The Relationship between Arterial Elasticity Parameters of Ascending Aorta, Abdominal Aorta and Carotid Arteries with Carotid Intima Media Thickness in Children with Bicuspid Aortic Valve

ABSTRACT

Background: Bicuspid aortic valve is a congenital cardiac malformation that affects not only the valve and ascending aorta but also the abdominal aorta and large central arteries like carotid arteries by damaging the elasticity of the vessel resulting in increased stiffness and reduced distensibility. Deterioration of aortic compliance disturbs functions of the left ventricle and triggers atherosclerosis determined with carotid intima-media thickness. The aim of this study was to assess the effect of the bicuspid aortic valve on the elastic properties of these parts of the arterial system in children.

Methods: Thirty-four children with bicuspid aortic valves with normal valvular functions or mild valvular dysfunction and a control group of 34 individuals with tricuspid aortic valves were included in the study. Echocardiographic measurements of the left ventricle, ascending aorta, and ultrasonographic measurements of the abdominal aorta and carotid arteries were performed, and elasticity indexes were calculated.

Results: The bicuspid aortic valve group had higher stiffness and lower distensibility in ascending aorta, abdominal aorta, and carotid arteries with higher carotid intima-media thickness values than the tricuspid aortic valve group. Aortic valvular z scores and ascending aorta and abdominal aorta stiffness were higher in patients with bicuspid aortic valves irrespective of valvular functions than in controls. Valvular dysfunction affected stiffness in carotid arteries. Dilatation of ascending aorta increased stiffness in the abdominal aorta. Distensibility was lower in ascending aorta and left carotid artery, with increased carotid intima-media thickness independent from ascending aorta dilatation. Stiffness of abdominal aorta revealed a positive correlation with the stiffness of the ascending aorta and the carotid arteries ($P < .05$, for all).

Conclusions: Elasticity indexes of children with bicuspid aortic valves were impaired in ascending aorta, abdominal aorta, and carotid arteries with an increase in carotid intima-media thickness.

Keywords: Abdominal aorta, aorta, bicuspid aortic valve, carotid intima-media thickness, children, echocardiography, elasticity, valvular and congenital heart disease

INTRODUCTION

Bicuspid aortic valve (BAV) represents the most common congenital cardiac malformation in the general population, with a reported incidence of 0.5–2%.1-4 Bicuspid aortic valve is the result of an altered aortic cusp formation process during valvulogenesis. It can manifest with or without raphe and is characterized by the presence of 2 commissures and 2 aortic cusps.15-9

Bicuspid aortic valve syndrome affects both the aortic valve and aortic wall. Valvular complications such as aortic stenosis (AS), aortic insufficiency (AI), and infective endocarditis can be seen when the valve is affected, while aortic coarctation, dilatation, and dissection can be present when the aortic wall is involved.10-15 Valvular and vascular hemodynamics may vary, depending on commissural fusion.1 Fusion of right and non-coronary (R-NC) cusps usually
This is the first study to evaluate AAo, CAs, and AbdAo together with CIMT in addition to the aortic valve and left ventricle in children with BAV. The purpose of this study was to evaluate valvular and ventricular functions and vascular changes in these vessels in terms of diameters and elasticity indexes.

**METHODS**

Thirty-four children patients with BAV and a control group of 34 individuals were included in the study, which was performed in a pediatric cardiology department. Detailed patient and family histories were taken, physical examinations were performed, and blood pressure, height, weight measurements, blood analysis, and 12-channel ECG records were recorded. Transthoracic two-dimensional (2D) echocardiography and Doppler echocardiographic evaluations were performed for all participants.

Individuals aged between 0 and 18 years, with normofunctional, mild AI (vena contracta <2 mm) and mild stenosis (peak flow velocity <3 m/s) valves who were consenting to participate were included in the study. The control group consisted of individuals with tricuspid aortic valve (TAV), matched with the patient group in terms of body surface area (BSA), age, and sex, who were consulted with the pediatric cardiology clinic for various reasons and with normal echocardiographic findings.

Children with BAV who were refusing to take part, BAV with moderate or severe valve stenosis, BAV more than minimal AI, diabetes, hypercholesterolemia, cardiovascular drug use, cardiomyopathy, genetic cardiovascular disease (Marfan syndrome, Turner syndrome, or Noonan syndrome), with other congenital or acquired heart diseases (aortic coarctation, endocarditis or a history of aortic balloon valvuloplasty), or a decreased left ventricular ejection fraction <55% were excluded.

**Study Protocol**

All patients underwent clinical evaluations, echocardiographic study, and ultrasonographic study. Blood pressure was measured with a sphygmomanometer by placing an age-appropriate cuff on the patient’s right arm. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded as the averages of 3 separate measurements like all echocardiographic and ultrasonographic measurements. The systolic and diastolic diameters of the vessels were calculated in M-mode. Systolic diameter (S) and diastolic diameter (D) values were then taken from inner face to inner face to calculate the elasticity parameters. Diastolic diameter was measured at the R peak of ECG, and systolic diameter at the maximal anterior motion of the artery. The stiffness index and distensibility of all the arteries investigated in this study were calculated with the same formula. The following indices of aortic elasticity were calculated:

\[ \text{Beta stiffness index} = \ln \left( \frac{\text{systolic pressure}}{\text{diastolic pressure}} \right) \]

