Effect of Transaortic Valve Intervention for Aortic Stenosis on Myocardial Mechanics

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Chronic afterload excess in aortic stenosis results in compensatory concentric hypertrophy which mitigates the increased systolic load. Surgical aortic valve replacement has been shown to decrease afterload and improve left ventricular (LV) ejection fraction (EF). The extent to which these changes take place in patients undergoing TAVI (transcatheter aortic valve intervention) may be different than what has been observed in the surgical aortic valve replacement patients who were generally younger with few co-morbidities. Accordingly, we analyzed indices of LV structure and ventricular mechanics pre- and 1-year after TAVI in 397 patients (mean age 81±9, 46% women) with severe symptomatic aortic stenosis, complete echocardiographic data was available in 156 patients and these patients compromised our study population. Our principal findings are: (1) LV remodeling occurs after TAVI; (2) afterload decreases significantly; (3) LV chamber and myocardial function, assessed by left ventricular ejection fraction and midwall fractional shortening, and stroke volume, respectively, remain unchanged or decrease. In conclusion, TAVI effects LV remodeling despite significant co-morbidities. Thus, TAVI reduces afterload and leads to LV remodeling. Surprisingly, however, systolic function does not improve. These data run counter to the paradigm that afterload reduction improves systolic function and suggest that the response to afterload reduction is complex in the TAVI population. **(Am J Cardiol 2021;146:56−61)**

Severe aortic stenosis (AS), the prototypical left ventricular (LV) afterload lesion, can result in LV hypertrophy as well as systolic and diastolic dysfunction.[1,2] If LV systolic dysfunction is due to afterload excess, such dysfunction should improve with relief of valve obstruction. Whether this paradigm is applicable to patients undergoing transcatheter aortic valve intervention (TAVI) is not clear. Studies have shown that LV afterload in patients with AS is affected by both the valve and the vasculature.[3] While TAVI improves outcome and relieves symptoms,[4−7] the typical patient undergoing this procedure has co-morbidities[8] which might independently lead to LV remodeling. Our aim was to examine changes in LV remodeling in patients with severe AS pre and 1-year after TAVI and if the response varied by gender and baseline LV ejection fraction (LVEF). We assessed LVEF, stroke volume (SV), midwall fractional shortening (FSmw) and afterload. We included FSmw because of prior work by our group[9,10] suggesting its superiority as an index of systolic function in pressure overload hypertrophy.

Methods

This was a single-center, retrospective study of clinical and echocardiographic data of all patients with severe AS prior to and 1-year after TAVI at The Christ Hospital Heart and Vascular Center from May 2011 to April 2017. Patients were included in the analysis if they had an echocardiogram at least one day prior to TAVI and up to 1-year after procedure. Demographic and clinical data of all patients were retrieved. In addition to analyzing data from the entire cohort, we performed 2 subgroup analyses: by LVEF, using the partition values <60% and ≥ 60%; and by gender. The study was approved by the Institutional Review Board at Christ Hospital.

All patients underwent a comprehensive 2-D echocardiogram according to the Intersocietal Accreditation Commission standards. Aortic valve area and valve gradients were recorded.[11] LV chamber dimensions and indices of structure were measured according to ASE standards.[12]

Total arterial load (TAL) was measured as indexed arterial elastance: 0.9 x systolic blood pressure (SBP)/SVI (stroke volume index). Pulsatile arterial load was measured by pulse pressure (PP): SBP-DBP (diastolic blood pressure).[3] Systemic arterial compliance (SAC, mL/mmHg) was calculated as SVI/PP[3]; circumferential end-systolic wall stress (eSS, g/cm2) was calculated as previously described.[9] Peak LV pressure was calculated by adding peak transaortic gradient x 0.7 to SBP to estimate LV ventricular end systolic pressure. Total LV load (Zva, $mmHg \bullet ml^{-1} \bullet m^{2}$), incorporating opposition due to both the stenotic aortic valve as well as the arterial load, was calculated by (MG + SBP)/SVI where MG is the mean gradient across the aortic valve.[13]

