

# Evaluation of left atrial mechanical function and atrial conduction abnormalities in patients with isolated bicuspid aortic valve

## Tek başına biküspit aort kapak hastalarında sol atriyum mekanik işlevleri ve atriyal ileti zamanlarının değerlendirilmesi

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### ABSTRACT

**Objective:** Present study is an evaluation of left atrial (LA) mechanical and conduction function in patients with bicuspid aortic valve (BAV) without significant valve dysfunction, and an investigation of relationship between LA function and aortic elasticity.

**Methods:** Study population consisted of 34 isolated BAV patients (mean age: 34±13 years) and 29 healthy, age- and sex-matched volunteers (mean age: 30±10 years). LA volume was measured using biplane area-length method and LA active and passive emptying volume and fraction was calculated. Intra- and interatrial atrial conduction time (ACT) was measured with tissue Doppler imaging. Aortic elasticity parameters were calculated including aortic strain, aortic stiffness index, aortic distensibility, and aortic elastic modulus.

**Results:** LA diameter, LA maximum volume, LA volume before atrial systole, and LA active emptying fraction were significantly higher in patients with BAV (33.2±3.2 mm vs 34.9±2.8 mm, p=0.030; 16.2±4.6 mL/m<sup>2</sup> vs 19.8±4.8 mL/m<sup>2</sup>, p=0.004; 10.2±3.7 mL/m<sup>2</sup> vs 12.1±4.9 mL/m<sup>2</sup>, p=0.029; and 30.4±12.0% vs 39.9±11.8%, p=0.003, respectively). ACT was similar between groups. Aortic distensibility was significantly lower and aortic stiffness index and aortic elastic modulus were significantly higher in patients with BAV (8.1±4.6 [10<sup>-6</sup>cm<sup>2</sup>dyn<sup>-1</sup>] vs 5.1±3.6 [10<sup>-6</sup>cm<sup>2</sup>dyn<sup>-1</sup>], p=0.006; 4.1±2.8 vs 7.3±4.9, p=0.003; 3.6±2.8 [dyn.cm<sup>-2</sup>10<sup>6</sup>] vs 5.9±3.9 [dyn.cm<sup>-2</sup>10<sup>6</sup>], p=0.010, respectively). In correlation analysis, LA active emptying fraction was significantly correlated with aortic stiffness index and mitral A- velocity (r=0.431, p<0.001; r=0.304, p=0.016, respectively).

**Conclusion:** The present study demonstrated that LA mechanical functions and aortic elasticity parameters were deteriorated, while atrial conduction time was preserved in patients with isolated BAV. Furthermore, LA mechanical functions were significantly correlated with aortic elasticity parameters and mitral inflow A-wave velocity.

### ÖZET

**Amaç:** Bu çalışmada, ciddi kapak işlev bozukluğu olmayan tek başına biküspit aort kapağı (BAK) bulunan hastalarda sol atriyum (SA) mekanik işlevlerini ve atriyal ileti zamanlarını (AİZ) değerlendirdik, ayrıca SA işlevleri ve aort esneklik parametreleri arasındaki ilişkiyi araştırdık.

**Yöntemler:** Çalışma popülasyonumuz tek başına BAK bulunan 34 hasta (ortalama yaş 34±13 yıl) ile yaş ve cinsiyet açısından uyumlu 29 sağlıklı gönüllüden (ortalama yaş 30±10 yıl) oluşmaktaydı. Sol atriyum hacimleri iki düzlemli alan uzunluk yöntemi kullanılarak ölçüldü. Ayrıca SA aktif, pasif boşalma hacimleri ve fraksiyonları hesaplandı. Atriyum içi ve atriyumlar arası AİZ'ler doku Doppler görüntüleme kullanılarak ölçüldü. Aort gerilimi, aort sertlik indeksi, aort gerilebilirliği ve aort esneklik katsayısı gibi aort esneklik parametreleri hesaplandı.

