ORIGINAL ARTICLE

Pulmonary artery and right ventricle function in patients with bicuspid aortic valve

Biküspit aort kapaklı hastalarda pulmoner arter ve sağ ventrikül fonksiyonları

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ABSTRACT

Objective: Bicuspid aortic valve (BAV) is a complex developmental anomaly caused by abnormal aortic leaflet formation during valvulogenesis. The present study is an assessment of the effects of BAV disease on the ascending aorta and pulmonary artery (PA), and an evaluation of the consequences for systolic and diastolic functioning of the left and right ventricles.

Methods: Total of 66 patients were eligible for inclusion. Pulmonary artery maximum diameter (PAD) was obtained 1 cm distal to the pulmonary annulus. Using pulsed-wave tissue Doppler imaging, left ventricular (LV) early diastolic velocity (E′) measurement was obtained at the annulus with placement of sample volume. Right ventricle (RV) peak global strain rate during systole (RV-SRS), early diastole (RV-SRE), and late diastole (RV-SRA) were calculated.

Results: In this study, 40.9% (n=27) of patients were female and average age was 35±11years. RV-SRS values (β=-.781, t=-2.723; p=0.010) and log-LV tissue Doppler imaging E' (β=-2.996, t=-5.405; p=<0.001) were negatively correlated, and log-PAD (β=4.861, t=3.052; p=0.005) was positively and independently correlated with ascending aortic diameter.

Conclusion: Ascending aorta diameter is positively correlated with PA diameter in BAV patients, and RV strain rate and LV diastolic parameters are affected before development of the valve disease.

ÖZET

Amaç: Biküspit aort kapağı, valvulogenez sırasında anormal aorti kapakçık oluşumu sonucunda ortaya çıkan gelişimsel bir anomalidir. Bu çalışmada, biküspit aort kapak hastalığının pulmoner arter ve çıkan aortaya etkileri, bu durumun sağ ve sol ventrikül sistolik ve diyastolik fonksiyonları üzerine etkisi değerlendirildi.

Yöntemler: Çalışmaya 66 hasta dahil edildi. Pulmoner arter en yüksek çapı (PAD), pulmoner anulusun 1 cm distalinden ölçüldü. Sol ventrikül (LV) erken diyastolik hızı, örnek hacim anulusa yerleştirilerek elde edildi. Sol ventrikül (LV) erken diyastolik hız (E'), doku Doppler görüntüleme tekniği kullanılarak ve örnek hacim anulusa yerleştirilerek elde edildi. Sağ ventrikül (RV) pik global strain hızı sistol (RV-SRS), erken diyastol (RV-SRE) ve geç diyastolde (RV-SRA) ölçüldü.

Bulgular: Hastaların %40.9'u (n=27) kadın ve ortalama yaşları 35±11'di. Sağ ventrikül sistolik pik global strain hızı (β=-0.781, t=-2.723; p=0.010) ve log-LV E' (β=-2.996, t=-5.405; p=<0.001) değerlerinin çıkan aorta çapı ile negatif, log-PAD (β=4.861, t=3.052; p=0.005) değerlerinin ise pozitif ve bağımsız ilişkili olduğu saptandı.

Sonuç: Biküspit aort kapaklı hastalarda çıkan aort çapı ile pulmoner arter çapı arasında pozirtif bir korelason olduğunu ve RV strain hızı ve LV diyastolik parametrelerinin kapak hastalığı gelişmeden önce etkilendiğini saptadık.

