Early Changes of Myocardial Function After Transcatheter Aortic Valve Implantation Using Multilayer Strain Speckle Tracking Echocardiography

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Transcatheter aortic valve implantation (TAVI) is an effective therapeutic option for severe symptomatic aortic valve stenosis (AS) with intermediate or high surgical risk. The purpose of this study was to examine the effects of TAVI on left ventricular (LV) mechanics using multilayer global longitudinal strain (GLS) by 2D speckle-tracking echocardiography. A total of 119 patients (mean age 83 ± 7.0 years, male 54%) with severe symptomatic AS and normal LV ejection fraction (LVEF) underwent echocardiography at baseline and 1 month after TAVI. Global longitudinal strain was measured from the endocardial layer (GLSendo), mid-ventricular layer (GLSmyo), epicardial layer (GLSepi) and full thickness of myocardium (GLSwhole). There was significant improvement in all 3 layers of GLS after TAVI compared with baseline, but there was no significant change in LVEF. The relative % increment in GLS in each layer strain were 11.2 ± 23.4% (GLSendo), 13.4 ± 33.0% (GLSmyo) and 18.0 ± 46.6% (GLSepi) with significant difference between GLSendo and GLSepi ($p < 0.05$). In conclusion, multilayer GLS is more sensitive than conventional LVEF to detect early improvement in LV systolic function after TAVI in patients with severe AS. There is a disproportional improvement in different layers with least improvement in the endocardium. Multilayer strain analysis may provide new insights into understanding mechanics of AS.
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Layer specific quantification of myocardial function may be more sensitive than transmural strain in detection of subclinical dysfunction in various cardiovascular diseases.[1−5] Recent studies have described the usefulness of layer specific strain analysis which have identified the early loss of endocardial global longitudinal strain (GLS) in asymptomatic severe aortic valve stenosis (AS).[6−8] GLS can improve after successful aortic valve replacement (AVR) by the new transcatheter aortic valve implantation (TAVI) approach.[9−11] However, there is limited data on the effects of TAVI on layer specific myocardial function. The aim of this study is to describe acute changes of multilayer strain at 1 month after TAVI in patients with severe AS and preserved left ventricular (LV) function.

Methods

This is a retrospective single-center study. Between October 2010 and November 2016, 301 patients with symptomatic severe trileaflet AS underwent successful TAVI at The Prince Charles Hospital in Brisbane. A flow diagram is shown in Figure 1 to demonstrate how we selected the patients for inclusion into the study. Exclusion criteria were; atrial fibrillation, transapical approach with poor ultrasound acoustic window, and absence of serial echo examination at 1 month after TAVI. One hundred and two patients were excluded due to atrial fibrillation (n = 12), transapical approach (n = 100), poor acoustic window (n = 24) and non−follow-up of echo examination (n = 46). A final total of 119 patients were included in the study which was approved by the local ethics committee.

All patients underwent preprocedural baseline echocardiographic examination 1 month before TAVI and serial postprocedural follow-up echocardiography 1 month after TAVI. Time difference between serial studies was mean 121.9 ± 89.3 days. Echocardiographic images were acquired by several different vendors (GE Vivid E95 [n = 46]; Philips EpiQ [n = 66]; Siemens SC2000 [n = 7]) and data stored in the Digital Imaging and Communications in Medicine format to allow offline postprocessing using vendor-independent software for multilayer strain analysis (TomTec Imaging Systems, Unterschleissheim, Germany).