\[ \text{Distensibility} = 2 \times \left( \frac{\text{systolic diameter} - \text{diastolic diameter}}{\text{diastolic diameter}} \right) / (\text{systolic pressure} - \text{diastolic pressure}) \]
Echocardiographic Study
The evaluation was performed in the left lateral decubitus position using a GE Vivid 7 Ultrasound device (GE Medical Systems, Horten, Norway) and a 2.5–3.5 MHz transducer with a transthoracic approach in both groups. Measurements were performed using 2D echocardiography and Doppler echocardiography. The bicuspid aortic valve was diagnosed based on the short-axis image of the aortic valve showing the presence of 2 commissures and 2 aortic valve cusps. Pulse wave (PW) and color Doppler were used to identify the aortic flow velocity, peak gradient, and degree of AI. The presence of AI was assessed on color Doppler images using standard criteria.21,27 Bicuspid aortic valve with AI, AS, and AI+AS were defined as BAV with valvular dysfunction (BAV-DYSF). Bicuspid aortic valve with normal functions was defined as BAV with normal function (BAV-NF). Aortic measurements were taken using 2D echocardiography at 4 different levels—annulus, sinus of Valsalva (SVS), sinotubular junction (STJ), and ascending aorta (AAo) at end-diastole.20 Measurements were normalized in accordance with BSA using z-scores with the Halifax method. BSA was calculated using the Haycock method.28 Z-scores between −2 and 2 were defined as normal, and z-scores > 2 as dilated for each level of the aorta. Patients with AAo z scores >2 were defined as BAV with AAo dilatation (BAV-D), and AAo z scores < 2 as BAV with non-dilated AAo (BAV-ND). Left ventricular systolic functions were measured on the parasternal long-axis using M mode.21,29 Mitral early diastolic flow velocity (E), its decreasing time (EDT) and late diastolic flow velocity (A), and the duration (A duration) were measured with the sample volume of PW placed on the level of the mitral annulus in apical 4-chamber view.30 M-mode records were taken at a rate of 50 mm/sec and Doppler records at a rate of 100 mm/sec.29,30

Tissue Doppler Imaging (TDI): Tissue Doppler imaging was recorded at a frame rate of >180 fr/sec and narrowest image sector angle (usually 30°) in an apical 4-chamber view. A sample volume was placed on the conjunction of the septal and lateral walls of the left ventricle with the mitral annulus. Peak septal and lateral early diastolic wave velocity (E’ septal and E’ lateral), peak septal and lateral late diastolic wave velocity (A’ septal and A’ lateral), E/A ratio, septal and lateral E/E’ ratios, and septal and lateral isovolumetric relaxation times (IVRT septal and IVRT lateral) were obtained.30,31

Ascending aorta elasticity measurements: The measurements were performed during an echocardiographic study. The probe was placed perpendicular to the AAo at the level of the right pulmonary artery and systolic and diastolic measurements of the vessel were obtained to calculate elasticity.21,22

Evaluation of CAs with Elasticity Measurements and Intima-Media Thickness
Carotid arteries were evaluated using a LOGIQ 7 ultrasonography device and a 7-12 Mhz linear probe. Patients were placed in the supine position with the head in hyperextension. CA diameter and CIMT measurements were performed on the same arterial segment, 1-2 cm proximal to the bifurcation of the right and left CAs to measure the arterial diameters.22,24,26 Carotid artery diameters were evaluated with 20 fr/sec for 10 seconds, while CIMT was evaluated with a frequency of 100 Mhz. Carotid intima-media thickness is defined as the distance from the leading edge of the lumen-intima interface to the media-adventitia interface of this wall. It was measured on the far and near walls of both the left and right CAs at end-diastole in the longitudinal and transverse planes using anterior, lateral, and posterior approaches.23,26,32,33

Evaluation of Abdominal Aorta with Elasticity Measurements
Abdominal aortic measurements were made in the supine position using LOGIQ 7 ultrasonography and a 3.5 MHz convex probe. The probe was placed on the subxiphoid area by viewing the AbdAo on the short axis and aortic diameters were measured.9,12

Statistics
All analyses were performed on Statistical Package for the Social Sciences 11.5 statistical software. Frequency and percentage were used for categorical variables. Data were expressed by using mean, standard deviation, median, minimum and maximum values for continuous variables. Normal distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. The relationship between categorical variables was assessed using the chi-square test. Continuous independent variables exhibiting normal distribution were evaluated using the t-test for 2-group comparisons, and with analysis of variance for more than 2 groups. Non-normally distributed variables were compared using the Mann–Whitney U test for 2 independent groups, and with the Kruskal–Wallis test for more than 2 groups. Correlation analysis for non-normally distributed variables was performed using Spearman correlation analysis. The post hoc Tukey test was performed for individual group differences in group comparisons. Ratios were compared using a 4 x 2 cross table and the chi-square test. P values <.05 were regarded as statistically significant.

RESULTS
No differences were determined in terms of age, gender, BSA, arterial blood pressure, or lipid parameters between patients with BAV and TAV. C-reactive protein and glucose values differed between the 2 groups but were still within normal ranges in both. Patients with BAV exhibited higher pulse pressure (PP) (P = .01) (Table 1).

