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Association Between Bicuspid Aortic Valve Phenotype and Patterns of Valvular Dysfunction and Bicuspid Aortopathy

Comprehensive Evaluation Using MDCT and Echocardiography

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OBJECTIVES We sought to define the clinical importance of an integrated classification of bicuspid aortic valve (BAV) phenotypes and aortopathy using multidetector computed tomography (MDCT).

BACKGROUND An association between BAV phenotypes and the pattern of valvular dysfunction or bicuspid aortopathy has yet to be definitely established.

METHODS The study cohort included 167 subjects (116 men, age 54.6 ± 14.4 years) who underwent both MDCT and transthoracic echocardiography from 2003 to 2010. Two BAV phenotypes—fusion of the right and left coronary cusps (BAV-AP) and fusion of the right or left coronary cusp and noncoronary cusp (BAV-RL)—were identified. Forty-five patients showed normal aortic dimensions and were classified as type 0. In the remaining patients, hierarchic cluster analysis showed 3 different types of bicuspid aortopathy according to the pattern of aortic dilation: type 1 (aortic enlargement confined to the sinus of Valsalva [n = 34]), type 2 (aortic enlargement involving the tubular portion of the ascending aorta [n = 49]), and type 3 (aortic enlargement extending to the transverse aortic arch [n = 39]).

RESULTS The prevalence of BAV-AP and BAV-RL was 55.7% and 44.3%, respectively. Comparing BAV-AP and BAV-RL, no differences in age or in the prevalence of male sex were determined. However, significant differences in the valvular dysfunction pattern were noted, with moderate-to-severe aortic stenosis predominating in patients with BAV-RL (66.2% vs. 46.2% in BAV-AP; $p = 0.01$), and moderate-to-severe aortic regurgitation in BAV-AP (32.3% vs. 6.8% in BAV-RL; $p < 0.0001$). A normal aorta was the most common phenotype in BAV-AP patients (33.3% vs. 18.9% in BAV-RL; $p = 0.037$), and type 3 aortopathy was the most common phenotype in BAV-RL patients (40.5% vs. 9.7% in BAV-AP; $p < 0.0001$).

CONCLUSIONS The patterns of valvular dysfunction and bicuspid aortopathy differed significantly between the 2 BAV phenotypes, suggesting the possibility of etiologically different entities. (J Am Coll Cardiol Img 2013;6:150–61) © 2013 by the American College of Cardiology Foundation

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Bicuspid aortic valve (BAV) is the most common congenital malformation, and it is responsible for a significant proportion of aortic valve replacements in adults (1–3). In addition to the marked phenotypic heterogeneity of BAV, there is a strong association with dilation of the ascending aorta (4–7). Indeed, aortopathy in BAV is a challenging clinical issue, and both pathogenesis and treatment are controversial. Moreover, not only is there marked variability in the phenotype of bicuspid aortopathy, but the presence and severity of the aortic dilation appear to be independent of the degree of valvular dysfunction (8–11). A sophisticated morphogenetic study showed that BAVs with different phenotypes develop at different embryonic stages and can, therefore, be viewed as etiologically distinct entities (12). It also has been suggested that the same etiological factors giving rise to the different BAV phenotypes are involved in the occurrence and progression of the associated valvular dysfunction or bicuspid aortopathy (12). However, although an integrated phenotypic classification that takes into account both BAV and the bicuspid aortopathy seems to be a logical approach to better understanding these pathologies, only a few clinical reports are available, and their therapeutic impact has not been fully explored (5,13–18).

See page 162

Echocardiography is the main imaging modality used to evaluate aortic valve and aortic pathology in patients with BAV, but this modality suffers from inherent flaws in terms of limited resolution and its inability to assess the entire aorta. Recently, excellent images of both the aortic valve and the aorta along its complete length have been obtained with computed tomography and magnetic resonance imaging in routine clinical practice. Accordingly, these techniques are being used with increasing frequency to better assess BAV and bicuspid aortopathy (17,18). Nonetheless, most studies published thus far have focused on pathology of either the aortic valve or the aorta itself, seldom considering the possible occurrence in both (5,13–15,17,18). Furthermore, those studies failed to thoroughly evaluate hemodynamic data obtained by echocardiography. Consequently, a potential association between BAV phenotypes and valvular dysfunction has not been seriously considered in the literature. Therefore, the aims of the present study were to: 1) evaluate bicuspid aortopathy phenotypes in patients with different types of BAV; and 2) assess the potential association between these 2 disease entities and clinical parameters, including hemodynamic variables. In this comprehensive evaluation, both echocardiography (to assess valvular dysfunction) and multidetector computed tomography (MDCT) (to phenotypically classify BAV and bicuspid aortopathy) were used.

METHODS

Subjects. From April 2003 to August 2010, 198 patients with BAV underwent MDCT to evaluate the coronary artery anatomy, aortic valve morphology including calcification, and aorta dilation for pre-operative evaluation. All patients were symptomatic or showed marked mediastinal widening and were referred for consultation of the timing of surgical intervention. From 2003 to 2006, 55 patients underwent MDCT examination with a 16-detector MDCT; from 2007 to 2010, 143 patients were evaluated with a dual-source MDCT scanner. Of these 198 patients, 31 were excluded from the study because the MDCT datasets did not cover the entire aortic arch and descending thoracic aorta. Thus, the study population consisted of 167 patients (mean age, 54.6 ± 14.4 years), of which 116 were men (69.0%). This retrospective study was approved by our institutional review board.

