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Evaluation of the Effect of Transcatheter Aortic Valve Implantation on Left Ventricular Function by 4-Dimensional Echocardiography

Transkateter Aort Kapağı İmplamantasyonunun Sol Ventrikül Fonksiyonlarına Etkisinin Dört Boyutlu Ekokardiyografi ile Değerlendirilmesi

ABSTRACT

Objective: Beneficial effects of transaortic valve implantation on left ventricular hemodynamics and prognosis of patients have been demonstrated. Although left ventricular systolic and diastolic function following transaortic valve implantation procedure have been examined in previous studies, 4-dimensional echocardiographic parameters have not been extensively studied, especially in patients with preserved ejection fraction aortic stenosis. In our study, we planned to evaluate the effect of transaortic valve implantation on myocardial deformation using 4-dimensional echocardiography.

Methods: A total of 60 consecutive patients who underwent transaortic valve implantation for severe aortic stenosis with preserved ejection fraction were prospectively enrolled in the study. Standard 2-dimensional echocardiography and 4-dimensional echocardiography were performed in all patients before and 6 months after the transaortic valve implantation procedure.

Results: Six months after valve implantation, significant improvement was observed in global longitudinal strain ($P < 0.001$), spherical circumferential strain ($P=0.022$), global radial strain ($P=0.008$), and global area strain ($P < 0.001$). In the regression analysis, global area strain and absence of diabetes mellitus were determined as independent predictors to show a 10% increase in the left ventricular ejection fraction.

Conclusions: In patients with preserved ejection fraction who underwent transaortic valve implantation, left ventricle deformation parameters have improved after 6 months, especially by using 4-dimensional echocardiography. The use of 4-dimensional echocardiography should be more common in daily practice.

Keywords: 4D-Strain, cardiac function, TAVI

ÖZET

Amaç: Transaortik kapak implantasyonunun (TAVI) sol ventrikül hemodinamiği ve prognozu üzerine yararlı etkileri gösterilmiştir. Önceki çalışmalarda TAVI prosedürünü takiben sol ventrikül sistolik ve diyastolik fonksiyonu incelenmiş olmasına rağmen, özellikle korunmuş ejeksiyon fraksiyonlu aort stenozu olan hastalarda dört boyutlu ekokardiyografik (4DE) parametreler kapsamlı bir şekilde çalışılmamıştır. Çalışmamızda TAVİ'nin miyokardiyal deformasyon üzerindeki etkisini 4DE kullanarak değerlendirmeyi planladık.

Yöntem: Korunmuş ejeksiyon fraksiyonlu ciddi aort stenozu nedeniyle TAVİ uygulanan ardışık toplam 60 hasta prospektif olarak çalışmaya alındı. Tüm hastalara TAVI işleminden önce ve 6 ay sonra standart iki boyutlu ekokardiyografi (2DE) ve 4DE uygulandı.

Bulgular: Kapak implantasyonundan 6 ay sonra, global longitudinal strain ($P < 0.001$), global sirkümferansiyel strain ($P=0.022$), global radyal strain ($P = 0.008$) ve global area strainde ($P < 0.001$) anlamlı iyileşme gözlendi. Regresyon analizinde, diabetes mellitus olmaması ve global area strain sol ventrikül ejeksiyon fraksiyonunda %10'luk bir artış göstermek için bağımsız belirleyiciler olarak belirlendi.

Sonuç: TAVİ uygulanan korunmuş ejeksiyon fraksiyonu olan hastalarda özellikle 4DE kullanımı ile 6 ay sonra sol ventrikül deformasyon parametrelerinde düzelme olmuştur. 4DE kullanımı günlük pratikte daha yaygın olmalıdır.

