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The Association between the Morphology of the Aortic Valve and the Dysfunction of the Aortic Valve in Pediatric Patients with a Diagnosis of Bicuspid Aortic Valve

Biküspid Aort Kapağı Tanısı Alan Pediatrik Hastalarda Aort Kapak Morfolojisi İle Aort Kapak Disfonksiyonu Arasındaki İlişki

Hüseyin Süslü[1], Ahmet Sert[2]

[1]Department of Pediatrics, Selçuk University Medical School, Konya, Turkey·
[2]Department of Pediatric Cardiology, Selçuk University Medical School, Konya, Turkey·

Abstract

Aim: The congenital heart malformation known as the bicuspid aortic valve is a prevalent condition. The objective of this study was to analyze the demographic, clinical, and echocardiographic characteristics of subjects who were children and adolescents with the bicuspid aortic valve condition. Additionally, we aimed to evaluate and compare the dimensions of the aortic root and ascending aorta as well as evaluate the level of aortic valve dysfunction in relation to the morphology of the aortic valve among the groups studied.

Material and Method: The prospective investigation was conducted among pediatric patients below the age of 18 years, who had been identified with bicuspid aortic valve through the use of echocardiography, at the Department of Pediatric Cardiology.

Results: Bicuspid aortic valve was detected in 1.42% (152 out of 10,691) of patients who underwent echocardiography. Among these patients, 72.4% (110) were male. The most frequent aortic valve morphology observed in patients with bicuspid aortic valve was the fusion of the left and right coronary cusps.

Conclusion: The results of our investigation have revealed that the diameter of the aortic annulus and sinotubular junction in the fusion of the right and non-coronary cusps cohort was markedly greater than that of the other groups. Moreover, it was observed that age, weight, and height exerted independent predictive effects on the diameters of the aortic root and ascending aorta in children diagnosed with bicuspid aortic valve.

Keywords: Adolescent, aortic root, aortic valve dysfunction, ascending aorta, bicuspid aortic valve, children

Öz

Amaç: Biküspit aort kapağı olarak bilinen konjenital kalp malformasyonu sık görülen bir durumdur. Bu çalışmanın amacı biküspid aort kapağı olan çocuk ve ergenlerin demografik, klinik ve ekokardiyografik özelliklerini analiz etmektir. Ek olarak, incelenen gruplar arasında aort kökü ve çıkan aort boyutlarını değerlendirmeyi ve karşılaştırmanın yanı sıra aort kapak fonksiyon bozukluğunun düzeyini aort kapak morfolojisi ile ilişkili olarak değerlendirmeyi amaçladık.

Gereç ve Yöntem: Prospektif çalışma, Çocuk Kardiyolojisi Bölümü'nde ekokardiyografi kullanılarak biküspit aort kapağı tanısı konulan 18 yaş altı pediatrik hastalarda gerçekleştirildi.

Bulgular: Ekokardiyografi yapılan hastaların %1,42'sinde (10.691 hastanın 152'sinde) biküspit aort kapağı tespit edildi. Bu hastaların %72,4'ü (110) erkekti. Biküspit aort kapağı olan hastalarda en sık gözlenen aort kapak morfolojisi, sol ve sağ koroner kasparın füzyonuydu.

Sonuç: Çalışmamızın sonuçları, sağ ve non-koroner kasp füzyon kohortunun aortik annulus ve sinotubüler bileşke çapının diğer gruplara göre belirgin şekilde daha büyük olduğunu ortaya koydu. Ayrıca biküspid aort kapağı tanısı alan çocuklarda yaş, kilo ve boyun aort kökü ve çıkan aort çapı üzerinde bağımsız prediktif etkiler oluşturduğu gözlendi.

Anahtar Kelimeler: Ergen, aort kökü, aort kapak disfonksiyonu, çıkan aort, biküspid aort kapağı, çocuklar

Corresponding *(İletişim)*: Ahmet Sert, Department of Pediatric Cardiology, Selcuk University, Faculty of Medicine, 42250, Konya, Turkey
E-mail *(E-posta)*: ahmetsert2@hotmail.com
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INTRODUCTION

Bicuspid aortic valve (BAV) is the most commonly found congenital cardiac disease. It is characterized by aortic valve regurgitation and aortic dilatation in approximately 50% of individuals.[1] BAV can occur either independently or in conjunction with other heart problems, and it can also manifest as part of a syndrome. In adults, valve dysfunction requiring intervention is frequently observed, and the severity of valve dysfunction is thought to be associated with the morphologic phenotype of BAV.[2] Researches exploring the link between BAV morphology, aortic root and ascending aorta measures, and aortic valve dysfunction in juveniles has yielded varying results in the literature.[3-5] Therefore, the purpose of this prospective study is to investigate the demographic, clinical, and echocardiographic aspects of children and adolescents diagnosed with BAV and to compare the measurements of the aortic root and ascending aorta, as well as the occurrence of aortic valve dysfunction, based on their aortic valve morphology within these groups.