MDCT technique. No patients needed pharmacological agents to control heart rate during the MDCT examinations, as their heart rates were <85 beats/min; however, all patients received 0.6-mg nitroglycerin sublingually 1 min before the examination to dilate the coronary arteries if the patients had no contraindication. Contrast agent was administered using a bolus-tracking technique. For all computed tomography (CT) studies, a dual-head power injector (Stellant D, Medrad, Indianola, Pennsylvania) was used to administer the 2-phase bolus at a rate of 3.5 to 4.0 ml/s, with a total volume of 100 ml of iomeprol that has the iodine concentration of 400 mg/ml (Iomeron 400, Bracco Imaging, Milan, Italy), followed by 40 ml of saline chaser. The bolus tracking method was used for the start of the scan; CT image acquisition was started 7 s after the signal density reached a pre-defined threshold of 120 Hounsfield units at the region of interest on the ascending aorta.

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation
AS = aortic stenosis
BAV = bicuspid aortic valve
BAV-AP = bicuspid aortic valve with fusion of the right and left coronary cusps
BAV-RL = bicuspid aortic valve with fusion of the right or left coronary cusp and noncoronary cusp
CT = computed tomography
ECG = electrocardiogram
MDCT = multidetector computed tomography
Vmax = peak systolic velocity

CT examinations were performed from 2003 to 2006 using a 16-detector MDCT scanner (Somatom Sensation 16, Siemens Medical Solutions, Erlangen, Germany), and from 2007 to 2010 using a dual-source MDCT scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany). A detector collimation was 16 × 0.75 mm (16-detector) and 2 × 32 × 0.6 mm (dual source), with a slice acquisition of 16 × 0.75 mm (16-detector) and 64 × 0.6 mm by means of a z-flying focal spot technique (dual source). The gantry rotation time was 375 ms (16-detector) and 330 ms (dual source), the pitch 0.2 (16-detector) and 0.20 to 0.43 (adapted to heart rate, dual-source), the tube voltage 100 to 120 kVp, and the tube current 600 mAs (16-detector) and 320 mAs per rotation (dual source). Electrocardiogram (ECG)-based tube current modulation was not implemented. Data acquisition was performed during an inspiratory breath-hold, while the ECG was recorded simultaneously for retrospective gating of the data. Radiation dose reports were available in 117 patients who had undergone CT exam using dual-source CT, and the mean estimated radiation dose was 16.49 ± 7.44 mSv.

CT image reconstruction and analysis. To assess the aortic valve, images were reconstructed parallel to the aortic valve plane with retrospective ECG gating at every 10% of the cardiac cycle. A monosegment reconstruction algorithm was used for image reconstruction. Reconstruction parameters consisted of an image matrix of 512 × 512 pixels, a section thickness of 3 mm in 3-mm increments, and a medium-smooth convolution kernel (B30f). Oblique-sagittal images, which were parallel to the aortic arch ("arch view"), were also reconstructed at the mid-diastolic phase for the aortic root and thoracic aorta measurement. Once the images were reconstructed, the image sets were transferred to the homemade picture archiving and communication system (Petavision, Asan Medical Center, Seoul, Republic of Korea), with which the evaluation of the phenotype of aortic valve and measurement of the thoracic aorta were performed.

BAV was defined as the presence of 2 cusps and commissures, with or without raphe in either structure. Each aortic valve was analyzed and characterized on the basis of the acquired orthogonal views. Systolic and diastolic images were used to identify the cusp separation and the site of leaflet fusion, with particular attention paid to the opening motion of the aortic cusp during systole. The 2 commissures were visualized only during systole, when there was clear separation of the leaflets. The remaining ridge and nonseparating border observed during systole represent the raphe. BAV phenotypes were defined by the presence and orientation of the cusps and raphes as follows (16,18):

1. Two completely developed cusps and commissures without a raphe. The orientation of the free edge of the cusp defined the anterior–posterior and right–left forms of BAV (BAV-AP and BAV-RL, respectively).
2. A malformed, more or less obliterated commissure, defined as a raphe, extending from the commissure to the free edge of the 2 underdeveloped conjoint cusps. With respect to the orientation of the raphe, the following phenotypes were distinguished: type 1 (fusion of the right and left coronary cusps); type 3 (fusion of the right and noncoronary cusps); and type 4 (fusion of the left and noncoronary cusps). In the absence of raphe, BAV with both coronary arteries originating from the anterior cusp was classified as type 2, and BAV with both coronary arteries originating from each cusp as type 5 (Figs. 1 and 2). Thus, types 1 and 2 represent BAV-AP with and without raphe, and types 3, 4, and 5, BAV-RL with and without raphe.

Two experienced cardiac radiologists (J.W.K. and D.H.Y.) independently analyzed the CT images for BAV phenotype. The results were identical in all patients except 1, for whom a consensus was subsequently reached. The degree of BAV calcification was scored as 0 (normal), 1 (mild), 2 (moderate), or 3 (severe) (18).

Thoracic aortic diameter was measured at 10 levels as previously described (Fig. 3) (17): A, aortic annulus; B, sinuses of Valsalva; C, sinotubular junction; D, tubular portion of the ascending aorta; E, proximal to the innominate artery or common trunk in case of a bovine arch; F, distal to the innominate artery or common trunk; G, proximal to the left subclavian artery; H, distal to the left subclavian artery; I, proximal descending aorta; and J, distal descending thoracic aorta at the level of the diaphragmatic hiatus as seen on the reconstructed oblique-sagittal datasets. The dimension of each level was determined as the maximum value measured at the oblique-sagittal image sets that was parallel to the aortic arch course ("arch view" images).

