Predictors and Changes in Cardiac Hemodynamics and Geometry With Transcatheter Aortic Valve Implantation

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The introduction of transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of patients with severe aortic stenosis (AS). However, despite the great clinical success of TAVI, less is known about the cardiac hemodynamics and structural changes to post-TAVI. We analyzed patients with AS who had a transthoracic echocardiography at most 6 months before index TAVI and follow-up transthoracic echocardiography 9 to 18 months later, performed at Duke University Medical Center from 2012 to 2014. A total of 152 TAVI patients with a median age of 81 years (median interquartile range 74 to 86) were included. TAVI resulted in the reduction of left ventricle (LV) mass index (g/m^2), median (interquartile range) 130 (115 to 157) pre versus 106 (85 to 135) post, p <0.001; LV end-diastolic volume (ml) 127 (105 to 143) pre versus 120 (100 to 143) post, p = 0.013; and LV end-systolic volume (ml) 55 (38 to 77) pre versus 45 (40 to 65) post, p = 0.027. TAVI also significantly improved LV global longitudinal strain (%) −14.4 (−11.3, −15.5) pre versus −14.8 (−12.2, −16.6) post (p <0.001, respectively). Post-TAVI LV mass regression was predicted by baseline LV mass and LV global longitudinal strain whereas post-TAVI LV ejection fraction was predicted by baseline LV ejection fraction, LV mass, and post-TAVI paravalvular leak. In conclusion, TAVI results in significant cardiac hemodynamic, geometrical, and functional changes at approximately 1-year postprocedure for patients with AS. Better baseline myocardial structure and function leads to more reverse remodeling. **(Am J Cardiol 2019;123:813−819)**

Aortic stenosis (AS) frequently results in left ventricular (LV) hypertrophy and remodeling, which is independently associated with cardiac morbidity and mortality.[1] Transcatheter aortic valve Implantation (TAVI) is now an increasingly available, minimally invasive option for symptomatic patients at intermediate to high surgical risk.[2] However, outside the immediate perioperative period, hemodynamic and structural changes to ventricular structure and function post-TAVI are not completely understood. Patient- and procedure-related factors that could affect postoperative ventricular remodeling have not been investigated in detail. To test the hypotheses that LV outflow obstruction relief post-TAVI and significant increase in effective orifice area would result in favorable changes in LV geometry and function and that patient-related clinical, hemodynamic, and echocardiographic factors would predict these changes, we conducted a single-center observational study in a cohort of TAVI patients at high-volume tertiary medical center.

Methods

The study population was derived from the Duke Echocardiography Laboratory Database (DELD) which houses digitally archived echocardiographic images, echocardiographic reporting data, clinical information, and outcomes data on >135,000 unique patients. The setup of DELD has been previously described.[3] All patients who underwent TAVI at Duke University Medical Center over the time period of 2012 to 2014 were eligible for inclusion. Patients who underwent TAVI procedures were matched by key identifiers and procedural date with transthoracic echocardiography (TTE) study dates within DELD to define a baseline TTE exam as the study that most recently preceded the TAVI, noting that the baseline TTE could be no more than 6 months before the procedure date.

Subsequently, DELD was searched to find a corresponding follow-up TTE study that occurred from 9 to 18 months after the valve replacement procedure, noting that if more than 1 follow-up echo study fell into that time frame, the study closest to 9 months after the procedure would be chosen for the analysis. Exclusion criteria applied to the study population

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included history of previous valve surgeries, severe aortic regurgitation present on baseline TTE study, and poor image quality preventing rereading and interpretation of either the pre or follow-up TTE study. For the cohort of patients remaining in the final analysis, demographic, hemodynamic, and diagnosis data were merged with electronic health record sources including the cardiac catheterization database, ECGs, patient demographics, and diagnosis database.

