ORIGINAL ARTICLE

Assessment of bicuspid aortic valve phenotypes and associated pathologies: A transesophageal echocardiographic study

Biküspit aort kapak fenotiplerinin ve ilişkili patolojilerin değerlendirilmesi: Bir transözofajiyal ekokardiyografi çalışması

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ABSTRACT

Objective: We investigated the frequency of different bicuspid aortic valve disease (BAV) phenotypes,the associated valvular pathologies, and the aortopathy phenotypes, using 2-dimensional (2D) transthoracic, 2D transesophageal echocardiography (TEE) and 3-dimensional (3D) TEE.

Methods: A total of 154 patients with BAV were included. Five BAV phenotypes were detected. To better define valvular pathologies, binary classifications of BAV were used: BAV with antero-posterior commisural line (BAV-AP) and right-left commissural line (BAV-RL). Aortopathy phenotype was classified according to the involved tract(s).

Results: Of the patients, 53.2% had type 1, 16.2% type 2, 15.6% type 3, 1.3% type 4, and 13.6% had type 5 BAV. The prevalence of BAV-AP and BAV-RL was 68.2% and 31.8%, respectively. No difference was detected with respect to aortic regurgitation between BAV-AP and BAV-RL (p=0.9), but the BAV-RL group had an increased propensity to have a stenotic aortic valve (p=0.003). The indexed aortic diameter was larger in BAV-AP cases than BAV-RL at the sinus of Valsalva (p=0.008). In patients with dilatation of the root and tubular portion, a predominance of BAV-AP versus BAV-RL was observed (85% vs 15%). A markedly low prevalence of the root phenotype (3.2%) was observed. In 90.1% of the patients, 2D TEE was sufficient to classify BAV phenotypes; further 3D imaging was needed in 9.9% of the cases.

Conclusion: There may be racial differences in the frequency of valvular and aortopathy phenotypes in patients with BAV. BAV phenotypes differ with respect to aortic stenosis and aortopathy phenotypes. TEE may have good diagnostic utility in differentiating BAV phenotypes.

ÖZET

Amaç: Farklı biküspit aort kapak (BAK) fenotiplerinin dağılımını, kapak patolojilerini ve aortopati fenotiplerininin dağılımını iki boyutlu (2B) transtorasik, 2B transözofajiyal ekokardiyografi (TÖE) ve 3B TÖE kullanarak araştırdık ve de bu incelemelerin BAK fenotiplendirmesinde kullanım yerini değerlendirdik.

Yöntemler: BAK'lı 154 hasta çalışmaya alındı. Beş BAK fenotipi saptandı. Kapak patolojilerini daha iyi tanımlamak için ikili BAK sınıflandırması şu şekilde kullanıldı: Ön-arka komissür çizgisinin olduğu BAK-ÖA ve sağ-sol komissür çizgisinin olduğu BAV-SS. Aortopati fenotipleri tutulum olan kısımlara göre sınıflandırıldı.

Bulgular: Hastaların %53.2'sinde tip 1, %16.2'sinde tip 2, %15.6'sında tip 3, %1.3'ünde tip 4 ve %13.6'sında tip 5 BAK alt tipi saptandı. BAK-ÖA ve BAK-SS'nin prevalansı sırasıyla %68.2 ve %31.8 idi. BAK-ÖA ve BAK-SS, kapak patolojileri açısından karşılaştırıldığında aort yetersizliği açısından fark yokken (p=0.9), BAK-SS grubunda daralmış bir kapak bulundurma eğilimi daha yüksekti (p=0.003). Sinüsler düzeyinde endekslenmiş aort çapı BAK-ÖA'da BAK-SS'ye göre daha genişti (p=0.008). Kök ve tübüler bölümün genişlediği hastalarda BAK-ÖA saptanma sıklığı BAK-SS saptanma sıklığına göre daha yüksekti (%85'e karşı %15). BAK popülasyonumuzda kök fenotipi (%3.2) belirgin olarak azdı. 2B TÖE hastaların %90.1'inde BAK fenotipini belirleyebildi ve 3B görüntülemeye olguların %9.9'unda ihtiyaç duyuldu.

Sonuç: BAK'lı hastalarda kapak ve aortopati fenotiplerinin sıklığında ırksal değişiklikler olabilir. BAK fenotipleri aort darlığı ve aortopati açısından farklılıklar göstermektedir. BAK fenotipini belirlemede TTE'nin düşük yararına karşın TÖE iyi bir tanısal fayda sağlayabilir.

