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Echocardiographic evaluation of aortic elasticity parameters in aortic stenosis patients with preserved ejection fractions undergoing transcatheter aortic valve implantation

Adil Bayramoglu[a], Hakan Tasolar[a,*], Siho Hidayet[a], Zeynep Ulutas[a], Julide Akaycan[a], Mehmet Cansel[a], Necip Ermis[a], Yucel Karaca[b], Yakup Yigit[a], Hasan Pekdemir[a]

[a] *Inonu University, Faculty of Medicine, Department of Cardiology, Malatya, Türkiye*
[b] *Elazig Fethi Sekin City Hospital, Clinic of Cardiology, Elazig, Türkiye*

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Abstract

Aim: Aortic stiffness is an important risk factor that reflects the mechanical tension and elasticity of the aorta and predicts cardiovascular mortality and morbidity. However, it has been found that aortic stiffness contributes to both symptom burden and clinical outcomes in patients with aortic stenosis (AS). In our study, we aimed to evaluate the effect of transcatheter aortic valve implantation (TAVI) on aortic elasticity parameters by echocardiography in patients with severe aortic stenosis, especially with preserved ejection fraction.

Materials and Methods: A total of 55 consecutive patients with symptomatic severe AS who underwent TAVI were included in the study. Demographic data, echocardiographic and aortic elasticity measurements of all patients were measured before and 6 months after the procedure. To evaluate the elastic properties of the aorta, aortic strain, distensibility and stiffness index were calculated.

Results: Left ventricular mass index (LVMI) ($p < 0.001$) and aortic stiffness ($p < 0.001$) were decreased, while aortic strain ($p < 0.001$) and aortic distensibility ($p < 0.001$) were found to be increased in the measurements performed at 6 months after TAVI. In the regression analysis, age and LVMI were found to be independent predictors for predicting improvement in aortic stiffness; on the other hand, LVMI also independently predicted the increase in aortic distensibility.

Conclusion: Improvement in aortic elastic properties and left ventricular functions were found in patients who underwent TAVI. Age and LVMI were observed to predict the improvement in stiffness and distensibility of the aorta in patients undergoing TAVI, especially in AS patients with preserved ejection fraction.

Introduction

Aortic stiffness reflects the mechanical stress and elasticity of the aorta and is an important risk factor for cardiovascular mortality and morbidity [1]. Increased aortic stiffness or decreased distensibility could be used as indicators of diffuse atherosclerotic involvement of the vascular system [2]. Evaluation of the mechanical properties of the aorta with non-invasive methods provides great benefit in the early diagnosis of atheroma [3]. Aortic elasticity parameters can be evaluated with three basic measurements based on aortic structure, hemodynamics, and tissue motion [4].

Aortic valve stenosis (AS), with an increasing incidence, is one of the most common valvular diseases in advanced age. In recent years, as an alternative to classical aortic valve surgery, transcatheter aortic valve implantation (TAVI) has been used in the treatment of high-risk patients for cardiovascular surgery [5]. However, the associations between aortic stenosis and increased aortic stiffness have been proven, leading to the theory that aortic stiffness can contribute to both symptom burden and clinical outcomes in this population [6, 7].

Studies on aortic stiffness and distensibility are insufficient for patients undergoing TAVI in the literature. Although the data of aortic stiffness in patients undergoing TAVI are early results, especially with B- and M-Mode measurements, which is a fast and easy-to-apply method [8], the number of patients in another study on follow-up results is also very limited [9]. In our study, we aimed to evaluate the effect of TAVI on aortic elasticity parameters

*Corresponding author:
Email address: hakantasolar@gmail.com (Hakan Tasolar)

by echocardiographically with short-term follow-up in patients with severe AS, especially with preserved ejection fraction (EF).