Digitally archived pre- and post-TAVI TTEs were analyzed. A series of parameters reporting on LV hemodynamic load, LV diastolic, and systolic function were measured. A calculation of effective aortic orifice area (AVA), Valvulo-arterial impedance (Zva), LV mass index, calculated mitral valve area, mitral regurgitation quantitation, aortic regurgitation quantitation, assessment of diastolic function, left atrial volumes, and Simpson's biplane calculation of LV ejection fraction (LVEF) was performed using previously published American Society of Echocardiography guidelines.[4] LV global longitudinal strain (GLS) was calculated with vendor independent speckle tracking strain analysis software (TomTec 2D Cardiac Performance Analysis, Munich, Germany: REF- Version 4.6 software).

Baseline clinical and TTE characteristics were described. For categorical variables, counts and percentages were used, whereas medians and interquartile ranges (IQR) were used for continuous variables. Within patient, changes from pre- to postprocedure by TTE parameters (post-pre) were calculated and p values for significant change were determined using Wilcoxon signed rank test for continuous variables and McNemar's test for binary variables. Four TTE characteristics were chosen a priori to describe cardiac remodeling and function pre- and post-TAVI procedure. These characteristics included LVEF (%), AVA in centimeters (cm^2), AVA index (cm^2/m^2), LV mass, LV mass index (g/m^2), and LV GLS (%). We measured each of these parameters on both pre- and post-TAVI TTE. For each of these characteristics, we then calculated the change post−pre-TAVI as a measure of cardiac remodeling.

A series of exploratory simple linear regression analyses was applied separately to each of the previously mentioned 4 remodeling characteristics to evaluate unadjusted relations in changes in the TTE characteristics and baseline patient/TTE characteristics. Exploratory variables included demographic, patient, and procedural characteristics. These were compared and included age, race (white vs nonwhite), body mass index, New York Heart Association classification, EuroSCORE, glomerular filtration rate (GFR), systolic blood pressure, diastolic blood pressure during a procedure, hypertension, diabetes mellitus, previous myocardial infarction, chronic obstructive pulmonary disease, history of coronary artery disease, renal disease, left bundle branch block, type of valve (self-expanding vs balloon-expandable) used, and valve size in millimeters (mm). A significant level of $p < 0.10$ for inclusion was used for the stepwise procedure. The final linear regression model presents the independent predictors of change in TTE characteristics from among the candidate variables. All statistical analyses were conducted using SAS Version 9.4 (www.sas.com, Cary, North Carolina).

A waiver of informed consent was obtained for use of retrospective data. The Duke Institutional Review Board approved this study. This study was funded in part by an investigator-initiated Boston Scientific-Duke Strategic Alliance for Research grant award to ZS. Boston Scientific was not involved in the study design, the collection, analysis and interpretation of data, the writing of the report, or in the decision to submit the article for publication.

Results

The final study population included a total of 152 patients who underwent first TAVI from 2012 to 2014. Detailed patient flow chart diagram and a comparison between excluded and included patient's characteristics appear in the Supplemental Material (Figure A and Table A). The median age was 81 (median [IQR] 74 to 86) years and 64% were men. The median (IQR) EuroSCORE was 14.9 (8.5, 26.4) and cardiovascular risk factors were prevalent in the cohort Table 1. A total of 116 (76%) patients underwent self-expandable, whereas 36 (24%) had balloon-expandable valve replacement. Table 2 summarizes the changes in hemodynamics pre- and post-TAVI. Measured parameters indicated improvement in aortic valve area and relief of LV outflow tract (LVOT) obstruction post-TAVI, as would be expected.

Post-TAVI, significant changes to LV geometry, including LV mass, LV end-diastolic volume, and end-systolic volume was observed and summarized in Table 2. No

Table 1
Baseline characteristics of patients with transcatheter aortic valve implantation