M-mode measurements were performed according to the criteria of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[12] Three consecutive cycles were averaged for every parameter. Left ventricular ejection fraction (LVEF) was estimated by biplane Simpson's rule. Maximum left atrial volume was calculated at end-systole of the left ventricle using the biplane Simpson's method and indexed to body surface area. Early (E) and late (A) wave velocities, E/A ratio, and E deceleration time were measured from the mitral inflow profile. To acquire tissue Doppler imaging data, the Nyquist limit was set at 15 to 20 cm/s, and minimal optimal gain was

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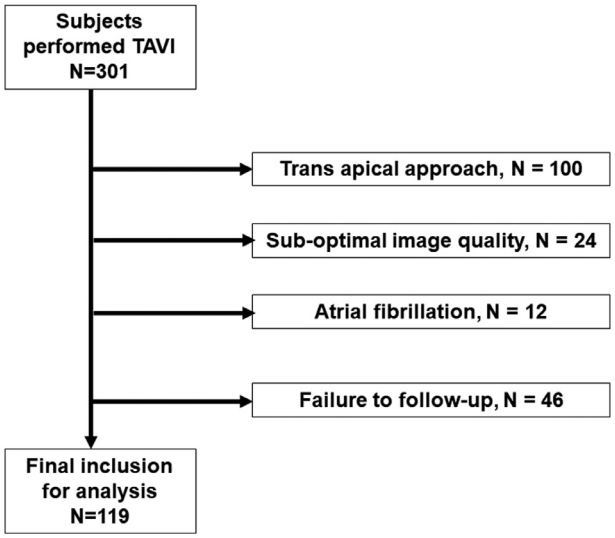

Figure 1. Flow chart of patients who met inclusion criteria for the study.

used. The myocardial early diastolic velocities (e') were obtained at the septal and lateral mitral annulus by placing a sample volume. The E/e' ratio was subsequently calculated for the average of septal and lateral measurements.

All speckle-tracking echocardiography-derived deformation measurements were performed by a blinded expert observer using vendor-independent postprocessing software package (2D Cardiac Performance Analysis [CPA], TOMTEC-Arena version 2.20, TomTec Imaging Systems, Unterschleissheim, Germany). For speckle tracking analysis, 3 cycles were recorded at a frame rate between 50 and 80 fps and were averaged for strain analysis. GLS was defined as the peak negative value from the strain curve at end-systole. From 3 manually selected landmark points (lateral and septal mitral annulus and LV apex) in apical views, LV endocardial borders were automatically detected by the software. Subsequently, automatic tracking of myocardial speckles was performed throughout the whole cardiac cycle. GLS was obtained for apical 4-chamber, 3-chamber, and 2-chamber views; subsequently, an offline vendor-independent software workstation provided LV model consisting of all segments. After the software automatically created a range of interest, which included endocardial, mid-myocardial and epicardial layers, then the range of interest was adjusted to include the myocardium as well (Figure 2). If the results were not satisfied, we calculated all the processes for global strain and multilayer strain repeatedly. The global and multilayer longitudinal strain value were obtained by averaging peak longitudinal strain of 16 segments (endocardial-layer GLS [GLSendo], midventricular-layer GLS [GLSmyo], epicardial-layer GLS [GLSepi] and transmural GLS [GLSwhole].[3,13]

LV afterload was measured by valvuloarterial impedance (Zva), which is the sum of systolic blood pressure and aortic valve mean gradient divided by the stroke volume indexed. Each component was recorded simultaneously both at baseline and after TAVI.

We randomly selected 20 cases to assess interobserver and intraobserver reproducibility of multilayer strain analysis by 2 independent blinded observers.

Continuous data are expressed as the mean ± SD. For continuous variables, Student's *t* test was performed, and for categorical variables, Chi-square test was used. Intraclass correlation coefficient was used for intra- and interobserver agreement. All statistical analyses were performed with SPSS version 12.0 statistical analysis software.

