ORIGINAL RESEARCH

Impact of Prosthesis-Patient Mismatch on Left Ventricular Myocardial Mechanics After Transcatheter Aortic Valve Replacement

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***Background*—**The aim of this study was to compare left ventricular (LV) remodeling using myocardial strain between patients with severe aortic stenosis (AS) treated with transcatheter aortic valve replacement (TAVR) with and without prosthesis-patient mismatch (PPM).

***Methods and Results*—**In a retrospective study, speckle-tracking echocardiography was used to measure global longitudinal strain (GLS) and strain rate (GLSR), circumferential strain, and rotation before and at mid-term follow-up post-TAVR. Moderate and severe PPM were defined as an effective orifice area ≤0.85 and <0.65 cm^2/m^2, respectively. A total of 102 patients (median age, 83 years [77–88]) with severe AS were included. At 6±3 months post-TAVR, moderate and severe PPM were found in 32 (31%) and 9 (9%) patients. Patients without PPM had a significant regression in LV mass (from 134±41 to 119±38 g/m^2; P=0.001) at follow-up whereas those with PPM did not. There was a significant improvement in LV GLS (−12.8±4.0 to −14.3±4.3%; P=0.01), GLSR (−0.61±0.20 to −0.73±0.25 $second^{-1}$; P<0.001), and early diastolic strain rate (0.52±0.20 to 0.64±0.20 $second^{-1}$; P<0.001) in patients without PPM, but not in those with PPM. After adjustment for pre-TAVR ejection fraction and post-TAVR aortic regurgitation, patients without PPM had greater improvement in LV longitudinal strain parameters compared to those with PPM. After a median follow-up of 46.1 months (interquartile range, 35.4–60.8), there was no difference in survival between patients with and without PPM.

***Conclusions*—**TAVR was associated with an incidence of PPM of 40%. Greater reverse LV remodeling using myocardial strain was evident in patients without PPM compared to PPM. Presence of PPM was not associated with mortality. **(*J Am Heart Assoc.* 2016;5:e002866 doi: 10.1161/JAHA.115.002866)**

Key Words: aortic stenosis • effective orifice area • prosthesis-patient mismatch • speckle-tracking echocardiography • strain • transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is now a common therapy for patients with severe aortic stenosis (AS) at high risk for open-heart surgery.[1] Although TAVR has better hemodynamics than surgical prostheses,[2] occurrence of prosthesis-patient mismatch (PPM) remains high, with reported incidence often >40%.[3–5] PPM after surgical aortic valve replacement (SAVR) negatively affects left ventricular (LV) remodeling and has an impact on morbidity and mortality.[6] Although the adverse clinical impact of PPM post-TAVR remains uncertain,[5] it is plausible that the higher residual afterload attributable to PPM also prevents LV structural and functional remodeling.

Speckle-tracking echocardiography (STE) allows sensitive assessment of global and regional myocardial deformation.[7] Several groups have demonstrated a recovery of LV longitudinal strain post-TAVR.[8–11] Larger improvement in global longitudinal strain (GLS) post-TAVR has been associated with lower mortality.[8] Whether there is a differential improvement in strain in patients with and without PPM post-TAVR has not been explored.

Our objective was to determine the impact of PPM on the recovery of LV function using myocardial strain at mid-term follow-up post-TAVR. Our secondary objective was to examine the association of PPM with all-cause mortality.

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An accompanying Figure S1 is available at http://jaha.ahajournals.org/content/5/2/e002866/suppl/DC1

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Methods

Study Population

This retrospective study included patients undergoing TAVR for symptomatic severe AS at 3 institutions (Toronto General Hospital, University of Toronto [Toronto, Ontario, Canada]; Cleveland Clinic Foundation [Cleveland, OH]; and Hôpital du Sacré-Coeur de Montréal, University of Montreal [Montreal, Quebec, Canada]). Patients were included if transthoracic echocardiograms (TTEs) pre-TAVR and at mid-term follow-up (between 2 and 12 months) were available. Exclusion criteria were (1) poor endocardial tracking with STE analysis in at least 2 adjacent myocardial segments and (2) atrial fibrillation during echocardiography. Twenty-one healthy patients ≥60 years of age served as the control group. A minimal amount of clinical follow-up of 6 months was required. The study protocol was approved by the local institutional research ethics boards. The requirement for informed consent was waived.

Transcatheter Aortic Valve Replacement

Eligibility for TAVR included the presence of symptomatic severe aortic stenosis with a valve area (AVA) ≤1.0 cm^2 and/or mean systolic aortic gradient >40 mm Hg. All patients were considered to be at high risk for death with conventional