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Bicuspid aortic valve disease (BAV) is the most common congenital heart anomaly, with an estimated prevalence of 1% to 2% in the general population.[1] BAV may be responsible for a greater mortality and morbidity rate than all other congenital heart defects.[2] It requires serious follow-up; most cases develop aortic dilation and have a ninefold increased risk of developing aortic dissection.[2] When a bicuspid aortic valve causes dilatation in the aorta, it is referred to as bicuspid aortopathy.[3] The disease represents a heterogeneous spectrum, leading to difficulties in the interpretation of follow-up and treatment options.[4] Genetic factors and racial and gender differences may contribute to this heterogeneity.[5] BAV has been divided into subgroups according to the orientation of the commissures and valve fusion patterns to determine the underlying reasons for the involvement of different segments of the aorta and to identify those patients with a tendency to develop valvular pathologies. In a few trials, on the basis of commissural orientation and cusp position in transthoracic echocardiography (TTE) images, binary classifications of BAV phenotypes were used.[6,7] A recent trial demonstrated 5 different BAV phenotypes.[8] TTE is the first-line imaging modality used for the diagnosis of BAV. It provides data regarding concomitant aortic and valvular pathologies; however, in some patients, limited resolution may prevent making a definite diagnosis or a clearer classification of BAV phenotype. A few investigators have used multidetector computed tomography (MDCT) to better determine valvular phenotypes in BAV.[8] Transesophageal echocardiography (TEE) provides better resolution and diagnostic accuracy than does TTE for BAV, leading to its acceptance as the mainstay for BAV diagnosis by some experts.[9,10] It also may have an advantage over TTE in differentiating BAV phenotypes by clearly demonstrating the presence/absence of a raphe, fusion of cusps, and detection of the orientation of commissures and coronary ostia. In some cases, 3-dimensional (3D) TEE rather than 2-dimensional (2D) TEE can lead to a definitive BAV diagnosis and better defines the morphological details of the aortic valve.[11,12]

Abbreviations:

2D	*Two-dimensional*
3D	*Three-dimensional*
AA	*Ascending aorta*
AR	*Aortic regurgitation*
AS	*Aortic stenosis*
BAV	*Bicuspid aortic valve disease*
BAV-AP	*BAV with antero-posterior commisural line*
BAV-RL	*BAV with right-left commissural line*
BSA	*Body surface area*
CoA	*Coarctation of the aorta*
LMCA	*Left main coronary artery*
LV	*Left ventricular*
LVOT	*Left ventricular outflow tract*
MDCT	*Multidetector computed tomography*
MRI	*Magnetic resonance imaging*
OFT	*Outflow tract*
RCA	*Right coronary artery*
SOV	*Sinus of Valsalva*
TEE	*Transesophageal echocardiography*
TP	*Tubular portion*
TTE	*Transthoracic echocardiography*
Vmax	*Maximum aortic peak velocity*

This study was an investigation of the frequency of BAV phenotypes, the related valvular pathologies, and the distribution of aortopathy phenotypes among the different BAV phenotypes using 2D TTE, and 2D and 3D TEE in a local Turkish cohort of BAV patients. The performance of 2D TTE and the additional role of 3D TEE in phenotyping BAV were also assessed. Furthermore, the concomitant congenital anomalies associated with BAV and the utility of echocardiographic imaging modalities in identifying BAV phenotypes were examined.

METHODS

Between January 2014 and January 2016, 171 consecutive patients with suspected BAV or with a previous diagnosis of BAV were evaluated. BAV was identified in 163 of these patients when only 2 cusps were unequivocally identified in systole and diastole in the short axis view with a clear "fish mouth" appearance during systole on TTE, and the diagnosis was verified. The BAV phenotype was determined by TEE, or less commonly, by cardiac magnetic resonance imaging (MRI). All patients were in sinus rhythm. Patients with any of the following were excluded: history of aortic root surgery (n=1), severe systolic dysfunction that would interfere with measurements of aortic valve function (n=1), history of endocarditis (n=1), inadequate TEE quality to determine a precise BAV phenotype due to severe calcification of the aortic valve (n=2), history of rheumatic fever or known rheumatic heart disease (n=1), and unwillingness to undergo TEE or cardiac MRI (n=3). In all, 154 patients were eligible for classification by BAV phenotype using TEE (n=151) and cardiac MRI (n=3).

TTE studies were performed using commercially available equipment (Philips iE33; Philips Healthcare, Inc., Andover, MA, USA). Left ventricular (LV) internal systolic and diastolic dimensions, posterior wall and interventricular septal thickness, and

left atrial diameter were determined according to the recommendations of guidelines.[13] In total, 3 to 5 measurements were made and averaged at each aortic level, and the results were indexed for body surface area (BSA). LV systolic function was assessed with the calculation of LV ejection fraction using Simpson's biplane method.[13]

The degree of aortic stenosis (AS) was graded using Doppler echocardiography. Severity of AS was graded as mild in patients with a maximum aortic peak velocity (Vmax) of 2.0 to 2.99 m/second and moderate-to-severe in those with a Vmax of ≥3 m/second to evaluate statistical differences, similar to a previous report.[14] Degree of aortic regurgitation (AR) was defined by a composite evaluation of the ratio of proximal jet width to the left ventricular outflow tract (LVOT) diameter, venae contracta, and the presence and severity of holodiastolic aortic flow reversal, according to guidelines.[15] Ratio of proximal jet width to LVOT diameter and venae contracta were calculated in TEE examinations for a more appropriate assessment of AR.