Results

One hundred and nineteen patients with symptomatic severe AS and preserved LV systolic function were included in the study. Baseline clinical demographics of the study population are shown in Table 1. Mean age of the patients was 83.2 ± 7.0 years, with a male prevalence of 53.8% and baseline LVEF of 58.6 ± 10.8%. Ninety six TAVI patients (80.7%) received Edwards balloon-expandable prosthesis (Edwards XT or S3, Edwards LifeSciences), 12 patients (10.0%) CoreValve self-expanding prosthesis (Medtronic), and 11 patients (9.2%) Lotus mechanically expanded prosthesis (Boston Scientific). Ninety three patients (78.2%) had TAVI performed by transfemoral approach and 26 patients (21.8%) by transaortic approach. Standard echocardiographic measurements were obtained at baseline and 1 month after TAVI and represented in Table 2. In the early after TAVI, transaortic peak, mean pressure gradient and Zva significantly decreased. LV mass index significantly decreased after TAVI. This suggested

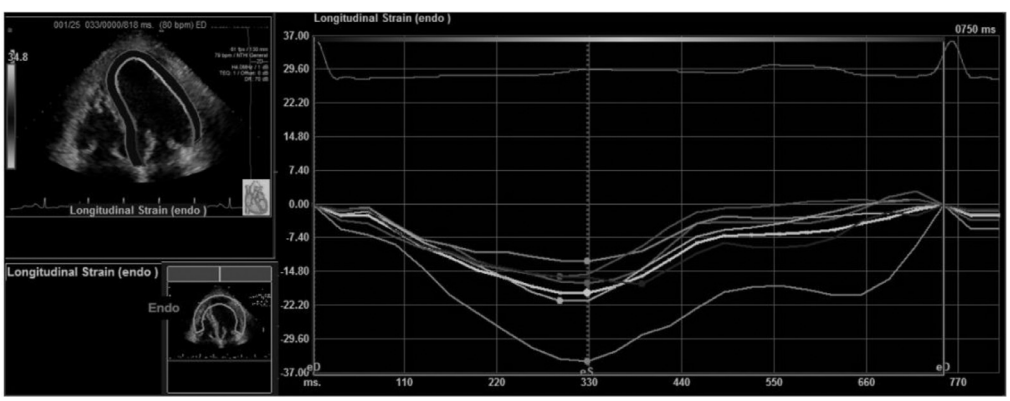

Figure 2. Representative longitudinal multilayer (endocardial layer) strain analysis.

Table 1
Demographic characteristics of patients

Variable	Patients n = 119
Age, (years)	83.2 ± 7.0
Men	64 (54%)
Height, (cm)	165.7 ± 9.6
Weight, (kg)	76.4 ± 16.3
Body surface srea, (m^2)	1.85 ± 0.22
Diabetes mellitus	24 (20%)
Hypertension	63 (53%)
Dyslipidemia	49 (41%)
Coronary artery disease	60 (50%)

Table 3
Multilayer global longitudinal strain (GLS) and the whole-myocardium GLS at baseline and after transcatheter aortic valve implantation (TAVI)

Variables	Baseline	1 month after TAVI	p Value
GLS endocardial layer (%)	−16.3 ± 3.9	−17.6 ± 3.6	0.0001
GLS midventricular layer (%)	−12.2 ± 3.1	−13.2 ± 3.2	0.0009
GLS epicardial layer (%)	−8.3 ± 2.3	−9.0 ± 2.4	0.002
GLS whole myocardium (%)	−16.8 ± 4.1	−17.7 ± 3.8	0.0006

that there was a significant morphological improvement of LV remodeling by TAVI. In contrast, LVEF and LV stroke volumes did not significantly change between the baseline and 1 month after TAVI. With LV diastolic function, there was a significant increase in e' septal, but significant change was not observed in average E/e'.

LV multilayer deformation parameters are shown in Table 3. Multilayer strain in all 3 layers significantly improved early after TAVI compared with baseline values. The relative percentage change of strain in 3 layers of the myocardium is shown in Figure 3. There was a significant difference between the percentage of strain change in GLSendo and GLSepi (11.2 ± 23.4% vs 18.0 ± 46.6%, $p < 0.05$).

Intra- and interobserver reliability is given in Table 4. Both intra- and interobserver variabilities in multilayer strain parameters showed excellent correlations in all layers of myocardium.