Characteristic	Total (n = 152)
Women	55 (36.2)
Men	97 (63.8)
Age (years), median Interquartile range (IQR), number of missing cases (nmiss)	81.0 (74.5-86.0) 0
Race	
White	139 (92.1)
Black	8 (5.3)
American Indian	3 (2.0)
Multiracial	1 (0.7)
New York Heart Association (NYHA) class	
Not available	24 (24.0)
1	0 (0.0)
2	17 (17.0)
3	47 (47.0)
4	12 (12.0)
EuroSCORE, median (IQR) nmiss	14.9 (8.5-26.4) 0
Glomerular filtration rate ml/min/1.73 m2, median (IQR) nmiss	54.1 (39.8-67.9) 2
Systolic blood pressure (mm Hg), median (IQR) nmiss	127.0 (113.0-140.0) 15
Diastolic blood pressure (mm Hg), median (IQR) nmiss	65.0 (60.0-77.0) 15
Hypertension	80 (52.6)
Diabetes mellitus	32 (21.1)
Myocardial infarction	22 (14.5)
Pulmonary disease	8 (5.3)
Coronary heart disease	92 (60.5)
Renal disease	27 (17.8)
Pacemaker	22 (14.5)

Table 2
Changes in cardiac hemodynamics, function, and geometry with transcatheter aortic valve implantation

Characteristic	Baseline (n = 152)	1-year follow-up (n = 152)	p
Aortic valve area (cm^2), median median Interquartile range (IQR), number of missing cases (nmiss)	0.77 (0.57-0.89) 2	1.71 (1.26-2.31) 11	<0.001
Aortic valve area index cm, median (IQR) nmiss	0.4 (0.3-0.5) 6	0.9 (0.6-1.2) 16	<0.001
Peak aortic valve gradients (mm Hg), median (IQR) nmiss	72 (61-87) 5	14 (12-18) 2	<0.001
Mean aortic valve gradients, median (IQR) nmiss	42 (37-54) 0	7 (6-9) 1	<0.001
Peak aortic valve velocity, median (IQR) nmiss	106 (85-112) 0	40 (36-54) 1	<0.001
End-diastolic volume (ml), median (IQR) nmiss	127 (105-143) 0	120 (100-143) 1	0.013
End-systolic volume (ml), median (IQR) nmiss	55 (38-77) 0	45 (40-65) 1	0.027
Left ventricle ejection fraction (LVEF) (%), median (IQR) nmiss	57.1 (44.3-65.8) 0	58.8 (49.6-66.1) 1	0.081
LVEF <30%	10 (7%)	7 (5%)	0.042
LVEF 30%-40%	16 (11%)	5 (3%)	
LVEF 41%-51%	27 (18%)	38 (25%)	
LVEF ≥52%	98 (65%)	101 (67%)	
Interventricular septum thickness (cm), median (IQR) nmiss	1.4 (1.4-1.7) 0	1.3 (1.1-1.5) 0	<0.001
Posterior wall thickness (cm), median (IQR) nmiss	1.4 (1.2-1.5) 0	1.2 (1.1-1.3) 0	<0.001
End-diastolic diameter (cm), median (IQR) nmiss	4.5 (4.1-4.9) 0	4.3 (4.0-4.8) 0	0.022
Left ventricle mass (g), median (IQR) nmiss	255.2 (207.8-300.2) 0	185.5 (151.3-258.2) 0	<0.001
Left ventricle mass index (g/m^2), median (IQR) nmiss	130.1 (115.4-156.5) 4	105.8 (84.9-135.1) 5	<0.001
Stroke volume, median (IQR) nmiss	76.6 (58.9-91.4) 2	72.3 (61.1-91.8) 10	0.985
Stroke volume Index, median (IQR) nmiss	39.4 (31.5-49.9) 6	36.4 (30.8-48.7) 15	0.549
E/prime, median (IQR) nmiss	18.3 (13.8-20.0) 9	16.0 (11.1-21.3) 6	<0.001
E/e' ≤14	37 (26%)	52 (37%)	<0.001
E/e' >14	103 (74%)	88 (63%)	
Valvulo-arterial impedance (Zva) %, median (IQR) nmiss	4.1 (3.5-5.4) 42	4.0 (3.0-4.7) 33	<0.001
Global longitudinal strain (GLS) %, median (IQR) nmiss	14.4 (11.3-15.5) 0	14.8 (12.2-16.6) 2	<0.001
GLS >−16	126 (84%)	100 (67%)	<0.001
GLS ≤−16	24 (16%)	50 (33%)	
Left bundle branch block	5 (3.4%)	32 (21.1%)	
QRS duration, median (IQR) nmiss	104.0 (92.0-134.0) 5	118.0 (96.0-154.0) 0	<0.001
Left atrial volume (ml), median (IQR) nmiss	84.0 (56.0-100.0) 0	75.0 (61.0-97.0) 1	0.282
Deceleration time, median (IQR) nmiss	210.0 (170.0-270.0) 4	220.0 (180.0-250.0) 5	0.136

