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The Association between Morphological and Functional Characteristics of the Bicuspid Aortic Valve and Bicuspid Aortopathy

Bo Hwa Choi[1], Sung Min Ko[2], Je Kyoun Shin[3], Hyun Keun Chee[3], Jun Seok Kim[3]

[1]Department of Radiology, National Cancer Center, Goyang, Korea; [2]Department of Radiology, Wonju Severance Christian Hospital, Yonsei Wonju College of Medicine, Wonju, Korea; [3]Department of Cardiovascular Surgery, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Korea

Objective: To identify the association between morphological and functional characteristics of the bicuspid aortic valve (BAV) and bicuspid aortopathy and to identify the determinants of aortic dilatation using transthoracic echocardiography (TTE) and cardiac computed tomography (CCT).

Materials and Methods: This study included 312 subjects (mean [SD] age, 52.7 [14.3] years; 227 males [72.8%]) who underwent TTE and CCT. The BAVs were classified by anterior-posterior (BAV-AP) or right-left (BAV-RL) orientation of the cusps and divided according to the presence (raphe+) or absence of a raphe (raphe-) based on the CCT and intraoperative findings. The dimensions of the sinus of Valsalva and the proximal ascending aorta were measured by CCT. We assessed the determinants of aortic root and proximal ascending aortic dilatation (size index > 2.1 cm/m^2) by Univariable and multivariable logistic regression analyses.

Results: Of the 312 patients, BAV-AP was present in 188 patients (60.3%), and 185 patients (59.3%) were raphe+. Moderate-to-severe aortic stenosis (AS) was the most common hemodynamic abnormality (54.8%). The most common type of aortopathy was the combined dilated root and mid-ascending aortic phenotype (62.5%). On multivariable analysis, age and AS severity were significantly associated with aortic root dilatation ($p < 0.05$), and age, sex, and AS severity were significantly associated with ascending aortic dilatation ($p < 0.05$). However, the orientation of the cusps, presence of a raphe, and severity of aortic regurgitation were not associated with aortic root and ascending aortic dilatation.

Conclusion: BAV morphological characteristics were not determinants of aortic dilatation. Age, sex, and AS severity were predictors of bicuspid aortopathy. Therefore, age, sex, and AS severity, rather than valve morphology, need to be considered when planning treatment for BAV patients.

Keywords: *Ascending aorta; Bicuspid aortic valve; Multidetector computed tomography; Transthoracic echocardiography*

INTRODUCTION

Bicuspid aortic valve (BAV) is the most frequent congenital cardiac abnormality and may present in as many as 2% of the general population [1]. BAV is defined by the presence of two commissures in systole. However, the morphology of BAV is highly variable and is classified according to the number and size of the cusps, the position and symmetry of the cusps, and the number of commissures [2,3]. Heterogeneity in the BAV morphology is related to the patterns and frequency of aortic valve dysfunction and aortic dilatation [4]. Compared to the general population, BAV aortopathy is associated with a six-to-nine-fold increased risk of aortic complications, such as rupture and dissection, and thus, represents a striking risk factor for these catastrophic clinical events that are associated with high mortality and morbidity [5-7]. Therefore, it is important to precisely diagnose BAV and determine whether it is accompanied by aortopathy before severe complications

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Corresponding author: Sung Min Ko, MD, Department of Radiology, Wonju Severance Christian Hospital, Yonsei Wonju College of Medicine, 20 Ilsan-ro, Wonju 26426, Korea.
• E-mail: ksm9723@yahoo.co.kr

develop.

Transthoracic echocardiography (TTE) has been considered as the standard imaging procedure for diagnosing BAV [8]. Most published studies on the relationship between BAV and aortopathy were based on TTE findings. However, the diagnostic accuracy of TTE is limited by operator dependency and possible impairment due to poor acoustic window, a large body habitus, limited field of vision, or technical artifacts. Recently, Hillebrand et al. [9] demonstrated that concomitant aortic aneurysms and the presence of severe aortic valve calcifications resulted in an inaccurate diagnosis of BAV with TTE. In contrast, cardiac computed tomography (CCT) allows for detailed and accurate assessment of aortic valve morphology and ascending aorta dimensions in patients with BAV [10,11]. However, only few studies have investigated the association between the morphological and functional characteristics of BAV and aortic dimensions using CCT [12,13]. Moreover, most reports on bicuspid aortopathy have been reported in Western countries. Therefore, the aims of this study were to identify the association between the morphological and functional characteristics of BAV and bicuspid aortopathy and to identify the determinants of aortic dilatation using CCT in Korean patients with BAV.

MATERIALS AND METHODS

Patient Population

The Institutional Review Board of Konkuk Universtiy Medical Center approved this retrospective study (KUMC-2020-02-014) and waived the requirement to obtain informed consent. From January 2008 to April 2019, 312 patients with BAV (mean [SD] age, 52.7 [14.3] years; 227 males [72.8%]) underwent both TTE and CCT within four weeks at our institution. CCTs were conducted to evaluate the preoperative coronary artery anatomy, aortic valve morphology, presence and extent of aortic valve cusp calcification, and ascending aortic dimensions.

CT Imaging Protocol

All CT examinations were performed using a dual-source CT scanner (Somatom Definition, Siemens Medical Solutions). Prior to the examination, heart rate (HR) was measured. Patients with a pre-scan HR > 65 beats per min (bpm) and without contraindications for beta-blockers were given 50–100 mg metoprolol orally one hour prior to CCT. All patients received 0.6 mg nitroglycerin sublingually one minute before the examination.