**Bulgular:** Sol atriyum çapı, en yüksek hacmi, atriyum sistolu öncesi hacmi ve SA aktif boşalma fraksiyonu BAK hasta grubunda anlamlı olarak yüksekti (sırasıyla, 33.2±3.2 mm ve 34.9±2.8 mm, p=0.030; 16.2±4.6 mL/m<sup>2</sup> ve 19.8±4.8 mL/m<sup>2</sup>, p=0.004; 10.2±3.7 mL/m<sup>2</sup> ve 12.1±4.9 mL/m<sup>2</sup>, p=0.029; %30.4±12.0 ve %39.9±11.8, p=0.003). Atriyal ileti zamanları her iki grup arasında benzerdi. Biküspit aort kapağı hasta grubunda; aort gerilebilirliği anlamlı olarak düşüken, aort sertlik indeksi ve aort esneklik katsayısı anlamlı olarak yüksekti (sırasıyla, 8.1±4.6 [10<sup>-6</sup>cm<sup>2</sup>dyn<sup>-1</sup>] ve 5.1±3.6 [10<sup>-6</sup>cm<sup>2</sup>dyn<sup>-1</sup>], p=0.006; 4.1±2.8 ve 7.3±4.9, p=0.003; 3.6±2.8 [dyn.cm<sup>-2</sup>10<sup>6</sup>] vs 5.9±3.9 [dyn.cm<sup>-2</sup>10<sup>6</sup>], p=0.010). Korelasyon analizinde SA aktif boşalma fraksiyonu, aort sertlik indeksi ve mitral A dalga hızı ile anlamlı derecede ilişkiliydi (sırasıyla, r=0.431; p<0.001, r=0.304; p=0.016).

**Sonuç:** Bizim çalışmamız tek başına BAK bulunan hastalarda AİZ'ler korunurken, SA mekanik işlevlerinin ve aort esneklik parametrelerinin bozulduğunu gösterdi. Dahası, SA mekanik işlevlerinin aort esneklik parametreleriyle ve mitral A dalga hızıyla anlamlı derecede ilişkili olduğu bulundu.

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**B**icuspid aortic valve (BAV) is the most common congenital cardiac malformation in adults, occurring in 1% to 2% of the population.<sup>[1]</sup> It is frequently associated with dilation, aneurysm, and dissection of the ascending aorta. Aortic annulus and ascending aorta dilation have been seen in patients with BAV, even in those with normally functioning valves.<sup>[2]</sup> Aortic complications are associated with progressive degeneration of the aortic media, and many studies have demonstrated that BAV is associated with reduced arterial elasticity and impaired aortic stiffness.<sup>[3,4]</sup> In addition, there is direct relationship between arterial stiffness and atrial conduction time and left atrial size.<sup>[5,6]</sup> Moreover, several studies have shown that BAV is associated with left ventricular (LV) systolic and diastolic dysfunction.<sup>[7-9]</sup> Ventricular mechanical function is directly related to left atrial (LA) size and function. Increased LA pressure and size may lead to fibrosis and structural changes in the atrium that can result in atrial arrhythmia.<sup>[10]</sup>

In this study, it was hypothesized that abnormal aortic elastic properties due to intrinsic aortic wall pathology and impairment of LV function may negatively affect LA function in patients with isolated BAV. Therefore, LA mechanical and conduction function in these patients was assessed.

## METHODS

### Study population

The study population consisted of 34 isolated BAV patients (17 women; mean age: 34±13 years) who were followed up at cardiology outpatient clinic. Control group consisted of 29 healthy, age- and sex-matched (12 women; mean age: 30±10) volunteers. Patients with aortic valve stenosis (aortic valve velocity >2 m/s) and more than mild aortic regurgitation, concomitant dysfunction of other heart valves, coronary artery disease, LV systolic dysfunction (LV ejection fraction [LVEF] <50%), LV hypertrophy, any arrhythmia, Marfan syndrome, any congenital heart defect, hypertension, diabetes mellitus, current smoking, or any systemic disease were excluded from the study. The study was approved by at the Medical School of Gaziosmanpasa University ethics committee and all subjects gave written, informed consent.