Materials and Methods

A total of 55 consecutive patients with symptomatic severe AS who met the study conditions and underwent TAVI between December 2018 and April 2021 were included in this prospective case-control study.study. Procedures were planned for all patients before TAVI was agreed upon by the heart valve team. The procedure was performed under general or local anesthesia. Percutaneous closure device was used in patients under local anesthesia [Perclose ProGlide system (Abbott Vascular, CA, USA)]. Self-expandable valves (medtronic evolute R or Abbott Portico valve) were implanted using standard protocols during the TAVI procedure in our study [10,11]. A balloon aortic valvuloplasty was performed before or after valve implantation, under rapid ventricular pacing if necessary. The bioprosthetic valve was then transfemorally placed in the native aortic valve position. Valve selection was left to the operator's preference. Patients under 65 years of age, patients with heart failure (EF $<$ %40), bicuspid aortic valve; those with pre-existing severe aortic insufficiency, patients with a history of percutaneous balloon valvuloplasty or surgical aortic valve repair/replacement/plastyand known aortopathy were excluded from the study.

Written informed consent was obtained from all patients before enrollment in the study. The study was approved by the local ethics committee and was conducted in accordance with the Helsinki Declaration. According to the power analysis results, at least 25 participants are required to work with 80% test power at 5% alpha level to determine 0.05 effect size.

Echocardiographic evaluation

All patients were evaluated by using Vivid S60 echocardiography device (Vivid S60, GE Vingmed Ultrasound, Horten, Norway) 3.5 MHz probe in the left lateral position. Detailed echocardiographic evaluation and elastic properties of the aorta were measured one week before TAVI and 6 months after TAVI procedure. All images were stored in a special system for echocardiographic analysis called the workstation (EchoPAC, version 202, GE Health-care, Waukesha, WI, USA). All examinations were performed by two cardiologists who were blind to clinical data (HT, AB).

The patients were monitored during the echocardiographic evaluation. 2D, pulsed, continuous wave and color Doppler examinations were performed using standard techniques [12,13]. Interventricular septal thickness (IVS) and posterior wall thickness (PWT), left ventricular (LV) end-diastolic (LVVD) and end-systolic dimensions (SVDs) were measured by M-Mode method. To calculate the mass of the SoV and LV mass index (LVMI) was calculated using the formula LV mass / BSA (body weight x 0.425 x height x 0.725 x 0.007184) validated by Devereux et al. [14]. Transmitral flow waves (E and A) were measured by flow Doppler during apical four-chamber imaging. Mitral annular velocities were measured by tissue Doppler imaging. Early diastolic velocity (Em) was measured separately from the septal and lateral annulus and averaged. The average Em value was used to calculate the E / Em ratio. Aortic regurgitation ratio was also calculated with color and CW doppler echocardiography according to the current guidelines. The LV ejection fraction (EF) was calculated by Simpson method [12, 13].

Measurement of aortic elasticity parameters

The diameters of the aorta were measured in the most distal part of the aortic root (approximately 3 cm above the aortic valve). Two-dimensional M-Mode transthoracic echocardiography data were recorded simultaneously with the electrocardiogram in the left parasternal long axis view. Before and after treatment measurements were made at the same distance from the aortic root. The aortic systolic diameter (AoS) was measured just before the end of the T wave on the ECG, while the aortic diastolic diameter (AoD) was measured at the peak of the QRS complex at the end of diastole.

At the same time, systolic (SBP) and diastolic (DBP) blood pressures were measured from the left brachial artery by sphygmomanometry within minutes of echocardiographic examination. Korotkoff sounds were used to describe SBP and DBP (phase-I, the emergence of the first sound, and phase-V, the disappearance of the sounds). The patients were kept in the supine position for 10 minutes before the examination. Subjects did not use tobacco, food, tea or coffee for 12 hours prior to assessment, and did not use any anti-hypertensive drugs for 24 hours.

Aortic strain, aortic distensibility and aortic stiffness index were calculated using the following formulas to evaluate the elastic properties of the aorta as described previously [7].

Aortic strain = 100 (AoS - AoD) / AoD,

Aortic distensibility = 2 x (AoS - AoD) / [AoD x (SBP - DBP)],

Aortic Stiffness Index (β) = ln (SBP / DBP) / [(AoS - AoD) / AoD].

Analysis of the data of 20 randomly selected patients was repeated by a second observer (HT, AB) to calculate inter-observer variability, and by the same observer (HT) 2 weeks later to calculate intra-observer variability, blindly to the demographic data of the patients.