The CCT scans were conducted 2 cm above the carina to the diaphragm excluding the entire aortic arch. Data were acquired in a craniocaudal direction with a detector collimation of 2 x 32 x 0.6 mm, slice acquisition of 2 x 64 x 0.6 mm, gantry rotation time of 330 ms, pitch of 0.20–0.43 adapted to HR, tube voltages of 100 or 120 kV for CCT, and a tube current-time product of 100–140 mAs per rotation for calcium scoring, and 100–280 mAs per rotation for CCT. A non-enhanced electrocardiography (ECG)-gated CCT scan, prospectively triggered at 75% of the R-R interval, was performed to measure the coronary artery and aortic valve calcium score. ECG-based tube current modulation was used for CCT, except for patients with mean HRs > 80 bpm or those with arrhythmia. The full dose window of 20–70% of the cardiac cycle was used in patients with HR ≤ 80 bpm. For all CT examinations, a Stellant D dual-head power injector (Medrad) was used to administer a 3-phase bolus at a rate of 4.5 mL/s. First, 70–80 mL iopromide (Ultravist 370®, Bayer Healthcare) was administered. Then, 45 mL of a 70%-to-30% blend of contrast media and saline was administered. Finally, 45 mL of saline was administered.

CT Image Reconstruction and Analysis

We reconstructed 10 transaxial CCT datasets at increments of 10% of the cardiac cycle from 0% to 90% of the R-R interval. The images were reconstructed with a slice thickness of 0.75 mm and a reconstruction increment of 0.4 mm. We reconstructed non-enhanced CT images with a section thickness of 3 mm and a reconstruction internment of 1.5 mm. After reconstruction, all datasets were transferred to a post-processing workstation (Vitrea 2, Vital Images).

We reconstructed cross-sectional transverse images during the whole cardiac cycle to acquire morphological aspects of the aortic valve using oblique coronal and oblique sagittal planes along the left ventricular outflow tract and an additional oblique transverse plane parallel to the aortic valve.

All images were reviewed by two radiologists with 16 and 5 years of experience, and the results were agreed upon. Both radiologists were blinded to the clinical and surgical data. The presence of BAV was confirmed by visualization of two cusps and commissures with or without a raphe during both systole and diastole. We adopted a simple dichotomous classification system using the orientation of the fused cusp and coronary ostium [14]. BAV was classified as type anterior-posterior (AP) orientation of the free edge of the cusps, with or without fusion of the right and left coronary cusps) or type right-left orientation (RL) of the free edge of the cusps, with or without fusion of the right or left coronary cusp and noncoronary cusps). BAV was further subdivided as the presence (raphe+) or absence of a raphe (raphe-) (Fig. 1) [13].

The measurement of the maximum dimension of the aortic sinuses of Valsalva was performed sinus to commissure in BAV with raphe and sinus to sinus in BAV without raphe in a double oblique transverse view of the aortic root. The maximum dimension of the tubular portion of the ascending aorta was measured in a double oblique transverse view obtained perpendicular to the aortic lumen (true short-axis image of the aorta) because the aorta had an oblique course [15]. The dimensions were measured with electronic calipers using an inner-edge to inner-edge technique at the mid-to-end systole (Fig. 2). We classified the ascending thoracic aorta into one of four main anatomical types depending on whether the segment of the vessel was predominantly involved in dilatation as follows [10]. In the normal aorta phenotype, all aortic dimensions were less than 2.1 cm/m^2 of body surface area (Fig. 3). Predominant aortic root dilatation (type 1) was defined as maximal aortic dilatation that exceeded 2.1 cm/m^2 at the level of the sinus of Valsalva. The middle ascending aortic phenotype (type 2) was defined as the maximal aortic dimension at the level of the middle