TEE was performed using a multiplanar probe allowing for 2D and 3D imaging (Philips X7-2t; Philips Healthcare, Inc., Andover, MA, USA). TEE views of the ascending aorta, aortic root, and the aortic valve were assessed at the high TEE long axis (at 120°–150°) and short axis (at 30°–60°). During TEE, the presence/absence of a raphe, orientation of the commissures, and coronary ostia were recorded. Kang's classification was used to determine BAV phenotypes using both 2D and 3D TEE images.[8] Accordingly, the orientation of the free edge of the cusp defined the anterior-posterior (AP) and right-left (RL) forms of BAV as BAV-AP and BAV-RL, respectively. A bicuspid aortic valve with fusion of the right and left coronary cusps with a raphe resulting in the AP orientation of the commissural line (BAV-AP), with both the right coronary artery (RCA) and left main coronary artery (LMCA) originating from the anterior cusp was classified as type 1 (BAV-AP with raphe). When the commissural line was in the AP position but with no raphe and both coronary arteries originated from the anterior cusp, this phenotype was classified as type 2 (BAV-AP without raphe). When fusion of the right and non coronary cusps with a raphe, resulting in a RL orientation of the commissural line (BAV-RL) with the RCA and LMCA originating from 2 separate cusps, was observed, this phenotype was classified as type 3. Fusion of the left and non coronary cusps with a raphe with 2 coronary ostia each originating from 2 separate cusps was classified as type 4. In the presence of RL orientation of the commissural line (BAV-RL) with 2 completely developed cusps and commissures without a raphe with coronary arteries originating from each separate cusp, the BAV phenotype was classified as type 5 (Fig. 1). Thus, BAV-AP had 2 subgroups, types 1 and 2, whereas BAV-RL had 3 subgroups, types 3, 4, and 5.

Aortic dimensions were measured at the end of the LV diastole as recommended by guidelines[16] at the following levels: (1) the annulus, (2) the mid-point of the sinus of Valsalva (SOV), (3) the sinotubular junction, and (4) the tubular portion (TP) of the ascending aorta (AA) at the level of its largest diameter using 2D TEE. In total, 3 to 5 measurements were taken and averaged at each aortic level, and the results were indexed for BSA. In patients with a BSA ≤1.68 m^2, the indexed diameters of AA and SOV were used to assess whether the relevant parameters exceeded the upper normal limits. Otherwise an AA diameter exceeding 39 mm[17] and a SOV diameter exceeding 40 mm were determined to be dilated.[8] In those with smaller BSA, when the indexed AA diameter and SOV diameter exceeded 2 standard deviations of the normal limits presented in the guidelines, they were determined to be dilated.[18] Thus, the upper limit was determined to be 22 mm/m^2 for the SOV diameter and 19 mm/m^2 for the AA diameter in patients with a small BSA. Three different patterns of bicuspid aortopathy were distinguished using Park's classification,[19] based on the tract(s) involved in the dilatation: enlargement of only the TP of the ascending aorta, enlargement of both the TP and root, and enlargement confined only to the root (sinuses) (Fig. 2). No complications were observed during or after the TEE examinations. This study was approved by institutional review board. Written informed consent was obtained from all participants before performing the TEE study.

All analyses were performed using SPSS for Windows, Version 15.0 software (SPSS Inc., Chicago, IL, USA). Homogeneity of variances was assessed using Levene's test. Normality tests were performed for all continuous variables. If the variable was normally distributed, it is presented as the mean±SD, otherwise, as the median and (minimum-maximum values).

