observers conducted tortuosity measurements in 53 randomly selected cases (15 BAV, 38 TAV). Intraclass correlation coefficients (ICC) to assess inter-observer and intra-observer reliability for the 2D measurements were calculated in R (v3.4.1. Vienna, Austria) using the *psych* package (v1.7.8. Chicago, IL) [29,30].

2.5. Statistical analysis

Univariable analyses explored differences in tortuosity measurements, as well as demographic and clinical characteristics between BAV and TAV subjects. For categorical variables, we used chi-squared or Fisher's exact tests where appropriate. For continuous variables, we assessed normality and computed *t*-tests if the data were normally distributed; otherwise, we computed Wilcoxon rank-sum tests. Any test with a *P*-value of <0.05 is considered statistically significant. A multivariable logistic regression model including aortic arch tortuosity and any significant variables in the univariable analyses was run to examine whether aortic arch tortuosity independently predicts BAV. Among BAV subjects, univariable and multivariable analyses were carried out in the same manner to explore the relationship between aortic arch tortuosity and TAD, and between arch tortuosity and BAV orientation. Analyses were conducted in STATA (v14. StataCorp LLC. College Station, TX).

3. Results

3.1. Study cohort

Three hundred and fifty-four subjects met the inclusion criteria (Table 1). One hundred twenty BAV subjects, 63 with TAD and 57 without TAD, were matched by age and gender to 234 TAV subjects, 63 with TAD and 171 without TAD.

The diagnosis of bicuspid aortic valve (BAV) was verified from imaging or operative reports (74 cases) or by direct visualization of cardiac echocardiograms (90 cases). Due to inadequate images, 139 subjects were excluded. CT scans were obtained between Feb 2003 and March 2017, including 185 angiograms, 83 with IV contrast, 54 pulmonary embolism protocol scans, and 32 coronary angiograms.

3.2. Validation of measurements

In two independent groups of 10 subjects, the correlation between 2D and 3D measurements was $R^2 = 0.95$ (UTHealth) and $R^2 = 0.84$