Bicuspid aortic valve (BAV) is a complex developmental anomaly caused by abnormal aortic leaflet formation during valvulogenesis.[1] BAV is the most commonly observed congenital heart malformation in adults, with prevalence of 1.3% in the general population.[2] Despite aortic stenosis and aortic insufficiency being the most widespread complications associated with BAV, dilatation of the ascending aorta

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from the root to the arch, known as bicuspid aortopathy, has been observed at rate of approximately 40% to 50%.[3,4] Presence of accelerated degeneration in medial layer of aorta has been reported in patients with bicuspid aorta.[5] Some studies have shown that elasticity of the ascending aorta is affected independently of the aorta's dilatation and valve dysfunction.[6] Having the same embryological origin, trunk of the pulmonary artery (PA) has shown the same histological degeneration in BAV patients, especially after application of Ross procedure.[7] Some studies indicate that BAV patients have drastic changes in both the ascending aorta and medial layer of the pulmonary trunk earlier than patients with tricuspid valve.[8] Taking this hypothesis as their starting point, Celik et al. demonstrated that elasticity of the pulmonary artery is affected in patients with BAV.[9]

The aim of the present study was to assess effects of BAV disease on the ascending aorta and PA, and to evaluate consequences of this condition for systolic and diastolic functioning of the left and right ventricles.

METHODS

This study was conducted between June and December of 2015 with sequentially included patients older than 18 years of age and diagnosed with BAV. Total of 93 patients were assessed for inclusion in the study. Exclusion criteria included aortic stenosis of hemodynamic significance (peak velocity >3 m/seconds); aortic insufficiency (vena contracta >2 mm); exposure to angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or beta-blocker therapy; Marfan syndrome and similar or related congenital abnormalities related to connective tissue; moderate or severe valve pathology; history of aortic valve intervention; inappropriate echogenicity; diagnosis of coarctation of the aorta; diagnosis of coronary artery disease; and rhythm other than normal sinus. After initial evaluation, 66 of total 93 patients were eligible for inclusion.

The study was approved by the institutional ethics committee, oral and written informed consent was obtained from all study participants, and all procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Clinical characteristics

Arterial hypertension was defined as present in patients with blood pressure value >140/90 mmHg or in patients receiving antihypertensive therapy. Diabetes mellitus was defined as fasting blood glucose level >126 or >200 mg/dL 2 hours after oral glucose tolerance test, and as present in patients receiving permanent medical antidiabetic therapy. Coronary artery disease was defined as history of myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, or an angiographic evidence of significant coronary artery stenosis (≥50%).

Abbreviations:

A	*Late ventricular velocity*
A'	*Late diastolic velocity*
BAV	*Bicuspid aortic valve*
E	*Early ventricular velocity*
E'	*Early diastolic velocity*
GLS	*Global longitudinal strain*
IVS	*Interventricular septum*
LA	*Left atrial*
LV	*Left ventricle*
LVEF	*Left ventricular ejection fraction*
MMP	*Matrix metalloproteinase*
PA	*Pulmonary artery*
PAD	*Pulmonary artery diameter*
PW	*Posterior wall*
RV	*Right ventricle*
S'	*Systolic velocity*
SRA	*Late diastolic strain rate*
SRE	*Early diastolic strain rate*
SRS	*Systolic strain rate*
TDI	*Tissue Doppler imaging*

Conventional echocardiographic examination

Echocardiographic examinations were performed offline by 2 experienced echocardiographers. Initial examination was performed by the first echocardiographer, followed by blinded analysis completed offline by the second echocardiographer. Conventional 2-dimensional (2-D) echocardiographic examinations were performed utilizing the Vivid 7 (GE Healthcare, Inc., Chicago, IL, USA) echocardiography system in accordance with recommendations of the American Society of Echocardiography.[10] Left ventricular (LV) diameter, interventricular septum (IVS), posterior wall (PW), and left atrial (LA) size and volume were measured. LV ejection fraction (LVEF) was calculated using biplane Simpson's method.[11]

i) Aortic measurement: Aortic diameter was obtained in 2-D from the interior of 1 wall to the interior of the opposite wall at the level of the aortic valve, the widest point of the sinus of Valsalva, the sinotubular junction and the ascending aorta. Measurements were performed at end-systole. Aortic diameter measurement was indexed to body surface area. Aortic elasticity of the ascending aorta was measured echocardiographically with M-mode at 3 cm above the aortic valve. Aortic systolic diameter was measured at the point of maximal movement of the anterior aortic wall toward the anterior. In order to define end-systole, measurement was performed at simultaneously recorded peak point of R-wave on electrocardiography.