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LVEF was calculated by the biplane method of disks summation (modified Simpson's rule).[12] FSmw was calculated using methods which have been described previously.[14]

Pressure-volume loops (PV loops) were created with Harvi (http://harvi.online, with permission of PV Loops LLC[15]). Two PV loops were generated using mean clinical and echocardiographic data: one to approximate the PV loop of the average patient pre-TAVI and a second to approximate the PV loop of the average patient after-TAVI. In the first PV loop, the input variables were LV contractility, LV lusitropy, LV volume, and vascular properties (see Supplementary Table 1). These input variables were adjusted to approximate the mean pre-TAVI blood pressure, heart rate, SV, LVEF, LV end diastolic volume, LV wall thickness, mean and peak AV gradient, and mean Zva of the study population (green PV loop). In the second PV loop, input variables were again adjusted to approximate the changes in LV end diastolic volume, LV wall thickness, mean and peak AV gradient, and SVR that were observed in the study population after-TAVI. To assess a potential explanation for the observed changes in SV and LVEF, we programed a 10% decline in contractility into the after-TAVI model and recorded the effects of this decline in contractility on SV and LVEF (orange PV loop).

Continuous variables are expressed as means and standard deviation (SD) and compared using paired sample T-test or Wilcoxon signed ranks test, based on the distribution of the data. Categorical variables are reported as absolute values with percentages and compared using the Chi-square statistic or Fisher's exact test. A 2-tailed p value of <0.05 is considered significant. Statistical analysis was performed using the SPSS (SPSS 25; SPSS Inc. Armonk, New York) software package.

Results

A total of 397 subjects who underwent TAVI were included in the demographic analysis. We had complete data for 160 patients regarding LV dimensions pre and 1-year after TAVI and complete data for 156 patients regarding LV mass pre and after TAVI. As expected, the population had a significant burden of co-morbidities, see Table 1. TAVI was associated with LV mass regression and remodeling as shown in Table 2. As expected, eSS dropped significantly. SV decreased significantly. There was a trend toward a decrease in FSmw and LVEF. Although there was a significant decrease in Zva at 1-year, this value remained high (i.e., >3.5 mm $Hg \bullet mL^{-1} \bullet m^2$).[13] Surprisingly, despite a reduction in transvalvular gradient and eSS, there was no meaningful increase in LVEF or FSmw. These directional changes are summarized in Figure 1.

We subdivided the population by LVEF, <60% (reduced LVEF group) and ≥ 60% (preserved LVEF group) based on previous work by Ito et al. who demonstrated that LVEF <60% in the presence of moderate AS predicts further deterioration of LVEF and appears to be represent an abnormal LVEF in AS.[16] LV remodeling occurred in both groups as shown in Table 3 but was more pronounced and statistically significant in the reduced LVEF group. End-systolic stress fell significantly in both subgroups. However, despite this significant reduction in ventricular afterload, FSmw values tended to decline. Surprisingly, LVEF did not increase, (and actually fell) in the preserved EF group while there was no significant change in the reduced EF group. These changes were accompanied by a significant reduction in SV and SAC in the group as a whole and in both subgroups. Consistent with the apparent reduction in SAC, TAL was higher at 1-year follow-up.

We found that wall thickness and LV mass index decreased at 1-year in both men and women as shown in Table 4. As was the case with the analysis by LVEF, there was a statistically significant decrease in SV in both groups. Afterload or eSS decreased significantly in both groups. While LVEF decreased in both men and women, FSmw decreased significantly in women but was relatively unchanged in men. SV was lower 1- year after TAVI in both groups. Zva decreased but remained high in both groups in men and women, respectively. TAL and SVR increased in both groups after TAVI but the change was significant only in men.