### Echocardiography

All participants were evaluated using transthoracic

echocardiography with 2–4 MHz transducer (Vivid S5; GE Healthcare, Inc., Chicago, IL, USA) during continuous electrocardiogram (ECG) monitoring. Echocardiographic examination consisted of standard, 2-dimensional echocardiogram, including M-mode and Doppler echocardiography according to

#### Abbreviations:

ACT	Atrial conduction times
BAV	Bicuspid aortic valve
ECG	Electrocardiogram
EF	Ejection fraction
IVRT	Isovolumic relaxation time
IVS	Interventricular septum
LA	Left atrium
LV	Left ventricle
LVEDD	Left ventricular end-diastolic diameter
LVESD	Left ventricular end-systolic diameter
LVEF	Left ventricular ejection fraction
PW	Posterior wall
Vmax	LA maximum volume
Vmin	LA minimum volume
Vp	LA volume before atrial systole

recommendations in the American Society of Echocardiography guidelines.<sup>[11]</sup> Morphology of the aortic valve was defined in parasternal short axis view. LV wall thickness (interventricular septum [IVS] and posterior wall [PW]) and LV end-diastolic (LVEDD) and end-systolic diameters (LVESD) were measured from parasternal long axis view with M-mode echocardiography. LA diameter was measured from apical 4-chamber view. LVEF was calculated using apical 4-chamber views using Simpson's method.

Mitral valve inflow patterns (E-wave, A-wave, E-wave deceleration time, E/A ratio, and isovolumic relaxation time [IVRT]) were measured using pulsed wave Doppler. LA volume was obtained from apical 4-chamber views using biplane area-length method. LA maximum volume (Vmax) at end-systolic phase, LA minimum volume (Vmin) at end-diastolic phase (onset of the mitral opening), and LA volume before atrial systole (Vp) were measured at the beginning of atrial systole and calculated indexed to body surface area. Parameters of LA function were calculated as follows:<sup>[12]</sup>

- LA passive emptying volume (mL) = Vmax–Vp,
- LA passive emptying fraction (%) = [(Vmax–Vp)/ Vmax] × 100%,
- LA active emptying volume (mL) = Vp–Vmin,
- LA active emptying fraction (%) = [(Vp–Vmin)/Vp] × 100%.

Atrial conduction time (ACT) was measured by using tissue Doppler echocardiography. ACT was defined as time between beginning of P-wave on the

ECG monitor to start of late diastolic wave. It was obtained from lateral mitral annulus, septal mitral annulus, and tricuspid annulus, and labeled lateral ACT, septal ACT, and tricuspid ACT, respectively. Difference between lateral ACT and tricuspid ACT was defined as interatrial ACT, difference between septal ACT and tricuspid ACT was defined as intra-right atrial ACT, and difference between lateral ACT and septal ACT was defined as intra-left ACT. All measurements were repeated 3 times, and average was calculated for each ACT value.

Aortic systolic and diastolic diameters were measured 3 cm above the aortic valve from parasternal long axis view. Parameters of aortic elasticity were calculated as follows:<sup>[13]</sup>

- Aortic strain (%) = (aortic systolic – diastolic diameter) x 100 / aortic diastolic diameter,
- Aortic stiffness index = (systolic / diastolic blood pressure [BP]) / aortic strain,
- Aortic distensibility ( $\text{cm}^2 \cdot \text{dyne}^{-1} \cdot 10^{-6}$ ) = 2 x aortic strain / (systolic – diastolic BP),
- Aortic elastic modulus ( $\text{dyne} \cdot \text{cm}^{-2} \cdot 10^6$ ) = (systolic – diastolic pressure) / aortic strain.

### Statistical analysis

All statistical analyses were conducted using SPSS software, version 21.0 (IBM Corp., Armonk, NY, USA). Categorical data were shown as number of cases and percentages, while descriptive statistics for continuous variables were expressed as mean±SD or me-