In a normal aorta, the diameter of the annulus was <3.0 cm, the sinus of Valsalva <4.0 cm, the tubular portion of the ascending aorta <4 cm, and

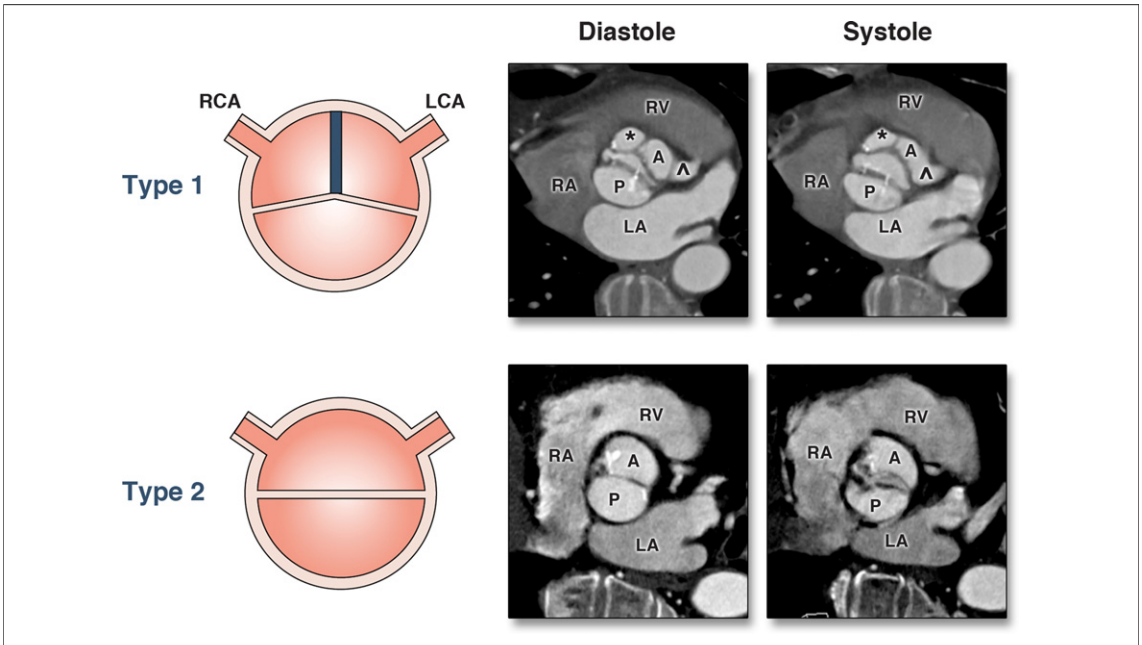

Figure 1. Diagrams and Representative MDCT Images of BAV-AP

Fusion of the right and left coronary cusps results in the anterior–posterior orientation of the commissural line, with the right coronary (RCA) and left coronary (LCA) arteries originating from the anterior cusp (A). The circumflex (^) indicates the LCA. Fusion of the right and left coronary cusps may show a raphe, indicated by an asterisk (*). BAV-AP = bicuspid aortic valve with fusion of the right and left coronary cusps; LA = left atrium; MDCT = multidetector computed tomography; RA = right atrium; RV = right ventricle.

the aortic arch and descending thoracic aorta <3.0 cm. An abnormal aorta was classified into 3 types according to hierarchical cluster analysis, using HCE (Hierarchical Clustering Explorer) version 3.5 (University of Maryland, College Park, Maryland) (17). Data were first plotted after normalization using the within-patient *z*-score. Complete linkage analysis with the Pearson correlation coefficient similarity measurement was used to generate the clustergram. Four different phenotypes of bicuspid aortopathy were thus defined: type 0, normal aorta; type 1, dilated aortic root; type 2, aortic enlargement involving the tubular portion of the ascending aorta; and type 3, diffuse involvement of both the entire ascending aorta and the transverse aortic arch (Fig. 3).

Echocardiography. All patients underwent comprehensive 2-dimensional and Doppler echocardiographic examinations using commercially available machines. Two echocardiography specialists reviewed all images (D.H.Kim and J.K.S.) to classify the severity of aortic valvular dysfunction according to the guidelines of the American Society of Echocardiography (19,20). Aortic stenosis (AS) or regurgitation (AR) of moderate or severe degree was defined as hemodynamically significant valvular dysfunction.

Statistical analysis. For descriptive statistical analysis, continuous variables were expressed as the mean ± SD, and categorical variables as frequencies or percentages. Analysis of variance and the unpaired Student *t* test were used to compare continuous variables among or between groups. Categorical variables were analyzed with the chi-square test and Fisher exact test. The Kruskal-Wallis test was used to compare patient age and peak systolic velocity (Vmax) with respect to aortopathy type. SPSS version 19.0 software (SPSS, Chicago, Illinois) was used for the statistical analysis. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics. Table 1 shows the clinical profiles of the subjects. More than 65% of the patients with BAV were men. Moderate-to-severe AS was the most common hemodynamic abnormality (55.1%), followed by moderate-to-severe AR (21.0%). Patients with normally functioning BAV or hemodynamically insignificant mild AS or AR comprised about 12% of the subjects. Open heart surgery to correct a defective aortic valve and/or a pathology involving the ascending aorta was done in 136 patients (81.4%).