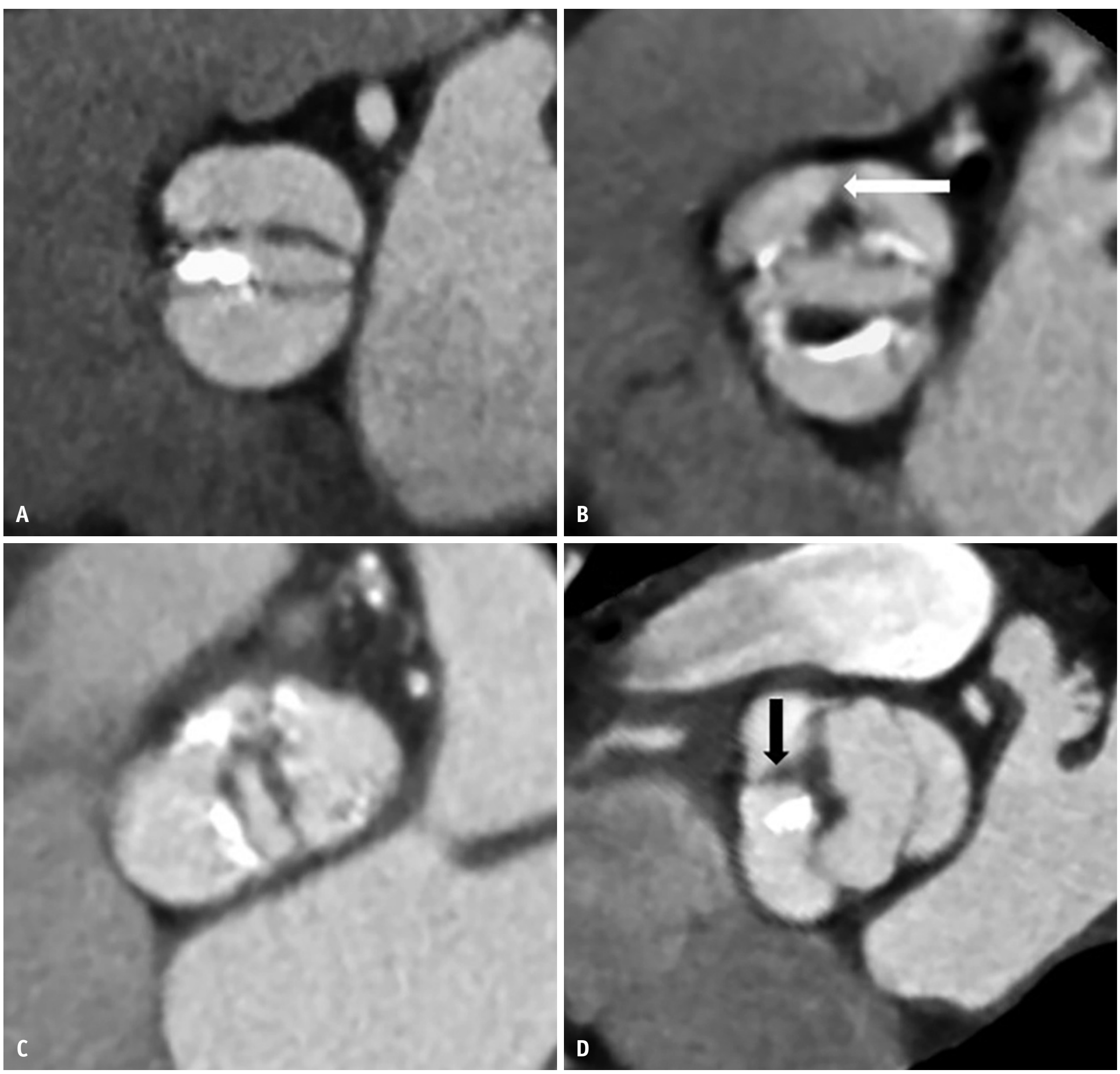

Fig. 1. BAV classification.
BAV-AP is defined as an AP orientation of the cusps **(A)** or a raphe (**B,** arrow). BAV-RL is defined as a RL orientation of the cusps **(C)** or a raphe (**D,** arrow). BAV is divided according to the presence **(B, D)** or absence **(A, C)** of a raphe. AP = anterior-posterior, BAV = bicuspid aortic valve, RL = right-left

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ascending tubular area exceeding 2.1 cm/m^2. The combined dilated root and mid-ascending aortic phenotype (type 3) was assigned when the maximal dimension measured at the level of the sinus of Valsalva and the middle ascending tubular aorta exceeded 2.1 cm/m^2 [16,17]. In addition, we also used the dichotomous classification of aortic root or mid-ascending aorta dilatation using aortic size index (2.1 cm/m^2) to determine the determinants of aortic dilatation