MATERIAL AND METHOD

During the period spanning from January 1, 2017 to December 31, 2019, children below the age of 18 who had been diagnosed with BAV via echocardiography conducted by the Department of Pediatric Cardiology within the Faculty of Medicine, were incorporated into this prospective study. Furthermore, an examination of these syndromes was also conducted, with the aim of revealing the frequency of any genetic syndromes that may be associated with BAV. Patients whose echocardiographic image was deemed suboptimal were excluded from the study. The ethical committee at our hospital provided the necessary authorization for the study protocols (as evidenced by approval number 2017/294), while signed informed consent papers were collected from the parents of the adolescent subjects. During the study, all patients underwent thorough interrogation of their medical and family histories, spanning over two generations. The registration and follow-up form documented the physical examinations conducted as per routine. The physical examination encompassed the patients' grievances during their first admission and follow-up, personal and family history, and any murmur/abnormal heart sound. Additionally, measurements of height, weight, and blood pressure values were taken. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared.

One experted pediatric cardiologist conducted examination via the Philips EPIQ 7C device from Philips Healthcare in Minnesota, United States to the transthoracic echocardiographic. The left lateral decubitus position was used to examine apical four- and five-chamber, parasternal long-axis and short-axis, and subcostal echocardiographic images of the patients. The aortic valve morphology during systole and diastole was examined in the parasternal short axis view. Patients were diagnosed with BAV if they exhibited aortic valves with distinct bipartite ends, the characteristic systolic fish-mouth appearance of the aortic valve leaflets, or two of the three supporting features of BAV, namely systolic dome, diastolic prolapse of aortic leaflets, and eccentric leaflet closure. True BAV (BAV without raphe) was segregated based on its orientation, i.e., horizontal or vertical. Furthermore, BAV was classified into three additional types depending on the location of the raphe, which were as follows: type fusion of the left and right coronary cusps, type fusion of the right and non-coronary cusps, and type fusion of the left and non-coronary cusps. The patients underwent regular echocardiographic examinations at six-month intervals for follow-up purposes.

The measurements of the diameter for the aortic annulus, sinus of valsalva, sinotubular junction (aortic root), and proximal ascending aorta 1 cm above the sinotubular junction were conducted in the parasternal long-axis view, which was perpendicular to the long axis of the vessel, and at the end of systole. The aortic Z scores were then calculated according to the method previously described by Cantinotti et al.[6] If the resulting Z-score value was greater than +2, it was accepted as an indication of enlargement in the aortic root or ascending aorta. The classification of aortic valve stenosis was based on the peak Doppler gradient measurement, which was determined to be mild (peak Doppler gradient <40 mmHg), moderate (peak Doppler gradient between 40-70 mmHg), or severe (peak Doppler gradient >70 mmHg).[7] In addition, the grading of aortic regurgitation (AR) ranged from first degree to fourth degree, with hemodynamically significant AR considered to be of the second degree or more severe, as defined by the measurement.[8]

Statistical Analysis

The utilization of Statistical Package for the Social Sciences 21.0 (SPSS Inc., Chicago, IL, USA) was implemented for all statistical analyses. Categorical variables were represented by numbers and percentages. The distribution of parameters was examined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Whether the data was normally distributed or not determined the usage of parametric or nonparametric tests in data analysis. Mean±standard deviation was employed for quantitative data presentation. In cases where parameters were not normally distributed, the median (minimum-maximum) was displayed. Depending on the distribution of the variables, differences in the means of the variables were examined using both parametric and nonparametric tests. The comparison of groups was conducted using the independent t test or the Mann-Whitney U test, while connections associations between parameters were investigated using the Pearson or Spearman correlation test. The Bonferroni-corrected Mann-Whitney U test was employed as a more stringent measure of statistical significance for multiple comparisons, in conjunction with the Kruskal-Wallis analysis of variance, to compare groups. To compare categorical variables between independent groups, the chi-square test was utilized. The mixed ANOVA test was employed to analyze

the group effect in repeated measurements. Subsequently, stepwise multivariate linear regression was used to ascertain which factors independently explained a significant ($p < 0.05$) proportion of the variation in the dependent variables. The Mc Nemar test was applied to compare categorical variables between dependent groups. The Wilcoxon signed rank test or the paired samples t-test were implemented to compare the research group's before and subsequent values. The significance of results was established when the value of p was less than 0.05, or when p was less than 0.05 divided by the number of comparisons made, denoted as k.