Table 1
Demographic and baseline patient characteristics

Baseline characteristics	All patients (*N*= 397)	Men (*N*= 216)	Women (*N*=181)
AGE (YEARS)	81 ± 9	80 ± 10	81 ±8
WOMEN	181 (45.6%)	n/a	n/a
HEIGHT (INCHES)	66 ± 4	69 ± 3	63 ± 3
WEIGHT (LBS)	176 ± 42	192 ± 38	158 ± 39
BODY SURFACE AREA (M2)	1.9 ± 0.3	2 ± 0.2	1.7 ± 0.2
BODY MASS INDEX (KG/M2)	28 ± 6	28 ± 5	28 ± 7
HYPERTENSION	360 (91%)	196 (91%)	164 (91%)
CORONARY ARTERY DISEASE	254 (64%)	162 (75%)	92 (51%)
DIABETES MELLITUS	140 (28%)	87 (40%)	53 (29%)
ATRIAL FIBRILLATION	132 (33%)	84 (39%)	48 (27%)
PERIPHERAL VASCULAR DISEASE	95 (24%)	62 (29%)	33 (18%)
CEREBROVACULAR ACCIDENT	55 (14%)	31 (14%)	24 (13%)
PRIOR CARDIAC SURGERY	268 (67.5%)	158 (73%)	110 (61%)
PRIOR PACEMAKER	48 (12%)	31 (14.4%)	17 (9.4%)

Table 2
Echocardiographic and hemodynamic variables Pre and 1-year after Transaortic Valve Intervention (TAVI)

Characteristic	Pre - TAVI		1-year after TAVI		p- value
Echocardiographic variable	Mean	SD	Mean	SD	
LV Internal Dimension, Diastole (mm)	46.9	8.2	46.7	8.0	0.89
LV Internal Dimension, Diastole (mm)	31.7	11	30.6	9.5	0.13
IVSTd (mm)	12.4	3.6	11.4	3.2	0.00
PWTd (mm)	11.8	2.5	10.7	2.3	0.00
Relative Wall Thickness	0.50	0.1	0.50	0.1	0.84
Left Ventricular Mass (gm)	210.6	59.5	178.3	62.9	0.00
Left Ventricular Mass Index (gm/m2)	113.5	33.1	96.6	31.8	0.00
Midwall Fractional Shortening (%)	0.19	0.80	0.17	0.50	0.06
Left Ventricular End-Diastolic Volume (ml)	128	46.3	114.9	41.4	0.00
Left Ventricular End-Systolic Volume (ml)	65.9	34.5	60.4	38.5	0.02
Stroke Volume (ml)	60.1	19.2	52.8	17.4	0.00
Left Ventricular Ejection Fraction (%)	50	12.6	48.3	10.4	0.11
Systolic Blood Pressure (mmHg)	131	22	132	21	0.55
Diastolic Blood Pressure (mmHg)	69	11	69	10	0.56
LV-Ao Peak Gradient (mmHg)	78.1	21.1	20.8	9.7	0.00
LV-Ao Mean Gradient (mmHg)	46.1	12.9	10.3	5.0	0.00
End Systolic Stress (g/cm2)	165.8	72.5	113.1	45.5	0.00
Valvulo-Arterial Impedance (mmHg•mL-1•m2)	6.1	1.9	5.4	1.7	0.00
Systemic Vascular Resistance (dyn*s/cm5)	1896	680.1	2141.3	679.9	0.00
Systemic Arterial Compliance (mL/mmHg)	1.1	0.5	0.9	0.4	0.00
Total Arterial Load (mmHg/ml/m2)	4	1.3	4.5	1.4	0.00