Table 1. Baseline Characteristics and Procedural Details

Clinical Characteristics	All Patients (N=102)	Patients With No Post-TAVR PPM (n=61)	Patients With Post-TAVR PPM (n=41)	*P* Value
Age, y	83 (77–88)	84 (78–88)	83 (77–88)	0.28
Men	59 (58)	36 (59)	23 (56)	0.77
Logistic EuroSCORE (%)	19±13	18.9±12.5	20.0±15.2	0.94
Body mass index, kg/m^2	24.8±8.0	23.7±6.2	26.5±10.0	0.08
Body surface area, m^2	1.80±0.21	1.77±0.19	1.84±0.23	0.13
NYHA class III or IV	90 (88)	55 (90)	35 (85)	0.46
LVEF (%)	54±12	54.0±11.7	54.3±12.1	0.87
Arterial hypertension	84 (82)	52 (85)	32 (78)	0.35
Dyslipidemia	79 (78)	48 (79)	31 (76)	0.72
Diabetes mellitus	30 (29)	17 (28)	13 (32)	0.68
Coronary artery disease	69 (68)	42 (69)	27 (66)	0.75
Peripheral vascular disease	15 (15)	7 (12)	8 (20)	0.26
Previous aortic valve replacement	4 (4)	2 (3)	2 (5)	0.68
CABG	44 (43)	27 (44)	17 (42)	0.78
Chronic lung disease	13 (13)	9 (15)	4 (10)	0.46
Procedural details				
Approaches/access				0.24
Transfemoral	50 (49)	27 (44)	23 (56)	
Transapical or direct transaortic	52 (51)	34 (56)	18 (44)	
Valve in valve procedure	4 (4)	2 (3)	2 (5)	1.0
Prosthesis				0.35
Edwards	90 (88)	52 (85)	38 (93)	
Corevalve	12 (12)	9 (15)	3 (7)	
Prosthesis size, mm	25.1±1.9	25.4±2.2	24.8±1.5	0.21
Prosthesis size				0.04
23	39 (38)	22 (36)	17 (41)	
26	55 (54)	31 (51)	24 (59)	
29 to 31	8 (8)	8 (13)	0 (0)	

Data are expressed as median (range), number (percentage), or mean±SD. CABG indicates coronary artery bypass graft; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PPM, prosthesis-patient mismatch; TAVR, transcatheter aortic valve replacement.

SAVR as determined by a multidisciplinary team. TAVR was performed with either the balloon-expandable Edwards SAPIEN (or SAPIEN XT; Edwards Lifesciences, Irvine, CA) or the self-expandable Medtronic CoreValve (Medtronic, Minneapolis, MN) devices available at the time of the procedures and per operator discretion. Device sizing was based on two-dimensional (2D) echocardiography-derived annular diameter before 2011 and on annular area measured by three-dimensional (3D) transesophageal echocardiography (TEE) or multidetector computed tomography (MDCT) from 2011 onward.

Clinical Data

Demographics, comorbidities, previous cardiac procedures, logistic European System for Cardiac Operative Risk Evaluation score (EuroSCORE), and functional status were prospectively collected. Mortality from time of TAVR to the censor date of May 1, 2014 was recorded by chart review at the 3 institutions and Social Security Death Index.

Echocardiography

TTEs were performed following the American Society of Echocardiography (ASE) guidelines before and at mid-term follow-up post-TAVR.[12–14] AVA was calculated using the continuity equation. The components of the continuity equation and linear aortic annulus diameter from a long-axis view were remeasured independently by 2 experienced observers (F.P., T.Y.) blinded to any other clinical data. Effective orifice area (EOA) post-TAVR was calculated at mid-term follow-up using the LV outflow tract (LVOT) diameter and the velocity measured just underneath the apical margin of the valve stent. In cases where the landing zone of the stent was low in the LVOT, diameter and velocity were both measured in the proximal portion of the stent.[15,16]

Prosthesis-Patient Mismatch

In the setting of a morphologically normal valve, PPM is considered to be hemodynamically insignificant if the indexed EOA (iEOA) is >0.85 cm^2/m^2, moderate if iEOA between 0.65 and 0.85 cm^2/m^2, and severe if <0.65 cm^2/m^2. For obese patients (body mass index ≥30 kg/m^2), lower criteria were used (severe PPM if EOA <0.60 cm^2/m^2 and moderate PPM if EOA between 0.60 and 0.70 cm^2/m^2).[16]

Aortic Regurgitation

Pre-TAVR, severity of native aortic valve regurgitation was ascertained as per ASE guidelines using an integrative approach.[14] Categorization of post-TAVR paravalvular aortic regurgitation (AR) was based mainly on the proportion of the circumference of the aortic prosthetic ring occupied by the regurgitant jet in the parasternal short-axis view: (1) mild, <10%; (2) moderate, 10% to 29%; and (3) severe, ≥30%.[16] Trivial paravalvular AR was defined as a pinpoint jet. Pulsed-wave signals of diastolic flow reversal in the descending thoracic aorta were also used: (1) mild, absent or brief early diastolic flow reversal; (2) moderate, intermediate finding between mild and severe AR; and (3) severe, prominent, and holodiastolic flow reversal.[16] Density of the AR jet on continuous-wave Doppler was also used: (1) mild, incomplete or faint AR jet density; or (2) moderate or severe, dense AR jet density.[16] In cases of both valvular and paravalvular regurgitation, grading of AR reflected the summation of both regurgitation. Consistent with our recent work, we defined significant post-TAVR AR as (1) new mild post-TAVR AR (ie, no or trivial pre-TAVR AR that becomes mild AR post-TAVR) or (2) any moderate or severe post-TAVR AR, because it was shown to be associated with adverse LV structural and functional remodeling.[9]