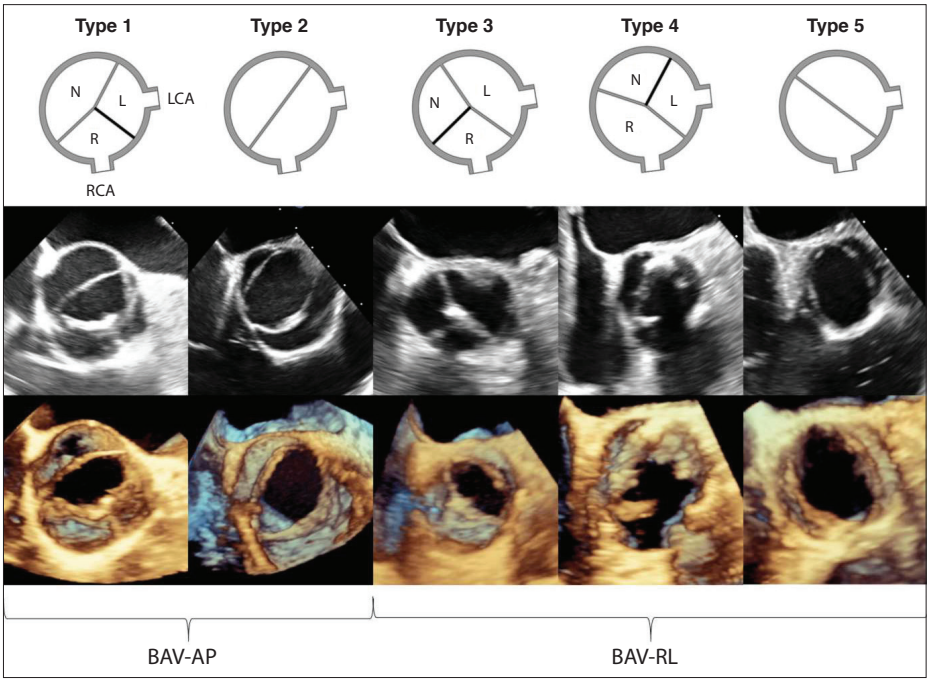

Figure 1. Top: Schematic diagram of the 5 different bicuspid aortic valve (BAV) phenotypes drawn according to the orientation of transesophageal echocardiographic (TEE) images. Middle: Two-dimensional TEE images of the 5 BAV phenotypes. Bottom: Three-dimensional echocardiographic images of the corresponding phenotypes.

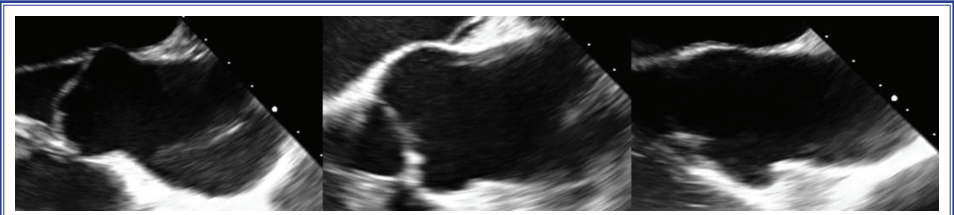

Figure 2. Three aortic phenotypes observed in patients with bicuspid aortic valve. Left: Dilatation of the tubular portion of the ascending aorta. Middle: Dilatation of the sinus of Valsalva (SOV) and the tubular portion of the ascending aorta. Right: Dilatation confined to the SOV alone (root phenotype).

Categorical data are presented as numbers and percentages. Comparisons of categorical data between 2 groups were performed using Pearson's chi-square test, continuous corrected chi-square test, or Fisher's exact test, as appropriate. To assess any difference between the BAV AP and BAV-RL groups with respect to the pattern of aortic dilatation, those with only root dilatation (5 patients) were excluded from the analysis due to the very low prevalence. Comparisons of normally distributed continuous data were performed using independent t test; otherwise, the Mann-Whitney U-test was used. The Kruskal-Wallis test was used to compare continuous variables with non-normal distributions with respect to aortopathy type. When the p value from Kruskal-Wallis test statistics was statistically significant, Bonferroni-adjusted Mann-Whitney U test was used to know which group differed from which others. A p value of <0.05 was considered to indicate statistical significance. However, in all possible multiple comparisons, the Bonferroni correction was applied to control Type I error.

RESULTS

Table 1 displays the baseline characteristics of the study population. Of the 154 patients, 71.4% (n=110)

Table 1. Demographic variables and echocardiographic findings in patients with bicuspid aortic valve

Age (years)	37 (17–70)
Male, n (%)	110 (71.4)
Height (cm)	169.9±9.42
Weight (kg)	73.9±13.33
BSA (m^2)	1.84±0.18
Arterial hypertension, n (%)	17 (11)
Diabetes mellitus, n (%)	10 (6.5)
Bicuspid aortic valve phenotypes, n (%)	
Type 1	82 (53.2)
Type 2	25 (16.2)
Type 3	24 (15.6)
Type 4	2 (1.3)
Type 5	21 (13.6)
Aortic stenosis, n (%)	
None	80 (51.9)
Vmax 200–299 cm/sec	42 (27.3)
Vmax ≥300 cm/sec	32 (20.8)
Aortic regurgitation, n (%)	
None	43 (27.9)
Mild	98 (63.6)
Moderate/severe	13 (8.4)
Aortic dilatation, n (%)	
None	68 (44.2)
Tubular portion	61 (39.6)
Root + tubular portion	20 (13)
Root type	5 (3.2)

Continuous data are expressed as mean±SD and categorical data as numbers and percentages.

BSA: Body surface area; Vmax: Maximum aortic peak velocity; SD: Standard deviation.

were men. The median age of the study group was 37 years (range: 17–70 years). Of these patients, 82 (53.2%) had the type 1 BAV phenotype, 25 (16.2%) had type 2, 24 (15.6%) had type 3, 2 (1.3%) had type 4, and 21 (13.6%) had the type 5 BAV phenotype. Thus, the prevalence of BAV-AP and BAV-RL was 68.2% and 31.8%, respectively. The frequency of hypertension, diabetes mellitus, and aortic valvular pathologies is presented in Table 1. In total, 32 (20.7%) patients had moderate-to-severe AS, and 13 (8.4%) had moderate-to-severe AR.