Discussion

We undertook this study to evaluate LV remodeling and changes in systolic function after TAVI in an older population with severe AS and multiple cardiac co-morbidities. Secondary aims were to analyze these changes by baseline LVEF and by gender. Since systolic hypertension adds a second load to the LV of patients with AS,[8] we used Zva, the sum of the mean pressure gradient across the aortic valve and the systolic pressure divided by the LV stroke volume, indexed to body surface area (BSA) as a measure of global LV afterload.[13] Our principal findings are: (1) LV remodeling occurs after TAVI, regardless of gender; such remodeling occurs more significantly in those with a baseline LVEF <60%; (2) afterload (eSS),decreases significantly, due to the drop in gradient; (3) surprisingly, both LV chamber and myocardial function either remained unchanged or decreased (LVEF in EF ≥60% subgroup, FSmw in women); and (4) paralleling this decrease in LVEF and FSmw, SV decreased in all subgroups.

Previous studies have shown that surgical aortic valve replacement is associated with regression of left ventricular hypertrophy and modest improvement in LVEF after

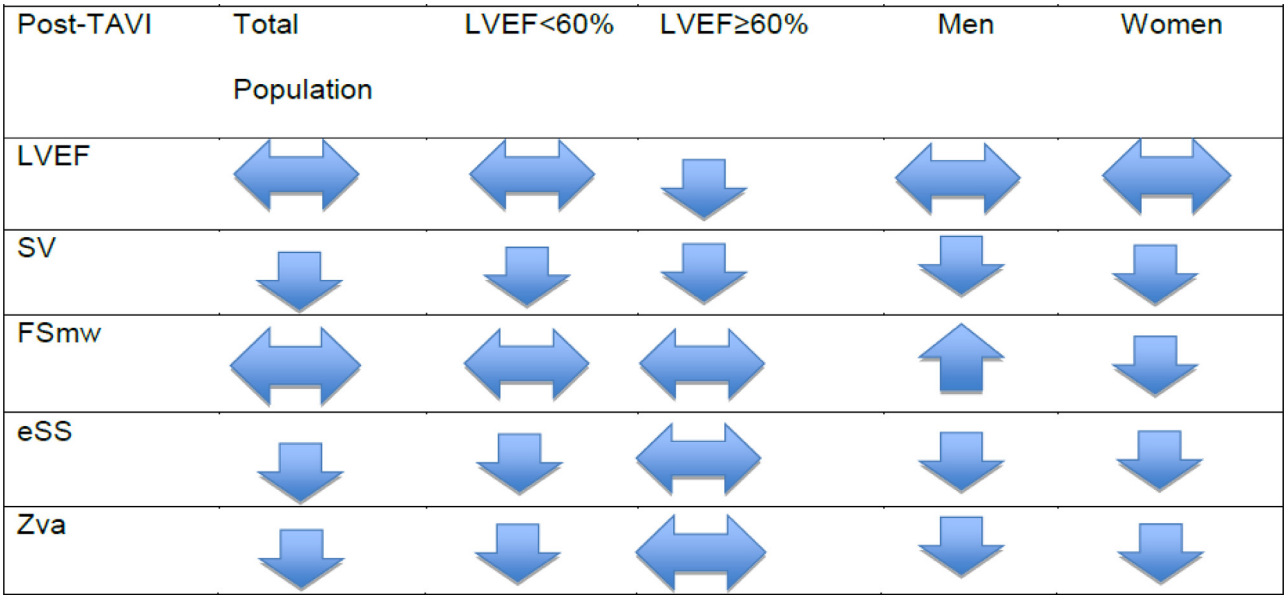

Figure 1. Summary of the directional changes in the total population and by subgroup.