Table 2. Comparison of Included vs Excluded Patients

Clinical Characteristics	Included Patients (n=102)	Excluded Patients (n=100)	*P* Value
Age, y	83 (77–88)	83 (77–86)	0.21
Men	59 (58)	52 (52)	0.49
Logistic EuroSCORE (%)	19±13	21±11	0.28
Body surface area, m^2	1.80±0.21	1.79±0.24	0.75
NYHA class III or IV	90 (88)	82 (82)	0.52
Arterial hypertension	84 (82)	82 (82)	0.92
Diabetes mellitus	30 (29)	30 (30)	1.0
Coronary artery disease	69 (68)	47 (47)	0.005
Chronic lung disease	13 (13)	20 (20)	0.23
Echocardiographic parameters			
Aortic valve area, cm^2	0.68±0.17	0.68±0.13	1.0
Aortic valve area index, cm^2/m^2	0.38±0.10	0.39±0.09	0.46
Aortic annulus (2D TTE), mm	21.1±2.2	21.6±2.4	0.18
LVEF (%)	54±12	56±10	0.34
Prosthesis-patient mismatch	41 (40)	37 (37)	0.67

Data are expressed as median (range), number (percentage), or mean±SD. 2D indicates two-dimensional; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TTE, transthoracic echocardiography.

Myocardial Mechanics

2D strain evaluations were done by a single operator (F.P.) blinded to clinical information. LV subendocardial mechanics by STE was measured pre- and post-TAVR using syngo Velocity Vector Imaging (version 3; Siemens Medical Solutions USA, Mountain View, CA), the accuracy of which has been previously validated with sonomicrometry.[17] Apical 4-, 3-, and 2-chamber views were used to obtain longitudinal strain and strain rate. Parasternal short-axis planes were used to obtain circumferential strain, strain rate, rotational angles, and maximal instantaneous basal to apical angle difference (net LV twist). Global peak systolic strain and strain rate and early diastolic strain rate values were derived from the time strain and strain rate curves, averaging the 16 myocardial segments.

Intra- and Interobserver Variability

Ten randomly selected studies were reanalyzed for all major strain parameters once by the same observer several months after the initial analysis. A second experienced observer, blinded to previously obtained data, analyzed the same patients and the same loops for interobserver variability. Ten post-TAVR studies were also analyzed for the reproducibility of the post-TAVR LVOT diameter measurement.

Statistical Analysis

Categorical variables are expressed as percentages and continuous variables as mean±SD or median (interquartile range; IQR). The proportion of patients with PPM post-TAVR during the first 4 and the last 3 years of the study were compared using the chi-square test. Echocardiographic parameters pre- and post-TAVR were compared using the McNemar test for categorical variables or the paired *t* test or the Wilcoxon signed-rank test for continuous variables. Comparisons of the change in echocardiographic parameters post-TAVR between patients with and without PPM were performed using ANCOVA, adjusting for the preprocedural value, LVEF, and presence of significant AR post-TAVR.[9] We chose to adjust for these variables based on past clinical knowledge of the significance of these variables on LV remodeling. Kaplan–Meier curves with a log-rank and Gehan–Breslow–Wilcoxon tests were used to assess survival differences between groups. Predictors of death were analyzed using the multivariable Cox proportional hazards model. The PPM variable (PPM/no PPM) was forced into the model followed by an automated forward selection algorithm (with a $P<0.05$ to enter a new variable in the model) to add other significant variables to the model. Candidate variables considered include those that were significant on a univariable

Table 3. Comparison in Echocardiographic Parameters Pre- and Post-TAVR According to PPM

Echocardiographic Parameters	Patients With No Post-TAVR PPM (n=61)			Patients With Post-TAVR PPM (n=41)			
	Baseline	Follow-up	*P* Value*	Baseline	Follow-up	*P* Value*	*P* Value†
Aortic annulus (2D TTE), mm	21.4±2.0	—	—	20.7±2.4	—	—	
Indexed aortic annulus, mm/m^2	12.2±1.7	—	—	11.3±1.3‡	—	—	
Aortic valve area, cm^2	0.69±0.17	1.93±0.34	<0.001	0.66±0.18	1.32±0.22	<0.001	<0.001
Aortic valve area index, cm^2/m^2	0.40±0.10	1.10±0.17	<0.001	0.36±0.09	0.72±0.11	<0.001	<0.001
Aortic mean gradient, mm Hg	49±17	10±4	<0.001	48±12	12±5	<0.001	0.01
LV end-diastolic diameter, cm	4.5±0.8	4.5±0.8	0.94	4.7±0.9	4.6±0.7	0.55	0.86
LV end-systolic diameter, cm	3.0±0.8	3.0±0.9	0.97	3.3±1.0	3.1±0.8	0.10	0.42
LV diastolic volume/BSA, mL/m^2	60±25	60±22	0.95	60±21	58±23	0.49	0.55
LV systolic volume/BSA, mL/m^2	29±17	27±17	0.39	29±17	27±16	0.15	0.65
LVEF (%)	54±12	57±12	0.08	54±12	56±11	0.36	0.58
LV mass index, g/m^2	134±41	119±38	0.001	133±41	124±38	0.15	0.36
Lateral E', cm/s	6.6±2.3	7.6±2.7	0.06	7.9±2.6‡	7.4±2.6	0.21	0.68
E/E' ratio	14.9±7.8	14.5±9.4	0.61	14.6±8.1	15.9±7.5	0.19	0.37
LA volume, mL/m^2	48±17	44±14	0.12	56±18	55±17	0.84	0.09
RVSP, mm Hg	43±13	41±14	0.35	46±12	41±14	0.07	0.78

Data are expressed as mean±SD. 2D indicates two-dimensional; BSA, body surface area; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; PPM, prosthesis-patient mismatch; RVSP, right ventricular systolic pressure; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiogram.