Anahtar Kelimeler: 4D-Strain, Kardiyak fonksiyon, TAVI

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Aortic stenosis (AS) is the most common valvular heart disease, and its incidence increases with age.[1] Aortic stenosis often causes left ventricular hypertrophy (LVH) and remodeling.[2,3] Transcatheter aortic valve implantation (TAVI) is an increasingly useful alternative to surgery for symptomatic patients at intermediate or high risk for surgery.[4] Hemodynamic and structural changes in ventricular structure and function after TAVI is still an area of interest. In previous studies, patients and procedural factors that may affect ventricular remodeling after TAVI were evaluated using conventional methods.[5,6]

Recent studies have shown that 4-dimensional speckle tracking echocardiography (4DSTE) could be a more reliable and sensitive test to evaluate subclinical left ventricle (LV) function in patients with various clinical disorders.[7,8] Four-dimensional speckle tracking echocardiography has the advantage to overcome the limitation of plane dependence during 2-dimensional (2D) imaging by obtaining practical 3-dimensional (3D) data simultaneously.[9,10]

The aim of our study is to evaluate the changes in left ventricular function after TAVI with 4DSTE in patients with preserved ejection fraction (EF), which is a method that could determine subclinical changes at an earlier point than 2D imaging.[11,12]

Materials and Methods

A total of 60 consecutive patients with preserved EF between August 2018 and May 2020 treated with self-expandable valves (Medtronic evolute-R or Abbott Portico valve) due to severe AS were prospectively included in the study. Three patients were excluded from the study because of poor image quality and 5 patients were lost at the 6th-month follow-up. Aortic valve prosthesis was retrogradely placed in all patients through transfemoral access. The study was performed according to the guidelines of the Declaration of Helsinki. The study protocol was approved by Malatya Clinical Research Ethics Committee (decision number: 2017/125; date: 20.12.2017). Written informed consent was obtained from all the participants included in the study. We performed standard 2D and 4D transthoracic echocardiography before and 6 months after the TAVI procedure to all patients. Functional response to TAVI after follow-up was defined as a 10% improvement in 3D left ventricle ejection fraction (LVEF) based on previous studies and available data on patients receiving cardiac resynchronization therapy.[13] Patients were divided into 2 groups based on real-time 3D LVEF increase of 10% or more (n=18) and not (n=42). Age, gender, EuroSCORE, hypertension (HT), diabetes mellitus (DM), history of stroke, coronary artery disease, dyslipidemia, chronic obstructive pulmonary disease, chronic renal disease, pacemaker status, New York Heart Association class, NT-Pro BNP level, waist circumference, smoking status, blood pressure, body mass index, and heart rate of all patients were evaluated and recorded.

Two-Dimensional and Doppler Echocardiography

Echocardiographic examinations of the participants were performed using the Vivid E95 system (GE Healthcare, Oslo,