Table 3
Echocardiographic and hemodynamic variables Pre and 1-year after Transaortic Valve Intervention (TAVI) by baseline ejection fraction

Characteristic	Left ventricular ejection fraction <60%					Left ventricular ejection fraction ≥ 60%				
	Pre- TAVI		1-Year after TAVI		p- value	Pre- TAVI		1-year after TAVI		p- value
Echocardiographic variable	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
LV Internal Dimension, Diastole (mm)	48.7	7.3	46.5	8.3	0.1	50.1	6.9	43.7	6.9	0.01
LV Internal Dimension, Diastole (mm)	34.1	10.1	32	8.5	0.02	28	7.2	29.7	7.5	0.32
IVSTd (mm)	12.8	2.9	11.7	2.6	0	12.9	3	12.1	3.1	0.28
PWTd (mm)	11.7	2.4	10.4	2.3	0	11.9	2.9	11.2	2.2	0.26
Relative Wall Thickness	0.51	0.1	0.5	0.1	0.77	0.47	0.1	0.52	0.1	0.17
Left Ventricular Mass (gm)	214.1	57.9	178.5	65.8	0	198.3	63.1	173.3	48.1	0.05
Left Ventricular Mass Index (gm/m2)	116.6	33.8	96.9	33.2	0	104.2	30.4	96.9	27.5	0.19
Midwall Fractional Shortening (%)	0.18	8	0.16	50	0.15	0.2	0.1	0.18	0	0.26
Left Ventricular End-Diastolic Volume (ml)	134.5	47.2	119.6	43.5	0	106.3	36.1	95.9	27.3	0.04
Left Ventricular End-Systolic Volume (ml)	74.9	34.1	64.8	29.4	0	36.3	12.9	45.9	19.5	0
Stroke Volume (ml)	58.2	18.7	53.8	18.5	0.01	65.85	19.8	49.38	12.7	0
Left Ventricular Ejection Fraction (%)	45.4	10	46.7	9.8	0.24	65.7	5.5	53.5	10.8	0
Systolic Blood Pressure (mmHg)	132	22	132	21	0.95	129	20	132	19	0.62
Diastolic Blood Pressure (mmHg)	70	11	69	11	0.43	68	10	67	9	0.79
LV-Ao Peak Gradient (mmHg)	78.3	20.6	21.1	8.9	0	83.1	21.4	20.9	12.6	0
LV-Ao Mean Gradient (mmHg)	46.1	12.6	10.9	4.5	0	48.9	13.4	11	6.4	0
End Systolic Stress (g/cm2)	170.3	69.4	115.5	45.5	0	141.8	65	104.9	47.6	0.07
Valvulo-Arterial Impedance (mmHg•mL-1•m2)	6.2	1.9	5.3	1.6	0	5.4	1.9	5.5	1.8	0.79
Systemic Vascular Resistance (dyn*s/cm5)	1996.2	684.5	2083.4	661.3	0.24	1567.3	560.8	2331	718.9	0
Systemic Arterial Compliance (mL/mmHg)	1.1	0.5	0.9	0.4	0.01	1.1	0.6	0.8	0.3	0
Total Arterial Load (mmHg/ml/m2)	4.1	1.3	4.4	1.4	0.08	3.6	1.4	4.6	1.5	0.01

surgery.[8,17] TAVI affords the ability to study the impact of rapid relief of valve obstruction, without the confounding effects of surgery. However, despite the widespread and rapid adoption of TAVI,[4,5,7,18] relatively little is known about its impact on LV mechanics. We have hypothesized that the LV of the typical TAVI patient might respond differently to relief of valve obstruction than that of a younger patient. We found that despite the presence of longstanding hypertension and coronary artery disease, the aged heart appears to respond to the relief of outflow obstruction with a significant reduction in LV mass index.[19]

Table 4
Echocardiographic and hemodynamic variables Pre and 1-year after Transaortic Valve Intervention (TAVI) in men and women