significant change was seen in LVEF. Statistically significant changes in LV diastolic function were observed with a reduction in the E/e' ratio and increase in E wave deceleration time post-TAVI (Table 2).

Table B (Supplementary Material) shows univariate relations between clinical characteristics and exploratory cardiac remodeling variables. After adjusting for other clinical and TTE variables, 4 multivariate models were derived with the exploratory cardiac remodeling variables as dependent variables.

Baseline AVA and LVEF predict change in AVA. Baseline AVA was significantly inversely correlated with AVA post-TAVI with smaller values of AVA at baseline resulting in larger decreases in AVA post-TAVI and smaller decreases in AVA for patients with larger baseline AVA (p <0.001). Patients with a normal LVEF at baseline had larger increase in AVA when compared with patients with reduced baseline LVEF post-TAVI (p = 0.035). Lower LVEF at baseline had smaller increase in AVA.

Although there was no significant change in median LVEF pre- and post-TAVI, there does appear to be evidence that post-TAVI have a higher LVEF (Table 2 and Figure 1A). Baseline LVEF, LV mass, and AVA predict significant change in LVEF post-TAVI. For example, patients with a normal LVEF at baseline do not have as much improvement in LVEF, whereas a patient with reduced LVEF at baseline had larger increase in LVEF post-TAVI, (p <0.001). Patients with LV mass >285 g at baseline had a significant inverse correlation with change in LVEF, such that patients with larger values of LV mass experience smaller changes in LVEF post-TAVI compared with patients with smaller values of LV mass at baseline (p = 0.017). Patients with moderate to severe paravalvular leak had less improvement in LVEF post-TAVI compared with the patients with trivial to mild paravalvular leak, (p = 0.042). Patients with a large AVA index at baseline had larger increase in LVEF post-TAVI when compared with a patient with a small value of baseline AVA index (p = 0.012).

In unadjusted analyses, there was a significant decrease in LV mass index from baseline (median = 130.1 g/m^2) to follow-up (median = 105.8 g/m^2) illustrating successful remodeling post-TAVI (Tables 2 and Figure 1B). Baseline LV mass index and LV GLS predict change in LV mass index. There was a significant inverse correlation between baseline LV mass index and change in LV mass index post-TAVI resulting in larger decreases in LV mass index post-TAVI in patients with smaller baseline LV mass index and smaller decreases in LV mass index post-TAVI with larger values of baseline LV mass index, (p <0.001). Interestingly, patients with a better LV GLS at baseline had larger decrease in LV mass index post-TAVI, when compared with a patient with a lower value of baseline LV GLS