Table 2 summarizes the comparisons of demographic and echocardiographic variables between patients with BAV-AP and BAV-RL. There was no difference between the 2 groups with respect to age, gender, height, weight, or BSA. Diameter of the aortic annulus and tubular AA was similar between the groups; however, the diameter of the SOV (p=0.014), indexed SOV diameter (p=0.008), and indexed sinotubular junction diameter (p=0.039) was larger in those in the BAV-AP group. In the BAV-AP group, 7 (6.7%) patients had moderate AR and 2 (1.9%) had severe AR, whereas no severe AR was observed in the BAV-RL group, and 4 (8.2%) patients had moderate AR. In the BAV RL group, a stenotic aortic valve was present in 65.3% of the patients, whereas it was 40% in the BAV-AP group (p=0.003). The prevalence of moderate-to-severe AS in the BAV-AP and BAV-RL groups was 16.2% (17/105) and 30.6% (15/49), respectively.

When the type of aortic dilatation was compared, the most commonly affected portion of the aorta was the TP in both phenotypes. The frequency of aortic root involvement was low in both the BAV-AP and BAV-RL groups (2.9% and 4.1%, respectively). Aortic enlargement confined to both the root and TP was detected in 16.2% of the patients with BAV-AP and 6.1% of the patients with BAV-RL. In the BAV-AP group, 40% of the patients had aortic dilatation confined to the TP. We further investigated the pattern of aortic dilatation and severity of AS and aortic regurgitation (AR) in the 5 different valvular phenotypes of BAV. In patients with the type 1 phenotype (n=82), 59.8% (49/82) of the patients were free of any degree of AS; however, only 24.4% (20/82) of the patients with the type 1 BAV were free of any degree of AR. In 2 patients with the type 4 phenotype, the aortic valve had a Vmax of ≥3 m/second. Among 13 patients with moderate or severe AR in our BAV group, 7 (53.8%) had type 1, 2 (15.4%) had type 2, and 4 (30.8%) patients had type 3 BAV phenotypes. No patients with type 4 or type 5 had moderate or severe AR.

The clinical characteristics of the patients according to BAV aortopathy phenotype were also analyzed (Table 3). With a prevalence of 3.2% (5/154), the root phenotype was rare in our BAV population. Thus, we excluded these 5 patients from the analysis and compared the characteristics of patients without aortic dilatation (n=68), those with only dilatation of the tubular segment of the aorta (n=61), and those with dilatation of both the root and the tubular segment of the aorta (n=20). Patients without aortic dilatation

Table 2. Comparison of demographic and echocardiographic variables in patients with BAV-AP phenotype and BAV-RL phenotype

Variable	BAV-AP (n=105)	BAV-RL (n=49)	*p*
Men, n (%)	75 (71.4)	35 (71.4)	1
Age (years)	37.5 (17–69)	36 (17–70)	0.906
Weight (kg)	73.9±13.1	74.5±14.5	0.853
Height (cm)	169.8±8.9	170.1±10.4	0.901
Body surface area (m^2)	1.84±0.17	1.84±0.2	0.918
Posterior wall (mm)	9 (7–14)	9 (7–14)	0.216
Interventricular septum (mm)	10 (7–16)	10 (7–16.5)	0.439
Left atrial diameter (cm)	33.8±4.18	34.7±4.56	0.298
Left ventricular end-diastolic diameter (cm)	47.6±5.84	47.4±6.33	0.812
Left ventricular end-systolic diameter (cm)	27.6±5.12	27.2±4.91	0.613
Left ventricular ejection fraction (%)	62.7±5.51	62.8±4.58	0.906
Aortic diameters			
Annulus (mm)	27.5±4.31	27.3±3.88	0.717
Sinus of valsalva (mm)	34.5±5.16	32.2±5.29	0.014
Sinotubular junction (mm)	30.1±4.92	28.5±4.79	0.091
Tubular portion (mm)	38.2±6.93	37.3±7.74	0.425
Indexed aortic diameters			
Sinus of valsalva (mm/m^2)	18.8±2.61	17.5±2.85	0.008
Sinotubular junction (mm/m^2)	16.4±2.72	15.5±2.51	0.039
Tubular portion (mm/m^2)	20.9±4.17	20.2±4.25	0.345
Aortic stenosis, n (%)			
None	63 (60)	16 (32.7)	0.006
Vmax 200–299 cm/sec	25 (23.8)	18 (36.7)	
Vmax ≥300 cm/sec	17 (16.2)	15 (30.6)	
Aortic stenosis (any degree), n (%)	42 (40)	32 (65.3)	0.006
Aortic velocity (cm/sec)	186 (80–547)	232 (113–449)	0.014
Aortic regurgitation, n (%)			
None	30 (28.6)	13 (26.5)	0.957
Mild	66 (62.9)	32 (65.3)	
Moderate/ severe	9 (8.6)	4 (8.2)	
Aortic regurgitation (any degree), n (%)	75 (71.4)	36 (73.5)	0.944
Aortic dilatation, n (%)			
None	43 (41)	25 (51)	0.315
Tubular portion	42 (40)	19 (38.8)	
Root+tubular portion	17 (16.2)	3 (6.1)	
Root type	3 (2.9)	2 (4.1)	