Left ventricular diameters were similar between the groups. However, EDT and IVRT septal were longer (P = .020 and P = .030, respectively) in BAV patients compared to TAV. E’ septal was lower and E/E’ septal was higher in patients with BAV than in TAV (P = .040, P = .010). Aortic diameters reflected by z-scores of the annulus, SVS, STJ, and AAo were higher in BAV children than in controls (Table 2).

Systolic and diastolic diameters of AAo were higher (P < .05 for both) in BAV patients with respect to controls, but AAo S-D was similar between the groups. Systolic and diastolic diameters of CAs were similar, while S-D was lower in both of the CAs in BAV than in TAV. Both of the CAs, AbdAo,
Table 1. Demographic and Laboratory Parameters of the Patients

|                  | BAV (n=34) (mean ± SD) | TAV (n=34) (mean ± SD) | P    |
|------------------|------------------------|------------------------|------|
| Age (years)      | 11.19 ± 4.37           | 10.88 ± 4.18           | .840 |
| Gender (F/M)     | 10/24                  | 10/24                  |      |
| BSA (m²)         | 1.24 ± 0.36            | 1.25 ± 0.36            | .880 |
| SBP (mmHg)       | 101.94 ± 9.79          | 99.50 ± 7.71           | .250 |
| DBP (mmHg)       | 59.50 ± 7.59           | 61.58 ± 5.76           | .200 |
| PP (mmHg)        | 42.44 ± 6.69           | 37.91 ± 7.49           | .010 |
| Glucose (mg/dL)  | 90.00 ± 8.49           | 93.69 ± 6.15           | .040 |
| LDL (mg/dL)      | 77.50 ± 22.20          | 81.03 ± 22.72          | .520 |
| Total cholesterol| 150.29 ± 23.85         | 156.63 ± 25.39         | .290 |
| Triglyceride     | 85.02 ± 36.30          | 74.42 ± 28.87          | .190 |
| CRP (mg/dL)      | 2.22 ± 1.55            | 1.55 ± 0.67            | .020 |

Significant P value <.05.

Table 2. Two-dimensional, Doppler, and Tissue Doppler Parameters in the Patients

|                  | BAV (Mean ± SD)/(Median (Min/Max) (n=34)) | TAV (Mean ± SD)/(Median (Min/Max) (n=34)) | P    |
|------------------|------------------------------------------|------------------------------------------|------|
| LVESd (cm)       | 0.88 ± 0.18                              | 0.83 ± 0.19                              | .270 |
| LVEDd (cm)       | 3.87 ± 0.44                              | 3.85 ± 0.63                              | .870 |
| LPWd (cm)        | 0.79 ± 0.19                              | 0.75 ± 0.16                              | .330 |
| FS (%)           | 40.20 ± 4.14                             | 38.73 ± 5.22                             | .100 |
| E (m/s)          | 1.03 ± 0.14                              | 1.01 ± 0.15                              | .450 |
| A (m/s)          | 0.58 ± 0.12                              | 0.55 ± 0.09                              | .270 |
| E/A              | 1.79 ± 0.41                              | 1.86 ± 0.40                              | .440 |
| E'/lateral       | 6.35 ± 1.74                              | 5.88 ± 1.25                              | .230 |
| EDT (ms)         | 157.12 ± 35.20                           | 141.85 ± 18.59                           | .020 |
| A duration (ms)  | 143.90 ± 0.03                            | 138.52 ± 0.61                            | .270 |
| E' lateral (m/s) | 0.18 ± 0.11                              | 0.17 ± 0.03                              | .710 |
| A' lateral (m/s) | 0.14 ± 0.21                              | 0.08 ± 0.09                              | .130 |
| IVRT lateral (ms)| 59.69 ± 12.20                            | 59.76 ± 8.9                              | .970 |
| E'/septal        | 8.15 ± 1.84                              | 7.11 ± 1.37                              | .010 |
| E' septal (m/s)  | 0.013 ± 0.02                              | 0.014 ± 0.02                             | .040 |
| A' septal (m/s)  | 0.06 ± 0.01                              | 0.06 ± 0.01                              | .600 |
| IVRT septal (ms)| 67.65 ± 14.23                            | 61.13 ± 9.12                             | .030 |
| Ann z-score      | 1.32 (−1.36/3.85)                        | −0.29 (−2.16/1.95)                       | .001 |
| SVS z-score      | 0.92 (−1.86/3.94)                        | 0.01 (−1.19/2.22)                       | .005 |
| STJ z-score      | 0.09 (−2.68/2.73)                        | −0.56 (−2.59/2.05)                       | .005 |
| AAO z-score      | 1.94 (−2.05/5.91)                        | −0.39 (−1.75/1.98)                       | .001 |

Significant P value <.05.