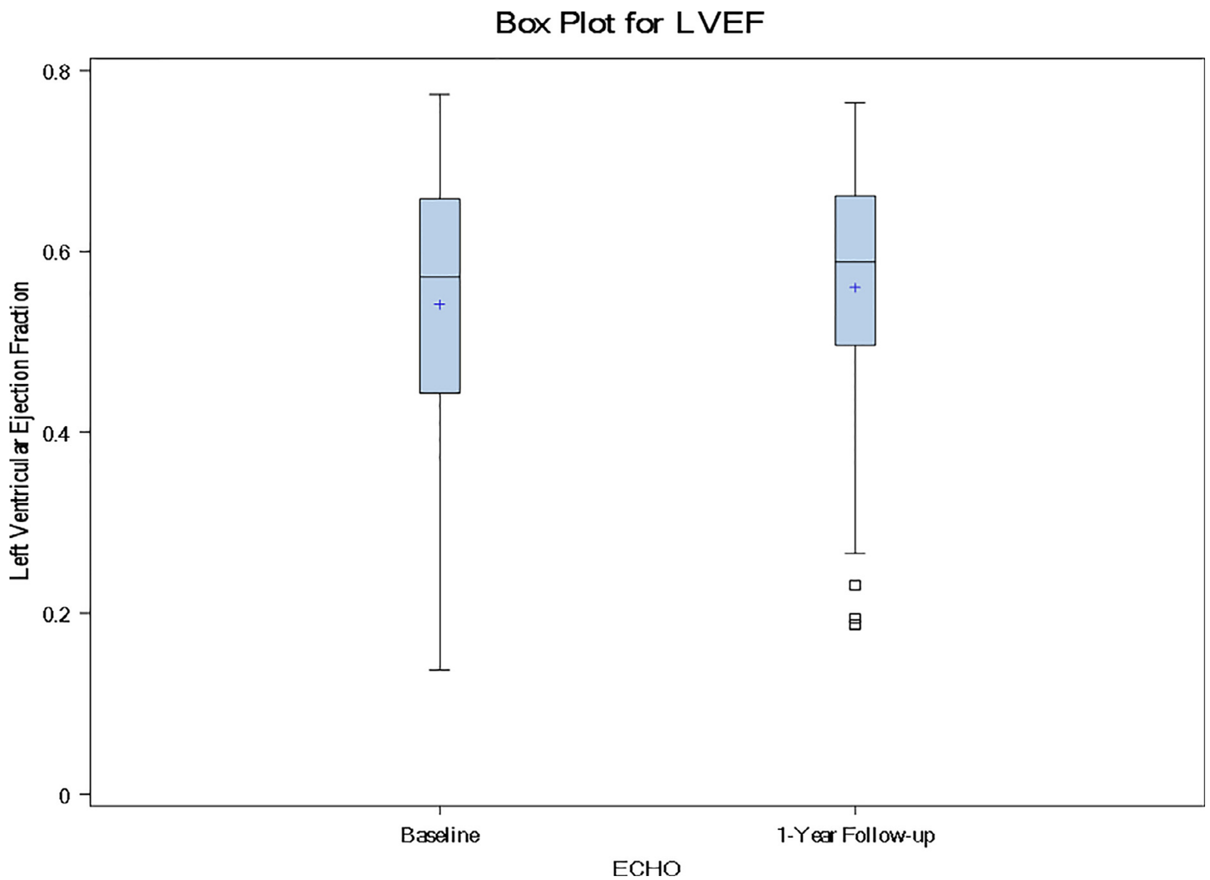

Figure 1A. Box plot for LVEF at the baseline and 1-year follow-up post-TAVI.