RESULTS

In the cohort of 10,691 patients presenting for initial assessment in the pediatric cardiology, a total of 152 (1.42%) individuals were identified as having been diagnosed with BAV. Among these, 42 (27.6%) were identified as female, while the remaining 110 (72.4%) were male. The mean age of the population was 7.8±4.6 years, ranging from 1 month to 17 years. Upon detailed inquiry regarding cardiovascular complaints, 115 (75.7%) of the patients with BAV reported no active symptoms during their initial presentation. However, the remaining cases exhibited a variety of symptoms, including sweating (26.3%), failure to gain weight (19.7%), chest pain (17.8%), exercise intolerance (15.1%), palpitations (15.1%), fatigue (14.5%), respiratory distress (13.2%), presyncope symptoms (10.5%), fainting (5.3%), hypoxic seizures (2.6%), and peripheral cyanosis (2%). Eight individuals, accounting for 5.2% of those with BAV, presented with syndromic conditions. Among the cohort, 2 (1.3%) had Down syndrome, 2 (1.3%) exhibited Klinefelter syndrome, 1 (0.6%) displayed Di George syndrome, 1 (0.6%) manifested Apert syndrome, 1 (0.6%) illustrated Gorlin-Goltz syndrome, and 1 (0.6%) was diagnosed with Sturge-Weber syndrome. In the family history of 33 (21.7%) of the patients, there was evidence of first-degree consanguinity. The vast majority, or 126 (82.9%), of the patients with BAV had no prior history of chronic disease. Co-occurrence of other diseases was noted in the remaining patients and included 12 (7.9%) who had allergic diseases, 4 (2.6%) who had rheumatological diseases, 3 (2.0%) who had nephrological diseases, 3 (2.0%) who had endocrinological diseases, 2 (1.3%) who had neurological diseases, 1 (0.7%) who had haematological disease, and 1 (0.7%) who had gastroenterological disease. Among the cohort of patients diagnosed with BAV, a majority of 126 (82.9%) were not using medication. Of the remaining patients, a small proportion of 15 (9.9%) were using antihypertensive drugs, while an even smaller proportion of 3 (2.0%) were using benzathine penicillin-G, 3 (1.3%) were using antiarrhythmic drugs, 2 (1.3%) were using asthma drugs, 2 (1.3%) were using colchicine, and 1 (0.7%) was using subcutaneous immunoglobulin. In terms of familial history, 33 (21.7%) patients with BAV had a history of consanguinity, with 119 (78.3%) of these cases being of the first degree. Furthermore, a large majority of 141 (92.7%) patients did not report a family history of sibling death, while a small minority of 11 (7.2%) reported such a history. In the sample population, a small percentage of individuals had a history of rhythm disorder (5.3%), sudden death (4.6%), congenital heart disease (2.6%), or syncope (1.3%). As far as it is learned from the family history, a number of individuals also had hypertension (6.6%), hyperlipidemia (2.6%), metabolic syndrome (15.8%), diabetes (13.2%), or both diabetes and hypertension (11.2%) in their relatives. Additionally, a small percentage of individuals had coronary artery disease (4.6%), thyroid dysfunction (0.7%), or neurological disease (1.3%) in their first and second degree relatives. In our study, we invited first-degree relatives of patients with BAV for family screening. BAV was diagnosed in 12 of the total 30 patients who visited our pediatric cardiology clinic through echocardiographic examination.

At the time of initial presentation, the average weight of the patient cohort (N:152) was 29.2±17.8 kilograms (median: 23, 3.7-83), while the mean height was 122.1±32.0 cm (median 124, 40-182). The patients' blood pressure was recorded as 100.6±12.4 mmHg (70-160 mmHg), with an average diastolic blood pressure of 64.9±10.5 mmHg (32-110 mmHg). The mean blood pressure of the patients was 76.9±10.4 mmHg.

When categorizing patients by age, we observed that 18 (11.8%) belonged to the infancy period (0-24 months), 27 (17.8%) to the pre-school period (2-5 years), 69 (45.4%) to the school age (5-12 years), and 38 (25%) were adolescents (>12 years old). The largest proportion of our cases was within the age group of 5-12 years. **Table 1** presents the demographic and anthropometric characteristics of the patients. In accordance with the Gomez malnutrition classification, 19 patients (12.5%) were deemed malnourished, 12 patients (7.8%) had mild malnutrition, and 7 patients (4.6%) had moderate malnutrition. There was an absence of severe malnutrition observed in our patient cohort. Within the sample, 21 individuals (13.8%) exhibited short stature. Among these, 17 patients (11.1%) demonstrated a range of -2 to -3 standard deviations (potentially indicative of a normal variant or pathological short stature), while 4 patients (2.6%) exhibited a -3-standard deviation (suggesting pathological short stature). Upon conducting cardiac auscultation examinations, 116 patients (76.3%) displayed no cardiac murmur or abnormal heart sounds. Among the remaining patients, 25 individuals (16.4%) exhibited systolic murmur and 11 patients (7.2%) displayed ejection click.

Of the patient cohort diagnosed with BAV, 65 individuals, representing 42.9% of the total sample, exhibited an isolated occurrence of the condition. Comorbid echocardiographic findings were present in the remaining patients. These included isolated trace mitral valve regurgitation in 26 patients (17.1%), ascending aorta dilatation in 19 patients (12.5%), aortic coarctation in 10 patients (6.6%), trace mitral valve regurgitation and dilatation of the ascending aorta in 8 patients (5.3%), trace mitral valve regurgitation and mitral valve prolapse in 7 patients (4.6%), atrial septal defect in 6 patients (3.9%), ventricular septal defect in 4 patients (2.6%),

trace mitral regurgitation and atrial septal defect in 2 patients (1.3%), dilatation of the ascending aorta and ventricular septal defect in 2 patients (1.3%), mitral valve prolapse and atrial septal defect in 1 patient (0.6%), mitral valve prolapse in 1 patient (0.6%), and other congenital heart anomalies in 1 patient (0.6%).