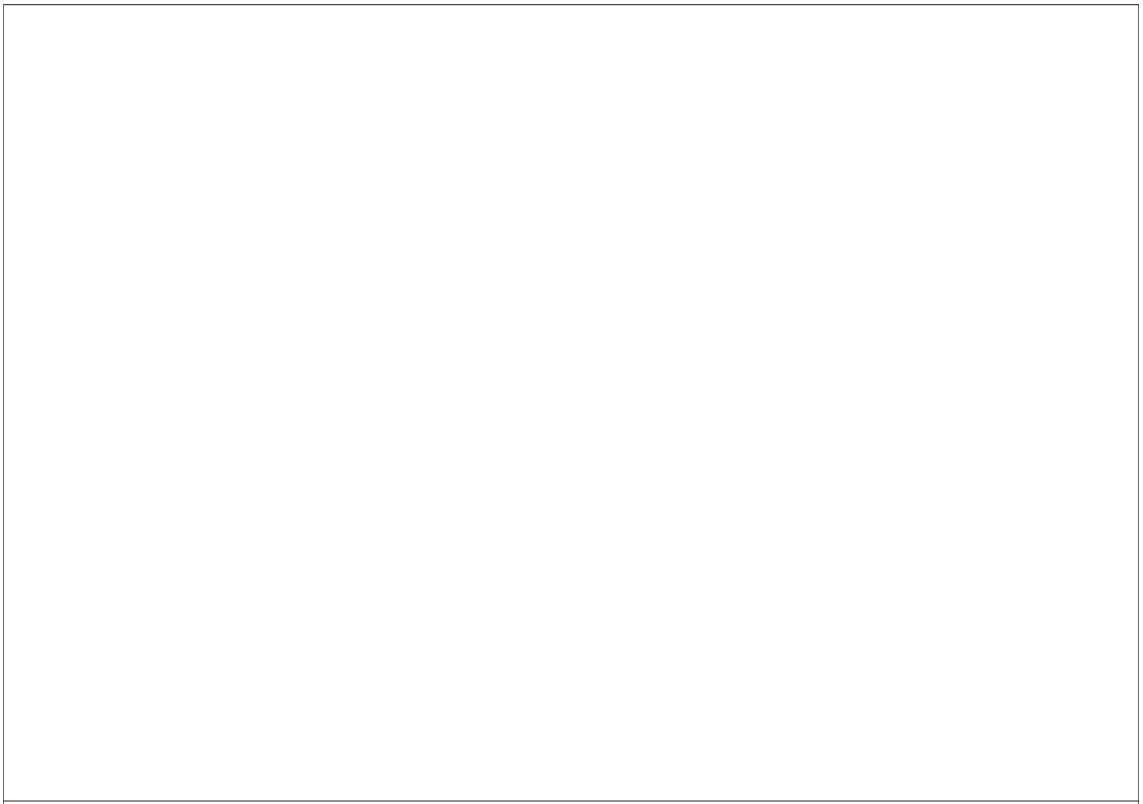

Figure 2. Diagrams and Representative MDCT Images of BAV-RL

Fusion of the right or left coronary cusps with noncoronary cusp results in a right–left orientation of the commissural line with the right and left coronary arteries originating from each cusp separately. The circumflex (^) indicates the LCA. The area of congenital leaflet fusion is defined as a raphe, indicated by an asterisk (*). BAV-RL = bicuspid aortic valve with fusion of the right or left coronary cusp and noncoronary cusp; L = left cusp; R = right cusp; other abbreviations as in Figure 1.

Phenotypes of BAV and bicuspid aortopathy. Among the BAV phenotypes, type 1 was the most common in our patients (44.3% [74 of 167]), followed by type 5 (36.5% [61 of 167]), type 2 (11.4% [19 of 167]), and type 3 (7.2% [12 of 167]). Type 4 was seen only in 1 patient. Thus, the prevalence of BAV-AP and BAV-RL was 55.73% (93 of 167) and 44.3% (74 of 167), respectively (Fig. 4).

Cluster analysis showed an ascending aorta of normal dimensions (type 0) in 45 patients (26.9%, 45 of 167). Three different patterns of bicuspid aortopathy were distinguished. Type 1, present in 34 patients (20.4%), was characterized by aortic enlargement confined to the aortic root. Type 2, observed in 49 patients (29.3%), consisted of aortic enlargement involving the aortic root and the tubular portion of the ascending aorta. In the 39 patients (23.4%) with type 3, there was diffuse involvement of both the entire ascending aorta and the transverse aortic arch (Fig. 5).

Table 2 summarizes the clinical features of patients with BAV-AP and those with BAV-RL, allowing comparison of the 2 types. Neither the mean age nor the male prevalence differed significantly between groups. The 2 groups also did not differ with respect to the prevalence of moderate-to-severe valvular dysfunction (AS, AR, or both) (89.2% [83 of 93] in BAV-AP vs. 85.1% [63 of 74] in BAV-RL; $p = 0.426$). However, there was a significant difference in the pattern of valvular dysfunction between the BAV-AP and BAV-RL groups ($p < 0.0001$). Moderate-to-severe AS was the predominant form of valvular dysfunction in patients with BAV-RL type (66.2% [49 of 74] vs. 46.2% [3 of 93] in BAV-AP), whereas moderate-to-severe AR was more common in BAV-AP (32.3% [30 of 93] vs. 6.8% [5 of 74] in BAV-RL). This trend was well represented by the significantly higher Vmax across the aortic valve in the BAV-RL group. Despite similar dimensions of the ascending aorta, the distribution of bicuspid aortopathy differed significantly between groups. A normal aorta was seen significantly more often in patients with BAV-AP (33.3% [31 of 93] vs. 18.9% [14 of 74] in