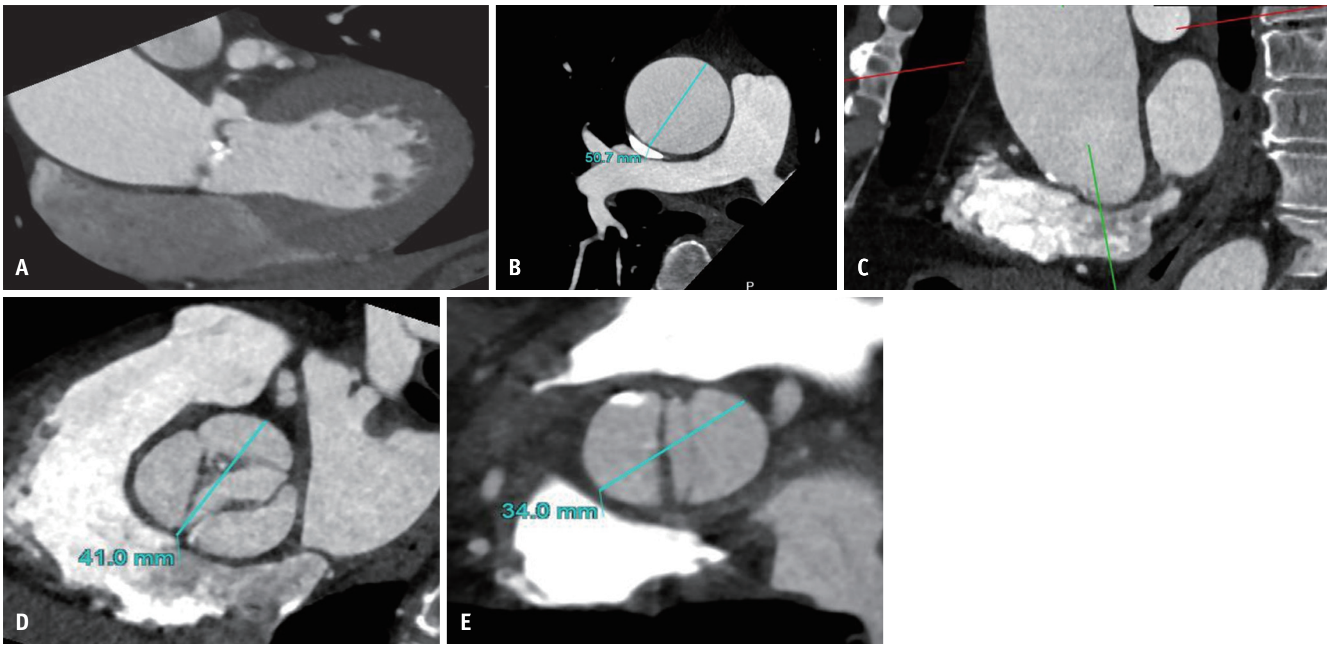

Fig. 2. Example of measurement of the aortic dimensions at different locations.
Oblique sagittal reformatted CT image shows sinus of Valsalva and tubular portion of ascending aorta at early-to-mid-systole **(A)**. The maximum dimension of the tubular portion of ascending aorta was measured in a double oblique transverse view **(B)** obtained perpendicular to the aortic lumen **(C)**. The maximum dimension of the sinus of Valsalva was measured sinus to commissure in BAV with raphe **(D)** and sinus to sinus in BAV without raphe **(E)** in a double oblique transverse view. The ascending aorta was assigned to one of four main anatomical phenotypes according to the vessel segment exclusively or predominantly involved in the dilatation. BAV = bicuspid aortic valve

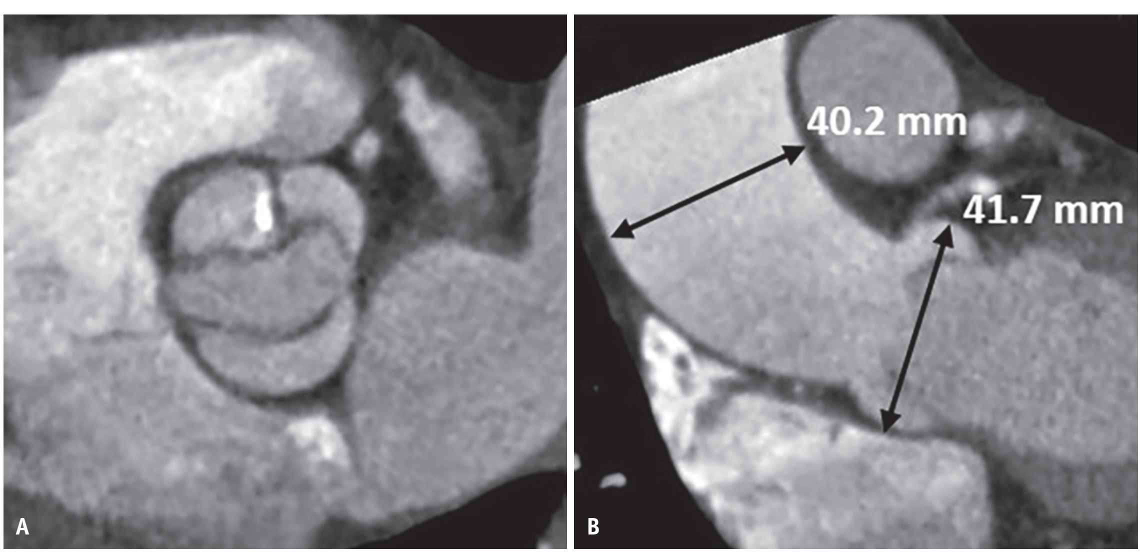

Fig. 3. BAV with anterior-posterior orientation of the free edge of the cusps with a raphe in a 47-year-old male. He had normal valvular function.
A. Double oblique CT reconstruction parallel to the aortic valve during systole demonstrates BAV with a fusion of the right and left coronary cusps. **B.** Double oblique coronal CT reconstruction through the left ventricular outflow tract during systole shows dimensions of the sinus of Valsalva (41.7 mm, 1.91 cm/m^2 of body surface area) and the tubular portion (40.2 mm, 1.84 cm/m^2 of body surface area). A normal aortic phenotype was considered because the two aortic dimensions were less than 2.1 cm/m^2 of the body surface area. BAV = bicuspid aortic valve

in statistical analyses. Aortic aneurysms were defined by dimensions greater than 50 mm.

Echocardiographic Evaluation

The aortic valve morphology and the severity of valvular dysfunction were recorded by cardiologists. Two-dimensional TTE was performed with a Vivid 7 device (GE Healthcare) and an Acuson Sequoia C512 apparatus (Siemens) with 2.5–3.5 MHz imaging transducers. The severity of aortic stenosis (AS) or regurgitation (AR) (mild, moderate, or severe) was assessed using parameters from the American College of Cardiology/American Heart Association guidelines [18]. Combined aortic stenosis and regurgitation (ASR) was classified as both AS and AR, and the severity of each valvular dysfunction was recorded. For example, combined severe AS and mild AR was classified as either "moderate or severe AS" and "non or mild AR." The left ventricular functional parameters were measured on 2D-TTE using a modified Simpson's method.