Clinical Characteristics and Aortic Measurements According To Aortic Valve Morphology

The BAV subtype of five patients could not be definitively determined by echocardiography. Of the remaining patients, the BAV types were categorized as follows: left-right fusion type in 100 patients (68%), right-noncoronary cusp fusion type in 32 patients (21%), and 13 patients (9%) without raphe. Left-noncoronary cusp fusion type was observed in only two patients (1%) and was not included in the statistical analysis due to the small sample size. The statistical analyses were conducted on a total of 145 patients. **Table 1** presents patients' clinical characteristics and echocardiographic measurements based on aortic valve morphology. The three groups showed no significant differences in sex (p: 0.913). Furthermore, no significant differences in aortic measurements were observed when analyzed by sex ($p>0.05$). When comparing the three groups based on age, weight, height, systolic blood pressure, aortic annulus, sinotubular junction, and ascending aorta measurements, a statistically significant difference was observed between the groups. However, no significant difference was noted in terms of the z-scores values of the aortic root and descending aorta diameters and diastolic blood pressure. Furthermore, when examining the three groups based on age, the left-right fusion type group exhibited a statistically significantly lower age than the right-noncoronary cusp fusion type group. Lastly, when comparing the groups based on systolic blood pressure, the right-noncoronary cusp fusion type group displayed a statistically significantly higher systolic blood pressure than the BAV without raphe group. When comparing the three groups in relation to the diameter of the aortic annulus, it was found that the aortic annulus diameter of the group with fusion of the right-noncoronary cusp type was significantly higher than that of the group with fusion of the left and right coronary cusps. Similarly, when examining the sinotubular junction diameter, the right-noncoronary cusp fusion type group exhibited a statistically significant increase compared to the BAV without raphe group. Furthermore, in terms of the diameter of the ascending aorta, the right-

Table 1. Comparison of patients' clinical features and echocardiographic measurements according to aortic valve morphology

	Total patients (N:145)	Type fusion of the left and right coronary cusps (N:100)	Type fusion of the right and non-coronary cusps (N:32)	Type without raphe (N:13)	Oneway ANOVA/ or Kruskal wallis test	P1 value	P2 value	P3 value
Sex (Male/Female)	105/40	72/28	24/8	9/4	NA			
Age (month)	96.4±56.3 96 (1-204)	89±55.4 (1-192)	122.8±54.9 (18-204)	87.1±49.5 (16-164)	**0.011**	**0.010**		
Weight (kg)	29.7±18 23 (3.7-83)	27.4±16.9 (3.7-76)	38.3±20.4 (10-83)	25.6±12.8 (9-51)	**0.019**	0.018		
Height (cm)	123±31 124 (40-182)	118±32.8 (40-175)	137±26 (75-182)	120±27 (73-155)	**0.024**	0.022		
Body Mass Index	17.07 (10.89-25.95)	16.86 (10.89-25.39)	17.93 (13.61-25.95)	16.53 (14.15-21.23)	0.404			
Systolic Bloood Pressure (mmHg)	101±12.7 100 (70-160)	100±12.8 (70-160)	105±12 (90-130)	96±12 (85-130)	**0.013**			**0.015**
Diastolic Bloood Pressure (mmHg)	65.2±10.7 60 (32-110)	64.5±10.6 (32-110)	68.9±11 (50-90)	62±8.5 (50-75)	0.100			
Aortic Annulus (mm)	15.15±3.69 15 (5.2-28)	14.67±3.86 14.70 (5.2-22.7)	17.05±3.86 16.65 (11-28)	14.36±1.57 14 (11.9-16.5)	**0.005**	**0.008**		0.037
Z score	-0.13±1.85 -0.09 (-4.62-9.87)				0.513			
Sinus Valsalva (mm)	20.79±5.10 20.65 (7.3-35.8)	20.55±5.54 20.65 (7.3-35.8)	22.29±4.13 22.5 (14-32.3)	19.13±3.14 18.80 (14.3-25.3)	0.075			
Z score	0.02±1.82 0.04 (-4.20-8.65)				0.457			
Sinotubular Junction (mm)	17.33±4.69 17.2 (6.4-30.7)	16.95±4.86 17.2 (6.4-29.6)	19.10±3.86 19 (11.8-30.7)	15.166±2.68 15.90 (10.6-19)	**0.007**	0.040		**0.012**
Z score	0.68±1.87 0.57 (-3.82-10.19)				0.119			
Ascending Aorta (mm)	21.46±5.97 20.75 (7.1-38.4)	20.67±6.1 19.90 (7.1-38.4)	24±4.97 23 (15-37.9)	21.19±5.95 20.20 (13.2-33.1)	**0.006**	**0.009**		
Z score	1.33±1.94 1.10 (-3.82-10.19)				0.581			

P1: Type fusion of the left and right coronary cusps versus type fusion of the right and non-coronary cusps, P2: Type fusion of the left and right coronary cusps versus type without raphe, P3: Type fusion of the right and noncoronary cusps versus type without raphe, Data were indicated mean±standart deviation, median (minimum-maximum). Normally distributed data were compared with the One-way ANOVA test. If the data do not fit the normal distribution, results were compared using the Kruskal–Wallis test followed by the Bonferroni-corrected Mann–Whitney U test. Significance was determined by $p<0.05$ for the Kruskal–Wallis test and $p<0.016$ ($p=0.05/3$) for the Bonferroni correction. Statistically significant differences are highlighted in bold.

noncoronary cusp fusion type group displayed a significantly higher diameter compared to the type fusion of the left and right coronary cusps group (**Table 1**).