Arterial readings of systolic and diastolic blood pressure were measured brachially.

Aortic strain (%) observed while investigating aortic elasticity was calculated with the formula 100 x (aortic systolic diameter - aortic diastolic diameter) / aortic diastolic diameter.

Aortic stiffness index (β) was calculated using the formula (systolic blood pressure / diastolic blood pressure) / [(aortic systolic diameter - aortic diastolic diameter) / (aortic diastolic diameter.)]

Aortic distensibility index (cm^{-2} $dyne^{-1}$ 10^{-6}) figure was 2 x (aortic systolic diameter - aortic diastolic diameter) / [(aortic diastolic diameter) x (systolic blood pressure - diastolic blood pressure)],[12] as described by Nistri et al.

ii) Pulmonary artery stiffness was calculated with recordings of pulmonary flow with pulse wave placed 1 cm distal to the pulmonary valve in parasternal short-axis view, and using formula of (kHz/sec) = maximal frequency shift of pulmonary flow / acceleration time.[13] Pulmonary artery acceleration time and maximal flow velocity values were measured with spectral Doppler. Maximum pulmonary artery diameter (PAD) was obtained 1 cm distal to the pulmonary annulus.

Fractional area change of the right ventricle (RV) was calculated through percentage area change of the RV at end-systole and end-diastole in apical 4-chamber view. Tricuspid annular plane systolic excursion was calculated by measuring distance of systolic movement of the RV annulus longitudinally with M-mode while passing the tricuspid annular plane and parallel to the lateral wall of the RV.

iii) RV and LV inflow measured with tissue Doppler imaging: Early (E) and late (A) wave ventricular filling velocities, E/A ratio, and E deceleration time were measured from the mitral inflow profile. Isovolumetric relaxation time was also measured with pulse wave Doppler using previously validated and recommended methods.[14] To acquire tissue Doppler imaging (TDI) data, Nyquist limit was set at 15–20 cm/second, and minimal optimal gain was used. Myocardial systolic (S′), early diastolic (E′), and late diastolic (A′) velocities were obtained at the septal and lateral mitral annulus with sample volume placement. E/E′ ratio was subsequently calculated for septal and lateral measurements and was also averaged. E, A, and DT measurements for tricuspid inflow were obtained in similar fashion. TDI measurements of the S', E', and A' velocities were performed by placing a sample volume on the free wall of the RV.

Speckle tracking echocardiography

Using dedicated software package (EchoPAC; GE Healthcare, Inc., Chicago, IL, USA) 2-D strain and strain rate were measured as previously described to obtain information on local myocardial function and velocity.[15]

i) LV: For speckle tracking analysis, 3 cycles were recorded at frame rate ≥45 fps and were averaged for strain analysis. Aortic valve opening and closing times were measured from LV outflow Doppler profile and were incorporated into speckle tracking strain profile in order to exclude post-systolic components. From 3 manually selected landmark points (lateral and septal mitral annulus and LV apex) in apical views, LV endocardial borders were automatically detected by the software. Subsequently, automatic tracking of myocardial speckles was performed throughout cardiac cycle. Manual corrections of border tracings were avoided as much as possible. Global longitudinal strain (GLS) and strain rate curves were obtained for apical 4-chamber, 3-chamber, and 2-chamber views, including all LV myocardial segments (6 segments per view). LV-GLS was calculated by averaging peak longitudinal strain of 16 segments. Similarly, peak global strain rate during systole (LV-SRS), early diastole (LV-SRE), and late diastole (LV-SRA) were calculated.

ii) RV: Using dedicated EchoPAC software, 2-D strain and strain rate were measured as previously described, to obtain information on local myocardial function and velocity. After manual tracing of endocardial border of the RV (about 10 to 16 points) over 1 frame, endocardial borders were automatically tracked throughout cardiac cycles. Myocardial velocity was derived as ratio between frame-to-frame displacement of speckles and time interval.[16]

After endocardial border of RV was manually traced, automatic tracing of entire endocardial border was performed throughout cardiac cycle. GLS and time to peak strain were measured. RV-GLS was calculated by averaging the 6 segments of the lateral and interventricular septum. RV free wall strain was calculated by averaging the 3 segments of the lateral. Similarly, peak RV-SRS, RV-SRE, and RV-SRA were calculated.