**Table 1. Demographic and echocardiographic findings of the groups**

	Control (n=29)			Bicuspid aortic valve (n=34)			p
	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			30.5±9.9			34.6±13.6	0.183
Sex (female)	12	42		17	50		0.494
Body mass index ( $\text{kg}/\text{m}^2$ )			25.1±4.47			23.4±4.4	0.188
Systolic blood pressure (mmHg)			104±10			108±10	0.134
Diastolic blood pressure (mmHg)			69±10			65±7	0.071
Heart rate (beats/min)			80±14			78±10	0.719
Left ventricular end-diastolic diameter (mm)			44±4			46±3	0.113
Left ventricular end-systolic diameter (mm)			28±3			30±3	0.096
Left ventricular ejection fraction (%)			65 [63–66]			65 [63–65]	0.989
Interventricular septum (mm)			8 [8–10]			9 [8–10]	0.175
Posterior wall (mm)			8 [8–10]			9 [8–10]	0.236
Mitral E (cm/s)			77±14			79±17	0.602
Mitral A (cm/s)			61±12			69±15	0.030
Isovolumic relaxation time (ms)			58±14			69±11	<0.001
Mitral deceleration time (ms)			205±33			189±42	0.090
E/A			1.3±0.2			1.2±0.3	0.197
E/E'			5.2±1.2			5.5±1.3	0.459
Systolic aortic diameter (cm)			29.4±3.8			32.6±4.9	0.005
Diastolic aortic diameter (cm)			26.1±3.9			29.9±5.2	0.002
Aortic strain (%)			13.1±6.7			9.9±7.1	0.079
Aortic stiffness index			4.1±2.8			7.3±4.9	0.003
Aortic distensibility ( $10^{-6} \text{cm}^2 \text{dyn}^{-1}$ )			8.1±4.6			5.1±3.6	0.006
Aortic elastic modulus ( $\text{dyn} \cdot \text{cm}^{-2} \cdot 10^6$ )			3.6±2.8			5.9±3.9	0.010

SD: Standard deviation.

dian (interquartile range), where applicable. Data were tested for normality using the Kolmogorov-Smirnov test. In statistical analysis for numeric variables, Student's t-test or Mann-Whitney U test was used, and for categorical data, chi-square test was used. Degrees of association between continuous variables were evaluated with Spearman's rank correlation test. Value of  $p < 0.05$  was considered statistically significant.

## RESULTS

According to basic clinical and demographic characteristics, study groups were similar with regard to age, sex, body mass index, and heart rate. All the participants were normotensive and no significant differences were observed in systolic or diastolic BP between the 2 groups. Basic echocardiographic measurements were also similar in both groups with regard to LVEDD, LVESD, LVEF, IVS, and PW thickness. Mitral A-wave velocity and IVRT were significantly higher in patients with BAV ( $61 \pm 12$  cm/s vs  $69 \pm 15$  cm/s,  $p=0.030$ ;  $58 \pm 14$  ms vs  $69 \pm 11$  ms,  $p<0.001$ , respectively), while mitral E-wave velocity, E-wave deceleration time, E/A ratio, E/E' ratio were similar between groups.

Ascending aorta systolic and diastolic dimensions were significantly higher in patients with BAV. Aortic strain was lower in BAV patients, but difference was not statistically significant ( $13.1 \pm 6.7\%$  vs  $9.9 \pm 7.1\%$ ;  $p=0.079$ ). Aortic distensibility was significantly lower in patients with BAV ( $8.1 \pm 4.6$  vs  $5.1 \pm 3.6$ ;  $p=0.006$ ). Aortic stiffness index and aortic elastic modulus were

significantly higher in patients with BAV compared with control group ( $4.1 \pm 2.8$  vs  $7.3 \pm 4.9$ ,  $p=0.003$ ;  $3.6 \pm 2.8$  [dyn.cm<sup>-2</sup>10<sup>6</sup>] vs  $5.9 \pm 3.9$  [dyn.cm<sup>-2</sup>10<sup>6</sup>],  $p=0.010$ , respectively). Demographic, clinical, and echocardiographic characteristics of participants are provided in Table 1.

According to LA function, LA diameter, LA Vmax, LA Vp, and LA active emptying fraction were significantly higher in BAV patient group when compared with control group ( $33.2 \pm 3.2$  mm vs  $34.9 \pm 2.8$  mm,  $p=0.030$ ;  $16.2 \pm 4.6$  mL/m<sup>2</sup> vs  $19.8 \pm 4.8$  mL/m<sup>2</sup>,  $p=0.004$ ;  $10.2 \pm 3.7$  mL/m<sup>2</sup> vs  $12.1 \pm 4.9$  mL/m<sup>2</sup>,  $p=0.029$ ; and  $30.4 \pm 12.0\%$  vs  $39.9 \pm 11.8\%$ ,  $p=0.003$ , respectively). LA Vmin and LA passive emptying fraction were not different between groups. In addition, according to atrial conduction features, Lateral ACT, septal ACT, tricuspid ACT, left intra-atrial ACT, right intra-atrial ACT and interatrial ACT were similar between groups. LA mechanical function and ACT can be seen in Table 2.