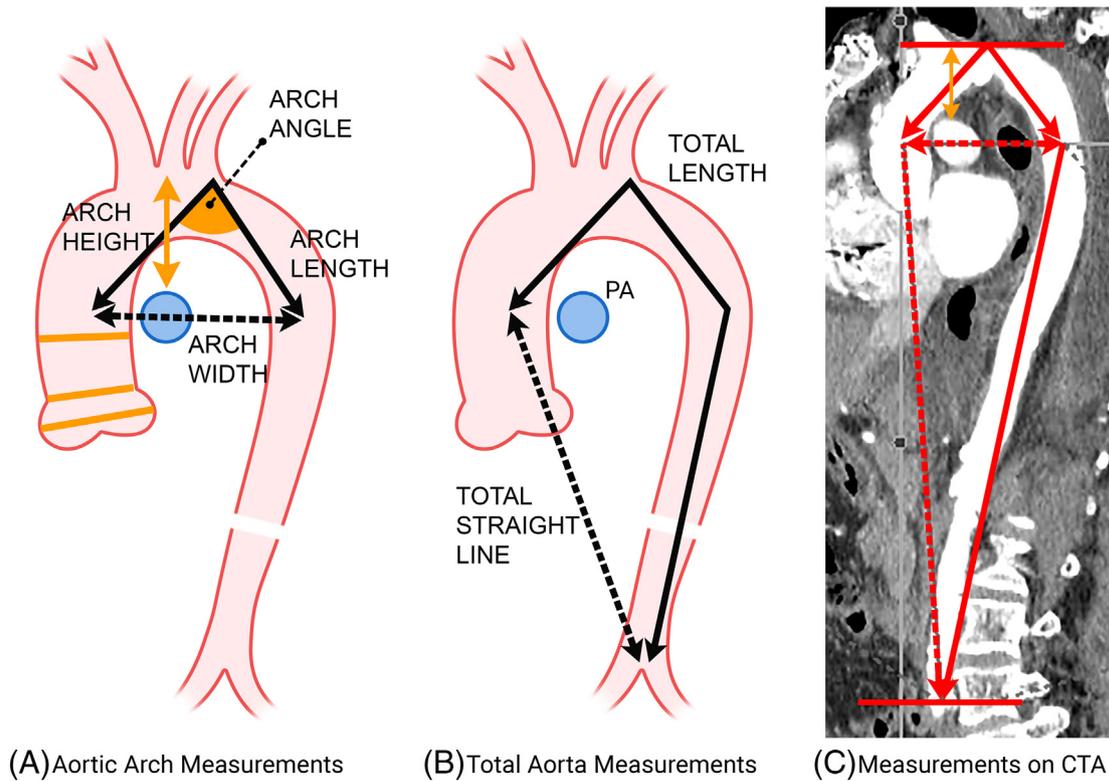


Fig. 1. Measurements of aortic tortuosity and geometry. PA: pulmonary artery. CTA: computed tomography angiogram. (A) Diagram illustrates aortic arch tortuosity measurements, including arch length, height, width and angle, as well as aortic diameters at the sinuses of Valsalva, sinotubular junction and mid-ascending aorta. Arch tortuosity is estimated as the ratio of arch length divided by width. (B) Diagram illustrates total aortic tortuosity measurements. Total tortuosity was estimated by total length divided by total straight-line distance. (C) Candy-cane view with superimposed measurements on a representative CTA.

(Vall d'Hebron). In UTHealth subjects, the mean difference in arch length between 2D and 3D measurements was 1.9 mm (95% CI of -0.4 to 4.2 mm). The limits of agreement were from -5.1 to 8.9 mm and no point of mean difference was outside the limits of agreement. In Vall d'Hebron subjects, the mean difference was 1.2 mm (95% CI of -5.5 to 3.0 mm). The limits of agreement were from -14.5 to 12.1 mm and one point (10%) of mean difference was outside the limits of agreement. In addition, our measurements proved to be reliable when assessed by two independent observers. Inter-observer ICC was 0.9 (95% CI 0.83–0.94). Intra-observer ICC was 0.87 (95% CI 0.7–0.94), and 0.94 (95% CI 0.93–0.99).

3.3. BAV and aortic arch tortuosity

The demographic and clinical characteristics of BAV and TAV subjects were appropriately matched (Table 1). The prevalence of smoking (35% vs. 47%, $P = 0.04$) and European ancestry (76% vs. 52%, $P < 0.01$) were the only significant differences between groups.

Eight (6%) BAV and 17 (7%) TAV underwent AVR before the first available image for analysis ($P = 0.8$). The overall incidence of AVR was significantly higher in BAV subjects (60, 50%) than in TAV subjects (49, 21%, $P < 0.01$). The most frequent reason for valve surgery was aortic stenosis. In addition, 60 (80%) BAV vs. 30 (13%) TAV subjects underwent AAI ($P < 0.01$). One BAV subject with aortic aneurysm and one TAV subject with dissection died during the follow up period.

Aortic arch tortuosity was significantly larger in BAV subjects compared to TAV subjects (median 1.76; interquartile range [Q1–Q3]: 1.62–1.95) vs. 1.63 [1.53–1.78], $P < 0.01$. Arch length (149 [136–160] vs. 135 [122–152] mm, $P < 0.01$) and height (46 [41–53] vs. 39 [34–47] mm, $P < 0.01$) were also significantly larger in BAV subjects. Correspondingly, the arch angle was more acute in BAV subjects (70 [61–77] vs. 75 [68–81] degrees, $P < 0.01$). There was no significant difference in arch width between the two groups (83 [76–92] vs. 82 [73–91] mm,

$P = 0.25$). As expected, the maximum aortic diameter was larger in BAV than TAV subjects (41 [37–49] vs. 34 [31–40] mm, $P < 0.01$).

We also compared total aortic tortuosity with arch tortuosity in a subgroup of 128 subjects (48 BAV, 80 TAV) whose images included the abdominal aorta. We found that aortic arch tortuosity is not highly correlated with total aortic tortuosity ($R^2 = 0.18$) and is not significantly different between BAV and TAV subjects ($P = 0.61$).

The prevalence of TAD and AAI among BAV subjects with arch tortuosity in the highest ($n = 30$, from 1.95 to 2.99) and lowest quartiles ($n = 30$, from 1.36–1.62) was identical, despite significantly lower rates of diabetes, hypertension and smoking in the high tortuosity subgroup. BAV subjects with high tortuosity were more likely to report a family history of TAD and to harbor other congenital heart defects.

In a multivariable analysis adjusting for maximum aortic diameter, race and smoking, increased arch tortuosity remained independently associated with BAV (Table 2). Arch tortuosity was not correlated with age, height, BSA or maximum aortic diameter (Fig. 2).