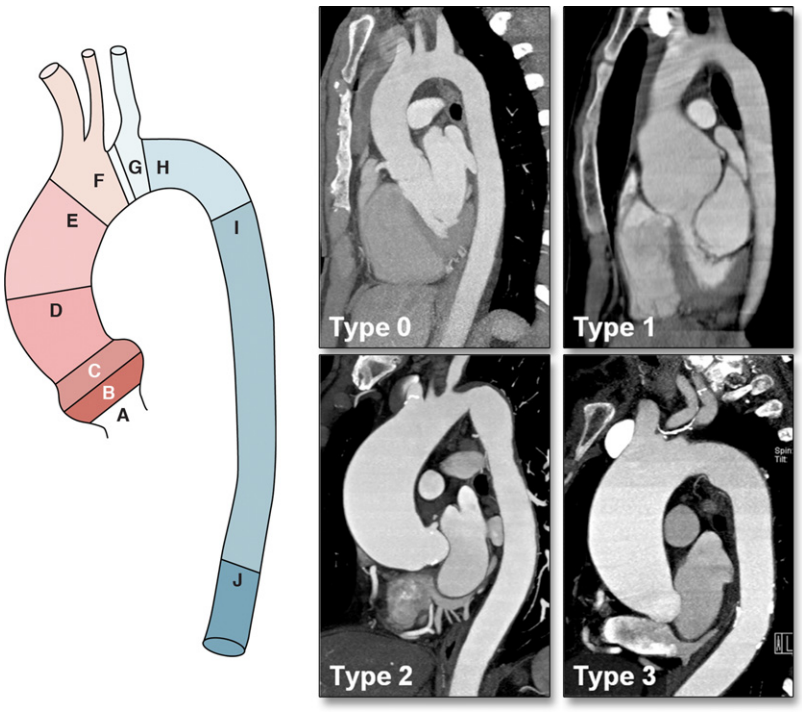

Figure 3. The 10 Levels Used in Aortic Dimension Measurements With Representative MDCT Images of Bicuspid Aortopathy Phenotypes

Type 0 is a normal aorta; type 1 is characterized by dilated aortic root. If the aortic enlargement involves the tubular portion of the ascending aorta, it is classified as type 2, whereas in type 3, there is diffuse involvement of the entire ascending aorta and the transverse aortic arch. A indicates the aortic annulus; B, sinuses of Valsalva; C, sinotubular junction; D, tubular portion of the ascending aorta; E, proximal to the innominate artery (or common trunk in case of a bovine arch); F, distal to the innominate artery (or common trunk); G, proximal to the left subclavian artery; H, distal to the left subclavian artery; I, proximal descending aorta, and J, distal descending thoracic aorta at the level of the diaphragmatic hiatus. MDCT = multidetector computed tomography.

BAV-RL), whereas the incidence of type 1 (24.7% vs. 14.9% in BAV-RL type) and type 2 (32.3% vs. 25.7% in BAV-RL) aortopathy did not differ between groups. The most striking difference was in the prevalence of type 3 bicuspid aortopathy, which was the most common pattern in the BAV-RL group, but occurred only rarely in the BAV-AP group (40.5% vs. 9.7% in BAV-AP type).

Table 1. Patient Characteristics (N = 167)

Age, yrs	54.6 ± 14.4
Men	115 (68.9)
Hypertension	47 (28.1)
Diabetes mellitus	16 (9.6)
Valvular dysfunction	
Moderate-to-severe AS	92 (55.1)
Moderate-to-severe AR	35 (21.0)
Moderate-to-severe ASR	19 (11.4)
Normal or mild AS or AR	21 (12.5)
Maximal systolic jet velocity through BAV (Vmax), m/s	4.5 ± 1.4

Values are mean ± SD or n (%).
AR = aortic regurgitation; AS = aortic stenosis; ASR = aortic stenosis and regurgitation; BAV = bicuspid aortic valve; Vmax = peak systolic velocity.

Table 3 summarizes the clinical features according to bicuspid aortopathy phenotype. Significant differences in age, prevalence of male sex, BAV phenotype, and types of valvular dysfunction were present depending on aortopathy phenotype. Compared with patients with type 0 and 1 phenotypes (normal or localized aortic root enlargement), those with type 2 and 3 phenotypes (more advanced aortic enlargement) were characterized by higher mean age (59.1 ± 11.7 years vs. 49.8 ± 15.5 years; $p < 0.0001$). If we combine phenotypes 0 and 1 as one group and phenotypes 2 and 3 the other, different clinical features can be more dramatically presented (Table 4). Hemodynamically significant AS was more frequently observed in patients with type 2 and 3 phenotypes than in those with types 0 and 1 (64.8% [57 of 88] vs. 44.3% [35 of 79]; $p = 0.008$), whereas moderate-to-severe AR was relatively more common in patients with type 0 and 1 phenotypes than those

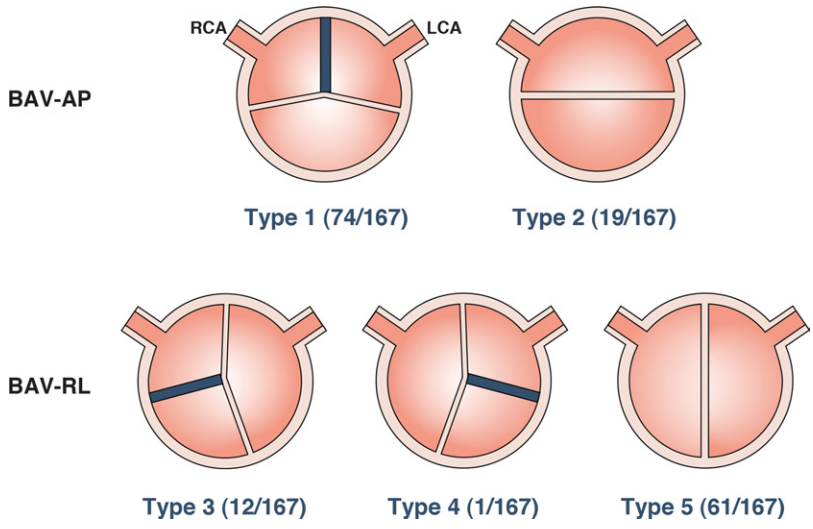

Figure 4. Morphologies Used to Define the Various BAV Phenotypes

BAV = bicuspid aortic valve; other abbreviations as in Figures 1 and 2.