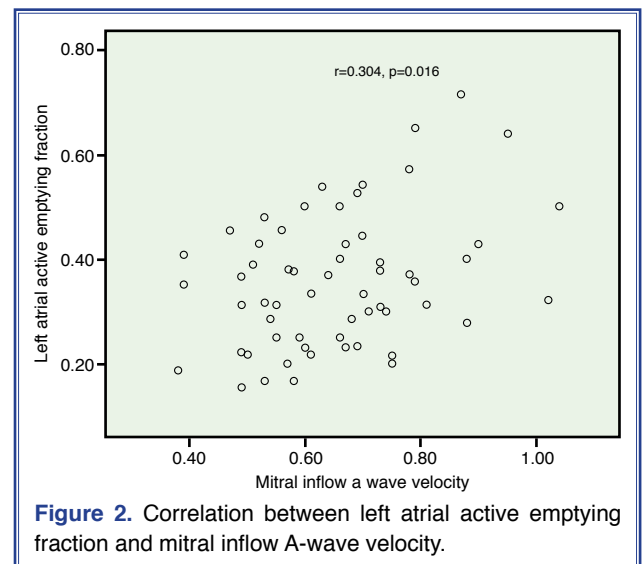
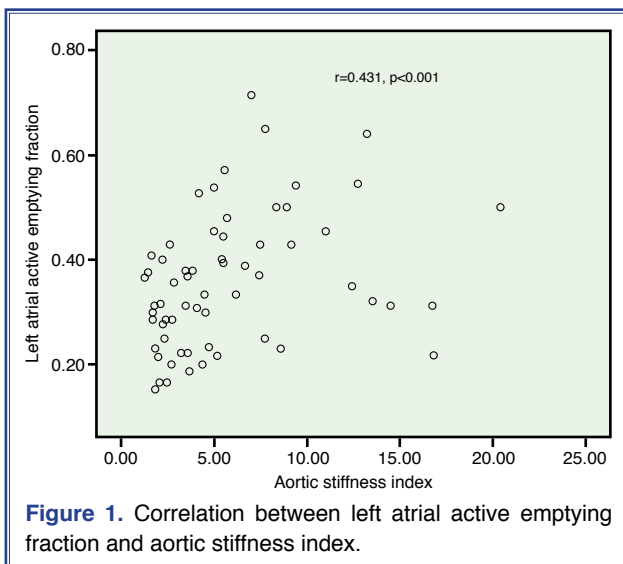
Correlation analysis revealed that LA active emptying fraction was significantly correlated with aortic stiffness index (Figure 1) and mitral A-wave velocity (Figure 2) ( $r=0.431$ ,  $p<0.001$ ;  $r=0.304$ ,  $p=0.016$ , respectively).

## DISCUSSION

The present study demonstrated that LA mechanical function and aortic elasticity parameters in patients

**Table 2. Left atrial mechanical functions and atrial conduction times of the study groups**

	Control (n=29)	Bicuspid aortic valve (n=34)	p
Left atrium diameter (mm)	33.2±3.2	34.9±2.8	0.030
Left atrium maximum volume (mL/m <sup>2</sup> )	16.2±4.6	19.8±4.8	0.004
Left atrium minimum volume (mL/m <sup>2</sup> )	6.9±2.3	7.4±2.6	0.430
Left atrium Volume at the beginning of atrial systole (mL/m <sup>2</sup> )	10.2±3.7	12.1±4.9	0.029
Left atrium active emptying fraction (%)	30.4±12.0	39.9±11.8	0.003
Left atrium passive emptying fraction (%)	37.2±10.1	36.7±13.3	0.856
Lateral atrial conduction time (ms)	34.7±12.1	33.4±11.7	0.673
Septal atrial conduction time (ms)	21.4±7.9	22.5±10.7	0.645
Tricuspid atrial conduction time (ms)	25.8±12.6	26.5±12.0	0.822
Left intra-atrial atrial conduction time (ms)	13.2±10.9	11.2±8.1	0.416
Right intra-atrial atrial conduction time (ms)	4.4±14.5	4.5±13.5	0.975
Inter-atrial atrial conduction time (ms)	11 [3-22]	8 [4-15]	0.335



with isolated BAV were deteriorated, while atrial conduction times were preserved. Furthermore, we found that LA mechanical function parameters were significantly correlated with aortic elasticity parameters and mitral inflow A-wave velocity.