3.4. TAD and aortic arch tortuosity

We compared the clinical characteristics and aortic measurements of 63 BAV subjects who presented with TAD to 57 BAV subjects without TAD. Subjects with TAD were significantly younger (50 SD 13 vs. 57 SD 13 years, $P < 0.01$) had increased body height (175 SD 7 vs. 168 SD 11 cm, $P < 0.01$) and had larger BSA (2.0 [1.9–2.2] vs. 1.9 [1.6–2.1] m², $P < 0.01$). Maximum aortic diameters were significantly larger in subjects with TAD (47 [43–53] vs. 37 [33–40] mm, $P < 0.01$), and these differences persisted after adjustment for body size (Z-score 4.30 [3.58–5.59] vs. 1.54 [0.79–2.36], $P < 0.01$). BAV subjects with TAD underwent aortic valve replacement (AVR) at similar rates to subjects without TAD (46% vs. 54%, $P = 0.36$). The most frequent indication for AVR in the subgroup with TAD was aortic regurgitation (AR, in 40%). In contrast, the most frequent indication for AVR in subjects without

Table 1
Patient characteristics.

	BAV (n = 120)	TAV (n = 234)	P value
Age (years)	54 ± 14	54 ± 14	0.84
Female	37 (31)	79 (34)	0.58
Hispanic ethnicity	31 (14)	25 (21)	0.10
Race			<0.01
Caucasian	91 (76)*	121 (52)	
African American	10 (8)*	60 (27)	
Other	18 (15)	40 (18)	
Patient height (cm)	175 [167–180]	172 [165–180]	0.69
BSA (m ²)	2.0 [1.8–2.2]	2.0 [1.8–2.2]	0.28
BMI (Kg/m ²)	29 [26–32]	29 [25–33]	0.88
Diabetes	20 (17)	58 (25)	0.09
Hypertension	70 (60)	156 (68)	0.15
Smoking	40 (35)^	107 (47)	0.04
FH aneurysm	3 (3)	5 (2)	0.71
FH dissection	0 (0)	1 (0.4)	1.00
FH BAV	0 (0)	0 (0)	–
Aortic coarctation	2 (2)	1 (0.4)	0.27
Ventricular septal defect	1 (0.9)	0 (0)	0.34
Atrial septal defect	0 (0)	1 (0.4)	1.00
Mitral valve prolapse	0	3 (1)	0.21
Arch tortuosity	1.76 [1.62–1.95]*	1.63 [1.53–1.78]	<0.01
Length (mm)	149 [136–160]*	135 [122–152]	<0.01
Width (mm)	83 [76–92]	82 [73–91]	0.25
Height (mm)	46 [41–53]*	39 [34–47]	<0.01
Angle (degree)	70 [61–77]*	75 [68–81]	<0.01
Diameter (mm)	41 [37–49]*	34 [31–40]	<0.01
Z-score	3.32 [1.52–4.72]*	0 [–0.06–0]	<0.01
Total aorta tortuosity (n = 128)	1.52 [1.46–1.57]	1.50 [1.46–1.56]	0.61
TAD	63 (52)	63 (26)	
Aneurysm	50 (41)*	35 (15)	<0.01
Dissection	13 (11)	28 (12)	0.75
Acute	10	23	
Chronic	3	5	
AVR before image	8 (6)	17 (7)	0.8
AVR	60 (50)*	49 (21)	<0.01
Stenosis	32	25	0.45
Regurgitation	15	4	
Other/unknown	13	20	
AAI	60 (50)*	30 (13)	<0.01
Aneurysm	50	12	
Dissection	10	18	
In-hospital death	1 (0.8)	2 (0.8)	

Data presented as Mean ± SD for data with normal distribution or median [interquartile range] for data with non-normal distribution, or n (%). BAV: bicuspid aortic valve; TAV: tricuspid aortic valve; BSA: body surface area; BMI: body mass index; FH: family history; TAA: thoracic ascending aorta; TAD: thoracic aorta aneurysm or dissection; AVR: aortic valve replacement; AAI: ascending aortic intervention.

^ P < 0.05.
* P < 0.01.

TAD was aortic stenosis (77%). All BAV patients in the TAD underwent AAI, except for 9 subjects (14%) with TAA aneurysm who deferred elective repair.