Continuous data are expressed as mean (± standard deviation) or median (minimum-maximum); Categorical data are expressed as numbers and percentages. BAV: Bicuspid aortic valve; AP: Antero-posterior; RL: Right-left; Vmax: Maximum aortic peak velocity; SD: Standard deviation.

were younger than those with dilatation of any tract(s) (p<0.001). The median age was not different between the other 2 groups including patients with two different aortopathy phenotypes (adjusted p value= 0.325). The BAV phenotype was not statistically different among the groups; however, in patients with root and

Table 3. Clinical features of patients according to BAV aortopathy phenotype

	No dilatation (Group 1) (n=68)	Dilatation of tubular portion (Group 2) (n=61)	Dilatation of tubular portion+root (Group 3) (n=20)	*p*
Age (years)	26 (17–68)	40 (19–70)*	46 (27–69)*	<0.001
Men (%)	49 (72.1%)	41(67.2%)	15 (75%)	0.752
BAV phenotype, n (%)				
BAV-AP	43 (63.2)	42 (68.9)	17 (85)	0.188
BAV-RL	25 (36.8)	19 (31.1)	3 (15)	
AS (any degree), n (%)	26 (38.2)	36 (59)*	12 (60)	0.036
Aortic velocity ≥ 300 cm/sec, n (%)	10 (14.7)	21 (34.4)*	1 (5)†	0.001
AR (any degree), n (%)	47 (69.1)	43 (70.5)	17 (85)	0.388
Aortic velocity (cm/sec)	176 (100–381)	230 (96–547)*	206 (80–332)	0.012

Continuous data are expressed as median (minimum-maximum), and categorical data as numbers and percentages. BAV: Bicuspid aortic valve; AP: Antero-posterior; RL: Right-left; AS: Aortic stenosis; AR: Aortic regurgitation.
*p<0.0167 group 2 or 3 vs group 1 and †p<0.0167 group 2 vs group 3 for comparison of age and aortic velocity.
*p<0.05 group 2 or 3 vs. group 1, †p<0.05 group 2 vs. group 3 for comparison of percentages of patients with AS or aortic velocity ≥ 300 cm/s.

tubular aortic dilatation, 85% of the patients had the BAV-AP subtype. BAV stenosis was more common in patients with aortic dilatation confining TP than in those without dilatation (p=0.039), also indicated by a higher median Vmax in patients with a dilated tubular aorta than in those without dilatation. Moderate-to-severe AS was less common in patients free of aortic enlargement. No difference was found with respect to the frequency of any degree of AR between the groups. Among the 5 patients with root phenotypes, 2 were in the BAV-AP group and 3 in the BAV-RL group. None of the 5 patients had AS (aortic velocity range 96–180 cm/second).

Additional congenital anomalies and the phenotypes of BAV noted in these patients are presented in Table 4. There were 3 patients with coarctation of the aorta (CoA), and all 3 had the type 1 BAV phenotype.

To determine the utility of echocardiographic imaging techniques in BAV diagnosis, the diagnostic performance of TTE was first assessed. An experienced echocardiographer (KT) who was blinded to the patients' BAV phenotypes assessed all of the TTE images of the 154 patients. The accuracy of TTE in BAV phenotyping was 47.4% (n=73), while it was 90.1% (n=136) for 2D TEE (3 patients who refused TEE and preferred cardiac MRI were excluded for 2D and 3D TEE accuracy analysis). In 9.9% of the patients, 3D TEE (n=15) was needed to obtain exact phenotyping. Among these 15 patients, 3D imaging was needed to make the exact diagnosis of BAV-AP

Table 4. Additional congenital anomalies or genetic syndromes detected in patients with bicuspid aortic valve

Anomaly	n	%	Bicuspid aortic valve type
Coarctation of aorta	3	1.9	Type 1
Atrial septal defect	2	1.29	Type 1 (n=1), Type 2 (n=1)
Ventricular septal defect	1	0.64	Type 2
Turner syndrome	1	0.64	Type 1
Kallmann syndrome	1	0.64	Type 1
Persistant left superior vena cava	1	0.64	Type 1
Horseshoe kidney (renal fusion)	1	0.64	Type 1
Absence of celiac artery	1	0.64	Type 3

subtypes in 4 (2.6%) patients and BAV-RL subtypes in 11 (7.3%) patients.