Statistical analysis

Data are presented as mean±SD and geometric mean for continuous variables, and as percentage (number of cases) for categorical variables. Normal distribution of the data was tested with Kolmogorov-Smirnov test. Log-transformation was used for variables aortic strain, aortic distensibility index, deceleration time, LV-TDI E', LV-TDI A', LV-TDI S', LV E/E', PAD, PA acceleration time, RV end-systolic area and RV inflow A, which had skewed distribution. Pearson's and Spearman's correlation analyses were used to test possible associations between ascending aorta dimension and study variables. Independent variables of ascending aortic dilatation in bicuspid aorta disease was obtained with age and hypertension- adjusted multiple linear regression analysis using stepwise model including significant variables at 25% level from univariate analysis as covariates. Multicollinearity was checked for variables used in regression analysis, since stiffness parameters were correlated with each other, which might cause bias in multivariate setting. Accordingly, variance inflation factor and tolerance values were used after regression analysis to check for multicollinearity. Tolerance value of 0.20 and above and/or variance inflation factor of 5 and less were acceptable for our model to ignore multicollinearity. Interobserver and intraobserver reliability were assessed with Bland-Altman plots. P value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPPS Statistics 22 (IBM Corp., Armonk, NY, USA) and MedCalc 12.4.0 (MedCalc Software, Ostend, Belgium) software.

RESULTS

Total of 93 consecutive patients were evaluated. Eight patients with inappropriate echogenicity, 2 patients with diagnosis of coarctation of the aorta, 2 patients with coronary artery disease, 7 patients with concomitant moderate to severe valvular disease, and 8 patients who were using beta-blocker or angiotensin converting enzyme inhibitor were excluded from the study. In all, 66 of total 93 patients were eligible for inclusion following initial evaluation.

Baseline demographic characteristics of the patients are shown in Table 1. Of all patients, 40.9% (n=27) were female and mean age of study group was 35±11 years. Hypertension was found in 19.7% (n=13) of participants, and 7.6% (n=5) had diabetes mellitus. Mean LVEF was determined to be 67±5.9% and mean aortic diameter was 3.6±0.61.

Correlation coefficients using Pearson's and Spearman's correlation analyses are presented in Table 2. Ascending aorta diameter was found by Pearson's and Spearman's, respectively, to be correlated with RV-TDI E' (r=-0.312, p=0.020; r=-317, p=0.019), RV-TDI A' (r=0.299, p=0.027; r=0.309, p=0.022), RV-free wall strain (r=-0.357, p=0.012; r=-0.309, p=0.031), log-LV TDI E' (r=-0.609, p<0.001; r=-0.602, p<0.001), log-PAD (r=0.438, p=<0.001; r=0.370, p=0.006), RV-SRS (r=-0.311, p=0.029; r=-0.344, p=0.015), log-aortic distensibility index (r=-0.208, p=0.102; r=-0.193, p=0.130), and tricuspid annular plane systolic excursion (r=-0.243, p=0.064; r=-0.313, p=0.016). Hypertension and age-adjusted multivariate linear regression analysis to determine relationship of ascending aorta diameter and echocardiographic parameters is provided in Table 3. RV-SRS values (β=-0.781, t=-2.723; p=0.010) and log-LV TDI E' (β=-2.996, t=-5.405; p:<0.001) were negatively correlated, and log-PAD (β=4.861, t=3.052; p=0.005) was positively and independently correlated with ascending aortic diameter.