*Pre- vs post-TAVR.

†Comparison of post-TAVR parameters between PPM vs no PPM.

‡$P<0.05$ for comparison of baseline characteristics between no PPM vs. PPM patients.

screen and others that are clinically associated with mortality: age, EuroSCORE, LVEF, relative reduction in mean transaortic gradient post-TAVR, and post-TAVR right ventricular systolic pressure (RVSP). The assumption of proportional hazards for the Cox model was assessed using Schoenfeld residual plots and tested by adding time-covariate interaction to the model for each covariate.

Sample-size calculation for ANCOVA was performed according to the method of Borm et al.[18] The SD in post-TAVR GLS was estimated at absolute 4%. Assuming a baseline GLS of −14.6% and an improvement in GLS from pre- to post-TAVR of ≈1.3% (based on our previous work[9]), an α=0.05, and 80% power, the sample-size requirement was 68. Intra- and interobserver variability was assessed using mean difference±2SD (Bland-Altman analysis), intraclass correlation coefficient (ICC) and the coefficient of variation (COV). A level of significance of 0.05 was used. Statistical analyses were conducted using SPSS software (version 20; IBM Corp, Armonk, NY).

Results

Study Population

Among the 202 patients who underwent a TAVR procedure from 2007 to 2012 at the Toronto General Hospital, 2009–2011 at the Cleveland Clinic, and in 2013 at Hôpital du Sacré-Coeur de Montréal, and had available preprocedural and mid-term follow-up TTEs, 102 were included. The excluded individuals consisted of 40 patients with atrial fibrillation during TTE and 60 patients with poor endocardial tracking with the VVI software or missing adequate views (flow diagram, Figure S1). Baseline characteristics are presented in Table 1. Median (IQR) age was 83 (77–88) years, and 57% were men. Mean logistic EuroSCORE was 19±13%. At baseline, there was no statistically significant difference between the 102 study patients and the 100 excluded patients with regard to age, sex, EuroSCORE, LVEF, and AVA. Excluded patients had a lower prevalence of coronary artery disease (47% vs 68%; *P*=0.005; Table 2). Incidence of PPM in the included versus excluded patients (40% vs 37%; *P*=0.67) was similar.

Prosthesis-Patient Mismatch

PPM post-TAVR was present in 41 patients (40%). It was moderate in 32 patients (31%) and severe in 9 (9%). No significant differences in baseline clinical characteristics were observed between patients with and without PPM (Table 2). In the last 3 years of the study (from 2011 to 2013), occurrence of PPM was significantly lower compared with the initial 4 years (from 2007 to 2010; 23% vs 46%; *P*=0.04).

Transcatheter Aortic Valve Replacement

Transapical or direct transaortic and transfemoral approaches were used in 52 (51%) and 50 (49%) patients, respectively, with no significant difference between the PPM and no-PPM groups (Table 1). Edwards SAPIEN valves were implanted in 90 patients (88%; including SAPIEN XT in 22 [21%]), and

Table 4. Comparison of Myocardial Mechanics Pre- and Post-TAVR According to PPM

		Patients With No Post-TAVR PPM (n=61)			Patients With Post-TAVR PPM (n=41)			
	Controls (n=21)	Baseline	Follow-up	*P* Value*	Baseline	Follow-up	*P* Value*	*P* Value†
Longitudinal								
GLS (%)	−19.4±2.7	−12.8±4.0	−14.3±4.3	0.01	−12.2±4.1	−13.0±3.6	0.13	0.042
GLSR, s^{-1}	−1.01±0.15	−0.61±0.20	−0.73±0.25	<0.001	−0.59±0.20	−0.63±0.17	0.07	0.006
Early diastolic SR, s^{-1}	0.93±0.17	0.52±0.20	0.64±0.30	<0.001	0.57±0.28	0.55±0.20	0.49	0.004
Circumferential								
GCS (%)	−31.2±4.3	−27.4±7.8	−28.1±8.2	0.58	−26.4±8.0	−26.3±6.2	0.92	0.26
GCSR, s^{-1}	−1.90±0.39	−1.77±0.63	−1.86±0.69	0.39	−1.71±0.65	−1.71±0.51	0.96	0.27
Early diastolic SR, s^{-1}	1.74±0.46	1.80±0.69	1.82±0.70	0.87	1.79±0.74	1.77±0.62	0.89	0.40
Apical rotation (degrees)	8.0±3.8	8.8±5.5	6.2±5.0	0.02	10.4±5.9	6.5±7.3	0.03	0.98
Peak twist angle (degrees)	11.0±4.5	13.5±6.3	11.6±6.1	0.08	15.0±7.6	11.3±5.6	0.07	0.75

Data are expressed as mean±SD. AR indicates aortic regurgitation; GCS indicates global circumferential strain; GCSR, global circumferential strain rate; GLS, global longitudinal systolic strain; GLSR, global longitudinal systolic strain rate; PPM, prosthesis-patient mismatch; SR, strain rate; TAVR, transcatheter aortic valve replacement.

*Pre- vs post-TAVR.