Statistical analysis

Statistical analysis was performed using JASP (version 0.14.1, JASP Team, 2019; jasp-stats.org) and JAMOVI (version 1.6.2, the jamovi project, Sidney, Australia) software programs. Distribution of the data was determined using the Shapiro-Wilk test. Continuous variables were given as mean ± standard deviation or IQR, and categorical variables as numbers and percentages. Differences between groups were evaluated with t-test or Mann-Whitney U test for continuous variables, and Chi-square or Fisher's exact test for categorical variables. Differences between data before and after 6 months were evaluated using the paired-t test or the Wilcoxon test. To evaluate the correlation between data, Pearson's or Spearman analysis was performed according to the data type. Age, BMI, E / Em ratio, EF, LVMI, Valve type, atrial fibrillation and paravalvular aortic insufficiency were taken into univariate analysis to determine independent predictors of aortic stiffness and distensibility. Variables with p value < 0.05 were included in multiple linear regression analysis. Blant-Altman analysis and ICC tests were performed to evaluate intra and inter-observer variability, reliability and agreement of the measurements. Intra-class correlation coefficients for the absolute fit of single measures were estimated using a two-way mixed-effect model. A value of $P < 0.05$ was considered statistically significant.

Results

Fifty-five consecutive transcatheter heart valve procedures that met the study criteria were included during the study period. Baseline demographic data of the patients included are given in Table 1.

56.4% of the patients were male and the mean age was 76.3 ± 5.5. Operations were mostly performed under conscious sedation. Fifteen patients had balloon prediltation before valve implantation and 8 patients also had post-dilatation with aortic balloon catheter.

Echocardiographic and aortic elasticity data of the patients performed before and 6 months after TAVI are given in Table 2.

In the measurements performed on the 6th month after the TAVI procedure, LVMI ($p < 0.001$), A wave ($p < 0.001$), AoS ($p = 0.038$), AoD ($p < 0.001$) and aortic stiffness ($p < 0.001$) were decreased, on the other hand, the E wave ($p < 0.001$), stroke volume index ($p = 0.018$), EF ($p < 0.001$), aortic strain ($p < 0.001$) and aortic distensibility ($p < 0.001$) were found to be statistically significantly increased.

A positive significant correlation was found between the amount of improvement in aortic stiffness and age, E/Em, EF and LVMI ($p < 0.05$ for all) (Table 3).

Negative correlation was also found between in improvement of aortic distensibility with age, E/Em, and LVMI, on the other hand, a positive significant correlation was found with EF ($p < 0.05$ for all) (Table 4).

In multiple linear regression analysis to identify independent predictors affecting aortic stiffness, age ($p = 0.001$) and LVMI ($p = 0.028$) were found to be the independent predictors for improvement in aortic stiffness (Table 3). In the multiple linear regression analysis performed to determine the independent predictors affecting aortic distensibility, it was also found that the LVMI ($p = 0.024$) was an independent predictor for predicting the increase in aortic distensibility (Table 4).

Both intraobserver and interobserver reproducibility of aortic stiffness index and aortic distensibility measurements was excellent. For the aortic stiffness index, the mean intra-observer ICC value was 0.986 and the inter-observer ICC value was 0.980, while for aortic distensibility, the mean intra-observer ICC value was 0.977 and the inter-observer ICC value was 0.946 (Table 5). Bland-Altman analysis also showed good agreement and low bias in both intra-observer and inter-observer measurements in terms of both aortic stiffness index and aortic distensibility measurements (Figure).