After the diagnosis of BAV, patients underwent regular echocardiographic examinations at 6-month intervals. The patients who came for the examination had two, three, or four measurements recorded. Unfortunately, the number of patients with three and four measurements was insufficient to conduct further statistical analysis. However, for the 58 patients in the BAV group with fusion of the left and right coronary cusps, 14 patients in the right-noncoronary cusp fusion type group, and 6 patients in the BAV without raphe group, we evaluated the repeated measurements using mixed ANOVA. The results showed that aortic valve morphology did not have a statistically significant effect on the measurements of the aortic root and ascending aorta.

The Relationship between Aortic Valve morphology and Aortic Valve Stenosis and Regurgitation

The study found that among 100 patients with BAV left-right leaflet fusion, 34 (34%) displayed hemodynamically insignificant AR, 13 (13%) displayed both aortic stenosis (AS) and AR, 9 (9.0%) displayed mild AS, 2 (2.0%) displayed moderate AS, and 1 (1.0%) displayed hemodynamically significant AR. In the case of 32 patients with BAV type fusion of the right and non-coronary cusps, 12 (37.5%) displayed hemodynamically insignificant AR, 8 (25%) displayed both AS and AR, 2 (6.25%) displayed mild AS, and 1 (3.1%) displayed hemodynamically significant AR. Moreover, among 13 patients with BAV without raphe type, 7 (53.85%) displayed hemodynamically insignificant AR, while 4 (30.7%) displayed both AS and AR. Finally, among 2 patients with BAV with type fusion of the left and non-coronary cusps, both AS and AR were found in 1 (50%) patient. Patients with hemodynamically significant AR were treated with an angiotensin converting enzyme inhibitor.

When the three groups were compared in terms of isolated AS, isolated AR, and both AS and AR, coexistence of AR and AS were found to be statistically higher in the right-noncoronary cusp fusion type group compared to the other groups (p: 0.016).

Aortic Valve Morphology and Accompanying Congenital Heart Diseases

In a total of 100 BAV types formed by type fusion of the left and right coronary cusps, 40 (40%) were observed to have no additional cardiac anomaly. The remaining patients displayed various cardiac anomalies, including 17 (17%) with mild mitral regurgitation, 13 (13%) with enlargement of the ascending aorta, 7 (7%) with coarctation of the aorta, 6 (6%) with atrial septal defect, 6 (6%) with trace mitral valve prolapse accompanied by mild mitral regurgitation, 3 (3%) with enlargement of the ascending aorta coupled with mild mitral regurgitation, 2 (2%) with ventricular septal defect, 2 (2%) with atrial septal defect accompanied by mild mitral regurgitation, 2 (2%) with ventricular septal defect and enlargement of the ascending aorta, and 1 (1%) with mitral valve prolapse.

In 46.9% of the 32 BAV types resulting from the fusion of the right and non-coronary cusps, no additional cardiac anomaly was observed. Among the remaining patients, 21.9% had trace mitral regurgitation, 12.5% had an enlargement of the ascending aorta, 9.4% had an enlargement of the ascending aorta with trace mitral regurgitation, 3.1% had coarctation of the aorta, 3.1% had mitral valve prolapse with trace mitral regurgitation, and both mitral valve prolapse and ventricular septal defect were observed in 3.1% of the patients.

In the subset of patients with BAV lacking a raphe, cardiac anomalies were absent in a majority of cases (61.5%, n=8 out of 13). However, in the remaining patients, various concomitant congenital heart diseases were present, including ventricular septal defect (15.4%, n=2), coarctation of the aorta (7.7%, n=1), enlargement of the ascending aorta (7.7%, n=1), and a combination of trace mitral regurgitation and enlargement of the ascending aorta (7.7%, n=1). Among the two BAV types characterized by left-noncoronary leaflet fusion, one displayed trace mitral regurgitation while the other exhibited enlargement of the ascending aorta. Upon statistical analysis, no significant differences were observed between the groups in terms of concomitant congenital heart diseases (p: 0.320).

Correlation between Aortic Root and Ascending Aorta Measurements And Other Parameters

A positive correlation was discovered between the diameters of the aortic root and ascending aorta and various patient factors, including age, weight, height, as well as systolic and diastolic blood pressures in BAV patients as depicted in **Table 2**.