†Post-TAVR PPM vs Post-TAVR no PPM. Comparisons of the change in echocardiographic parameters post-TAVR between patients with PPM and those with no PPM were performed using ANCOVA with the absolute difference from baseline as the outcome and preprocedural value, LVEF, and significant post-TAVR AR as the covariates.

Medtronic CoreValves were implanted in 12 (12%). PPM was not observed in patients with 29- or 31-mm prostheses.

Echocardiography

The pre-TAVR absolute and body surface area (BSA)-indexed diameters of the aortic annulus were smaller in the PPM group (20.7±2.4 vs 21.4±2.0 mm; P=0.06; and 11.3±1.3 vs 12.2±1.7 mm/m^2; P=0.01, respectively). The correlation between the native BSA-indexed aortic annular diameter and the post-TAVR EOA was modest (R=0.31; P=0.001). At baseline, there was no other significant difference in echocardiographic measurements between PPM and no-PPM patients, except for a higher lateral E' in the former (Table 3).

Follow-up TTE studies were performed 6.0±3.0 months post-TAVR, with no significant difference between the PPM and no-PPM subgroups (6.3±2.9 vs 5.7±3.1 months; P=0.39). The increase in iEOA was lower (P<0.001) in the PPM subgroup (from 0.36±0.09 to 0.72±0.11 cm^2/m^2; P<0.001), compared to the no-PPM subgroup (from 0.40±0.10 to 1.10±0.17 cm^2/m^2; P<0.001). This was accompanied by a smaller decrease (P=0.01) in the mean transaortic pressure gradient in the PPM subgroup (from 48±12 to 12±5 mm Hg; P<0.001), compared to the no-PPM subgroup (from 49±17 to 10±4 mm Hg; P<0.001), post-TAVR. LV mass regression was significant only in patients without PPM (Table 3). Overall, LV dimensions, ejection fraction, and conventional parameters of diastolic function did not change significantly post-TAVR in patients with or without PPM.

Postprocedural AR

Severity of post-TAVR AR was none or trivial in 40 patients (39%), mild in 43 (42%), moderate in 18 (18%), and severe in 1 (1%). Among the 41 patients with PPM, significant post-TAVR AR was found in 7 (17%) versus 25 patients (41%) among the 61 with no-PPM (P=0.01).

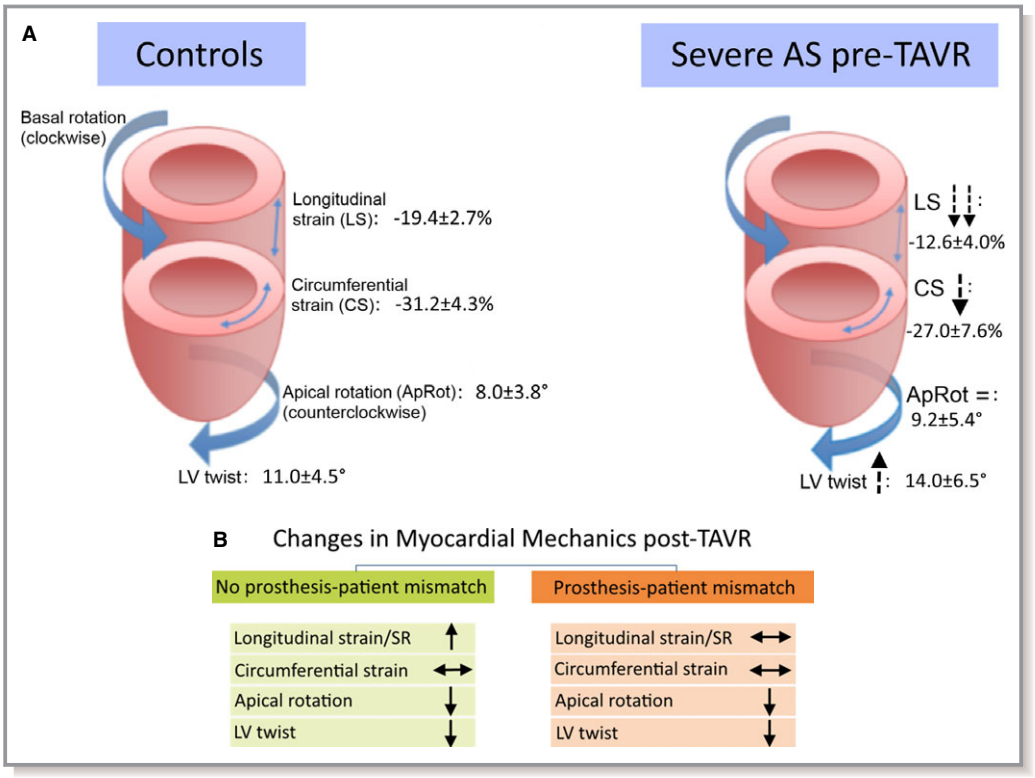

Figure 1. Summary of the pre-TAVR alterations in myocardial mechanics (compared to the controls) and the expected changes post-TAVR according to the presence of PPM. A, Multidirectional myocardial mechanics in control subjects (left panel) and in patients with severe AS (right panel). Increased (↑) parameters of myocardial deformation, as compared to healthy controls, represent compensatory mechanisms. See text for details. B, Changes in myocardial mechanics post-TAVR in patients with severe AS and post-TAVR PPM versus no-PPM. Arrows represent the change in myocardial mechanics compared to the mechanics preceding TAVR (↑: "increases", ↓: "decreases", and ↔: "no change"). ApRot indicates apical rotation; AS, aortic stenosis ; CS, circumferential strain; LS, longitudinal strain; LV, left ventricle; PPM, prosthesis-patient mismatch; SR, strain rate; TAVR, transcatheter aortic valve replacement.