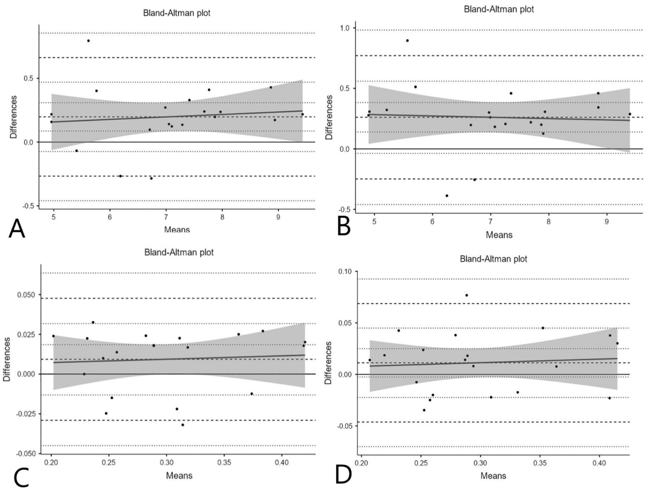

Figure 1. Bland-Altman plots show both intra- (A) and interobserver (B) good agreement and low bias for aortic stiffness, and intra- (C) and interobserver (D) good agreement and low bias for aortic distensibility.

Discussion

The principal findings of the present investigation were as follows; (i) the evaluation performed 6 months after the TAVI procedure showed improvement in left ventricular functions and elastic properties of the aorta, (ii) It was observed that the degree of improvement in aortic stiffness was predicted independently by age and pre-procedure LVMI, and improvement in aortic distensibility was also predicted by LVMI, (iii) Good agreement and low bias was found in aortic elasticity measurements, both in intraobserver and interobserver measurements.

Aortic stiffness and distensibility could be assessed using three basic measurements based on aortic structure, hemodynamics, and tissue motion. In general, structural-based measurements include B-Mode and M-Mode ultrasonographic measurements, tissue motion-based measurements include tissue Doppler and speckle tracking imaging, and finally hemodynamic-based measurements include color and speckled doppler imaging and pulse wave velocity measurements [7]. Although, hemodynamic-based measurements, especially aortic pulse wave velocity, are the gold standard in evaluating aortic stiffness, structural-based measurements can be preferred in daily cardiology practice because of their easy application and technical availability. There are many formulas in literature to measure aortic stiffness and distensibility using B-Mode and M-Mode ultrasonographic methods, in particular, correlation between blood pressure and changes in aortic diameter or wall thickness was used to reflect aortic stiffness [7, 15]. In our study, we used structural-based B- and M-Mode ultrasonographic methods to evaluate aortic stiffness and distensibility in patients who underwent TAVI. In addition, we found excellent agreement and reliability results for both intra- and interobservers measurement of the stiffness and distensibility parameters of the aorta in the ICC and Blant-Altman analyzes.

It is known that impairment in aortic elasticity is detrimental to coronary perfusion and is associated with fu-

Table 1. Demographic data of the patient population.

Age (years)		76.3±5.5
Gender (male) (n, %)		31 (56.4)
Body mass index kgm-2		25.3±5.2
Hypertension (n, %)		43 (78.2)
Diabetes mellitus (n, %)		32 (58.2)
History of stroke (n, %)		1 (1.8)
Coronary artery disease (n, %)Previous PCIPrevous CABG		24 (43.6) 8 (14.5)
Smoking (n, %)		19 (34.5)
Dyslipidemia (n, %)		31 (56.4)
COPD (n, %)		14 (25.5)
Chronic renal disease (n, %)		1 (1.8)
Atrial Fibrillation (n, %)		12 (21.8)
Pacemaker implantation (n, %)		15 (27.3)
NYHA functional class	I (n, %)	-
	II (n, %)	12 (21.8)
	III (n, %)	36 (65.5)
	IV (n, %)	7 (12.7)
Hb (mg/dL)		11.9±2.2
Creatinine (mg/dL)		1.05±0.63
NT-proBNP (pg/ml)		587 (112-2156)
LDL cholesterol (mg/dL)		103.1(46-241)
HDL cholesterol (mg/dL)		45.5 (35-66)
Triglyceride (mg/dL)		132.6(61-323)
EuroSCORE II (%)		7.55± 6.13
STS Mortality (%)		6.72±4.12
AVA (cm2)		0.81±0.11
Implanted valve size (mm)		25.6±1.4
Anesthesia (n, %)GeneralConscious sedation		4 (7.3) 51(92.7)
Valve type (n, %)Evolut RPortico		14(25.4) 41(74.6)
Paravalvular AR (n, %)		7 (12.7)

PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass grafting, AVA: Aortic valve area, AY: Aortic insufficiency.