BAV is a common congenital heart disease that is not only a product of valvulogenesis but is also a genetic disorder of the aorta and cardiac development.<sup>[3]</sup> Pathogenesis of the malformation is still unclear. BAV is associated with considerable rates of morbidity and mortality, as well as aortic complications, including dilation, aneurysm formation, and dissection.<sup>[3,14]</sup> Although hemodynamic stress as a result of turbulent flow over the malformed valve contributes to the aortic malformation, valvular dysfunction is not solely responsible for the vascular complications. More than half of patients with normally functioning BAV have aortic dilation.<sup>[2]</sup> Fibrillin-1, endothelial nitric oxide synthase deficiencies, and increased matrix metalloproteinase activity result in degeneration of the aortic media as well as structural weakness in aortic wall in these patients.<sup>[3]</sup> Several studies have demonstrated that BAV is associated with reduced arterial elasticity and impaired aortic stiffness.<sup>[4,15,16]</sup> In addition, there is a known relationship between arterial stiffness, atrial conduction times, and LA size.<sup>[5,6]</sup> Consistent with previous data, the patients in this study had higher aortic dimensions compared to control group, despite having normally functioning BAV. In addition, BAV patients have impaired aortic elasticity, and there was positive correlation between aortic stiffness and LA emptying fraction in our study.

LV function is directly related to LA function, and ventricular remodeling is an important determinant of LA size and function.<sup>[17]</sup> Previous studies have demonstrated that LV function can be affected in BAV patients. For example, Kocabay et al.<sup>[7]</sup> reported that patients with isolated BAV had early features of subclinical LV diastolic dysfunction, as measured by 2-dimensional speckle-tracking echocardiography. Santarpia et al.<sup>[8]</sup> found that LV longitudinal, circumferential, and radial strain were lower in patients with BAV without significant valvular dysfunction. Kurt et al.<sup>[9]</sup> also reported that some BAV patients had lower levels of LV longitudinal strain compared with healthy subjects. In general, the hemodynamic effects of bicuspid valve and impaired aortic elasticity could affect LV function. In this study, we found that mitral A-wave and IVRT were significantly higher in BAV patients than in controls, but diastolic echocardiographic parameters were similar between BAV and control groups. Our results suggest that LV diastolic function is slightly affected by BAV; however, conventional echocardiographic methods were used to assess LV function. More sensitive echocardiographic methods may have revealed diastolic function in this study.

Increased LA pressure and size may lead to fibrosis and to development of atrial arrhythmia. Despite recent developments, measurement of LA volume and size is still the most commonly used method to estimate atrial function. In addition, many studies have reported that atrial electromechanical delays can reflect the electrophysiological and structural features



of the atria, and that delays are related to atrial fibrillation.<sup>[18,19]</sup> Although many studies have investigated LV function and aortic elastic properties, there is insufficient data on LA function in patients with BAV. Recently, Bilen et al.<sup>[20]</sup> reported that BAV is associated with longer P-wave duration and increased P-wave dispersion, both of which are related to aortic elasticity. Similarly, in this study, we found that LA function was disturbed in patients with BAV, while ACTs were similar between the 2 groups. Furthermore, LA active emptying fraction correlated with aortic stiffness and mitral inflow A-wave. Based on our results and previous data, we believe that present study results may be explained by change in LV diastolic function and impairment of aortic elastic properties.

### Study limitations

This study had several limitations. The primary limitation is that it was a single-center study with a small study population. In addition, we used a cross-sectional design and did not perform patient follow-up. The patients could not be followed prospectively for arrhythmic episodes. Another limitation is that we assessed LA function by conventional echocardiographic methods; more sensitive echocardiographic methods would have been better.

In conclusion, we found that BAV without significant valve dysfunction was associated with impairment of LA mechanical functions. These results suggest that BAV patients may be more likely to develop atrial arrhythmias.

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**Keywords:** Aortic elasticity; bicuspid aortic valve; left atrium.

**Anahtar sözcükler:** Aortik esneklik; biküspit aort kapak; sol atriyum.