Myocardial Mechanics

Longitudinal deformation

Compared to the control group, the 102 patients with severe AS had lower GLS (−12.6±4.0% vs −19.4±2.7%; $P<0.001$), lower GLSR (−0.61±0.20 vs −1.01±0.15 second^{-1}; $P<0.001$), and lower early diastolic strain rate (0.54±0.24 vs 0.93±0.17 second^{-1}; $P<0.001$; Table 4). At baseline, there was no significant difference in LV myocardial mechanics between PPM and no-PPM patients. At mid-term follow-up, patients without PPM showed consistent improvement in longitudinal systolic and diastolic deformation despite a higher incidence of significant post-TAVR AR: GLS from −12.8±4.0% to −14.3±4.3% ($P=0.01$); GLSR from −0.61±0.20 to −0.73±0.25 second^{-1} ($P<0.001$); and early diastolic strain rate from 0.52±0.20 to 0.64±0.20 second^{-1} ($P<0.001$). In contrast, the changes in longitudinal strain parameters did not reach statistical significance in the PPM group. After adjusting for pre-TAVR strain and strain rate values, LVEF, and significant post-TAVR AR, patients with no PPM had greater improvement of LV longitudinal systolic and diastolic function by STE at follow-up compared with those with PPM (Figures 1 and 2; Table 4).

Circumferential deformation, rotation, and net LV twist angle

At baseline, patients with AS had significantly lower global circumferential strain (−27.0±7.6% vs −31.2±4.3%; $P=0.02$) than healthy controls. However, at mid-term follow-up post-TAVR, there was no significant improvement in circumferential deformation in either the PPM or no-PPM subgroups (Table 4). Apical rotation and net LV twist, a compensatory mechanism in severe AS, which was supraphysiological pre-TAVR (14.0±6.5 degrees in patients vs 11.0±4.5 degrees in controls; $P=0.05$), decreased toward normal values post-TAVR in both the PPM and no PPM subgroups (Table 4).

Survival

During a median follow-up of 46.1 months (IQR, 35.4–60.8; range, 11.1–84.6), there were 14 (34%) deaths in the PPM