ture cardiovascular events [16]. Therefore, measurements of aortic stiffness and distensibility are increasingly used as a prognostic indicator in clinical practice. The elastic properties of the aorta are regulated by the structure of the aortic wall, the autonomic nervous system, and the perfusion of the aortic wall through the vasa vasorum. In previous studies, in the evaluations made immediately after aortic valve surgery, it was shown that aortic elasticity was impaired due to damage to the vaso-vasorum and autonomic innervation in the aorta by clamps and manipulations [17-19]. It was shown in a study, with a limited number of patients, that this situation did not cause deterioration in aortic elasticity in the early period in patients who underwent TAVI [8]. In our study, we showed that this improvement in elastic properties, which was not seen in previous studies, changed significantly in the measurements performed 6 months after the TAVI procedure. In another study, Vizzardi et al. evaluated aortic elasticity parameters in TAVI patients with a low population of 15 patients [9], and found improvement in aortic elasticity parameters in accordance with our study. However, the fact that they did not perform multiple regression analysis

Table 2. Echocardiographic and aortic elasticity data of the patients measured before the procedure and at the 6th month

	Before TAVI	After TAVI	P value
2D Ejection Fractione (%)	58.7±4.3	60.1±3,6	< 0.001
LVESD (mm)	36.1±3.7	36.5±3.8	0.269
LVEDD (mm)	51.1±3.7	51.3±3.6	0.357
LV mass index (g/m2)	137.8±9.1	117.0±10.4	< 0.001
E wave (cm/s)	58.2±3.8	54.6±5.4	< 0.001
A wave (cm/s)	75.1±3.7	68.3±3.8	< 0.001
Em (cm/s)	8.8±0.4	8.9±1.0	0.733
E/Em ratio	6.6±0.4	6.2±0.9	0.007
Stroke volume index (mL/m2)	33.1±2.0	34.7±1.9	0.018
Systolic pulmonary artery pressure (mmHg)	48.9±11.0	45.8±10.4	< 0.001
Peak aortic valve gradients (mmHg)	75.5±20.7	13.9±3.4	< 0.001
Mean aortic valve gradients (mmHg)	46.2±12.4	7.7±1.9	< 0.001
Aortic systolic diameter (mm)	36.6±1.7	36.8±1.9	0.038
Aortic diastolic diameter (mm)	34.2±1.9	32.9±1.1	< 0.001
Systolic blood pressure (mmHg)	132.0±9.1	132.8±10.2	0.490
Diastolic blood pressure (mmHg)	77.0±10.4	78.1±9.1	0.569
Pulse pressure (mmHg)	55.8±5.4	54.1±13.7	0.357
Aortic strain (%)	7.3±2.8	12.0±6.1	< 0.001
Aortic stiffness	8.6±4.0	5.4±5.5	0.001
Aortic distensibility (×10—3 mmHg—1)	2.6±1.0	4.8±2.8	< 0.001

EF: Ejection fraction, LVESD: left ventricular end systolic size, LVEDD: left ventricular end-diastolic size.

Table 3. Univariate and multiple linear regression analysis of factors predicting aortic stiffness index

	Univariate Analysis		Multivariate Analysis			
	r	P value	β	OR	95%CI	P value
Age	0.595	< 0.001	0.499	0.412	0.791 − 0.207	0.001
BMI	0.129	0.349				
E/Em	0.439	0.001				
EF	-0.406	0.002				
LVMI	0.440	0.001	0.175	0.261	0.331 − 0.019	0.028
Valve type	0.082	0.554				
Paravalvular AR	-0.012	0.930				

AR: Aortic insufficiency, BMI: Body mass index, EF: Ejection fraction, LVMI: Left ventricular mass index.

affecting the aortic elasticity parameters in their studies and also included patients with low EF into their studies constitute major differences between our studies. In addition, the agreement and reliability analyzes on the aortic elasticity parameters that we did in our study were not included in their study. So, we also found that age and LVMI were the independent predictive factors affecting the improvement in aortic stiffness, and LVMI was the predictor of the aortic distensibility.