Reliability analysis

LV-GLS and RV-GLS were re-measured by first echocardiographer and second echocardiographer who was blinded to the first measurement in 28 randomly selected patients. Agreement analysis of inter- and intra-observer variability for LV-GLS measurements revealed high agreement; mean difference of 0.1 (95% limits of agreement [LoA], 2.2 to -2.0) and mean difference of -0.37 (95% LoA, 1.28 to -2.02), respectively. For intra-observer reliability, intraclass correlation coefficient was significant for LV-GLS at 0.95, (0.911–0.980). Agreement analyses of inter- and intra-observer reliability for RV-GLS revealed high agreement with mean difference of -0.5 (95% LoA, -3.5 to 2.5) and -0.2 (95% LoA, -2.6 to 2.1), respectively. Bland-Altman plotting of the 2 echocardiographers' results were within agreement limits of 1.96 (95% confidence interval) (Figure 1).

DISCUSSION

Our study led us to 3 essential conclusions. First, there was positive correlation between dilatation of the as-

Table 1. Clinical and echocardiographic determinants of baseline

Age (years)	35±11	TDI S' cm/s	8.55*
Female gender, n (%)	27 (40.9)	E:E'	6.56*
BMI (kg/m^2)	1.87±0.19	LV-SRS	-0.90±0.19
Diabetes mellitus, n (%)	5 (7.6)	LV-SRE	1.00±0.27
Hypertension, n (%)	13 (19.7)	LV-SRA	0.76±0.23
Hyperlipidemia, n (%)	3 (4.5)	LV -GLS	-17.26±2.8
Smoking, n (%)	12 (18.2)	Pulmonary artery diameter (cm)	2.21*
Echocardiographic data		PA acceleration time	114*
LV ejection fraction (%)	67±5.9	PA maximum velocity	0.94±0.17
Endsystolic diameter (cm)	2.9±0.39	PA stiffness	8.8±3.1
Enddiastolic diameter (cm)	4.7±0.49	RV end-diastolic area (cm^2)	15.81±2.88
Interventricular septum (cm)	0.98±0.19	RV end-systolic area (cm^2)	8.47*
Posterior wall (cm)	1.02±0.18	RV fractional area change (%)	44±7.14
Ascending aorta (cm)	3.6±0.61	TAPSE (cm)	2.13±0.32
Ascending aorta (mm/m^2)	1.94±0.36	RV-GLS	-21.62±3.5
Aortic strain (%)	7.60*	RV-SRS	-1.18±0.24
Aortic distensibility index (10^{-6} cm^{-2} dyne^{-1})	3.35*	RV-SRE	1.06±0.33
Aortic stiffness index	2.2±0.20	RV-SRA	0.96±0.26
Left atrial diameter (cm)	3.2±0.33	RV free wall strain	-26.32±5.97
Mitral E (m/s)	0.81±0.18	RV inflow E	0.59±0.11
Mitral A (m/s)	0.67±0.18	RV inflow A	0.40*
E:A	1.2±0.37	RV inflow E:A	4.3±1.41
IVRT (unit)	87±19	RV TDI E'	13.16±2.52
Deceleration time (s)	188*	RV TDI A'	12.63±3.17
TDI septal E' cm/s	9.79*	RV TDI S'	13.85±1.98
TDI septal A' cm/s	9.62*	RV E:E'	4.3±1.4

*Geometric mean was given. A: Late ventricular velocity; A': Late diastolic velocity; BMI: Body mass index; E: Early ventricular velocity; E': Early diastolic velocity; GLS: Global longitudinal strain; IVRT: Isovolumetric relaxation time; LV: Left ventricle; PA: Pulmonary artery; RV: Right ventricle; SRA: Late diastolic strain rate; SRE: Early diastolic strain rate; SRS: Systolic strain rate; TAPSE: Tricuspid annular plane systolic excursion; TDI: Tissue Doppler imaging.

cending aorta and dilatation of the PA. The second and third are that RV-SRS and LV-TDI E' negatively correlated with dilatation of the ascending aorta. No connection was established between dilatation of the aorta and parameters related to aortic and PA elasticity, or speckle tracking parameters of the LV.