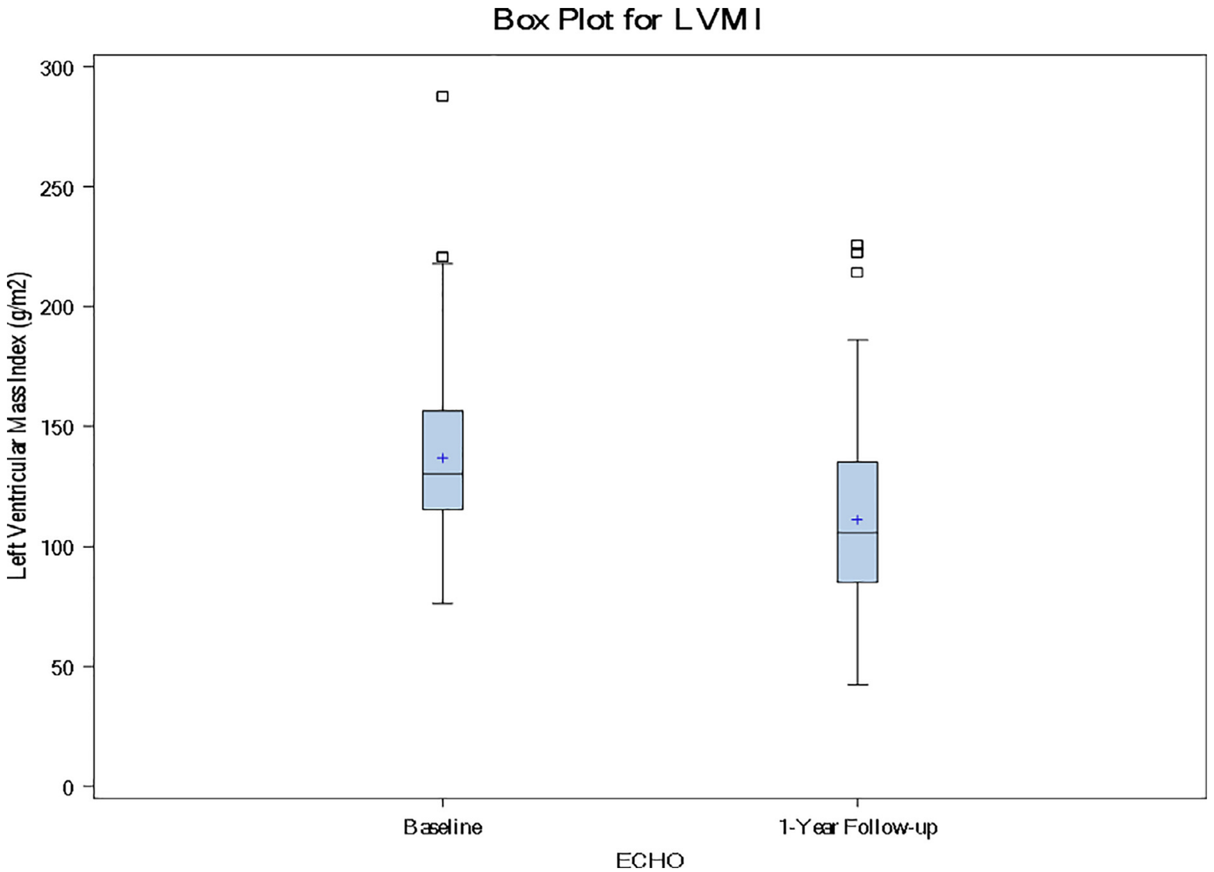

Figure 1B. Box plot for LVMI at the baseline and 1-year follow-up post-TAVI.