with types 2 and 3 (32.9% [26 of 79] vs. 10.2% [9 of 88]; $p < 0.0001$). The tubular portion of the ascending aorta was significantly dilated in patients with type 2 and 3 phenotypes compared with those with types 0 and 1 (45.2 ± 7.0 mm vs. 37.5 ± 7.2 mm; $p < 0.0001$). BAV-RL was relatively more common in patients with type 2 and 3 phenotypes than in those with types 0 and 1 (55.7% [49 of 88] vs. 31.6% [25 of 79]; $p = 0.003$), whereas BAV-AP was more common in patients with type 0 and 1 phenotypes than in those with types 2 and 3 (68.4% [54 of 79] vs. 44.3% [39 of 88]; $p = 0.002$).

DISCUSSION

On the basis of high-quality MDCT data, variable phenotypes of BAV and aortic enlargement were identified in a series of 167 patients. Importantly, in this group, the type of valvular dysfunction was associated with both BAV phenotypes and the bicuspid aortopathy type. Specifically, patients with BAV-AP had a relatively higher prevalence of hemodynamically significant AR, but a normal ascending aorta, whereas hemodynamically significant AS and aortic enlargement involving the entire

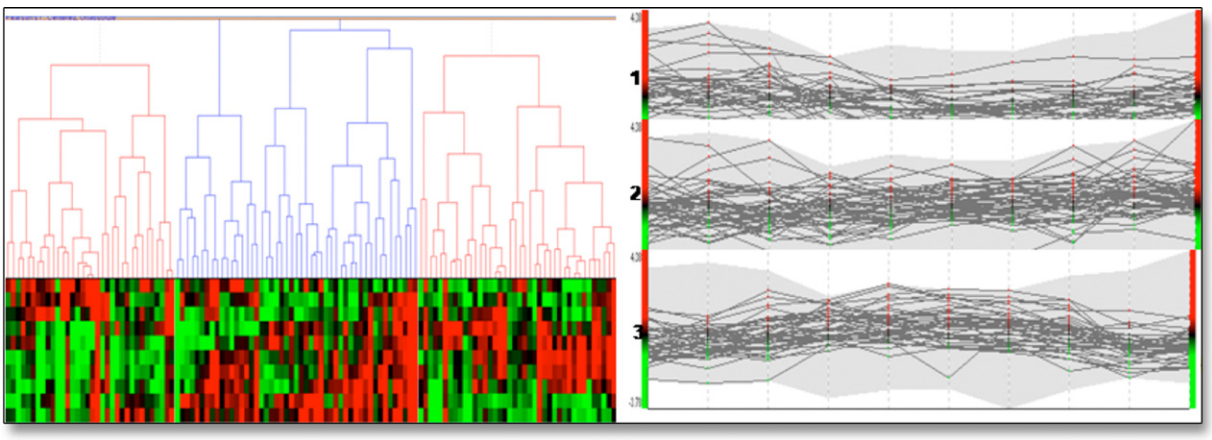

Figure 5. Hierarchical Clustering of the Data Shows Aortopathy Types 1, 2, and 3

The **left panel** shows a heat map in which each column represents a patient and each row represents aortic diameters that have been color coded according to the calculated within-patient *z*-scores from annulus **(top)** to distal descending thoracic aorta **(bottom)**. The 3 types of aortopathy are shown in the **right panel**, which demonstrate the measured diameters at each level for individual patients.

Table 2. Clinical Characteristics: BAV-AP Versus BAV-RL Type

	BAV-AP (n = 93)	BAV-RL (n = 74)	p Value
Age, yrs	54.6 ± 14.9	54.8 ± 13.7	0.910
Men	69 (74.2)	46 (62.2)	0.150
Hypertension	31 (35.2)	16 (22.2)	0.072
Calcification			0.390
None	32 (34.4)	21 (28.4)	
Mild	12 (12.9)	12 (16.2)	
Moderate	10 (10.8)	14 (18.9)	
Severe	39 (41.9)	27 (36.5)	
Valvular dysfunction			<0.0001
Normal, mild AS, or mild AR	10 (10.8)	11 (14.9)	
Moderate-to-severe AS	43 (46.2)	49 (66.2)	
Moderate-to-severe AR	31 (32.3)	5 (6.8)	
Moderate-to-severe ASR	10 (10.8)	9 (12.2)	
Vmax, m/s	4.2 ± 1.5	4.9 ± 1.2	0.005
Ascending aorta dimension, mm			
Annulus	23.1 ± 3.7	22.1 ± 3.6	0.074
Sinus of Valsalva	38.1 ± 6.6	38.7 ± 6.3	0.522
Sinotubular junction	30.2 ± 5.3	31.8 ± 6.4	0.070
Tubular portion	41.0 ± 8.1	42.3 ± 8.0	0.284
BAV aortopathy			<0.0001
Type 0	31 (33.3)	14 (18.9)	
Type 1	23 (24.7)	11 (14.9)	
Type 2	30 (32.3)	19 (25.7)	
Type 3	9 (9.7)	30 (40.5)	

Values are mean ± SD or n (%).
BAV = bicuspid aortic valve; BAV-AP = bicuspid aortic valve with fusion of the right and left coronary cusps; BAV-RL = bicuspid aortic valve with fusion of the right or left coronary cusp and noncoronary cusp; other abbreviations as in Table 1.

ascending aorta and the transverse arch were more often seen in patients with BAV-RL. Patients with more extensive aortic enlargement (type 2 and 3 bicuspid aortopathies) had a higher mean age and a higher prevalence of moderate-to-severe AS. The close association between BAV phenotype and certain types of valvular dysfunction or bicuspid aortopathy suggests a common pathophysiological link. Accordingly, a comprehensive evaluation of BAV and bicuspid aortopathy phenotypes should be the first step in the evaluation of these patients, as it will contribute to a better understanding of the marked phenotypic variability inherent to this complicated disease entity.