Pre-operative echocardiograms were available for 48 BAV subjects with TAD and 42 subjects without TAD. The prevalence of valve configurations other than Sievers 1 (L-R) was increased in subjects who presented with TAD (25% vs. 10%, *P* = 0.05). Subjects with TAD were more likely to present with AR (91% vs. 69%, *P* < 0.01) and had lower mean transaortic gradients (*P* = 0.04) and lower VD scores (2 [1–4] vs. 4 [2–7], *P* = 0.01).

Total aortic tortuosity, but not aortic arch tortuosity, was significantly greater in BAV subjects who presented with TAD (*P* = 0.04, *n* = 48). However, the contribution of total aortic tortuosity was not independently associated with TAD after adjustment for diameter, age and BSA in multivariable models.

3.5. BAV orientation and aortic arch tortuosity

Pre-operative transthoracic (42) and transesophageal (48) echocardiograms were available for 90 BAV subjects. Sievers 1 (R-L) was the

Table 2
Multivariable analysis.

Variable	Odds Ratio (95% CI)	P value
Aortic arch tortuosity	5.23 (1.67–16.36)	0.004
Maximum aortic diameter	1.13 (1.07–1.19)	<0.001
African American race	0.36 (0.15–0.86)	0.02
Smoking	0.64 (0.34–1.18)	0.15

CI: confidence interval.

most prevalent configuration (74, 82%). We defined atypical valve configurations as Sievers 2 (N-R) (14, 15%) or Sievers 3/unicuspid (2, 2%). Subjects with Sievers 1 and atypical orientations presented with similar clinical characteristics and aortic diameters (41 [36–47] vs. 47 [40–48] mm, *P* = 0.2). The prevalence of AS (58% vs 67%, *P* = 0.68), AR (81% vs. 73%, *P* = 0.95), and mean VD score (4 [1–5.5] vs. 3 [1.5–3.5], *P* = 0.3) were similar in both groups. However, subjects with atypical cusp orientations were more likely to develop TAD requiring aortic surgery than Sievers 1 subjects (75% vs. 48%, *P* = 0.05). However, arch tortuosity was not significantly increased in subjects with Sievers 2 or 3 orientations (*P* = 0.59).

4. Discussion

Arterial tortuosity is uniformly increased in patients with heritable TAD [23]. Markedly increased tortuosity is prevalent in patients with Loey-Dietz syndrome who develop early onset thoracic aortic dissections [31]. Vertebral artery tortuosity is also linearly associated with aortic events in patients with Marfan syndrome [22]. Aortic arch and total descending aortic tortuosity predicted survival and aortic events in patients with Type B aortic dissections [24]. These data highlight the potential prognostic impacts of tortuosity that merits follow up in larger prospective studies. However, the requirement for dedicated prospective imaging to quantitate tortuosity in 3D reconstructions of MR or CT images may limit the applicability of this approach.

In this study, we developed and validated a new approach to estimate aortic arch tortuosity using archival 2D images and implemented this method to investigate tortuosity in a hospital-based cohort of BAV patients. While BAV is associated with a 5–10 fold increased lifetime risk for TAD, aortic events occur in only 25% of patients during long-term follow up [6–8,10,32]. Current guidelines recommend surveillance of all BAV patients as if they are at equal risk for complications [1,2]. There is an urgent clinical need for reproducible biomarkers besides aortic diameter that can identify the high-risk subgroup, who could then be targeted for increased surveillance or early interventions. We hypothesize that arch tortuosity is increased in BAV and can serve as an accessible clinical indicator of vascular risk.

We found that aortic arch tortuosity was significantly increased in BAV patients and remained independently associated with BAV after adjusting for common clinical factors that are known to influence the incidence and progression of TAD. The most prevalent arch phenotype of our BAV cohort, characterized by increased length and vertex angle acuity, resembles the predominant arch morphology of patients with Turner syndrome, another genetically mediated disorder that confers a high risk for TAD [33,34]. Arch tortuosity may result from accelerated arterial elongation, which is a property of normal aging [35]. These effects may be more pronounced in BAV patients because of abnormal helical flow and increased shear stress in the ascending aorta [19,20].