Characteristic	Men					Women				
	Pre- TAVI		1-Year after TAVI		p- value	Pre- TAVI		1-year after TAVI		p- value
Echocardiographic Variable	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
LV Internal Dimension, Diastole (mm)	45.1	7.7	49.1	7.4	0.00	49.2	8.4	43.5	7.6	0.00
LV Internal Dimension, Diastole (mm)	34.5	12.2	32.3	10.1	0.04	28.8	8.9	28.7	8.6	0.95
IVSTd (mm)	12.4	3.8	11.5	3.6	0.02	12.4	3.3	11.4	2.9	0.02
PWTd (mm)	11.9	2.8	10.8	2.3	0.01	11.7	2.2	10.5	2.3	0.00
Relative Wall Thickness	0.53	0.1	0.49	0.1	0.10	0.46	0.1	0.52	0.2	0.02
Left Ventricular Mass (gm)	230.0	62.0	200.6	65.7	0.00	192.7	51.3	157.7	52.7	0.00
Left Ventricular Mass Index (gm/m2)	118.2	36.7	102.8	33.7	0.00	108.5	28.5	90.4	28.8	0.00
Midwall Fractional Shortening (%)	0.16	0.08	0.18	0.04	0.39	0.21	0.10	0.16	0.10	0.00
Left Ventricular End-Diastolic Volume (ml)	147.0	48.3	131.0	46.5	0.00	109.2	35.6	97.5	27.2	0.00
Left Ventricular End-Systolic Volume (ml)	78.4	37.9	71.0	33.3	0.10	53.6	25.7	50.1	17.7	0.20
Stroke Volume (ml)	66.8	19.5	58.8	17.7	0.00	53.3	16.4	47.1	15.1	0.00
Left Ventricular Ejection Fraction (%)	48.0	12.3	47.4	11.0	0.67	52.1	12.6	49.1	9.9	0.08
Systolic Blood Pressure (mmHg)	131	22	130	21	0.80	131	22	134	21	0.30
Diastolic Blood Pressure (mm Hg)	70	10	68	10	0.28	69	11	69	11	0.90
LV-Ao Peak Gradient (mm Hg)	74.7	19.3	19.5	8.6	0.00	83.3	22.1	22.0	10.7	0.00
LV-Ao Mean Gradient (mmHg)	43.6	11.5	10.3	4.4	0.00	49.3	13.6	11.2	5.4	0.00
End Systolic Stress (g/cm2)	180.7	76.4	110.8	39.0	0.00	146.0	62.5	116.2	53.2	0.01
Valvulo-Arterial Impedance (mmHg•mL-1•m2)	5.7	1.8	5.1	1.6	0.02	6.4	2.0	5.7	1.7	0.01
Systemic Vascular Resistance (dyn*s/cm5)	1749.8	547.3	2022.7	685.9	0.01	2062.4	775.1	2271.5	655.3	0.09
Systemic Arterial Compliance (mL/mmHg)	1.2	0.6	1.1	0.5	0.02	0.9	0.5	0.8	0.3	0.00
Total Arterial Load (mmHg/ml/m2)	3.8	1.3	4.2	1.4	0.08	4.1	1.3	4.7	1.4	0.02

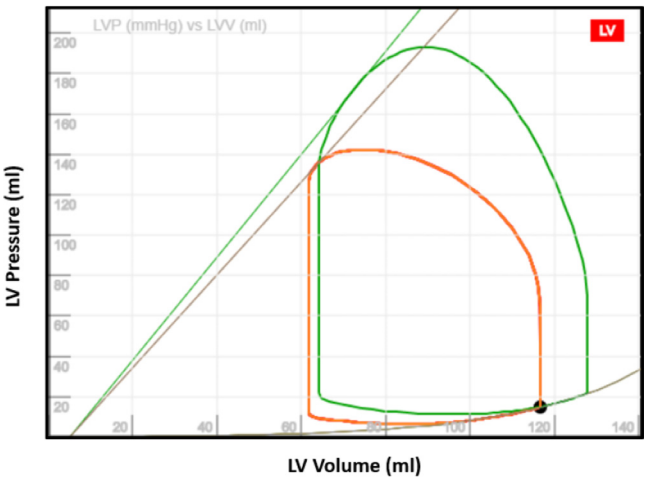

Figure 2. Pressure volume loops green: pre-TAVI: orange: after TAVI with modeling of a 10% decrease in contractility. decreased mean and peak AV gradients. and increased SVR. The overall reduction in Z_{VA} resulted in a downward and leftward shift of the pressure volume loop, representative of an after-TAVI decline in peak and end-systolic LV pressure and a decline in LVEDV. The decline in contractility, together with an increase in TAL, resulted in a decline in stroke volume and ejection fraction.