In order to determine the independent variables influencing aortic anulus, sinus Valsalva, sinotubuler junction, and ascending aorta in patients with BAV, a multiple regression analysis model was utilized. Furthermore, a multiple stepwise regression was conducted to reveal the distinct contributions of sex, age, systolic blood pressure, and aortic valve morphology groups. The independent variables found to impact aortic anulus were weight (β=0.205, p=0.032, adjusted R square 0.670, Confidence Interval 0.004-0.081) and height (β=0.637, p <0.0001, Confidence Interval 0.052-0.096). The age (β=0.302, p=0.025, adjusted R square 0.617, Confidence Interval 0.004-0.052) and height (β=0.501, p <0.0001, Confidence Interval 0.038-0.123) were the independent variables for sinus valsalva. Similarly, weight (β=0.298, p=0.007, adjusted R square 0.574, Confidence Interval 0.041-0.104) and height (β=0.490, p<0.0001, Confidence Interval 0.022-0.134) were the independent variables for sinotubuler junction. The independent variables for ascending aorta were age (β=0.313, p=0.032, adjusted R square 0.548, Confidence Interval 0.003-0.064) and height (β=0.446, p=0.002, Confidence Interval 0.030-0.138).

Table 2. The Pearson correlation analysis of a cohort of 145 patients with bicuspid aortic valve, showing the relationship between multiple parameters and measurements of the aortic root and ascending aorta

Variable	r	p
Aortic anulus		
Sex	0.125	0.135
Age	0.770	<0.0001
Weight	0.754	<0.0001
Height	0.815	<0.0001
Systolic Blood Pressure	0.573	<0.0001
Diastolic Blood Pressure	0.465	<0.0001
Sinus valsalva	0.866	<0.0001
Sinotubular Junction	0.853	<0.0001
Ascending aorta	0.767	<0.0001
Sinus valsalva		
Sex	0.092	0.271
Age	0.766	<0.0001
Weight	0.707	<0.0001
Height	0.781	<0.0001
Systolic Blood Pressure	0.507	<0.0001
Diastolic Blood Pressure	0.396	<0.0001
Sinotubular Junction	0.900	<0.0001
Ascending aorta	0.761	<0.0001
Sinutubular junction		
Sex	0.093	0.268
Age	0.744	<0.0001
Weight	0.732	<0.0001
Height	0.758	<0.0001
Systolic Blood Pressure	0.527	<0.0001
Diastolic Blood Pressure	0.491	<0.0001
Aurtic anulus	0.853	<0.0001
Sinus Valsalva	0.900	<0.0001
Ascending aorta	0.864	<0.0001
Ascending aorta		
Sex	0.095	0.26
Age	0.719	<0.0001
Weight	0.685	<0.0001
Height	0.734	<0.0001
Systolic Blood Pressure	0.559	<0.0001
Diastolic Blood Pressure	0.497	<0.0001
Aortic anulus	0.767	<0.0001
Sinus Valsalva	0.761	<0.0001
Sinotubular Junction	0.864	<0.0001

DISCUSSION

This prospective investigation proffers evidence demonstrating the commensurability of the frequency of BAV with that reported in the literature. Furthermore, the study ascertained that the incidence of BAV was more prominent among males. The most frequently detected aortic valve morphology type amongst patients with BAV was observed to be the fusion of the left and right coronary cusps fusion type. Our study evinced that the aortic annulus and sinotubular junction diameter of the right-noncoronary cusp fusion type cohort was significantly higher in a statistical sense than those of the other groups. Additionally, we demonstrated that aortic valve dysfunction was markedly more frequent in the right-noncoronary cusp fusion type group relative to the other aortic valve morphologic groups. Age, weight, and height were also independent prognosticators of aortic root and ascending aortic diameters in children with BAV, as was discovered.

The estimated occurrence of BAV among the general population is 1-2%, with a noticeable male predominance reflected in a sex ratio of 3:1. Nistri et al.[9] expounded upon a comprehensive register of echocardiographic investigations that were conducted during the military screening of 20,946 young men in the northeastern region of Italy. Correspondingly, they were able to detect BAV in 0.8% of the subjects. Furthermore, Basso et al.[10] documented an echocardiographic frequency of 0.5% in children.[9,10] It is estimated that the frequency of BAV in first-degree relatives of individuals diagnosed with BAV is 8-10%.[11,12] In our investigation, the frequency of BAV was determined to be within the range reported in the literature, with a prevalence of 1.4%. Our study also revealed that the frequency of BAV was 2.6 times higher in males as compared to females, which corresponds to previous research findings.

The 2014 guidelines published by the American Heart Association/American College of Cardiology and European Society of Cardiology recommended the implementation of echocardiographic screening for first-degree relatives of patients with BAV. However, limited data from relatively small studies have investigated the effectiveness of familial screening for first-degree relatives of patients with BAV and have reported conflicting outcomes. Recently, Massardier et al. conducted a study revealing that the prevalence of BAV was 6.6% among first-degree relatives of patients with BAV.[11] In our study, although not all first-degree relatives of patients with BAV underwent echocardiographic screening, the diagnosis of BAV was confirmed in 12 individuals who presented to us. Although we cannot draw definitive conclusions based on these findings, it remains crucial to perform echocardiographic examinations for first-degree relatives of patients with BAV.