BAV is a complex developmental anomaly caused by abnormal aortic leaflet formation at valvulogenesis.[1] BAV is the most commonly observed congenital heart malformation in adults, with prevalence of 1.3% in the general population.[2] Despite aortic stenosis and aortic insufficiency being the most widespread complications associated with BAV, widening of the ascending aorta from the root to the arch, known as bicuspid aortopathy, has been observed at rate of approximately 40% to 50%.[3,4] Compared with those with tricuspid aortic valve, BAV patients have higher rate of dilatation of the aorta and increased risk of aortic aneurysm, dissection, and rupture.[17,18] Previous studies of BAV patients have reported rates of dilatation of 8% to 59% at level of the aortic annulus, 16% to 78% at level of the sinus of Valsalva, 15% to 79% at level of the sinotubular junction, and 35% to 68% in the proximal ascending aorta.[5,19–21] BAV can affect the PA and pulmonary valve alongside the aorta, ascending aorta, and aortic arch.[22–24] However much the intrinsic pathologies of the aorta may be responsible for dilatation of the aorta, an increasing body of evidence shows that aortic flow anomalies

Table 2. Correlation of ascending aorta diameter to echocardiographic measurements

Variable	r		*p*	
	Pearson's	Spearman's	Pearson's	Spearman's
RV TDI E'	-0.312	-0.317	0.020	0.019
RV TDI A'	0.299	0.309	0.027	0.022
RV free wall strain	-0.357	-0.309	0.012	0.031
Log-LV TDI E'	-0.609	-0.602	<0.001	<0.001
Log-PAD	0.438	0.370	<0.001	0.006
RV-SRS	-0.311	-0.344	0.029	0.015
Log-aortic distensibility index	-0.208	-0.193	0.102	0.130
TAPSE	-0.243	-0.313	0.064	0.016

A': Late diastolic velocity; E': Early diastolic velocity; LV: Left ventricle; PAD: Pulmonary artery diameter; RV: Right ventricle; SRS: Systolic strain rate; TAPSE: Tricuspid annular plane systolic excursion; TDI: Tissue Doppler imaging.

may also be responsible.[25,26] According to a study by Bissell et al., the most important additional parameter in aortic dilatation is that of abnormal flow.[27] Additionally, they confirmed intrinsic pathologies of the medial layer, elastic tissue-collagen, and smooth muscle cell loss with accompanying accelerated degradation and found increased wall stiffness and decreased aortic distensibility.[28] BAV patients were shown to have abnormal aortic distensibility and stiffness.[17] Parameters of aortic elasticity were reported to be independent of aortic dilatation and valve pathology.[6] Another study evaluated aortic maximum systolic distension and maximum diastolic recoil with magnetic resonance imaging. Although they found that both were lower in BAV patients than in control group, they were unable to find any difference between BAV patients with or without dilated aortas.[29]

In our study, it was observed that aortic elasticity indexes were more affected than reported in the literature. We attempted to explain cystic medial degeneration and intrinsic aortic pathologies in patients with isolated BAV. Similarly to results of Donato Aquaro et al., elasticity indexes were found to be abnormal independently of diameter of the ascending aorta. No difference was found between patients with dilated and undilated aortas in terms of elasticity indexes, suggesting that basic pathological agent in aortic dilatation may be turbulent flow.

We have also demonstrated that LV-TDI E' value decreased as diameter of the ascendant aorta increased. BAV group with normal valve functions showed dia-

Table 3. Multivariate linear regression analysis to determine independent predictors of ascending aorta dilation in bicuspid aortic disease

	Unstandardized coefficients	t	*p*	95 % CI
First step				
Log-LV TDI E'	-3.395	-5.167	<0.001	-4.730 – (-2.060)
Second Step				
Log-LV TDI E'	-2.971	-4.904	<0.001	-4.203 – (-1.738)
Log-PAD	5.263	3.038	0.005	1.738 – 8.789
Third Step				
RV-SRS	-0.781	-2.723	0.010	-1.365 – (-.197)
Log-LV TDI E'	-2.996	-5.405	.<0.001	-4.126 – (-1.867)
Log-PAD	4.861	3.052	0.005	1.617 – 8.104

CI: Confidence interval; LV-TDI E': Left ventricle tissue Doppler early diastolic velocity; PAD: Pulmonary artery diameter; RV-SRS: Right ventricle peak systolic strain rate.