Table 3. Elasticity Parameters Related with Bicuspid Aortic Valve in Central Arteries

| Parameter                                | BAV-DYSF (n=18) (Mean ± SD) | BAV-NF (n=16) (Mean ± SD) | TAV (n=34) (Mean ± SD) | P    |
|------------------------------------------|-------------------------------|---------------------------|------------------------|------|
| Total wall thickness (mm)                | 2.84 ± 0.68                   | 2.83 ± 0.68               | 2.73 ± 0.59            | .040 |
| Near wall thickness (mm)                 | 2.68 ± 0.66                   | 2.70 ± 0.67               | 2.65 ± 0.57            | .040 |
| Far wall thickness (mm)                  | 2.96 ± 0.75                   | 2.90 ± 0.73               | 2.87 ± 0.69            | .040 |

Significant P value <.05.
**Table 3. Arterial Diameters and Elasticity Parameters of Aortic and Carotid Arteries of the Patients**

|                          | BAV (mean ± SD) (n = 34) | TAV (mean ± SD) (n = 34) | P  |
|--------------------------|--------------------------|--------------------------|----|
| AAo S (mm)               | 24.00 ± 5.20             | 20.90 ± 3.60             | .007|
| AAo D (mm)               | 20.90 ± 4.80             | 17.5 ± 3.3               | .001|
| AAo S-D (mm)             | 3.10 ± 1.10              | 3.40 ± 0.9               | .810|
| AAo SI                   | 4.48 ± 2.86              | 2.75 ± 1.46              | .003|
| AAo DIS (10^-6 cm² dyn^-1) | 7.53 ± 3.47             | 10.62 ± 3.43             | .001|
| RCA S (mm)               | 5.82 ± 0.45              | 5.93 ± 0.50              | .356|
| RCA D (mm)               | 4.95 ± 0.44              | 4.87 ± 0.46              | .476|
| RCA S-D (mm)             | 0.86 ± 0.26              | 1.05 ± 0.25              | .004|
| RCA SI                   | 3.41 ± 1.01              | 2.40 ± 0.81              | .001|
| RCA DIS (10^-6 cm² dyn^-1) | 8.51 ± 3.32             | 11.97 ± 4.18             | .001|
| LCA S (mm)               | 5.77 ± 0.50              | 5.76 ± 0.54              | .920|
| LCA D (mm)               | 4.93 ± 0.47              | 4.73 ± 0.48              | .090|
| LCA S-D (mm)             | 0.83 ± 0.21              | 1.02 ± 0.26              | .002|
| LCA SI                   | 3.58 ± 1.39              | 2.46 ± 1.12              | .001|
| LCA DIS (10^-6 cm² dyn^-1) | 8.38 ± 3.03             | 12.01 ± 4.25             | .001|
| AbdAo S (mm)             | 11.15 ± 2.89             | 10.51 ± 2.50             | .341|
| AbdAo D (mm)             | 9.01 ± 2.62              | 8.23 ± 1.98              | .173|
| AbdAo S-D (mm)           | 2.13 ± 0.75              | 2.28 ± 0.79              | .432|
| AbdAo SI                 | 2.81 ± 1.77              | 1.86 ± 0.63              | .005|
| AbdAo DIS (10^-6 cm² dyn^-1) | 12.30 ± 5.67             | 15.20 ± 4.73             | .027|
| RCFIMT (mm)              | 0.42 ± 0.04              | 0.41 ± 0.10              | .480|
| RnCIMT (mm)              | 0.44 ± 0.04              | 0.40 ± 0.02              | .001|
| LFCIMT (mm)              | 0.43 ± 0.04              | 0.39 ± 0.02              | .001|
| LnCIMT (mm)              | 0.42 ± 0.04              | 0.39 ± 0.02              | .001|

**Significant P value <.05.**

AbdAo, abdominal aorta; AAo, ascending Aorta; BAV, bicuspid aortic valve; D, diastolic diameter; DIS, distensibility; LCA, left carotid artery; LFCIMT, left carotid artery far wall intima media thickness; LnCIMT, left carotid artery near wall intima media thickness; n, number; RCA, right carotid artery; RCFIMT, right carotid artery far wall intima media thickness; RnCIMT, right carotid artery near wall intima media thickness; S, systolic diameter; S-D, difference in diameter; SI, stiffness index; TAV, tricuspid aortic valve.

**Table 4. Valve Functions in Patients with BAV Based on Raphe Location**

| Raphe in BAV | BAV–DYSF (n = 26) | TAV (n = 34) | Total (n = 34) |
|--------------|------------------|-------------|---------------|
|              | Al (n = 17)      | AS (n = 2)  |                |
| R-NC         | 1                | 16          | 17 (50%)      |
| R-L          | 7                | 9           | 16 (47%)      |
| L-NC         | 0                | 1           | 1 (3%)        |
| Total        | 8 (24%)          | 26 (76%)    | 34 (100%)     |

Al, aortic insufficiency; AS, aortic stenosis; BAVs, patients with bicuspid aortic valve; BAV-DYSF, BAV with valvular dysfunction; BAV-NF, BAV with normal functioning valves; L-NC, raphe between the left and non-coronary cusp; n, number; R-NC, raphe between the right and non-coronary cusp; R-L, raphe between the right and left coronary cusp.

**DISCUSSION**

The relationship between aortic elastic properties and aortopathy in pediatric patients with BAV has only recently been investigated. Impaired elasticity is important as the cause of vascular hypertrophy with an increase in wall thickness, and dilatation of the artery with an increase in arterial length known as remodeling. This leads to degeneration in fibers and results in a vicious cycle. When arterial stiffness increases, the majority of the pulse volume is sent to the periphery, and the quick return of the waves reflected from the periphery is followed by a decrease in buffering mechanisms. This situation increases the late systolic afterload that affects thick-thin myofilament interactions and cross-bridge dissociation, which leads to impaired relaxation. As a result increase in SBP, decline in DBP and increase in PP are determined that leads to left ventricular hypertrophy and a decreased capillary/myositis ratio. These findings support the idea that aortic diameters are enlarged and aortic elasticity is impaired even in BAV patients with normal function or only mild dysfunction. As a result of the inverse correlation between aortic SI and DIS, changes may occur in left ventricular systolic and diastolic functions, and abnormal left ventricular remodeling may be seen. In the present study, SBP and DBP values were similar between the groups, but PP was higher in the patients with BAV, showing that PP may be affected as a result of the nature of BAV. Impairment in diastolic functions indicated by EDT, E’ septal, E/E’ septal, and IVRT septal also confirmed the knowledge in the previous literature. Weismann et al also demonstrated lower E’ parameters in children with BAV than in controls. However, this was not associated with diastolic dysfunction because it was within the normal range for age.