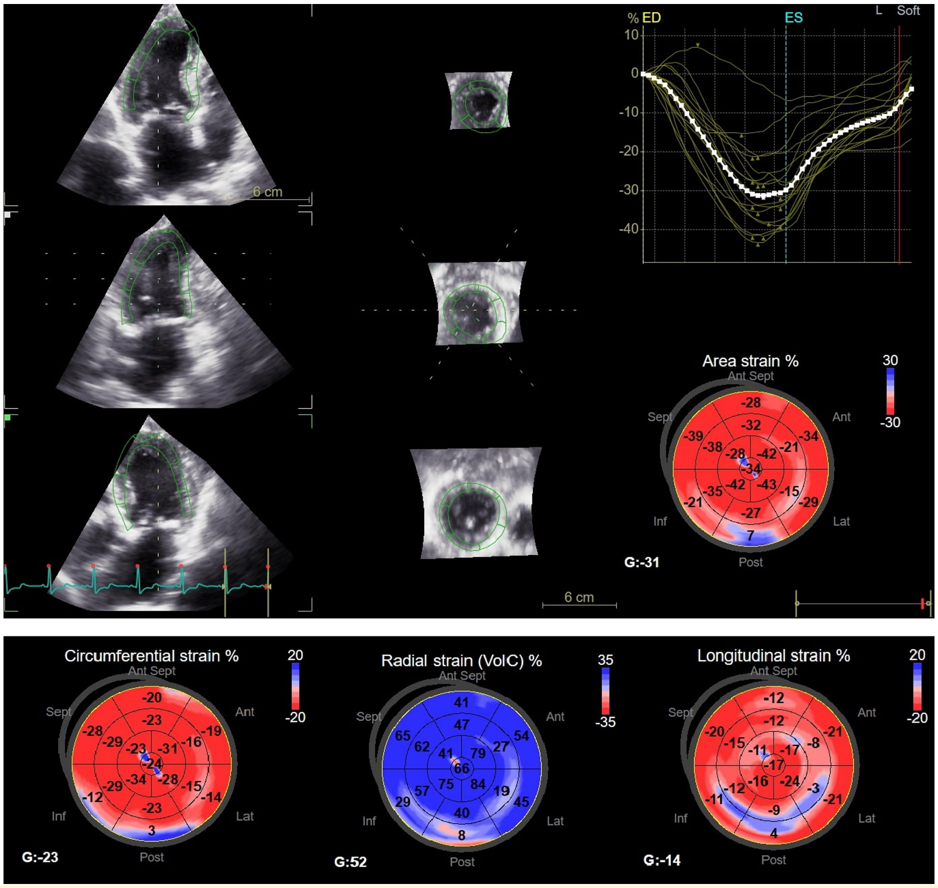

Figure 1. Four-dimensional (4D) speckle tracking echocardiography showing the measurements of the left ventricular global area strain (GAS), global circumferential strain (GCS), global radial strain (GRS), and global longitudinal strain (GLS)

Norway). All examinations were performed by 2 cardiologists blinded to clinical data, and the data were evaluated as recommended by the American/European communities. Two-dimensional imaging, pulsed wave, continuous wave, and color Doppler evaluations were performed using standard techniques.[14,15] Interventricular septal thickness (IVST), posterior wall thickness (PWT), LV end-diastolic dysfunction (LVDD), and Left ventricle sistolic diameter (LVDS) were measured by M-Mode method. Transmitral flow velocities (E and A) were measured by pulsed-wave Doppler from the apical 4-chamber view and the E/A ratio was calculated. Mitral annular velocities were measured by tissue Doppler imaging. Early diastolic velocity (Em) was measured from the septal and lateral annulus and averaged. The average Em value was used to calculate the E/Em ratio. Left ventricle ejection fraction was calculated by Simpson's method. Left ventricle mass was calculated using the formula originally validated by Devereux et al.[16] Left ventricle mass index (LVMI) was defined as LV mass/body surface area (body weight × 0.425 × height × 0.725 × 0.007184).

Four-Dimensional Echocardiography

In the multi-cardiac cycle mode from the apical 4-chamber view, adjustments were made to allow breath-hold and full inclusion of the left ventricular cavity and walls in the image for at least 3 cardiac cycles, and a 4D full volume scan was performed.[17] The depth and width of the images were adjusted to cover the entire full volume of LV 4D image. The transducer was held in a fixed position, at a frame rate of > 25 frame/sec at all times. If the quality of the first image was poor, the full volume image was repeated. The images obtained were stored digitally for offline analysis [EchoPAC software workstation (4D Auto LVQ)]. Midpoint of the mitral valve annulus and apex in the 2 orthogonal apical views were taken as reference points. Left ventricle mass measurement was made as follows. The 3D volume was positioned to be cut longitudinally from the center axis LV range. Left ventricle ejection fraction was calculated using 4D Auto LVQ algorithm of the software. Myocardial and endocardial borders were manually adjusted to reduce the error rate. The 4D strain region was obtained by automatically drawing the endocardial and epicardial borders at the end of systole. In addition, strains of each LV segment were obtained with global longitudinal strain (GLS), global circumferential strain (GCS), global radial strain (GRS), and global area strain (GAS) software, which are the means of longitudinal, radial, and circumferential peak systolic values (Figure 1).

Statistical Analysis

Statistical Package for Social Sciences (SPSS 21.0; SPSS Inc., Chicago, Ill, USA) software was used for all statistical analyses. Continuous variables are expressed as mean ± standard deviation, while categorical variables are shown as percentages. Categorical variables were compared using Pearson's chi-square or Fisher's exact test. Direct correlations between continuous variables were assessed using Pearson's and Spearman's correlation analyses. Paired test was used to compare parameters before and after the TAVI procedure. Age, gender, DM, HT, hyperlipidemia, smoking, coronary artery disease, EuroSCORE, LVESD, LVEDD, LV mass index, left atrium (LA) volume index, *E/A*, *E/Em*, aortic valve area, systolic pulmonary arterial pressure (sPAB), stroke volume index (SVI), GLS, GCS, GRS, and GAS were included in the univariate analysis. To predict LVEF improvement, the parameters with $P < 0.05$ were included in the multiple logistic analysis. A P value < 0.05 was considered significant.