We also compared aortic geometry and tortuosity between subgroups of BAV subjects. Subjects with the highest levels of arch tortuosity developed significant TAD with fewer cardiovascular risk factors and were more likely to have a family history of TAD or other congenital heart defects. These observations were replicated in clinical outcome studies investigating associations between cusp orientation, valve dysfunction and TAD [15,16]. Tortuosity may therefore identify BAV

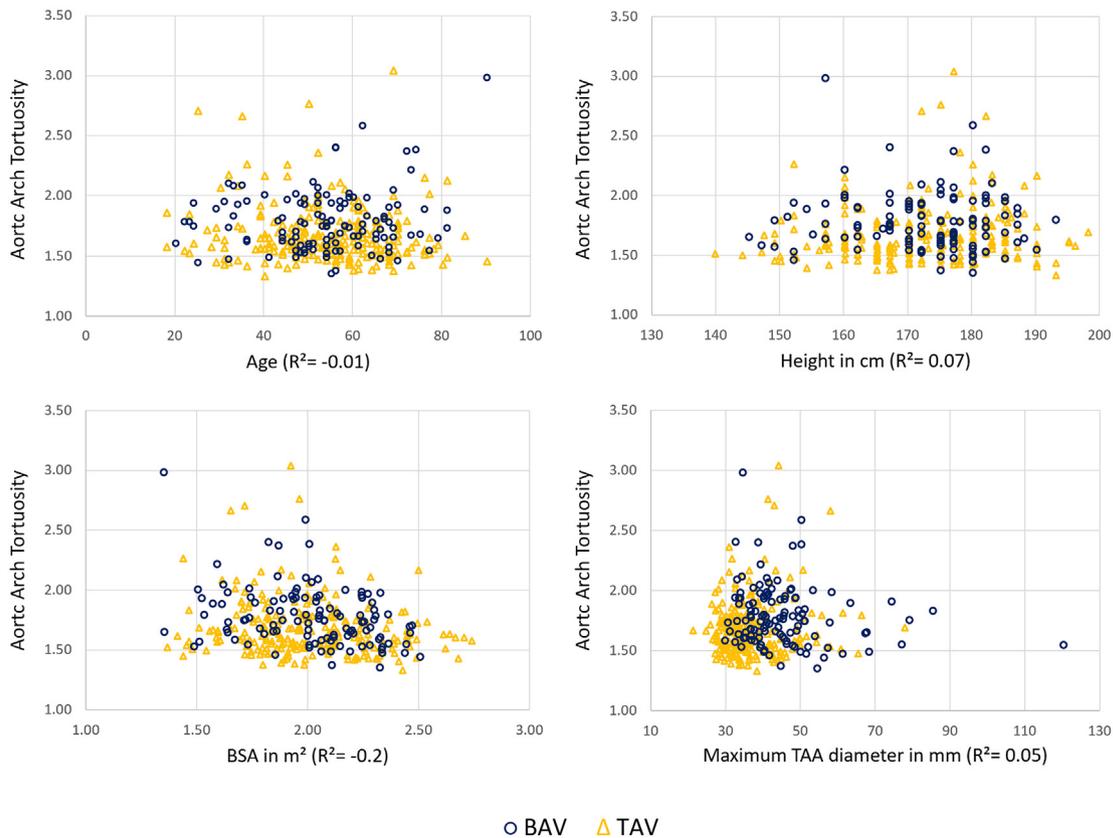


Fig. 2. Aortic arch tortuosity correlations. Correlation between aortic arch tortuosity and age, patient height, body surface area (BSA), and maximum thoracic ascending aorta (TAA diameter) in both bicuspid (BAV) and tricuspid aortic valve (TAV) subjects.

patients with an increased genetic predisposition to TAD, resulting in more aggressive valvular and aortic disease.

4.1. Limitations

This retrospective study of a hospital-based cohort may not accurately represent the natural history of other BAV patients. Because images were obtained for routine clinical indications and not for research, imaging protocols and image quality were not always optimal for measurement. 2D measurements may significantly underestimate tortuosity in cases where arch elongation occurs in more than one plane. Complete clinical data was not available for all ($n = 15$) of subjects, but the prevalence of missing data was not significantly different between BAV ($n = 8$) and TAV ($n = 7$) groups.

5. Conclusions

We found that aortic arch tortuosity is significantly increased in BAV subjects after adjustment for clinical and anatomic characteristics. Tortuosity is a promising metric to identify BAV patients who are at increased risk for thoracic aortic dilation or acute aortic dissection. This could result in improved surveillance and optimal timing of interventions. Prospective studies are in progress to investigate the impact of arch tortuosity on aneurysm progression and aortic dissection in younger patients.

Conflicts of interest

None.

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