Analysis of the relationships between the elasticity parameters of AAo, CA, and AbdAo revealed a positive correlation between SI of AbdAo and SI of AAo, RCA, and LCA (P < .01, for all) (Table 8).

**Table 4. Valvular Functions in Patients with BAV Based on Raphe Location**

| Raphe in BAV | BAV–DYSF (n = 26) | TAV (n = 34) | Total (n = 34) |
|--------------|------------------|-------------|---------------|
|              | Al (n = 17)      | AS (n = 2)  |                |
| R-NC         | 1                | 16          | 17 (50%)      |
| R-L          | 7                | 9           | 16 (47%)      |
| L-NC         | 0                | 1           | 1 (3%)        |
| Total        | 8 (24%)          | 26 (76%)    | 34 (100%)     |

P = .030). Dilated and non-dilated AAo had higher SI and lower DIS in LCA than in TAV (P < .05, for all). The right carotid artery had higher SI in BAV-D than in BAV-ND and also than in TAV (P = .045, P = .001), with lower DIS in BAV-D than in TAV (P = .001). Beta stiffness index of AbdAo was higher in BAV-D (P = .029), with similar DIS values compared to TAV. Carotid intima-media thickness values were higher in near walls of CAs and left far wall in both dilated and non-dilated AAo than in TAV (P < .05, for all) (Table 7).

**DISCUSSION**

The relationship between aortic elastic properties and aortopathy in pediatric patients with BAV has only recently been investigated. Impaired elasticity is important as the cause of vascular hypertrophy with an increase in wall thickness, and dilatation of the artery with an increase in arterial length known as remodeling. This leads to degeneration in fibers and results in a vicious cycle. When arterial stiffness increases, the majority of the pulse volume is sent to the periphery, and the quick return of the waves reflected from the periphery is followed by a decrease in buffering mechanisms. This situation increases the late systolic afterload that affects thick-thin myofilament interactions and cross-bridge dissociation, which leads to impaired relaxation. As a result increase in SBP, decline in DBP and increase in PP are determined that leads to left ventricular hypertrophy and a decreased capillary/myositis ratio. These findings support the idea that aortic diameters are enlarged and aortic elasticity is impaired even in BAV patients with normal function or only mild dysfunction. As a result of the inverse correlation between aortic SI and DIS, changes may occur in left ventricular systolic and diastolic functions, and abnormal left ventricular remodeling may be seen. In the present study, SBP and DBP values were similar between the groups, but PP was higher in the patients with BAV, showing that PP may be affected as a result of the nature of BAV. Impairment in diastolic functions indicated by EDT, E’ septal, E/E’ septal, and IVRT septal also confirmed the knowledge in the previous literature. Weismann et al also demonstrated lower E’ parameters in children with BAV than in controls. However, this was not associated with diastolic dysfunction because it was within the normal range for age. Santarpia et al demonstrated that LV longitudinal, circumferential, and radial strains were lower in subjects with BAV. Stefani et al suggested that young trained athletes with BAV have a normal LV performance but that these athletes also tend to have a lower strain in LV basal segments than healthy subjects. Bilen et al suggested that left atrial volume and E/e’ ratio are increased in BAV patients. Pees et al reported higher annulus and AAo z-scores in patients with BAV. Oulego-Erooz et al and Nistri et al also determined increased annulus, SVS, and STJ diameters in addition to proximal aortic dilatation in BAV with higher AAo S and AAo D, higher SI, and lower AAo S-D in BAV compared to TAV. We observed similar
results to the previous literature, supporting the idea that BAV exerts a negative effect on aortic diameters in all segments of the aorta.

Studies have reported abnormal elasticity characteristics of the aorta, sometimes resulting in dissection. However, thoracic and abdominal aortic dissections are rare with BAV during childhood. One case with BAV was reported with dissection in the celiac artery, this being attributed to systemic disease rather than to local factors. In a study from Turkey, Gürses et al reported decreased DIS and increased SI in the abdominal aorta of the children with BAV compared to TAV.

Endothelial dysfunction with increased PP and increased SI causes atherosclerosis with thickening of the intima and media layers of large and medium-sized muscular arteries and CAs. A close relationship exists between SI and CIMT. A study involving patients with Fallot tetralogy reported an increase in SBP and a decrease in DBP with increased PP, causing stiffening of the central arteries with lower compliance and with a reduced difference in the diameters of CAs.