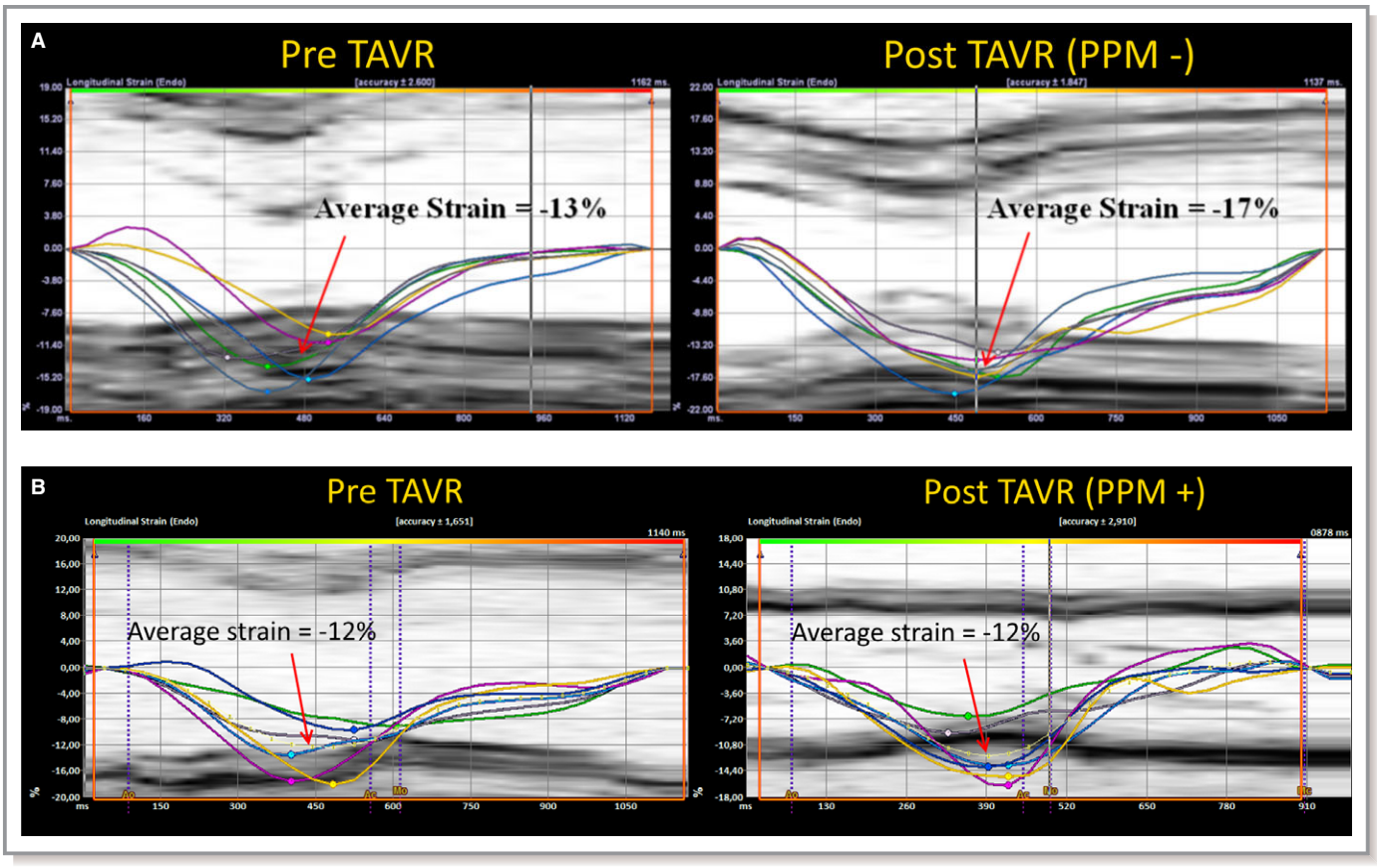

Figure 2. Segmental longitudinal strain curves (apical 2-chamber view) in representative patients pre- versus post-TAVR. A, In a representative patient without PPM, longitudinal systolic strain is reduced at baseline with near normalization post-TAVR. B, In a representative patient with PPM, longitudinal systolic strain is reduced at baseline with no change post-TAVR. PPM indicates prosthesis-patient mismatch; TAVR, transcatheter aortic valve replacement.

group and 21 (34%) in the no-PPM group. Median survival time was 75.4 versus 56.1 months, respectively (Figure 3). There was no difference in survival between the groups (log-rank test, *P*=0.49; Gehan–Breslow–Wilcoxon test, *P*=0.48). On univariable Cox regression analysis, the relative reduction in mean transaortic gradient postprocedure and post-TAVR right ventricular systolic pressure were predictors of mortality (Table 5). Neither the presence of moderate or severe PPM, severe PPM, nor post-TAVR iEOA (as a continuous variable) predicted all-cause mortality. Even in the 70 patients with no significant post-TAVR AR, PPM remained unassociated with survival. In a multivariable Cox model including PPM and the potential confounders, PPM did not independently predict mortality (hazard ratio [HR], 0.80; 95% CI, 0.36–1.77; *P*=0.59). In the final model, the relative reduction in mean transaortic gradient postprocedure was the only other significant predictor of mortality (HR, 0.67 per 10% reduction; 95% CI, 0.49–0.91; *P*=0.01). The linearity assumption for the mean transaortic gradient in the final model was tested by entering the square of the term along with the linear term into the final model. The squared term was not significant (*P*=0.52) and hence removed from the model. The assumption of proportional hazards was met for the covariates in the final model.

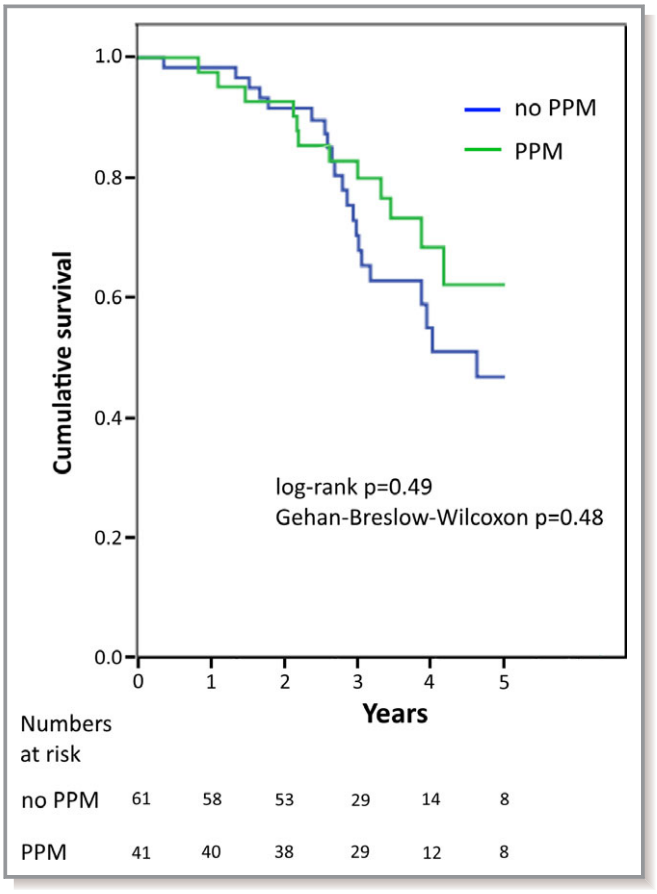

Figure 3. Kaplan–Meier survival curves stratified by the presence or absence of PPM. Kaplan–Meier curves were truncated at 5 years because of the paucity of data beyond 5 years. There was no difference in overall survival between the PPM and no-PPM groups (log-rank test, *P*=0.49; Gehan–Breslow–Wilcoxon test, *P*=0.48). PPM indicates prosthesis-patient mismatch; TAVR, transcatheter aortic valve replacement.

Inter- and Intraobser Variability

Analysis of intra- and interobserver variability demonstrated very good agreement between observations (Tables 6 and 7).