Consanguinity is recognized to concentrate autosomal recessive genes in the offspring, however, the contribution of these genes to the heritability of cardiac malformations remains incompletely comprehended.[13] Konya, situated in Central Anatolia, has been reported to have a consanguineous marriage rate of about 22%.[14] In the family history of 33 (21.7%) of the parents of BAV patients, there was consanguinity of the first and second degree. Our study's findings demonstrate a notably higher proportion of parental first-cousin marriage among patients with BAV.

Some patients who have BAV are diagnosed based on the presence of a murmur, while others may experience symptoms as a result of valvular dysfunction. There are also cases where the condition may remain unnoticed until adulthood, potentially leading to sudden death or severe

cardiovascular deterioration due to aortic dissection or rupture.[15] In our research, we observed that individuals with BAV presented with varying complaints at differing frequencies. Specifically, approximately 16% of patients had a murmur, 13% had malnutrition, and 11% had short stature. In the realm of medical diagnosis, BAV may present itself as an independent lesion or in conjunction with certain genetic syndromes, such as Turner syndrome, as noted in previous research.[16] Our current study reveals that 5.2% of patients afflicted with BAV also exhibit co-occurring syndromes.

The phenomenon of right-left cusp fusion is well established as being more prevalent, occurring in approximately 70% of cases, when compared to right-noncoronary fusion. Conversely, left-noncoronary fusion is noted to be the least common.[5] Our study aligns with existing literature, as the overwhelmingly dominant BAV type found in patients with BAV is the fusion of the left and right coronary cusps, accounting for 68% of cases.

The presence of BAV has been linked to early onset of valvular dysfunction and dilation of the proximal aorta, which exhibits high heterogeneity.[17] Previous literature has suggested that the diverse subtypes of BAV cusp fusion morphology may be correlated with varying degrees and levels of aortic dilatation, consequently having a differential impact on treatment and prognosis. Patients with fusion of the left coronary cusp and right coronary cusp commonly experience dilatation of the ascending aorta, in addition to aortic root dilation. Conversely, individuals with fusion of the right coronary and noncoronary cusps rarely exhibit aortic root dilation, with the ascending aorta being the primary area of concern. However, the current data is insufficient to establish the strength of the aforementioned relationships. A recent meta-analysis has demonstrated that the morphology of right and left cusp fusion in BAV is positively associated with a larger aortic diameter at the level of the sinuses of Valsalva. However, no significant impact was observed on the differences in ascending aorta diameter between the two most common BAV subtypes.[18] In our study, we have identified that the aortic annulus diameter of the right-noncoronary cusps fusion type group is significantly higher than that of the type fusion of the left and right coronary cusps group. Additionally, the sinotubular junction diameter of the right-noncoronary cusps fusion type group is significantly higher than that of the BAV without raphe group. Furthermore, our findings have revealed that the ascending aorta diameter of the right-noncoronary cusps fusion type group is significantly higher than that of the type fusion of the left and right coronary cusps group. In a study conducted by Gurvitz et al. encompassing 80 cases, it was demonstrated that the augmentation of aortic root sizes corresponded with an increase in height and body surface area rather than age.[19] Additionally, another study showed that a significant correlation existed between height, weight, body surface area, aortic root, and clinical parameters.[20] Our investigation found a favorable correlation between the dimensions of the aortic root and ascending aorta and various factors such as age, weight, height, systolic and diastolic blood pressures in BAV patients. Our study further established that age, weight, and height were autonomous predictors of aortic root and ascending aortic diameters, emphasizing the relevance of utilizing z-score values.

Previous research has indicated that the prevalence of valve dysfunction is greater in individuals with the right-left valve phenotype, characterized by the fusion of the right and left coronary cusps, while aneurysm of the ascending aorta is more common in those with the right-non-coronary cusps phenotype, characterized by the fusion of the right and non-coronary cusps, in cases of BAV.[15] A more recent study conducted by Blais et al. found that there was no significant difference in the rate of proximal aorta dilatation between various leaflet fusion patterns. However, it was observed that the fusion of the right and non-coronary cusps and complex fusion types tended to be associated with a greater proportion of children exhibiting more than mild aortic valve dysfunction.[21] A recent meta-analysis has demonstrated that patients with BAV who have fused right and left cusps are prone to develop AR, while those with fused right and non-coronary cusps are more likely to develop AS.[22] Moreover, Ward et al. have revealed that aortic valve insufficiency and stenosis are more prevalent in patients with fused right and non-coronary cusps. In their investigation, the median aortic sinus z score was higher in patients with fused left and right coronary cusps than in those with fused right and non-coronary cusps.[23] However, there were no significant differences in the median ascending aorta z score between the groups. Furthermore, we have found that aortic valve dysfunction is significantly more common in patients with fused right-noncoronary cusp than the other morphologic groups of aortic valve.

The heterogeneity of our study group should be acknowledged, as we opted to incorporate all patients diagnosed with BAV in our analysis. However, we aim to carry out a subsequent investigation on this topic, where we will expand our patient sample size.