The present study represents the first evaluation of CAs stiffness together with CIMT and AbdAo elasticity parameters in children with BAV. We determined higher SI and lower DIS of CAs with lower CAs S-D but similar AbdAo S-D in patients with BAV, suggesting that CAs may be affected more easily than AbdAo, in association with the short distance between the valve and CAs, which is more easily exposed to valvular hemodynamics than AbdAo. The positive correlation between SI of AbdAo with SI of AbdAo and CAs supports the idea that stiffening of the aorta is not localized only in a restricted region but affects the entire arterial system. The present study represents the first evaluation of CAs stiffness together with CIMT and AbdAo elasticity parameters in children with BAV. We determined higher SI and lower DIS of CAs with lower CAs S-D but similar AbdAo S-D in patients with BAV, suggesting that CAs may be affected more easily than AbdAo, in association with the short distance between the valve and CAs, which is more easily exposed to valvular hemodynamics than AbdAo. The positive correlation between SI of AbdAo with SI of AbdAo and CAs supports the idea that stiffening of the aorta is not localized only in a restricted region but affects the entire arterial system. The present study represents the first evaluation of CAs stiffness together with CIMT and AbdAo elasticity parameters in children with BAV. We determined higher SI and lower DIS of CAs with lower CAs S-D but similar AbdAo S-D in patients with BAV, suggesting that CAs may be affected more easily than AbdAo, in association with the short distance between the valve and CAs, which is more easily exposed to valvular hemodynamics than AbdAo. The positive correlation between SI of AbdAo with SI of AbdAo and CAs supports the idea that stiffening of the aorta is not localized only in a restricted region but affects the entire arterial system. The present study represents the first evaluation of CAs stiffness together with CIMT and AbdAo elasticity parameters in children with BAV. We determined higher SI and lower DIS of CAs with lower CAs S-D but similar AbdAo S-D in patients with BAV, suggesting that CAs may be affected more easily than AbdAo, in association with the short distance between the valve and CAs, which is more easily exposed to valvular hemodynamics than AbdAo. The positive correlation between SI of AbdAo with SI of AbdAo and CAs supports the idea that stiffening of the aorta is not localized only in a restricted region but affects the entire arterial system.

### Table 5. Evaluation of Children with BAV According to Valvular Function

|                         | BAV-NF (n = 8) (Mean ± SD)/Median (Min/Max) | BAV-DYSF (n = 26) (Mean ± SD)/Median (Min/Max) | TAV (n = 34) (Mean ± SD)/Median (Min/Max) | P          | P BAV-NF vs BAV-DYSF | P BAV-NF vs TAV | P BAV-DYSF vs TAV |
|-------------------------|---------------------------------------------|-----------------------------------------------|------------------------------------------|------------|---------------------|-----------------|------------------|
| SBP (mm Hg)             | 102.37 ± 9.36 (92–130)                      | 101.80 ± 10.10 (95–120)                       | 99.50 ± 7.71 (91–120)                    | 0.520      | NS                  | NS              | NS               |
| DBP (mm Hg)             | 59.12 ± 8.85 (41–110)                       | 59.61 ± 7.35 (41–120)                        | 61.58 ± 5.76 (58–78)                     | 0.440      | NS                  | NS              | NS               |
| PP (mm Hg)              | 43.25 ± 5.44 (35–55)                        | 42.19 ± 7.11 (35–55)                         | 37.91 ± 7.49 (35–50)                     | 0.030      | NS                  | 0.040           | 0.040            |
| Ann z-score             | 1.46 (−1.21/2.32)                           | 1.32 (−1.36/3.85)                            | −0.29 (−2.16/1.95)                       | 0.001      | NS                  | 0.001           | 0.001            |
| SVS z-score             | 1.17 (−0.36/3.94)                           | 0.75 (−1.86/3.24)                            | 0.10 (−1.91/2.22)                       | 0.010      | NS                  | 0.001           | 0.001            |
| STJ z-score             | 0.26 (−0.64/2.27)                           | 0.02 (−2.68/2.73)                            | −0.56 (−2.59/2.05)                      | 0.010      | NS                  | 0.001           | 0.001            |
| AAO z-score             | 1.39 (−0.73/4.69)                           | 2.07 (−2.05/5.91)                            | −0.39 (−1.75/1.98)                      | 0.001      | 0.010               | 0.010           | 0.010            |
| Aortic gradient (mm Hg) | 7.00 ± 1.32 (5.97–8.00)                     | 16.50 ± 0.52 (16.00–17.00)                    | 5.00 ± 1.23 (4.50–5.50)                  | 0.001      | 0.001               | NS              | 0.001            |

Significant P value < .05.

AAo, ascending aorta; AbdAo, abdominal aorta; Ann, annulus; Ao, aorta; BAV-NF, bicuspid aortic valve with normal functioning valves; BAV-DYSF, bicuspid aortic valve with valvular dysfunction; DBP, diastolic blood pressure; DIS, distensibility; L Ca left carotid artery; n, number; NS, Non significant; RCA, Right carotid artery; SBP, systolic blood pressure; SI, stiffness index; STJ, sinotubular junction; SVS, sinus of Valsalva; TAV, tricuspid aortic valve.