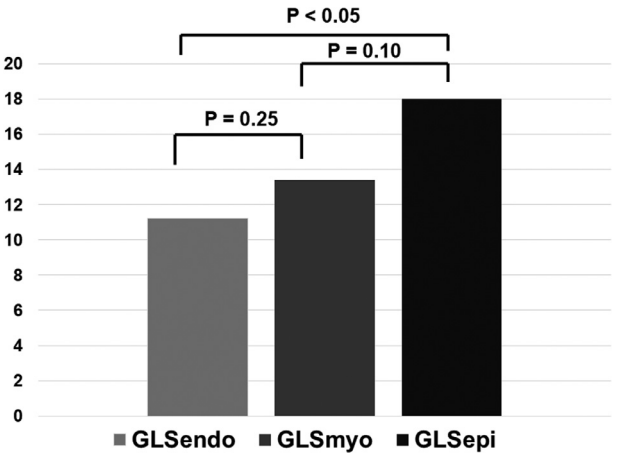

Figure 3. Comparison of percentage of strain change between 3 layers.

Discussion

TAVI is a guideline recommended therapeutic alternative to surgical aortic valve replacement for patients deemed to have high or intermediate surgical risk score. Previous studies have shown that long-term prognostic outcome of patients who had undergone TAVI is at least equivalent to surgical AVR in terms of survival, symptoms, and hospitalization[14,15] (The seminal papers to quote are PARTNER II and SURTAVI). Serial improvement in LV function after TAVI can be objectively quantified using LVEF by echocardiography.[16,12,13] However, this method can be limited when patients undergoing TAVI have preserved LVEF at baseline. There is emerging data showing that GLS is a more sensitive echocardiographic parameter than LVEF to assess subtle changes in LV function after TAVI.[9,17] In addition, layer-specific strain analysis is innovative for detailed assessment of LV wall mechanics in subendocardial ischemia and LV

Table 2
Standard echocardiographic parameters at base line and 1 month after transcatheter aortic valve implantation (TAVI)

Variables	Baseline	1 month after TAVI	p Value
LV ejection fraction (%)	58.6 ± 10.8	58.9 ± 9.8	0.81
LV end-diastolic volume(ml)	104.9 ± 39.4	102.9 ± 33.2	0.14
LV end-systolic volume (ml)	45.2 ± 26.0	45.4 ± 22.1	0.42
Intraventricular septum (mm)	13.6 ± 2.7	12.8 ± 2.7	0.049
LV posterior wall (mm)	11.7 ± 3.4	11.1 ± 2.4	0.020
LV mass index (g/m^2)	132.4 ± 40.4	122.6 ± 32.4	<0.002
Stroke volume index (ml/m^2)	47.5 ± 12.4	49.7 ± 13.6	0.09
Maximum pressure gradient (mm Hg)	74.0 ± 18.6	20.7 ± 7.2	<0.0001
Mean pressure gradient (mm Hg)	45.0 ± 12.0	11.0 ± 4.0	<0.0001
Aortic valve area (cm^2)	0.86 ± 0.18	1.94 ± 0.42	<0.0001
Valvuloarterial impedance (mm Hg/ml/m^2)	4.1 ± 1.3	3.2 ± 0.9	<0.0001
Septal peak early diastolic velocity (e') (cm/s)	4.7 ± 1.5	5.4 ± 2.1	<0.005
Lateral peak early diastolic velocity (e') (cm/s)	6.6 ± 2.5	7.2 ± 2.2	0.09
Average E/e' ratio	20.3 ± 10.3	19.4 ± 8.4	0.78

Table 4
Intraobserver and interobserver reproducibility of multilayer global longitudinal strain (GLS)