Statistical Analyses

The data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical data are presented as frequencies and percentages. Continuous variables are presented as mean ± SD or median with range. Independent *t* tests were used to compare continuous variables, and Fisher's exact test or chi-square tests were used to compare categorical variables between the groups with respect to BAV morphology and the presence of aortic dilatation. Variables with a $p < 0.05$ on Univariable logistic regression analysis were included in the multivariable logistic regression analysis to identify the independent determinants of aortic root or tubular dilatation. A p value of < 0.05 indicated significance for all analyses. All analyses were conducted using SAS v.9.2 (SAS Institute).

RESULTS

Patient Characteristics

Basic patient characteristics are summarized in Table 1. Detailed surgical findings on BAV morphology were available for 240 patients (76.9%). CCT was used to assess the BAV morphology in 72 patients (23.1%) not treated surgically because of insignificant valvular dysfunction. Of 312 patients with BAV, BAV-AP was present in 188 patients (60.3%), and a raphe was present in 185 patients (59.3%). Moderate-to-severe AS was the most common hemodynamic

Table 1. Patient Characteristics (n = 312)

Variables	
Age (years)	52.7 ± 14.3
Male, n (%)	227 (72.8)
Body surface area (m^2)	1.7 ± 0.2
Hypertension, n (%)	97 (31.1)
Hyperlipidemia, n (%)	52 (16.7)
Diabetes mellitus, n (%)	23 (7.4)
COPD, n (%)	13 (4.2)
Smoking, n (%)	117 (37.5)
NYHA class, n (I/II/III/IV)	149/97/58/8
Coronary artery disease, n (%)	29 (9.3)
Coronary calcium score, median (range)	0 (0–3,660)
Valve calcium score, median (range)	615 (0–14,073)
BAV morphology	
Raphe+/raphe–, n (%)	185 (59.3)/127 (40.7)
BAV-AP/BAV-RL, n (%)	188 (60.3)/124 (39.7)
Aortic phenotype, n (%)	
Normal	39 (12.5)
Root dilatation	33 (10.6)
Mid ascending aorta dilatation	45 (14.4)
Combined root and ascending aorta dilatation	195 (62.5)
Aorta aneurysm, n (%)	72 (23.1)
AS, n (%)	
None or mild	141 (45.2)
Moderate or severe	171 (54.8)
AR, n (%)	
None or mild	212 (67.9)
Moderate or severe	100 (32.1)
Aortic root	
Dimension (mm)	39.6 ± 6.1
Size index (cm/m^2)	2.3 ± 0.3
Size index > 2.1 cm/m^2	228 (73.1)
Tubular portion	
Dimension (mm)	43.0 ± 7.6
Size index (cm/m^2)	2.5 ± 0.5
Size index > 2.1 cm/m^2	240 (76.9)
Echocardiographic data	
LVEF (%)	63.1 ± 12.1
End diastolic volume (mL)	148.4 ± 73.4
End systolic volume (mL)	57.8 ± 44.8
AR/AS/ASR/Normal, n	104/97/92/19
Aortic valve surgery, n (%)	240 (76.9)
Aortic surgery, n (%)	121 (38.8)

AP = anterior-posterior, AR = aortic regurgitation, AS = aortic stenosis, ASR = aortic stenosis and regurgitation, BAV = bicuspid aortic valve, COPD = chronic obstructive pulmonary disease, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, RL = right-left abnormality (54.8%). Sixty patients (19.2%) had normally functioning BAVs or hemodynamically insignificant mild AS or AR, and 273 patients (87.5%) had dilated aortic root or ascending aortas, including 72 patients (23.1%) with ascending aortic aneurysms. The most frequent pattern of aortic dilation was type 3 aortopathy (195 [62.5%] patients), followed by type 2 (45 [14.4%] patients) and type 1 (33 [10.6%] patients). Aortic valve surgery was performed in 240 patients (76.9%), and ascending aortic grafts or wrapping surgery was performed in 121 patients (38.8%) to correct defective aortic valves and/or pathology involving the ascending aorta.

Determinants for Aortic Root and Ascending Aortic Dilatation

Patients with dilated aortic roots were older (p = 0.016), more likely to be female (p = 0.024), and had an increased frequency of RL-type BAVs (p = 0.029) (Table 2, Fig. 4). In multivariable regression analysis, a younger age and insignificant AS were significantly associated with aortic root dilatation ($p < 0.05$) (Table 3). Patients with ascending aorta dilatation were older ($p < 0.001$), were more likely to

Table 2. Comparison of Patients with and without Aortic Root Dilation Greater than 2.1 cm/m^2

	≤ 2.1 cm/m^2 (n = 84)	> 2.1 cm/m^2 (n = 228)	P
Age (years)	49.5 ± 14.7	53.8 ± 14.0	0.016
Male, n (%)	69 (82.1)	158 (69.3)	0.024
Hypertension, n (%)	23 (27.4)	74 (32.5)	0.390
BAV calcium score	1515.5 ± 2053.3	1806.4 ± 2446.8	0.333
BAV type, n (%)			0.062
No raphe	27 (32.1)	100 (43.9)	
Raphe	57 (67.9)	128 (56.1)	
BAV type, n (%)			0.029
AP	59 (70.2)	129 (56.6)	
RL	25 (29.8)	99 (43.4)	
AS severity, n (%)			0.992
None or mild	38 (45.2)	103 (45.2)	
Moderate or severe	46 (54.8)	125 (54.8)	
AR severity, n (%)			0.424
None or mild	60 (71.4)	152 (66.7)	
Moderate or severe	24 (28.6)	76 (33.3)	