DISCUSSION

In this study, we classified BAV phenotypes using 2D and 3D TEE and found a predominance of the type 1 subtype, accounting for >50% of our patients. In our study population, no difference was detected between the BAV-AP and BAV-RL groups with regard to AR, whereas BAV-RL patients more frequently had a stenotic aortic valve than did those with the BAV-AP phenotype. The prevalence of moderate-to-severe AS was also higher in the BAV-RL group. When we investigated the presence and distribution of aortopathy in our patients, the most common BAV aortopathy was enlargement of the TP of the aorta. Enlargement of the root alone was rare in our patients. A predominance of BAV-AP was observed in those with dilatation of the root and TP. Aortic dilatation was more prominent in older patients.

Several attempts have been made to demonstrate that BAV is not a simple disease, but rather a complex one with different phenotypes. Although some studies failed to show any relationship between phenotype and disease progression or valvular dysfunction,[20–22] animal studies showed that different BAV phenotypes (BAV-AP and BAV-RL) were distinct embryological entities.[23,24] These studies suggested that BAV-AP is caused by defective formation of the outflow tract (OFT) cushion, which might be a result of an alteration in the neural crest, whereas BAV-RL seems to be the result of defective OFT septation, which might occur during the nitric oxide-dependent stage of endothelial-to-mesenchymal transformation. Moreover, different valvular BAV phenotypes were shown to cause different aortopathy phenotypes, which are, in addition to valvular dysfunction, another factor affecting outcomes in patients with BAV.[25]

To better classify valvular phenotypes, recently Kang et al.[8] determined 5 phenotypes of BAV, their prevalence, and association with different types of aortopathy in a BAV population using MDCT. Similar to the findings of Kang et al., the most common phenotype in our BAV group was type 1. The second most common BAV phenotype in the former study was type 5, with a prevalence of 36.5%. In our BAV population, the prevalence of type 2, 3, and 5 were comparable. Type 4 was the rarest form of BAV phenotype in both studies. Overall, BAV-AP was more common in our population, similar to previous reports,[14,26–28] but in contrast to Ceccioni's[29] (higher prevalence of BAV-RL) report. The distribution of types 2, 3, and 5 phenotypes in our population differed from the findings of Kang et al.[8] The difference in prevalence might be due to racial differences in the populations studied. Larger epidemiology studies are needed to estimate the frequency of the different BAV phenotypes.

In the current study, we determined BAV phenotypes using TEE instead of MDCT. Half of our population was under 38 years old, which led us to choose TEE for phenotyping BAV and the associated aortopathy to avoid radiation exposure in these younger patients. Using TTE alone would not have provided accurate data. Determining presence/absence of a raphe or the origins of coronary arteries is mostly limited when TTE alone is used. Moreover, in patients with normally functioning aortic valves, one can even miss the diagnosis of BAV when a raphe exists between fusioned valves. TEE is accepted as a semi-invasive technique; however, in experienced laboratories, the value of the data provided by 3D visualization of cardiac structures should not be underestimated. Using 3D TEE, an experienced echocardiographer would see a similar anatomical view to that of the cardiac surgeon. 3D TEE determines exactly the size and features of cusps, the fusion of the commissures, the presence of thickening and calcification of a BAV, and the orientation of the coronary ostia, and it is a unique technique that shows the morphological details of a bicuspid valve with the same quality as a pathological examination.[12] In recent guidelines, TEE was suggested to be a reliable and cost-effective method for visualization of the aorta.[30] In our study, we could define valvular phenotype only in 47.4% of the patients with TTE but in 90.1% of the patients with 2D TEE. Our findings support that in phenotying BAV, TTE seems to be an insufficient technique. The studies in the literature have mostly presented data obtained using TTE in phenotyping BAV, which in fact, seems to be a serious limitation.[7,31] Performing TEE or MDCT in BAV phenotyping seems to be necessary to better understand the prognostic importance of morphologic types in BAV. In 9.9% of the patients even 2D TEE images failed to determine the precise phenotyping

where 3D TEE was used. Our data support that even in a small proportion of the patients with BAV, 3D imaging provides benefit in distinguishing valvular phenotypes. It has previously been demonstrated that the measurement of the area or diameter of the aortic annulus by 3D TEE was superior to 2D TEE measurements since the aortic annulus is not a simple circle, but rather eccentric in most aortic valve pathologies, as in BAV.[32–34] However, according to the results of our study, in phenotyping BAV, 3D TEE imaging only provided an additional benefit in a small proportion of patients where the raphe was short or the accumulation of calcification in the aortic leaflets led to the disappearance of the raphe. The aortic valve is difficult to image with 3D TEE because of its relative anterior position and thin pliable cusps, which might have contributed to its limited benefit in phenotyping; however, in experienced hands it provides important features about valve structure.[11]