### Table 6. The Relationship Between Raphe Location and Ascending Aortic Diameters

| Raphe Location in BAV Patients | BAV Without AAo Dilatation (n = 17) | Total (n = 34) |
|-------------------------------|-------------------------------------|---------------|
| R-NC (n = 17)                 | 7 (41%)                             | 17 (50%)      |
| R-L (n = 16)                  | 9 (53%)                             | 16 (47%)      |
| L-NC (n = 1)                  | 1 (6%)                              | 1 (3%)        |
| TOTAL (n = 34)                | 17 (100%)                           | 34 (100%)     |

AAo, ascending aorta; BAV, bicuspid aortic valve; L-NC, raphe between the left and non-coronary cusp; n, number; R-L, raphe between the right and left coronary cusp; R-NC, raphe between the right and non-coronary cusp.
DIS in pediatric patients with BAV-AI than BAV-AS and BAV-NF. These results could arise from the profound differences between congenital and acquired forms of AS accompanied by differences in flow pattern due to distinct BAV morphology. Our results were compatible with the literature suggesting that BAV increases aortic valvular z-scores and SI of AAo independently of valvular function. We also stated higher SI of AbdAo in both no and mild valvular dysfunctioning BAV in our study. Aortic velocity and peak gradient were higher in both subgroups in Nistri et al’s study compared to TAV, similarly to our study, supporting the idea that abnormal flow patterns exist in BAV even with normal functions. In addition, detected higher SI of CAs in the valvular dysfunction group, suggested that valve hemodynamics have an impact on the other parts of big central arteries, such as CAs. Pees et al reported higher AAo z-scores in patients with R-NC cusp fusion compared to those with R-L cusp fusion, although no differences were determined in other segments of the aorta. Girdauskas et al stated that fusion of R-L cusps orients the aortic flow toward the convexity of the AAo, resulting in the right-front systolic jet. Right and non-coronary cusp fusion causes left-back eccentric flow as a result of extension towards the proximal aortic arch. This could explain the increased proximal AAo and aortic arch diameters as a result of flow with left-back orientation in patients with BAV with R-NC fusion, and higher aortic root diameters as a result of flow with right-front orientation in patients with BAV with R-L fusion. Erolu et al reported higher z scores of SVS and STI in R-L morphology than R-NC morphology. We stated AAo dilatation in half of our patients.

| Table 7. Evaluation of Patients with BAV According to Ascending Aortic Diameters |
|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
|                                    | BAV-D (mean ± SD) (n = 17) | BAV-ND (mean ± SD) (n = 17) | TAV (mean ± SD) (n = 34) | P         | P BAV-D vs BAV-ND | P BAV-D vs TAV | P BAV-ND vs TAV |
|-------------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------|------------------|----------------|------------------|
| SBP (mm Hg)                         | 113.17 ± 10.47             | 100.7 ± 9.22                | 99.5 ± 7.71                 | .380      | NS               | NS             | NS               |
| DBP (mm Hg)                         | 61.17 ± 7.96               | 57.82 ± 7.03                | 61.58 ± 5.76                | .150      | NS               | NS             | NS               |
| PP (mm Hg)                          | 42.00 ± 6.39               | 42.88 ± 7.14                | 37.91 ± 7.49                | .037      | NS               | .050           | .050             |
| AAo S (mm)                          | 27.00 ± 4.60               | 21.11 ± 4.10                | 20.90 ± 3.60                | .001      | .001             | .001           | NS               |
| AAo D (mm)                          | 23.50 ± 4.40               | 18.30 ± 3.70                | 17.50 ± 3.30                | .001      | .001             | .001           | NS               |
| AAo S-D (mm)                        | 3.50 ± 0.90                | 2.70 ± 1.00                 | 3.40 ± 0.90                 | .035      | .050             | NS             | NS               |
| AAo SI                              | 4.00 ± 1.88                | 4.97 ± 3.59                 | 2.75 ± 1.46                 | .001      | NS               | NS             | .001             |
| AAo DIS (10⁻⁶ cm² dyn⁻¹)            | 7.66 ± 3.24                | 7.39 ± 3.78                 | 10.62 ± 3.43                | .001      | .010             | .001           | .003             |
| LCa S (mm)                          | 5.68 ± 0.49                | 5.86 ± 0.50                 | 5.76 ± 0.54                 | .590      | NS               | NS             | NS               |
| LCa D (mm)                          | 4.86 ± 0.52                | 5.01 ± 0.42                 | 4.70 ± 0.48                 | .163      | NS               | NS             | NS               |
| LCa S-D (mm)                        | 0.81 ± 0.25                | 0.85 ± 0.16                 | 1.02 ± 0.26                 | .008      | NS               | .016           | NS               |
| LCa SI                              | 3.68 ± 1.74                | 3.47 ± 0.97                 | 2.46 ± 1.12                 | .003      | NS               | .006           | .029             |
| LCa DIS (10⁻⁶ cm² dyn⁻¹)            | 8.53 ± 3.58                | 8.22 ± 2.45                 | 12.01 ± 4.25                | .001      | NS               | .008           | .003             |
| RCA S (mm)                          | 5.96 ± 0.53                | 5.68 ± 0.31                 | 5.93 ± 0.50                 | .151      | NS               | NS             | NS               |
| RCA D (mm)                          | 5.17 ± 0.46                | 4.74 ± 0.31                 | 4.87 ± 0.46                 | .013      | .014             | NS             | NS               |
| RCA S-D (mm)                        | 0.78 ± 0.27                | 0.94 ± 0.24                 | 1.05 ± 0.25                 | .003      | NS               | .003           | NS               |
| RCA SI                              | 3.79 ± 0.93                | 3.03 ± 0.96                 | 2.40 ± 0.81                 | .001      | .045             | NS             | .001             |
| RCA DIS (10⁻⁶ cm² dyn⁻¹)            | 7.34 ± 2.71                | 9.67 ± 3.53                 | 11.97 ± 4.18                | .001      | NS               | NS             | .003             |
| AbdAo S (mm)                        | 11.35 ± 3.41               | 10.94 ± 2.34                | 10.51 ± 2.50                | .579      | NS               | NS             | NS               |
| AbdAo D (mm)                        | 9.23 ± 2.91                | 8.80 ± 2.37                 | 8.23 ± 1.98                 | .344      | NS               | NS             | NS               |
| AbdAo S-D (mm)                      | 2.12 ± 0.81                | 2.14 ± 0.71                 | 2.28 ± 0.79                 | .733      | NS               | NS             | NS               |
| AbdAo SI                            | 2.93 ± 1.98                | 2.68 ± 1.58                 | 1.86 ± 0.63                 | .018      | NS               | .029           | NS               |
| AbdAo DIS (10⁻⁶ cm² dyn⁻¹)          | 11.78 ± 5.14               | 12.83 ± 6.27                | 15.20 ± 4.73                | .075      | NS               | NS             | .040             |
| LfCIMT (mm)                         | 0.43 ± 0.04                | 0.43 ± 0.04                 | 0.39 ± 0.02                 | .001      | NS               | .001           | .001             |
| LnCIMT (mm)                         | 0.43 ± 0.04                | 0.42 ± 0.03                 | 0.39 ± 0.02                 | .001      | NS               | .001           | .004             |
| RfCIMT (mm)                         | 0.43 ± 0.04                | 0.42 ± 0.03                 | 0.41 ± 0.10                 | .640      | NS               | NS             | NS               |
| RnCIMT (mm)                         | 0.45 ± 0.04                | 0.43 ± 0.02                 | 0.40 ± 0.02                 | .001      | NS               | .001           | .040             |