Results

Baseline demographic characteristics of 60 consecutive patients with EF greater than 50% between August 2018 and May 2020 are shown in Table 1. Mean age of the patients was 77.2 ± 5.3 years. Echocardiographic findings of the patients performed before and 6 months after the TAVI are given in Table 2. While LV mass index (139.2 ± 9.8 g/m^2 vs. 117.3 ± 10.8 g/m^2, $P < 0.001$), IVS (1.3 ± 0.4 cm vs. 1.0 ± 0.3 cm; $P < 0.001$), A wave velocity (76.1 ± 4.5 cm/s vs. 69.7 ± 3.8 cm/s; $P < 0.001$) decreased, and E wave velocity (54.3 ± 4.5 cm/s vs. 58.4 ± 4.1 cm/s; $P <$ 0.001), SVI (32.3 ± 2.1 mL/m^2 vs. 33.1 ± 2.0 mL/m^2, $P < 0.001$), and 3D LVEF (58.1 ± 2.0 vs. 62.7 ± 4.3; $P < 0.001$) significantly increased. Comparing basal and 6 months values, GLS (−15.0 ± 1.3 vs. −16.1 ± 1.4; $P < 0.001$), GCS (−19.5 ± 1.7 vs. −18.7 ± 1.6; $P=0.022$), GRS (46.6 ± 3.2% vs. 48.1 ± 2.6%; $P=0.008$), and GAS (−25.6 ± 3.0% vs. −28.0 ± 2.9%; $P < 0.001$) values were found to be statistically different.

Table 1. Baseline Demographic and Clinical Data of Study Patients (n=60)

Age (years ± SD)	77.2 ± 5.3
Gender (female) (%)	27 (45.0)
Body mass index (kg/m^2)	25.3 ± 5.2
EuroSCORE	14.1 ± 2.2
Hypertension, n (%)	47 (78.3)
Diabetes mellitus, n (%)	33 (55.0)
History of stroke, n (%)	2 (3.4)
Coronary artery disease, n (%)	26 (43.4)
Smoking, n (%)	13 (21.7)
Dyslipidemia, n (%)	26 (43.4)
COPD, n (%)	16 (26.7)
Chronic renal disease, n (%)	4 (6.7)
Pacemaker, n (%)	17 (28.3)
Bicuspid valve, n (%)	8 (13.3)
NYHA class (%)	-
I, n (%)	15 (25)
II, n (%)	39 (65.1)
III, n (%)	6 (13.3)
IV, n (%)	
NT-Pro BNP (pg/mL)	702 (112-2432)
SBP (mm Hg)	134 ± 9.7
DBP (mm Hg)	77 ± 10.9
Implanted valve size	25.9 ± 1.2

COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

Table 2. Echocardiographic Changes at Baseline and After TAVI

	Before TAVI	After TAVI	P
Peak aortic valve gradient (mmHg)	75.2 ± 23.2	13.3 ± 3.0	**<0.001**
Mean aortic valve gradient (mmHg)	45.9 ± 14.9	7.3 ± 2.0	**<0.001**
sPAB (mmHg)	47.7 ± 11.0	45.7 ± 10.3	**<0.001**
2D LVEF (%)	58.7 ± 4.3	61.1 ± 4.3	**<0.001**
LVESD (mm)	35.8 ± 3.7	36.7 ± 3.8	0.106
LVEDD (mm)	50.5 ± 4.0	51.2 ± 3.8	0.219
LV mass index (g/m^2)	139.2 ± 9.8	117.3 ± 10.8	**<0.001**
LA volume index (ml/m^2)	47.9 ± 17.0	43.2 ± 7.9	0.073
E wave (cm/s)	54.3 ± 4.5	58.4 ± 4.1	**<0.001**
A wave (cm/s)	76.1 ± 4.5	69.7 ± 3.8	**<0.001**
Em (cm/s)	8.87 ± 0.4	8.98 ± 1.0	0.700
SVI (mL/m^2)	32.3 ± 2.1	33.1 ± 2.0	**0.018**
3D LVEF %	58.1 ± 2.0	62.7 ± 4.3	**<0.001**
GLS %	−15.0 ± 1.3	−16.1 ± 1.4	**<0.001**
GCS %	−19.5 ± 1.7	−18.7 ± 1.6	**0.022**
GRS %	46.6 ± 3.3	48.1 ± 2.6	**0.008**
GAS %	−25.6 ± 3.0	−28.0 ± 2.9	**<0.001**

The bold values indicate a statistically significant difference between groups. Data are expressed as mean ± SD.
3D, three-dimensional; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; sPAB, systolic pulmonary artery pressure; SVI, stroke volume index; SD, standard deviation; TAVI, transcatheter aortic valve implantation.