Age has an important role in the deterioration of aortic elastic properties. Decrease in aortic elasticity with increasing age is a known condition [21, 22]. Li et al. found that the stiffness of the ascending aorta increased and the distensibility decreased as the age progressed in a healthy population [23]. In another study conducted by Musa et al. observed that, unlike our study results, there was no improvement in aortic stiffness parameters 6 months after TAVI when compared with aortic surgery [24]. Cardiac

Table 4. Univariate and multiple linear regression analysis of factors predicting aortic distensibility

	Univariate Analysis		Multivariate Analysis			
	r	P value	β	OR	95%CI	P value
Age	-0.380	0.004				
BMI	-0.083	0.543				
E/Em	-0.287	0.034				
LV EF	0.281	0.037				
LVMI	-0.432	0.001	-0.009	-0.320	-0.016 – -0.001	0.024
Valve type	0.111	0.419				
Paravalvular AR	0.068	0.620				

AR: Aortic insufficiency, BMI: Body mass index, EF: Ejection fraction, LVMI: Left ventricular mass index.

Table 5. Reliability of aortic stiffness and distensibility measurements

	Intraobserver	Interobserver
Aortic Stiffness		
Coefficient of variation (%)	3.06	3.68
Cronbach α	0.981	0.978
ICC (%95 GA)	0.986 (0.917 – 0.996)	0.980 (0.824 – 0.995)
Aortic distensibility		
Coefficient of variation (%)	5.02	7.30
Cronbach α	0.977	0.946
ICC (%95 GA)	0.973 (0.925 – 0.990)	0.942 (0.850 – 0.977)

ICC = Intragroup correlation coefficient.

magnetic resonance imaging was also used as a method of evaluating aortic elasticity in this study. In another study, Goudzwaard et al. [25] stated that there was a significant improvement in the aortic stiffness index measurements, which they evaluated with the arterial pulse wave velocity, made immediately after the procedure in patients who underwent TAVI, and this improvement was more pronounced, especially in patients who had higher basal aortic stiffness index. In another study, Terentes-Printzios et al concluded that there was an increase in aortic stiffness after TAVI and this increase continued in the long term, which contradicted with previous studies [26]. In our study, we found a significant improvement in aortic elasticity characteristics in the 6th month after the TAVI procedure. We also found that age is an independent predictor for the recovery of aortic elastic properties after TAVI. The facts that the patients who underwent TAVI in our study were younger compared to previous studies, the patients' ejection fraction were normal, and the mechanical properties of the valves used could explain these differences.

LV hypertrophy is considered to be an adaptive response that keeps LV wall stress close to normal in response to increased afterload due to stenosis in the aortic valve in patients with AS. However, this adaptation mechanism disrupts the myocardium in the chronic process, causing changes in the ventricular mass and myocardial cellular structure that lead to the development of fibrosis. Previous studies have shown that high LV mass or the presence of a high LVMI is an independent predictor of increased cardiovascular morbidity and mortality in both the general population and in patients with AS [27, 28]. It was also found in previous studies that both surgical treatment and TAVI resulted in a decrease in the risk of cardiovascular events by causing a decrease in LVMI in this patient group [29, 30]. As in previous studies, it was observed in our study that LVMI, which is known to be associated with LV dysfunction, increased and significantly regressed 6 months after the procedure. In addition, it was shown that the LVMI measured before the procedure independently predicts the improvement in the elasticity parameters of the aorta.

The small number of patients and the short follow-up period are one of the most important limitations of our study. Another limitation may be that the elasticity of the aorta is not measured using the pulse wave velocity. Other limitations of our study are not using valves that can be opened with balloon and excluding patients with low EF from the study in patients with TAVI.

Conclusion

As a result aortic elastic properties and left ventricular functions were found to be improved after TAVI in our study. It was also observed that age and LVMI are predictors of improvement in stiffness and distensibility of the aorta in AS patients, especially with preserved EF, undergoing TAVI. To support our findings, randomized studies with more patients in which the elastic properties of the aorta are followed for a longer period are needed.

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Ethics approval

Ethical approval for this study was obtained from the Malatya Clinical Research Ethics Committee (Protocol code: 2017/125)

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