AP = anterior-posterior, AR = aortic regurgitation, AS = aortic stenosis, BAV = bicuspid aortic valve, RL = right-left

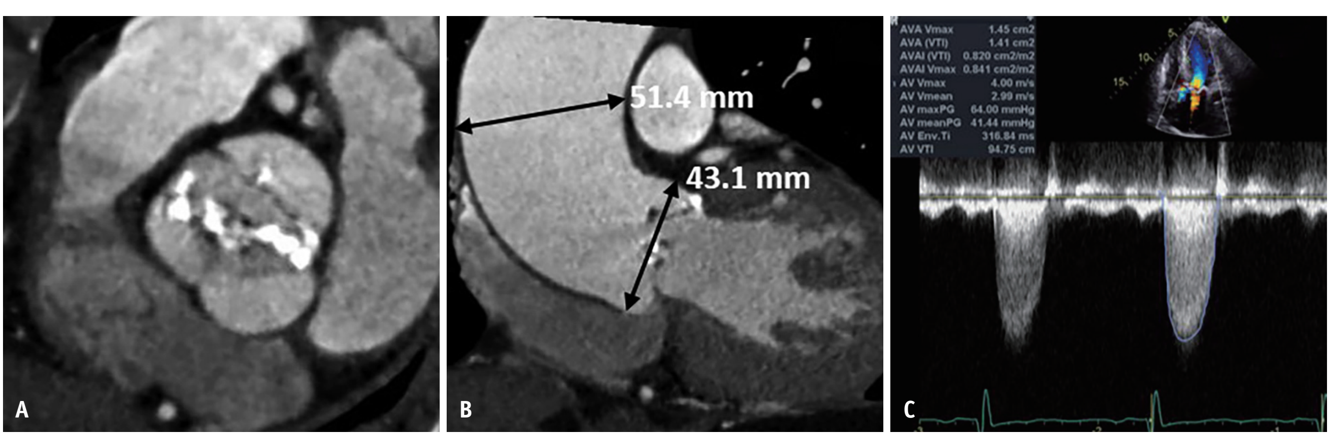

Fig. 4. BAV with right-left orientation of the free edge of the cusps without raphe in a 61-year-old female.
A. Double oblique CT reconstruction parallel to the aortic valve during systole demonstrates thickened, calcified cusps of the BAV with a fusion of the right and noncoronary cusps. **B.** Double oblique coronal CT reconstruction through the left ventricular outflow tract during systole shows dimensions of the sinus of Valsalva (43.1 mm, 2.51 cm/m^2 of body surface area) and the tubular portion (51.4 mm, 2.99 cm/m^2 of body surface area). A combined dilated root and mid-ascending aortic phenotype (type 3) was considered because the two aortic dimensions exceeded 2.1 cm/m^2 of body surface area. **C.** Continuous-wave Doppler recording of the aortic stenosis jet from an apical approach shows a maximum velocity of 4.0 m/sec. The continuity equation of the aortic valve area was 1.41 cm^2, corresponding to moderate aortic stenosis. BAV = bicuspid aortic valve

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be female ($p < 0.001$), had higher valve calcium scores ($p < 0.001$), more likely without raphe ($p = 0.011$), an increased frequency of RL-type BAVs ($p = 0.008$), moderate-to-severe AS ($p < 0.001$), and no or mild AR ($p < 0.001$) (Table 4). In multivariable regression analysis, older age, more likely to be female, and moderate-to-severe AS were significantly associated with ascending aortic dilatation ($p < 0.05$) (Table 5). Hypertension, orientation of the cusps, presence or absence of a raphe, and AR severity were not significant determinants of aortic root and ascending aortic dilatation.

DISCUSSION

The major findings of this study are as follows. First, the morphological characteristics of BAV, such as the orientation of the cusps and the presence or absence of a raphe, and the severity of AR were not associated with aortic root and ascending aortic dilatation in the multivariable regression analysis. Second, age and AS severity were the only determinants of aortic root. Third, age, sex, and AS severity were the only determinants of ascending aortic dilatation.

Inconsistent results have been reported on the association between specific BAV configurations and aortopathy (Table 6). Different BAV morphologies may lead to altered flow patterns, different wall strains, shear stress, and other stress factors that can affect the integrity of the aortic media differently. Ruzmetov et al. [19] suggested connections between the RL-type and ascending aortic dilatation and between the AP-type and aortic root dilatation. Kang et al. [13] showed that patients with AP-

Table 3. Univariable and Multavariable Regression Analyses of the Association between Aortic Root Dilatation and Variables

	Univariable			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (years)	0.94	0.92–0.97	< 0.001	0.97	0.94–1.00	0.025
Sex (male 1, female 0)	6.81	1.60–29.07	0.010	2.87	0.61–13.60	0.184
Hypertension	0.92	0.42–2.00	0.823			
AS severity (moderate or severe 1)	0.09	0.03–0.26	< 0.001	0.19	0.06–0.64	0.007
AR severity (moderate or severe 1)	4.70	2.22–9.96	< 0.001	1.54	0.46–5.08	0.482
BAV raphe	2.43	1.06–5.56	0.035	1.13	0.40–3.20	0.812
BAV cusps orientation (AP 0, RL 1)	0.51	0.23–1.13	0.099			
End diastolic volume	1.01	1.00–1.01	0.002	1.00	0.99–1.02	0.636
End systolic volume	1.01	1.00–1.01	0.034	0.99	0.97–1.01	0.445