Variable	Intraobserver coefficient	95% confidence level	Interobserver coefficient	95% confidence level
GLS endocardial layer	0.93	0.81-0.97	0.82	0.55−0.93
GLS midventricular layer	0.89	0.71-0.96	0.91	0.75−0.97
GLS epicardial layer	0.85	0.61-0.93	0.86	0.65−0.95

pressure overload.[3,6,7,18] The main findings of this study are (1) there was significant improvement in GLS in all 3 layers of the myocardium at 1 month after TAVI in the presence of preserved LVEF; (2) multilayer strain analysis demonstrated a consistent pattern of layer-specific strain improvement after TAVI with the epicardial layer demonstrating the most significant improvement and the endocardial layer with the least improvement; (3) there was no significant change in LVEF after TAVI in patients with normal LVEF at baseline. Our study clearly highlights the potential benefit of using GLS for more sensitive serial assessment of LV systolic function over conventional LVEF. Our study also gives some insight into the changes of layer specific myocardial mechanics in AS. Before TAVI, the baseline GLS in all 3 layers of the myocardium are reduced in our patient population compared with the published normal multilayer strain values in control subjects in the study by Nagata et al.[19] This suggests that the myocardium of patients with severe AS is already intrinsically dysfunctional despite preserved LV function by LVEF criteria. GLS is more sensitive than LVEF to detect myocardial dysfunction in aortic stenosis. Strain is load dependent and reduction in GLS can be partially explained by an increase in LV pressure afterload. The improvement of pressure hemodynamics provided by TAVI enabled an immediate improvement in transaortic valvular gradient and reduction of LV pressure loading which can also translate into an early improvement of LV remodeling.[17,20] This is consistent with the results of our study which demonstrated an improvement in Zva and subsequent reduction in LV mass at 1 month follow-up. Moreover, we demonstrated that there is a disproportional improvement in different layers of the myocardium with least improvement in the endocardial layer. This suggests that the endocardium may be the most subjected to the adverse effects of chronic LV pressure overload from AS. Previous studies have suggested the presence of ischemia and myocardial fibrosis in the endocardium as a result of sustained pressure loading in severe aortic stenosis.[21,22] The extent of biopsy proven myocardial fibrosis in aortic stenosis is directly related to the reduction in GLS.[23] In our study, the relatively smaller improvement in endocardial GLS after TAVI suggests fibrotic changes may be more prominent in the endocardium. Histology and cardiac magnetic resonance (CMR) have been conventionally used for detecting myocardial fibrosis.[19,24,25] Kvernby et al has previously demonstrated a reduction of myocardial fibrosis after aortic valve surgical replacement using CMR.[26] Multilayer strain analysis by echocardiography has the potential to be an alternative method to histology and CMR in detecting layer-specific differences of LV myocardial mechanics. One value in strain may be in the identification of patients who remain at risk for a poor long-term outcome after TAVI but more research is needed.

There are several limitations in this study. Firstly, this was a single center and retrospective study with limited short-term follow-up period of only 1 month. A future longer study is desirable to determine whether the observed changes in myocardial strain can be sustained and clinical outcomes of patients can be changed in the long term. Nonetheless this study was designed to assess the short-term acute effects of TAVI on LV strain. Secondly, we excluded patients with transapical approach of TAVI because of the potential limitations of apical imaging. Thirdly, we used echocardiographic images acquired by several different vendors, so there was a need to use vendor-independent software for multilayer strain analysis. Finally, we do not have CMR or histologically biopsy proven correlations between strain imaging and cardiac pathology. Different valves were also used with different effective orifice areas that may impact on load and hence GLS.

In conclusion, GLS is more sensitive than conventional LVEF to detect early improvement in LV systolic function after TAVI in patients with severe AS and preserved LV systolic function. There was significant improvement in GLS in all 3 layers of the myocardium but there was a disproportional improvement in different layers. Endocardial strain showed the least improvement. This may suggests endocardial strain lags behind improvement strain in the other layers. These findings can provide new insights into the understanding of LV mechanics and pathophysiology in patient with AS.

Disclosures

The authors declare that there are no conflicts of interest to disclose.

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