The comparison of the groups with and without improvement of 10% or more in 3D LVEF is shown in Table 3. The mean age (*P*=0.018) and E/Em ratio (*P*=0.005) were lower in the group with increased EF. The group with a 10% or more improvement in 3D LVEF had a lower rate of DM (*P*=0.001). Global longitudinal strain (14.7 ± 1.2% vs. 15.5 ± 1.4%; *P*=0.034), GCS (−17.9 ± 1.7% vs. −18.6 ± 1.7%; *P*=.139), and GAS (−24.3 ± 2.1 % vs. −28.7; ± 2.6%; *P* < 0.001) had higher wavelengths. In the regression analysis, absence of DM and GAS were observed to be independent strong predictors to show a 10% increase in the LVEF obtained by 3DE (Table 4). Intra- and inter-observer variability for GAS was 5.1% (Interclass correlation coefficient [ICCs] 0.901) and 6.2% (ICCs 0.851), respectively.

Discussion

In our study, we evaluated left ventricular function with 4DE before and 6 months after TAVI in patients with aortic stenosis, who had preserved EF. In addition to favorable effects on systolic pulmonary artery pressure and LV mass index, significant increases were observed in 3D LVEF, GLS, GAS, GRS, and GCS, 6 months after the procedure. Also, it has been shown that higher GAS and the absence of DM history are predictive factors for improvement in 3D LVEF.

Table 3 Comparison of Those With and Without a 10% Improvement in 3D LVEF After TAVI

	Without 10% Improvement	With 10% Improvement	P
Age (year)	78.3 ± 5.0	74.8 ± 5.3	**0.018**
Gender (female), n (%)	19 (45.2)	14 (77.8)	**0.020**
Diabetes mellitus, n (%)	29 (69)	4 (22.2)	**0.001**
Hypertension, n (%)	34 (81.0)	13 (72.2)	0.504
Smoking, n (%)	9 (21.6)	4 (22.2)	0.427
Coronary artery disease, n (%)	21 (50)	5 (27.8)	0.157
EuroSCORE	14.1 ± 2.2	13.9 ± 2.4	0.554
LVESD (mm)	35.3 ± 3.0	36.9 ± 4.9	0.129
LVEDD (mm)	50.2 ± 2.9	51.2 ± 5.5	0.375
LV mass index (g/m^2)	139.3 ± 8.7	138.7 ± 12.5	0.846
LA volume index (ml/m^2)	47.6 ± 18.3	48.7 ± 13.6	0.820
E/A ratio	0.71 ± 0.06	0.70 ± 0.1	0.720
E/Em ratio	6.3 ± 0.5	5.7 ± 0.9	**0.005**
Aortic valve area (cm^2)	0.84 ± 0.3	0.91 ± 0.4	0.486
sPAB (mmHg)	47.0 ± 11.4	49.4 ± 10.1	0.445
SVI (mL/m^2)	32.1 ± 1.9	32.7 ± 2.4	0.257
GLS %	−14.7 ± 1.2	−15.5 ± 1.4	0.034
GCS %	−17.9 ± 1.7	−18.6 ± 1.7	0.139
GRS %	46.3 ± 3.0	47.4 ± 4.0	0.247
GAS %	−24.3 ± 2.1	−28.7 ± 2.6	**<0.001**

The bold values indicate a statistically significant difference between 2 groups. Data are expressed as mean ± SD.
3D, three-dimensional; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; sPAB, systolic pulmonary artery pressure; SVI, stroke volume index; SD, standard deviation; TAVI, transcatheter aortic valve implantation.

Table 4 Univariate Analysis and Independent Predictors for 10% Increase in 3D LVEF in Multiple Logistic Regression Analysis

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR 95% CI	P
Age	0.875 (0.778-0.983)	0.025		
Gender	4.237 (1.134-15.034)	0.023		
Diabetes mellitus	0.128 (0.035-0.465)	0.002	3.447 (1.318-7.480)	0.033
E/Em ratio	0.195(0.051-0.745)	0.017		
GLS %	1.517 (1.013-2.270)	0.043		
GAS %	3.189 (1.741-5842)	<0.001	1.255 (1.322-9.302)	0.012

3D, three-dimensional; GAS, global area strain; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction.