BAV phenotype and clinical features. Although it is well known that BAV is characterized by variable patterns of leaflet fusion, the binary classification of BAV-AP and BAV-RL types has persisted (5,13–16). In addition, only a few studies have sought to determine whether this morphologically based classification is of prognostic value. The major findings of those studies are summarized in Table 5, which highlights the marked differences, including the prevalence of each BAV phenotype and its correlation with valvular dysfunction and aortic enlargement.

With 1 exception (13), a significantly higher prevalence of BAV-AP was reported. In our study, the prevalence of both types was comparable (55.7% [93 of 167] in BAV-AP and 44.3% [74 of 167] in BAV-RL). The correlation between BAV phenotype and valvular dysfunction is controversial. In young children and adolescents (5,14), BAV-RL is associated with a higher risk of significant valvular dysfunction and more rapid development of AS or AR with shorter time of intervention. However, in adult patients with BAV, recent clinical investigations failed to document such correlation (16,18). In our cohort, the distribution of AS or AR differed according to BAV phenotype. Despite the similar prevalences of hemodynamically significant valvular dysfunction among the 2 disease types, moderate-to-severe AS predominated in patients with BAV-RL, and moderate-to-severe AR in those with BAV-AP. Although previous investigators were unable to demonstrate a statistically significant

Table 3. Clinical Characteristics According to Bicuspid Aortopathy Phenotype

	Type 0 (n = 45)	Type 1 (n = 34)	Type 2 (n = 49)	Type 3 (n = 39)	p Value
Age, yrs	49.3 ± 15.3	50.5 ± 16.0	61.5 ± 10.9	56.2 ± 12.2	<0.0001
Men	30 (66.7)	27 (79.4)	39 (79.6)	19 (48.7)	0.008
Hypertension	11 (25.6)	11 (33.3)	16 (34.8)	9 (23.7)	0.617
Calcification					0.490
None	17 (37.8)	13 (38.2)	11 (22.5)	12 (30.8)	
Mild	6 (13.3)	6 (17.7)	5 (10.2)	7 (17.9)	
Moderate	3 (6.7)	5 (14.7)	10 (20.4)	6 (15.4)	
Severe	19 (42.2)	10 (29.4)	23 (46.9)	14 (35.9)	
BAV phenotype					<0.0001
AP type	31 (68.9)	23 (67.6)	30 (61.2)	9 (23.1)	
RL type	14 (31.1)	11 (32.4)	19 (38.8)	30 (76.9)	
Valvular dysfunction					0.007
Normal, mild AS, or mild AR	4 (8.9)	5 (14.7)	3 (6.1)	9 (23.1)	
Moderate-to-severe AS	22 (48.9)	13 (38.2)	31 (63.3)	26 (66.6)	
Moderate-to-severe AR	15 (33.3)	11 (32.4)	8 (16.3)	1 (2.6)	
Moderate-to-severe ASR	4 (8.9)	5 (14.7)	7 (14.3)	3 (7.7)	
Vmax, m/s	4.5 ± 1.7	4.2 ± 1.5	4.7 ± 1.1	4.6 ± 1.2	0.480

Values are mean ± SD or n (%).
AP = fusion of the right and left coronary cusps; RL = fusion of the right or left coronary cusp and noncoronary cusp; other abbreviations as in Tables 1 and 2.

association, they also noted that proportionally more patients with BAV-RL type had significant AS, which, they believed, contributed to local aortic dilation (16,21). Although we cannot explain why patients with a specific BAV phenotype have a propensity to develop a certain type of valvular dysfunction, a recent animal experiment provided strong evidence that BAV-AP and BAV-RL are distinct etiological entities (12). The authors clearly demonstrated that BAV-RL results from the defective development of the endocardial cushions of the cardiac outflow tract, probably during the nitric oxide–dependent stage of endothelial-to-mesenchymal transformation. By contrast, BAV-AP reflects the anomalous septation of the embryonic outflow tract due to altered neural crest cell behavior. However, further investigation is necessary to determine whether these molecular abnormalities are related to the development of certain types of valvular dysfunction.

Another notable finding in our study was the association between the frequency of a specific bicuspid aortopathy and a particular BAV phenotype. The association between BAV-RL and aortic enlargement has been previously reported (5,16) and was confirmed by the findings of our study. Although the mechanism underlying bicuspid aortopathy is unknown, differences in aortic shape may reflect differences in aortic development and tissue composition. Alternatively, the higher frequency of moderate-to-severe AS, with a higher Vmax, in BAV-RL patients suggests that the hemodynamic burden contributes significantly to the development of bicuspid aortopathy. However, because progressive aortic dilation occurs in many patients with normal valve function (9,13,22), and aortic enlargement was observed in our patients with normally functioning BAV, mild AS, or mild AR, the hemodynamic burden caused by valvular dysfunction cannot entirely explain the full spectrum of bicuspid aortopathy. Instead, differences in the flow-jet direction due to the different orientations arising from the various BAV phenotypes are an important etiological consideration. Recently, 4-dimensional flow magnetic resonance imaging showed abnormal helical systolic flow in the ascending aorta of patients with BAV, including those without aneurysmal dilation or AS (23). One interesting characteristic of BAV is that the direction of helical flow differs according to phenotype, with right-handed helical flow as the predominant pattern in BAV-AP, and left-handed helical flow in BAV-RL (23). Thus, as proposed in a previous study (16), variations in segmental aortic dilation that correlate with specific changes in valve morphology may be related to differences in eccentric flow jets that lead to a differential distribution of wall shear stress. Longitudinal follow-up is needed to determine whether an abnormal helical flow pattern correlates with bicuspid aortopathy phenotype. Such studies will