We hypothesized that, given the afterload-shortening relationship,[20–23] LVEF and even FSmw would improve, as has been shown in the PARTNER trials.[24,25] However, as noted above, neither LVEF nor FSmw improved despite the significant reduction in transvalvular gradient and afterload. Indeed, while most studies show an improvement in LVEF after TAVI,[26–28] some have shown that the LVEF remains unchanged or had decreased. In fact, our patients with a baseline LVEF ≥ 60 experienced a frank decline in EF.

To better understand these surprising findings, we considered the three principal factors which influence LVEF and FSmw: afterload, preload, and contractility. First, as far as afterload is concerned, while the mean gradient across the aortic valve decreased by more the 75%, Zva only decreased by 11%. The increase in total arterial load, driven by a decrease in SAC (i.e., increase in pulsatile load) and an increase in SVR (i.e. increase in resistive load), provides an explanation for this, as has been demonstrated by Yotti et al.[19] Patient-prosthesis mismatch can also contribute to elevated afterload after TAVI. Secondly, we think that major changes in fiber preload are unlikely to be present in a chronically remodeled heart, especially when there is concentric hypertrophy.[24] Finally, it is conceivable that contractility declined following TAVI. Regression of concentric hypertrophy may unmask underlying myocardial dysfunction. Krayenbuhl et al, in a seminal study, found a relative increase in interstitial fibrosis in the intermediate term (e.g., 12 months) suggesting that contractile elements regress faster than fibrous content.[29] It is also conceivable that LV contractility was supported by heightened adrenergic tone when the patient was suffering from severe AS and that such adrenergic tone might have declined by 1 year following TAVI; this is the putative mechanism for the lack of improvement in EF following treatment for hypertensive pulmonary edema.[30] We generated models to test the plausibility of these explanations using Harvi.[15] (Figure 2) Beta-blocker use and pacemaker implantation can adversely affect systolic function. In our study population, pacemaker implantation increased by only 5% after TAVI (12.6 to 17.6%). However, we found that the LVEF >60% group had a higher incidence of pacemaker implantation after TAVI (2.3% pre TAVI vs. 16.3% after TAVI) compared with the LVEF <60% group. Beta-blocker use actually decreased after TAVI by 22.4%.

The limitations of our study include the retrospective design and the reliance on the accuracy of the medical history and echocardiographic data that were documented. The size of the population and that the data was derived from a single center is also a limitation as well as limited data regarding these above findings with regard to clinical outcome. Finally, only patients with serial echocardiograms were included in the analysis and analysis was not performed by a core laboratory.

To summarize, our data suggest that improvement in LVEF in following TAVI cannot be counted on as a benefit of the procedure. The mechanisms at play affecting the change in LVEF are complicated and may be differ depending on the individual patient.

Credit Author Statement

Conception or Design of Work: Colleen Harrington, Matthew Gottbrecht, Eugene Chung and Gerard Aurigemma. **Data Collection:** Vien Truong**; Data Analysis and Collection**: Nouran Sorour, Ahmed Nagy, Colleen Harrington, Gerard Aurigemma, Matthew Gottbrecht, Eugene Chung**; Drafting the Article**: Colleen Harrington, Gerard Aurigemma**; Critical Revision of the Article**: Colleen Harrington, Lara Kovell, Matthew Gottbrecht, Eugene Chung, Gerard Aurigemma**; Final Approval of the version to be published**: Colleen Harrington, Nouran Sorour, Ahmed Nagy, Vien Truong, Lara Kovell, Matthew Gottbrecht, Eugene Chung, Gerard Aurigemma.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.01.021.

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