Aortic stenosis is characterized by LV pressure overload, which may lead to LV hypertrophy and impaired coronary flow reserve.[18,19] These changes can cause subendocardial ischemia even in the absence of epicardial coronary artery disease and over time affect systolic and diastolic functions.[19] In clinical practice, TAVI is performed for symptomatic patients at high surgical risk. Benefits of TAVI in terms of hemodynamic improvement and reverse LV remodeling are significant.[20] Studies have shown that left ventricular GLS is impaired in patients with AS with preserved EF and is an independent predictor of major cardiac events.[21] In another study, GLS values obtained before TAVI were observed to be predictors of improvement in LV function in long-term follow-up.[20] Alenezi et al[22] found that there was a significant improvement in GLS after TAVI compared to before TAVI. Longitudinal, circumferential, radial, and area of strain can be obtained by real-time 3D STE reconstruction using 4D STE. Four-dimensional echocardiography was introduced because it overcomes the limitation of plane dependence during 2D strain imaging and is more useful for obtaining simultaneous 3D strain data.[9,10] In a study comparing 4D Magnetic resonance (MR) with 2DE and 4DE on rats, it was shown that the correlation between 4D echocardiography and magnetic resonance imaging was better than 2D.[12] In our study, strain parameters were obtained using 4DE, which is easier to use and more reliable compared to 2D. In our study, in accordance with previous studies, GLS was observed to improve significantly 6 months after TAVI.

Global area strain determination using 4D STE, which cannot be obtained with 2D STE, could be a more sensitive marker demonstrating subendocardial dysfunction. Global area strain (also called area change rate), with its longitudinal and circumferential strain components, is of interest as a new parameter.[9] This is more sensitive to changes in regional distortion and can reduce tracking error due to higher signal-to-noise ratio compared to GLS and GCS. In a study, it was shown that the correlation of GAS with pro-BNP and disease duration was better than GLS in Sjögren's syndrome patients.[23] In our study, it was observed that GAS improved significantly 6 months after the treatment.

Left ventricular mass index has been shown to be associated with mortality and morbidity in patients with AS.[24] Again, it was observed that the rate of increase in the LV mass index level was very important.[25] In our study, it was observed that the LV mass index decreased significantly after TAVI. Various studies have shown that there is a change in EF at different rates (3%-20%) after TAVI. Similarly, age, female gender, absence of DM, baseline E/*Em,* and GAS were found to be significantly different when comparing patients who had a 10% increase in EF after TAVI with those without improvement.[20,21] In our study, it was determined that GAS value, which could not be obtained by conventional 2D echocardiography, was a strong independent predictor of improvement in 3D-LVEF.

Conclusions

In our study, it was observed that there was a significant improvement in 2D LVEF and 3D LVEF and 4D deformation parameters after TAVI. It was shown that GAS obtained before the procedure was a predictor of improvement in 3D LVEF. Therefore, evaluation with 4D STE may be helpful in predicting patients whose EF may improve after TAVI.

Study Limitations

1. Our study is a single-center study with a limited sample size.
2. Patients with low EF were not included in the study. The extent of the changes in this patient group was not observed.
3. Four-dimensional speckle tracking echocardiography also relies on good image quality, and 4 patients were excluded because of inadequate images.
4. Echocardiographic evaluation at 6 months after transaortic valve implantation may be early to show improvement in cardiac functions. Long-term follow-up studies may provide more reliable data.
5. The use of a single type of self-expandable valve is a limitation in our study.

Ethics Committee Approval: Ethics committee approval was received for this study from Malatya Clinical Research Ethics Committee(decision number: 2017/125; date: 20.12.2017).

Informed Consent: The written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.B.; Design – A.B., J.A.; Supervision – J.A., M.C., N.E.; Fundings - M.C., N.E., M.C., F.G.; Materials – M.C., F.G.; Data Collection and/or Processing – Z.U.; Analysis and/or Interpretation – Z.U.; Literature Review – Ş.H.; Writing – Ş.H.; Critical Review – H.T.

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