Significant P value <.05.
AAo, ascending aorta; AbdAo, abdominal aorta; BAV-D, bicuspid aortic valve with ascending aortic dilatation; BAV-ND, bicuspid aortic valve with non-dilated ascending aorta; D, diastolic diameter; DBP, diastolic blood pressure; DIS, distensibility; S, systolic diameter; S-D, difference in diameter; SI, stiffness index; LCa, left carotid artery; LfCIMT, left carotid artery far wall intima media thickness; LnCIMT, left carotid artery near wall intima media thickness; n, number; NS, Non significant; PP, pulse pressure; RCo, right carotid artery; RfCIMT, right carotid artery far wall intima media thickness; RnCIMT, right carotid artery near wall intima media thickness; SBP, systolic blood pressure; TAV, tricuspid aortic valve.
They had raphe between R and L cusps in 9 patients and between R-NC cusps in 7 patients. Even though R-NC cusp fusion seems as it was predominantly present in our study, differently from the literature, the number of the patients was close to each other and it can be attributed to the limited number of patients included in the study.

Aortic wall anomalies in patients with BAV are usually associated with cystic medial necrosis. Arterial stiffness increases as elastic fibers are degraded and replaced with collagen fibers in the aortic media. Intrinsic aortic wall pathology, hemodynamic flow anomalies in the proximal aorta, and pulsatile stress also play a role in aortic dilatation.

Impairment of elasticity parameters of CAs in both BAV-DYSF and BAV-D group show the adverse effect of valvular hemodynamics and aortic diameters on elasticity parameters of CAs. Both of the dilated and non-dilated groups in our study exhibited lower AAo and Ca DIS and higher CIMT than TAV, thus supporting the relationship between elasticity and atherosclerosis detected in childhood. BAV with Aao dilatation exhibited increased stiffness of AbdAo, indicating that dilatation has an additional impact on elasticity indexes in farther places from the origin. Similarly, systolic and diastolic arterial diameters being observed in AbdAo and left carotid artery suggested that SI and DIS can be affected independently of diameters and can lead the vessels to the next step to thickening and atherosclerosis.

**Study Limitations**

The study could be performed in a large patient group performed in multicenters. Therefore the patient number included in all the subgroups could be higher and the influence of other factors like the rate of aortic growth or cardiovascular risk factors can be defined more confidently. Another limitation of the study is that blood pressure was measured by cuff sphygmomanometry of the brachial artery and non-invasively in the ascending aorta. However, PP measured by using brachial artery pressure was significantly related to central PP obtained with radial artery tonometry and pulse wave analysis. It was stated that using brachial pressure results would not bias follow up changes in distensibility.

**CONCLUSION**

The measurements showed that children with BAV exhibited increased PP, aortic valvular and AAo diameters, and impaired elasticity parameters, irrespective of valvular functions, with increased CIMT triggering atherosclerosis. In addition, the presence of mild valvular dysfunction and Aao dilatation exerted adverse effects on the elasticity parameters of different parts of the central arteries. Patients with BAV should therefore be carefully evaluated in terms not only of the aortic valve and adjacent structures but also of the CAs and AbdAo, even if the diameters are within normal ranges. Aortic elasticity parameters can be easily measured using transthoracic echocardiography, and the findings may serve as a clinical indicator of aortic wall deterioration. The detection of clear and definitive impaired elasticity at early ages may help in the selection of patients who may benefit from closer follow-up, especially in terms of cardiovascular risk prevention, and eventually preventive drug therapy if indicated.

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