Some studies have suggested a BAV phenotype role in the rapid progression of valvular dysfunction and a link between BAV phenotype and aortopathy;[7] however, the findings in the literature are still ambiguous. The discrepancies among studies[7,14] have precluded creation of a guideline to suggest performing precise valvular phenotyping of BAV and arranging specific follow-up intervals for different phenotypes, so the use of TEE for this approach was not advised specifically.[30] Recently, a retrospective study of 829 BAV patients suggested no additional role for valve phenotype in enlargement of the aorta.[35] The study lacked follow-up and used a surgical classification of valvular phenotype, which is quite different from what we preferred to use. It seems that discrepancies between studies will remain unresolved if a unique, international method of phenotyping is not used in all studies. There are no data in the literature comparing the use of 2D and 3D TEE with MRI or MDCT in BAV phenotyping. The classification of BAV phenotypes proposed by Kang et al.[8] seems reproducible even when using different imaging modalities. Standardization of the BAV phenotype may help provide better comparisons of findings from different centers and contribute to a pooling of the clinical features of each phenotype. The use of TEE or MDCT/MRI for phenotyping BAV in follow-up studies might reveal more accurate data to determine the prognostic importance of aortic valve morphology during the disease course.

To determine BAV aortopathy in our group, we used Park's classification,[19] which is reasonable in clinical practice and shows the tract(s) involved in BAV aortopathy. The classification first proposed by Park et al.[19] lacked a cut-off value for aortic enlargement; however, Della Corte et al.[17] later adopted Park's classification to compare it with their classification by determining a cut-off value of an aortic size index >2.1 cm/m^2 (corresponding to 39 mm in a patient with a BSA of 1.85 m^2) and demonstrated that these 2 classifications had a prognostic value. We used the same cut-off value as that of Della Corte et al. in our study by assuming that a tubular aorta >39 mm in size was dilated. Using Park's classification in their own BAV cohort, Della Corta et al. determined in a BAV population (with a mean age of 48±16 years) that 35% of the patients had non-dilated aortas, 45% had dilatation of the TP, 13% had dilatation of both the aortic root and the TP, and 7% had dilatation confined to the root.[17] Our results are comparable with those frequencies presented by Della Corte, except that the root phenotype was rarer in our population. Because of a very small number of patients with the root phenotype, we cannot comment on determinants of this aortopathy, but the obvious differences in the prevalence of root phenotypes may indicate racial differences or genetic factors involved in the development of BAV and specific types of aortopathy in different races.

With growing evidence, it has been assumed that the BAV fusion type alters flow patterns in the aorta, which may play a role in the enlargement of different segments.[36–39] A study investigating the elastic properties of the aorta in BAV reported increased dimensions and stiffness of the SOV in the BAV-AP versus the BAV-RL phenotype, but with no difference in the elastic properties or dimensions of the AA.[39] In our BAV population, an increased diameter of the SOV was seen in the BAV-AP group despite similar TP dimensions in the BAV-RL group, as in previous reports.[14,39] Moreover, we determined a predominance of BAV-AP in those with dilatation of the root and TP, supporting the findings of previous studies. The most common BAV aortopathy phenotype was enlargement of the TP of the ascending aorta, similar to previous reports,[17] and these patients had higher aortic velocities than did those without dilatation, suggesting a contribution of hemodynamic factors in the development of BAV aortopathy.

The association of valvular involvement with the BAV phenotype is still not well understood. Valvular dysfunction and disease progression were assumed to be independent of the valve phenotype in previous reports.[20–22] In contrast to these reports, Fernandes et al.[27] determined that patients with BAV-RL had more than twice the risk of AS and AR compared with other types of BAV in a population <18 years old. Kang et al. reported a predominance of moderate-to-severe AR in BAV-AP, but a predominance of moderate-to-severe AS in BAV-RL.[8] In our study, we detected no difference between the BAV-AP and BAV-RL groups with respect to AR; however, the presence of a stenotic valve was more frequent in those with BAV-RL. In the BAV-RL group, moderate-to-severe AS was also more common than that in the BAV-AP group. It seems that patients with BAV-RL have a greater tendency to develop AS.

In this study, we also presented congenital anomalies detected in our BAV population. Among congenital heart diseases, the prevalence of CoA was 1.9%, that of atrial septal defect was 1.29%, and that of ventricular septal defect in our patients was 0.64%. All 3 patients with CoA had type 1 BAV. We also detected the presence of Kallmann syndrome and the absence of a celiac artery in 2 patients. We cannot explain whether these 2 congenital anomalies were detected coincidentally or have some link with BAV. Further reports are needed to clarify this issue.

Study limitations

There are several limitations to this study. This study was performed in a population of adults with a prediagnosis of BAV who were referred for echocardiography. Patients with BAV without valvular dysfunction or lack of symptoms might have been less well represented in our study. Although our study provides important data about BAV, our findings should not be generalized to all BAV populations.

Conclusion

There may be racial differences in the frequency of valvular and aortopathy phenotypes in patients with BAV. BAV phenotypes differ with respect to AS and aortopathy phenotypes. TEE may have good diagnostic utility in differentiating BAV phenotypes.

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