CONCLUSION

In our investigation, it was demonstrated that the frequency of children with BAV was preponderant in males, with a rate similar to that which has been documented in the literature. Additionally, the most prevalent aortic valve morphology was identified as type fusion of the left and right coronary cusps. Our data revealed that aortic root and ascending aorta measurements, as well as aortic valve dysfunction, were more elevated in the right-noncoronary cusps fusion type than in other aortic valve types. Furthermore, age, weight, and height were established as independent predictors of aortic root and ascending aorta measurements. We recommend that the exactitude of our findings can be disclosed through longitudinal studies involving a substantial cohort on this matter.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocols were approved by our hospital's ethics committee (approval number 2017/294)

Informed Consent: All participants included in the study signed the Informed Consent Form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Siurana JM, Sabaté-Rotés A, Ayerza A, et al. Adolescents with bicuspid aortic valve:Which criteria should we use for aortic dilatation? Int J Cardiol 2021;333:90-3.
2. Merkx R, Duijnhouwer AL, Vink E, Roos-Hesselink JW, Schokking M. Aortic diameter growth in children with a bicuspid aortic valve. Am J Cardiol 2017;120(1):131-6.
3. Pees C, Michel-Behnke I. Morphology of the bicuspid aortic valve and elasticity of the adjacent aorta in children. Am J Cardiol 2012;110(9):1354-60.
4. Ciotti GR, Vlahos AP, Silverman NH. Morphology and function of the bicuspid aortic valve with and without coarctation of the aorta in the young. Am J Cardiol 2006;98(8):1096-1102.
5. Nadorlik H, Bowman JL, Fitzgerald-Butt S, et al. Abnormal longitudinal growth of the aorta in children with familial bicuspid aortic valve. Pediatr Cardiol 2017;38(8):1709-15.
6. Cantinotti M, Giordano R, Scalese M, et al. Nomograms for two-dimensional echocardiography derived valvular and arterial dimensions in Caucasian children. J Cardiol 2017;69(1):208-15.
7. Sievers H-H, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc 2007;133(5):1226-33.
8. Yener N, Oktar GL, Erer D, Yardimci MM, Yener A. Bicuspid aortic valve. Ann Thorac Cardiovasc Surg 2002;8(5):264-7.
9. Nistri S, Basso C, Marzari C, Mormino P, Thiene G. Frequency of bicuspid aortic valve in young male conscripts by echocardiogram. Am J Cardiol 2005;96(5):718-21.
10. Basso C, Boschello M, Perrone C, et al. An echocardiographic survey of primary school children for bicuspid aortic valve. Am J Cardiol 2004;93(5):661-3.
11. Massardier C, Desroches F, Singbo N, et al. First-degree relatives screening of patients with bicuspid aortic valve:effectiveness and feasibility in pediatric cardiology daily practice. Pediatr Cardiol 2020;41(8):1645-50.
12. Cozijnsen L, Braam R, Bakker-de Boo M, et al. Family screening in patients with isolated bicuspid aortic valve. Neth Heart J 2022;30(4):207-11.
13. Nabulsi MM, Tamim H, Sabbagh M, Obeid MY, Yunis KA, Bitar FF. Parental consanguinity and congenital heart malformations in a developing country. Am J Med Genet A 2003;116(4):342-47.
14. Reisli I, Keles S, Calıskaner Z. Past and Future of J Project Meetings in Turkey:Evaluatıon of Last 10 Years. Immunology and Genetics Journal 2020:8-11.
15. Erolu E, Akalın F, Çetiner N, Şaylan BÇ. Aortic elasticity and the influence of valve morphology in children with bicuspid aortic valve. Cardiol Young 2018;28(11):1338-44.
16. Niaz T, Fernandes SM, Sanders SP, Michelena H, Hagler DJ. Clinical history and management of bicuspid aortic valve in children and adolescents. Prog Cardiovasc Dis 2020;63(4):425-33.
17. Evangelista A, Gallego P, Calvo-Iglesias F, et al. Anatomical and clinical predictors of valve dysfunction and aortic dilation in bicuspid aortic valve disease. Heart 2018;104(7):566-73.
18. Miśkowiec D, Lipiec P, Szymczyk E, et al. Bicuspid aortic valve morphology and its impact on aortic diameters—A systematic review with meta-analysis and meta-regression. Echocardiography 2018;35(5):667-77.
19. Gurvitz M, Chang R-K, Drant S, Allada V. Frequency of aortic root dilation in children with a bicuspid aortic valve. Am J Cardiol 2004;94(10):1337-40.
20. Schäfers H-J, Schmied W, Marom G, Aicher D. Cusp height in aortic valves. J Thorac Cardiovasc 2013;146(2):269-74.
21. Blais S, Meloche-Dumas L, Fournier A, Dallaire F, Dahdah N. Long-Term Risk Factors for Dilatation of the Proximal Aorta in a Large Cohort of Children With Bicuspid Aortic Valve. Circ Cardiovasc Imaging 2020;13(3):e009675.
22. Mai Z, Guan L, Mu Y. Association between bicuspid aortic valve phenotype and patterns of valvular dysfunction:A meta-analysis. Clin Cardiol 2021;44(12):1683-91.
23. Ward RM, Marsh JM, Gossett JM, Rettiganti MR, Collins RT. Impact of bicuspid aortic valve morphology on aortic valve disease and aortic dilation in pediatric patients. Pediatr Cardiol 2018;39(3):509-17.