AP = anterior-posterior, AR = aortic regurgitation, AS = aortic stenosis, BAV = bicuspid aortic valve, CI = confidence interval, OR = odds ratio, RL = right-left

Table 4. Comparison of Patients with and without Ascending Aortic Dilation Greater than 2.1 cm/m^2

	≤ 2.1 cm/m^2 (n = 72)	> 2.1 cm/m^2 (n = 240)	*P*
Age (years)	41.4 ± 14.8	55.9 ± 12.4	< 0.001
Male, n (%)	69 (95.8)	158 (65.8)	< 0.001
Hypertension, n (%)	16 (22.2)	81 (33.8)	0.064
BAV calcium score	632.2 ± 1625.1	2056.9 ± 2432.6	< 0.001
BAV type, n (%)			0.011
No raphe	20 (27.8)	107 (44.6)	
Raphe	52 (72.2)	133 (55.4)	
BAV type, n (%)			0.008
AP	53 (73.6)	135 (56.3)	
RL	19 (26.4)	105 (43.8)	
AS severity, n (%)			< 0.001
None or mild	60 (83.3)	81 (33.8)	
Mod or severe	12 (16.7)	159 (66.3)	
AR severity, n (%)			< 0.001
None or mild	30 (41.7)	182 (75.8)	
Mod or severe	42 (58.3)	58 (24.2)	

AP = anterior-posterior, AR = aortic regurgitation, AS = aortic stenosis, BAV = bicuspid aortic valve, RL = right-left

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Table 5. Univariable and Multivariable Regression Analyses of the Association between Ascending Aortic Dilatation and Variables

	Univariable			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (years)	1.08	1.06–1.11	< 0.001	1.06	1.03–1.09	< 0.001
Sex (male 1, female 0)	0.08	0.03–0.27	< 0.001	0.01	0.02–0.46	0.003
Hypertension	1.78	0.96–3.30	0.066			
AS severity (moderate or severe 1)	9.82	5.00–19.28	< 0.001	5.34	2.28–12.51	< 0.001
AR severity (moderate or severe 1)	0.23	0.13–0.40	< 0.001	1.02	0.37–2.83	0.966
BAV raphe	0.48	0.27–0.85	0.012	1.01	0.41–2.44	0.991
BAV cusps orientation (AP 0, RL 1)	2.17	1.21–3.89	0.009	0.83	0.37–1.90	0.664
End diastolic volume	0.99	0.99–1.00	< 0.001	0.99	0.98–1.01	0.277
End systolic volume	0.99	0.99–1.00	0.002	1.01	0.99–1.03	0.254

AP = anterior-posterior, AR = aortic regurgitation, AS = aortic stenosis, BAV = bicuspid aortic valve, CI = confidence interval, OR = odds ratio, RL = right-left

Table 6. Association between BAV Morphology and Aortopathy: A Literature Review

References	Published Year	Mean Age	No. of Patients	Major Findings	Modality
Kang et al. [13]	2013	54.6	167	Patients with AP morphotype had a relatively normal ascending aorta, whereas ascending aorta and aortic arch dilatation was more often seen in patients with RL morphotype	CT
Ruzmetov et al. [19]	2015	15	642	A connection between RL morphotype and ascending aorta dilatation, and between AP morphotype and aortic root dilatation	TTE
Shin et al. [12]	2015	51.7	209	AP morphotype was associated with a larger annulus and smaller ascending aorta	CT
Sievers et al. [20]	2016	56.8	828	It is insufficient to predict the morphology of BAV aortopathy only in relation to the BAV phenotype	Intraoperative finding
Kong et al. [21]	2017	47	2118	The presence of a raphe was associated with a higher prevalence of significant aortic stenosis and regurgitation, but was not associated with the pattern of aortic dilation	TTE

AP = anterior-posterior, BAV = bicuspid aortic valve, CT = computed tomography, RL = right-left, TTE = transthoracic echocardiography

type BAVs had relatively normal ascending aortas, whereas ascending aortic and aortic arch dilatation was seen more often in patients with RL-type BAVs. Recent large-scale studies, however, suggested that predicting the pattern of BAV aortopathy only in relation to BAV morphology is insufficient [10,20,21]. Our results are consistent with these large-scale studies. Interestingly, Schnell et al. [22] investigated the differences in aortic shape and blood flow patterns between BAV relatives and healthy controls using four-dimensional flow MRI. This study showed that BAV relatives exhibited altered aortic shapes and increased blood flow, despite the absence of valvular disease or aortic dilatation, suggesting that an inheritable component of BAV-related aortopathy affected the aortic shape and aberrant blood flow.

BAV is frequently associated with valve dysfunction. However, controversy exists over whether combined valvular dysfunction in patients with BAV affects the pattern of aortopathy [13,21]. Sievers et al. [20] found that stenotic BAVs showed significantly more ascending aortic dilatation and less combined root and ascending aortic dilatation, whereas insufficient BAVs were associated with significantly more dilated aortic root and combined root and ascending aortic dilatation. However, we found that the most common pattern of bicuspid aortopathy was combined root and ascending aortic dilatation. Furthermore, a high frequency of indexed ascending aortic dilatation was significantly associated with AS severity. In contrast, insignificant AS was associated with indexed aortic root dilatation. Sievers et al. [20] also reported that several patients showed a combined root and ascending aortic dilatation despite having trace AR, suggesting a minimal association between AR and bicuspid aortopathy. Therefore, we assume that the flow disturbance caused by AS may be related to ascending aortic dilatation.