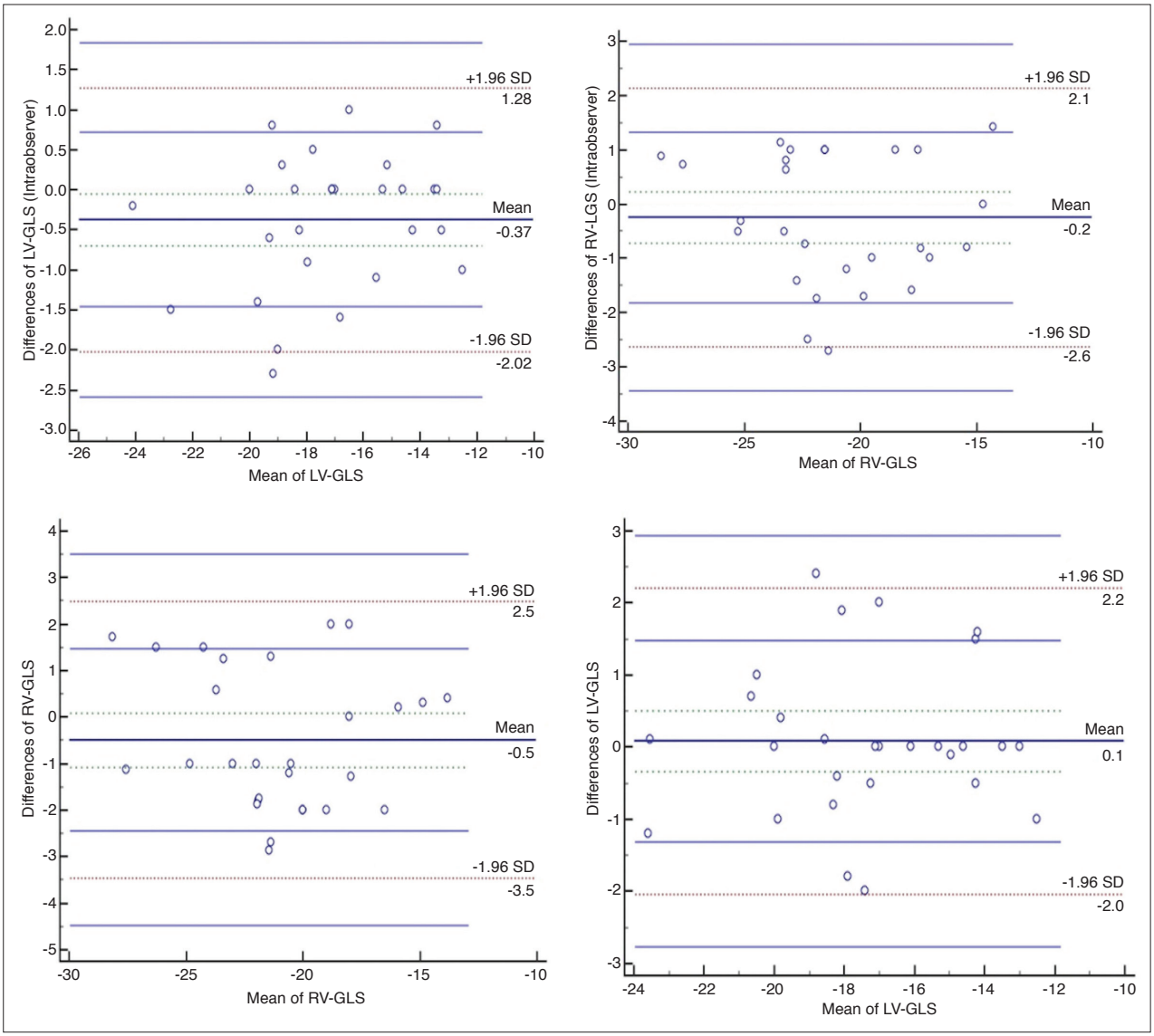

Figure 1. Intraobserver and interobserver Bland-Altman plots of left ventricular global longitudinal strain (GLS) and right ventricular GLS, with representation of the limits of agreement (dotted line), -1.96s to +1.96s.