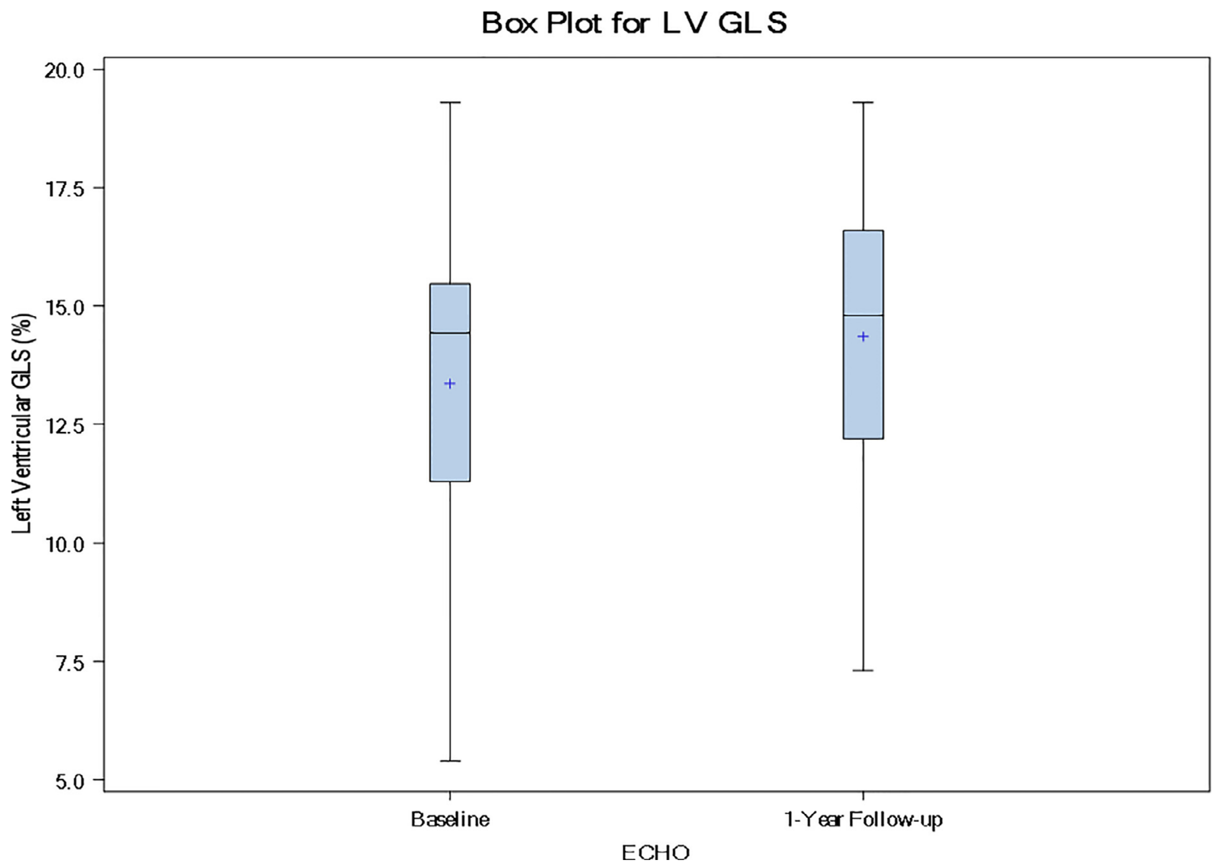

Figure 1C. Box plot for LV GLS at the baseline and 1-year follow-up post-TAVI.

(p <0.001). Patients with a large aortic peak gradient at baseline had larger reduction in LV mass index, when compared with a patient with a smaller baseline value of aortic peak post-TAVI (p =0.044).

In unadjusted analyses, there was a significant improvement in absolute value of LV GLS post-TAVI. This increase (more negative) in absolute values translates to a decrease in patients being classified as abnormal GLS (GLS >−16%) post-TAVI compared with pre-TAVI (Table 2 and Figure 1C). Baseline LV GLS, GFR, and DBP predict change in LV GLS. There was a significant inverse correlation between baseline LV GLS and change in LV GLS post-TAVI (in absolute value), with patients having normal LV GLS (LV GLS ≤−16) at baseline experiencing a smaller increase in absolute value of LV GLS, whereas a patient with abnormal baseline LV GLS (LV GLS >−16%) at baseline experiencing a larger increase (more negative) in absolute value of LV GLS post-TAVI (p <0.001). Patients with higher values of baseline GFR have larger improvement in LV GLS post-TAVI compared with patients with lower values of baseline GFR (p = 0.0019). Patients with DBP ≤65 mm Hg at baseline had no significant correlation with change in LV GLS. However, in patients with DBP >65 mm Hg at baseline, there was a significant inverse correlation with change in LV GLS post-TAVI such that larger values of baseline DBP resulted in smaller increases in absolute value of LV GLS post-TAVI compared with values of baseline DBP ≤65 mm Hg (p = 0.0156).

Discussion

This work highlights the important changes to cardiac structure, function, and hemodynamic profile and the predictors of these changes that occur with TAVI. At 1 year, TAVI resulted in continued favorable changes to the hemodynamic profile of the aortic valve and the LV structure; these include increases in aortic valve area, and a reduction in LV mass. This analysis also demonstrated significant improvements in LV systolic and diastolic function, specifically observed as improvements in LVEF, and LV GLS. In addition, we found that the baseline LV mass and LV GLS predict changes in LV mass regression and baseline LVEF, LV mass and paravalvular leak predict changes in LVEF.