Table 4. Comparison of Clinical Characteristics: Aortopathy Types 0 and 1 Versus Types 2 and 3

	Types 0 and 1 (n = 79)	Types 2 and 3 (n = 88)	p Value
Age, yrs	49.8 ± 15.5	59.1 ± 11.7	<0.0001
Men	57 (72.2)	58 (65.9)	0.384
Hypertension	22 (28.9)	25 (29.8)	0.910
Calcification			0.252
None	30 (38.0)	23 (26.1)	
Mild	12 (15.2)	12 (13.6)	
Moderate	8 (10.1)	16 (18.2)	
Severe	29 (36.7)	37 (42.0)	
Valvular dysfunction			0.004
Normal, mild AS, or mild AR	9 (11.4)	12 (13.6)	
Moderate to severe AS	35 (44.3)	57 (64.8)	
Moderate to severe AR	26 (32.9)	9 (10.2)	
Moderate to severe ASR	9 (11.4)	10 (11.4)	
Vmax, m/s	4.3 ± 1.6	4.7 ± 1.2	0.172
Ascending aorta dimension, mm*			
Annulus	23.0 ± 3.9	22.3 ± 3.3	0.19
Sinus of Valsalva	38.0 ± 6.9	38.6 ± 6.0	0.57
Sinotubular junction	30.0 ± 6.1	31.8 ± 5.5	0.048
Tubular portion	37.5 ± 7.2	45.2 ± 7.0	<0.0001
BAV type			0.002
BAV-AP	54 (68.4)	39 (44.3)	
BAV-RL	25 (31.6)	49 (55.7)	

Values are mean ± SD or n (%). *These comparisons are for illustrative purposes only since the groupings are influenced by aortic dimensions.
AP = fusion of the right and left coronary cusps; RL = fusion of the right or left coronary cusp and noncoronary cusp; other abbreviations as in Tables 1, 2, and 3.

provide further insight into the complicated nature of bicuspid aortopathy.

The advantages conferred by the use of high-quality cardiac imaging modalities cannot be overstated, as they are essential to an integrated, systematic, phenotypic classification of BAV and bicuspid aortopathy. Unlike conventional echocardiography, MDCT and cardiac magnetic resonance provide motion pictures of the aortic valve, with better image quality, and as such, have become promising diagnostic imaging tools (17,18). The deficiencies of echocardiography alone when a systematic approach is required is evidenced by the fact that using echocardiography, phenotypic classification is impossible in up to 20% of patients with BAV (24). Moreover, because involvement of aortic enlargement up to the transverse aortic arch is frequent, it is obvious that bicuspid aortopathy cannot be accurately assessed by echocardiography.

Table 5. Summary of Clinical BAV Phenotype Studies

First Author (Ref. #)	Mean Patient Age (yrs)	Number of Patients (AP/RL Type)	Major Findings
Fernandes et al. (5)	3	1,135 (70%/30%)	More significant valvular dysfunction in BAV-RL.
Cecconi et al. (13)	23.6	162 (55%/45%)	Only patients without significant valvular dysfunction were included. No correlation between BAV type and aortic enlargement.
Fernandes et al. (14)	16.1	310 (65%/35%)	More rapid progression of AR and AS with shorter time of intervention in BAV-RL.
Thanassoulis et al. (15)	33.1	156 (61%/38%)	Increased risk of rapid aortic dilation in BAV-AP.
Schaefer et al. (16)	Mid 40s	192 (80%/20%)	No association with valvular dysfunction; BAV-RL was associated with ascending aorta dilation.
Buchner et al. (18)	54	105 (72%/13%)	No correlation with aortopathy phenotype or valvular dysfunction.

Abbreviations as in Tables 1, 2, 3, and 4.

Study limitations. As the comprehensive MDCT and echo-Doppler evaluations were done in a tertiary referral hospital, our study potentially suffers from selection bias. In addition, more than 80% of the patients underwent surgical intervention due to significant valvular dysfunction with or without bicuspid aortopathy; consequently, our cohort comprises a highly selected group of patients with BAV. Thus, the extent to which our findings can be generally applied to BAV patients with mild valvular dysfunction is unclear.

Cluster analysis is a relatively new approach for classification of aortopathy. However, use of arbitrary cutoff values based on our clinical experience to define pathological aortic enlargement and failure to use a true short-axis view in a 3-dimensional dataset can be limitations of this study. The advantage of objective and accurate assessment of different patterns of phenotypes using well-established computer-based software needs to be tested in different patient populations by other investigators. The efficacy of CT imaging using ECG-based tube current modulation to further reduce the radiation dose can be another interesting topic.

CONCLUSIONS

Because comprehensive evaluation of BAV phenotypes and bicuspid aortopathy is feasible, and a meaningful association has been established between BAV phenotypes and the various types of valvular dysfunction or aortopathy, a systematic approach to the detailed classification of these diseases should become a routine clinical practice, offering new insights into this common disease entity.

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Key Words: bicuspid aortic valve ■ bicuspid aortopathy ■ computed tomography ■ echocardiography.