stolic dysfunction.[30] Kocabay et al. reported diastolic dysfunction, abnormal left atrium strain parameters and volume index with increased LV E/E' in isolated BAV patients.[31] Abnormal force parallel to the aortic wall exerted by shear stress acts upon endothelial surface in terms of friction, which may activate cellular signaling cascades and result in overexpression of extracellular matrix degenerating substances, including matrix metalloproteinases (MMPs) and their endogenous tissue inhibitors.[32,33] Tzemos et al. have shown that MMP2 levels are higher in BAV patients with dilated ascending aorta.[34] Increased MMP-2 levels seen in patients with dilatation of the ascending aorta may also be the cause of diastolic dysfunction. Previously, study by Martos et al. reported that MMP-2 created myocardial fibrosis.[35] Yasmin et al. indicated that MMP-2 was the cause of heart failure preserved ejection fraction.[36] As a result, elevated MMP-2 levels may cause diastolic dysfunction through increased fibrosis and stiffness.

Another finding was positive correlation between increased diameter of the ascending aorta and PA. Dilatation of the main PA has been demonstrated in BAV patients even in the absence of pulmonary valve disease.[23] Embryologically, the aorta and the PA share their origin in the sole outflow tract, the cono-

truncus.[37] Ross procedure and the complications that may follow suggest that the aorta may be affected by the pulmonary bed beside it, especially in bicuspid valve patients. Ross procedure is a method in which the pulmonary valve is used as autograft replacement for the aortic valve. The most frequent problem after Ross procedure in BAV patients is late dilatation of the autograft. BAV patients are known to exhibit neoaortic sinus dilatation and increase in diameter of the annulus after Ross procedure.[38] PA, which shares the same embryological origin with the aorta, might have the potential to exhibit the same intrinsic pathologies in BAV patients. In a another study comparing isolated BAV patients with control group it was demonstrated that elasticity of the PA was as abnormal as that of the aorta.[9]

Using PA stiffness index as a new, non-invasive parameter, it was determined that if distensibility of the PA is established as abnormal, ejection and acceleration times of the RV and PA would also be reduced.[39]

We did not find growth in diameter of the ascending aorta and PA stiffness very meaningful. Despite increase in PAD, pulmonary stiffness didn't change. This finding may have resulted from lack of standard cut-off value and not taking PAD into account when measuring stiffness. It is necessary to find a new, steady echocardiographic parameter for this area of focus. We considered that lack of change in PA stiffness values in our study might be connected to our quandary. Only new echocardiographic parameters that include PAD and longitudinal values would be able to shed light on this problem.

Another result of the present study was finding of decreased RV-SRS with increased dilatation of ascending aorta. To the best of our knowledge, RV systolic functions in the bicuspid aortic valve have not been evaluated so far. Santarpia et al. reported that compared to control group, BAV patients had lower LV longitudinal, circumferential, and radial strain.[40] RV systolic dysfunction has been demonstrated in patients with heart failure preserved ejection fraction.[41] It was suggested that increased LV pressure results in elevated PA wedge pressure, which in turn causes pressure overload for RV.[42] Our findings indicate that RV and PA parameters in BAV patients may be important in terms of clinical monitoring and that their prognostic value should also be investigated.

Limitations

The most important limitation of our study was relatively small number of patients. In addition, role of MMP-2, if any, was not investigated. Aortic elasticity was studied only with echocardiographic parameters. Another limitation was that, although small in number, patients diagnosed with hypertension and diabetes mellitus were included in the study and an isolated group was not created by ruling out co-morbidities. As the other limiting parameters, left atrial volume and tricuspid regurgitant jet were not evaluated in definitions of diastolic dysfunction. Although numerous parameters were used for RV function, tricuspid regurgitant jet was not assessed and pulmonary arterial pressure was not specified in many patients due to missing data.

Conclusion

In this study, we concluded that ascending aorta diameter is positively correlated with PAD in BAV patients and that RV strain rate and LV diastolic parameters are affected before development of the valve disease.

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