Patient characteristics and hemodynamic changes noted before and after TAVR in this tertiary care center cohort that comprised both balloon-expandable and self-expanding valves are consistent with previous findings from the PARTNER trial[5] as well as a review comparing hemodynamic changes post- surgical aortic valve replacment (SAVR) or TAVI.[6]

In an observational study of just over 200 patients, Sato et al noted that a lack of improvement in LV end-diastolic volume index and LV mass index portended increased risk of mortality within the year post-TAVI.[7] However, previous analyses have not examined the baseline predictors of post-TAVI hemodynamic changes. Our results indicate that age is not a predictor of hemodynamics or geometry changes in TAVI patients, which is consistent with previous studies.[1,8] In addition, data from single- or multicenter registries have also shown that age does not significantly impact on the mid- and long-term outcomes of patients who underwent TAVI.[9,10]

Gender-associated differences may play an important role in the way the LV adapts to pressure overload in AS patients, and the response of the LV to similar degrees of overload varies.[11,12] Gender-related differences in LV mass/volume ratio persist, even after adjusting for age, the severity of AS, and LV function. Our results showed that gender was not associated with changes in cardiac hemodynamics and geometry in post-TAVI patients. Previous studies have shown that LV geometry is altered in women with AS when compared with men after undergoing aortic balloon valvuloplasty.[13] However, these studies also highlight that female patients have a distinctive risk profile compared with male patients, with more frequent co-existent moderate or severe mitral valve disease, New York Heart Association functional class III/IV symptoms, porcelain aorta, lower body surface area, and GFR.[14,15]

Other important clinical covariates, such as EuroSCORE and GFR, also were examined to see whether their baseline values predicted cardiac hemodynamic and geometric changes. Due to the differing definitions of renal impairment used in the literature, the reported incidence of renal impairment post-TAVI varies widely.[16] Our study did not find any association between GFR and LVEF, AVA, or LV mass index. However, we find that patients with higher values of baseline GFR have larger improvement in LV GLS post-TAVI compared with patients with lower values of baseline GFR. We can only speculate that this association may be mediated by co-existent paraproteinemia, fibrosis, or infiltrative disease, which was not evaluated in this study and requires further investigation.[17]

We found that patients who had a lower initial LVEF were more likely to benefit in terms of cardiac geometry and hemodynamics from TAVI. We also found that patients who had higher AVA index at baseline had more improvement in LVEF, which may be explained by the LV obstruction relief offered by TAVI. AS results in increased LV systolic pressure and wall stress, which leads to hypertrophy of the cardiomyocytes and development of interstitial fibrosis.[18] LV mass index regression after valve replacement is presumed to be a favorable effect of LV unloading.[19] A number of studies have evaluated the extent and timing of LV mass index regression after surgical valve replacement and it is often used as a criterion by which to compare the performance of prosthetic valves.[20] However, little is known about the factors that associated with LV mass index regression post-TAVI. In addition, we found that changes in LV mass were predicted by baseline LV mass and LV GLS. Patients with higher baseline LV mass and LV GLS had more mass regression. Much remains to be understood about the long-term predictor of changes and what is more valuable and the best predictor of cardiac remodeling.

The strengths of the study include the consistent ability to measure comprehensive echocardiographic parameters, with inclusion of a high number of subjects in the final analysis. Our findings are also more generalizable representing the "real world" experience outside of a structured clinical trial setting. We have identified predictors of changes in cardiac hemodynamics and geometry with TAVI, which we have not seen described before. Limitations of this study include its retrospective nature, single-center study, and some selection bias due to only including patients with available TTE in the pre- and post-TAVI timeframes specified.

In conclusion, in AS patients, TAVI results in significant favorable cardiac hemodynamic and geometrical changes at 1-year postprocedure. TAVI also significantly improved LV function assessed by GLS. Better baseline myocardial structure and function lead to more reverse remodeling.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.11.038.

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