Among the clinical factors of patients with BAV, only age was a determinant of both aortic root and ascending aortic dilatation. Most previous studies have shown that older patients with BAV more frequently had aortopathy than younger patients with BAV, but the association between age and the type of aortopathy is controversial [13,23,24]. Interestingly, in our study, older age had a positive effect on aortic root dilatation and a negative effect on ascending aortic dilatation. In addition, bicuspid aortopathy occurs more frequently in males than in females [25-27]. According to a recent multicenter study, males more frequently had isolated dilatation of the sinus of Valsalva or sinotubular junction and diffuse dilatation of the aortic root and ascending aorta than females [25]. However, our results suggested that sex was not a significant determinant of aortic root dilatation but of ascending aortic dilatation. One reason underlying these differences is that our study included a smaller proportion of female patients (27.2%) and patients with insignificant aortic valvular dysfunction (19.2%). A second reason could be inter-ethnic differences. Kong et al. [28] reported that Europeans with BAV had a diffusely dilated type of bicuspid aortopathy, unlike Asians. Our study included only Korean patients. Therefore, further studies are required to validate our results on the association between aortopathy and clinical variables, such as age and sex.

Most studies on the relationship between BAV and aortopathy have used TTE, which is a non-invasive and standard diagnostic tool [19,21,29,30]. However, TTE had suboptimal sensitivity for diagnosing BAV because of operator dependence [9,31]. Moreover, TTE has limitations in evaluating the morphology of BAVs with severe valvular calcifications and in assessing the dimensions of the distal ascending aorta and aortic arch [9,32,33]. In contrast, CCT provides a detailed morphology of BAVs and the patterns of valvular calcifications [34-37]. In particular, CCT provides clues regarding the difference between a raphe in BAV and a degenerative commissural fusion in the tricuspid aortic valve in patients with severe valvular calcifications [35]. Previously, we reported that the accuracy of CCT in evaluating the orientation of the cusps and the presence of a raphe in patients with BAV was 93.5%, using surgical findings as a reference [12]. CCT can accurately measure the dimensions of the aortic root. In our study, the maximum dimension of the aortic sinuses of Valsalva was measured on a cross-section perpendicular to the long axis of the aortic root at the level of the maximal dimension because the aortic root was not symmetric [38]. In addition, CCT may be useful to rule out co-existing congenital abnormalities, such as coarctation of the aorta and coronary artery stenoses. For these reasons, we evaluated bicuspid aortopathy using CCT.

According to our results, the clinical heterogeneity of BAV aortopathy necessitates individualized treatment that considers a patient's specific characteristics, such as age, sex, and comorbidity of AS, rather than valve morphology. Therefore, we recommend periodic CCT imaging follow-up in patients with BAV and moderate-to-severe AS.

Our study had several limitations. First, this study was limited by its retrospective and single-center design. We could not explain the influence of age, which accounted for the flaw in our analysis of BAV morphological properties and the association with dilatation of the aorta. Therefore, prospective and multicenter studies are needed to clarify the relationship between BAV and aortopathy. Second, most included patients had significant valvular dysfunction requiring surgery, and only 60 patients (19.2%) showed normal or insignificant valvular dysfunction. This may not be free from selection bias. Third, our CCT protocol did not scan the distal ascending aorta or aortic arch. Further studies need to include more patients without valvular dysfunction and a CT protocol that covers the entire aorta. Finally, the patients' genetic variant information was not available; therefore, we could not consider this factor when analyzing the determinants of aortopathy.

In conclusion, the morphological characteristics of BAV were not associated with bicuspid aortopathy. Age and AS severity were determinants of bicuspid aortopathy. Sex was only associated with ascending aortic dilatation. Further studies are needed to investigate the discrepancy between our results and previous studies on the importance of morphological and functional characteristics of BAV in predicting bicuspid aortopathy phenotypes.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Sung Min Ko, Jun Seok Kim. Data curation: Bo Hwa Choi, Sung Min Ko, Jun Seok Kim. Formal analysis: Bo Hwa Choi, Sung Min Ko. Investigation: Bo Hwa Choi, Je Kyoun Shin. Methodology: Bo Hwa Choi, Sung Min Ko. Project administration: Sung Min Ko. Resources: Sung Min Ko, Je Kyoun Shin, Hyun Keun Chee. Supervision: Sung Min Ko. Validation: Sung Min Ko, Je Kyoun Shin, Jun Seok Kim. Visualization: Sung Min Ko, Hyun Keun Chee. Writing—original draft: Bo Hwa Choi. Writing—review & editing: Bo Hwa Choi, Sung Min Ko, Hyun Keun Chee.

ORCID iDs

Bo Hwa Choi
https://orcid.org/0000-0001-7276-1579
Sung Min Ko
https://orcid.org/0000-0002-7420-6269
Je Kyoun Shin
https://orcid.org/0000-0003-4499-939X
Hyun Keun Chee
https://orcid.org/0000-0001-7041-352X
Jun Seok Kim
https://orcid.org/0000-0002-2547-9674

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