Discussion

Despite the hopes that PPM would be obsolete in the era of TAVR, we identified PPM in 40% of our patients (including 9% severe PPM). Improvement in LV longitudinal systolic and diastolic deformation and LV mass regression was significantly lower at mid-term follow-up in the presence of moderate or severe PPM post-TAVR. We did not identify an association between PPM and all-cause mortality.

Incidence and Predictors of PPM

Occurrence of PPM post-SAVR is well recognized. Compared to SAVR, the valves used for TAVR have better hemodynamic performance, contributing to a reduction in PPM.[2,3,5,19] In the randomized comparison of patients from the PARTNER trial A cohort, TAVR was associated with less PPM (46% vs 60%) and severe PPM (20% vs 28%), compared to SAVR.[5] The difference in severe PPM was particularly important in patients with small aortic annuli (<20 mm).[5,20]

In our study, the incidence of moderate (31%) and severe (9%) PPM was consistent with the literature. There was an association between a smaller native aortic annulus diameter and PPM and between BSA-indexed native aortic annulus size and post-TAVR EOA, similar to the study by Clavel et al.[15] However, this association has not been consistent among all studies,[21–24] suggesting that the annulus size is only one factor among the interplay of several other causes, such as bulky calcifications, suboptimal valve positioning, and valve deployment.

In our study, when treatment was divided into 2 periods (2007–2010 and 2011–2013) to reflect the routine use of MDCT or 3D TEE for annular sizing at our institutions from 2011 onward, we detected a 50% reduction in the proportion with PPM during the recent period. Although our data are only hypothesis generating, this may reflect larger-size prosthesis and better prosthesis selection guided by 3D modalities[25,26] in the latter period. In our study, no case of PPM occurred with the largest prostheses (Edwards SAPIEN 29 mm or Medtronic CoreValve 29–31 mm), which were typically not available during most studies reporting PPM post-TAVR.

Table 5. Univariable Cox Regression Proportional Hazards Model

Variables	Death	
	HR (CI)	*P* Value
Baseline clinical characteristics		
Age	0.987 (0.950–1.027)	0.53
Body mass index	0.959 (0.900–1.022)	0.15
Male sex	0.881 (0.447–1.736)	0.71
Logistic EuroSCORE (%)	0.986 (0.954–1.019)	0.41
Diabetes mellitus	1.173 (0.581–2.369)	0.66
Coronary artery disease	0.664 (0.333–1.322)	0.24
Peripheral vascular disease	1.243 (0.475–3.251)	0.66
Previous CABG	0.696 (0.343–1.411)	0.32
Chronic lung disease	1.216 (0.426–3.467)	0.72
Procedural details		
Apical or direct transaortic	1.716 (0.846–3.483)	0.14
Medtronic CoreValve	1.939 (0.670–5.617)	0.22
Baseline echocardiographic parameters		
Indexed aortic annulus, mm/BSA	1.006 (0.815–1.241)	0.96
Aortic valve area index, cm^2/m^2	4.653 (0.192–111.062)	0.35
Aortic mean gradient, mm Hg	0.995 (0.971–1.019)	0.69
LV diastolic volume/BSA, mL/m^2	0.987 (0.970–1.004)	0.13
LV systolic volume/BSA, mL/m^2	0.977 (0.953–1.002)	0.07
Stroke volume, mL/m^2	0.995 (0.960–1.033)	0.81
LVEF (%)	1.03 (0.997–1.064)	0.08
LV mass index, g/m^2	0.998 (0.989–1.007)	0.67
RVSP, mm Hg	0.976 (0.945–1.009)	0.15
Absolute GLS (%)	1.033 (0.954–1.119)	0.42
Post-TAVR		
Presence of PPM	0.786 (0.399–1.549)	0.48
Severe PPM	0.790 (0.240–2.596)	0.70
iEOA, cm^2/m^2	1.108 (0.276–4.448)	0.89
Change in iEOA, cm^2/m^2	0.834 (0.194–3.581)	0.81
% reduction change in mean gradient (10%)	0.717 (0.540–0.953)	0.02
LVEF (%)	1.012 (0.985–1.040)	0.39
Stroke volume, mL/m^2	1.026 (0.991–1.062)	0.15
LV mass index, g/m^2	0.998 (0.988–1.008)	0.63
Absolute GLS (%)	1.028 (0.947–1.116)	0.51
Relative increase in GLS	0.997 (0.990–1.004)	0.36
Significant aortic regurgitation	1.189 (0.593–2.385)	0.63
RVSP, mm Hg*	1.037 (1.013–1.063)	0.003

BSA indicates body surface area; CABG, coronary artery bypass graft; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GLS, global longitudinal strain; HR, hazard ratio; iEOA, effective orifice area indexed to BSA; LV, left ventricular; LVEF, left ventricular ejection fraction; PPM, prosthesis-patient mismatch; RVSP, right ventricular systolic pressure; TAVR, transcatheter aortic valve replacement.
*Multiple imputation was performed for the variable post-TAVR right ventricular systolic pressure (14% missing data).

Impact of PPM Post-TAVR: Current Knowledge

Most studies describing the impact of PPM post-TAVR have been small and yielded variable conclusions. Similar to our findings, Ewe et al. reported less LV mass regression in 30 patients (18.2%) with PPM at 6 months post-TAVR with Edwards SAPIEN prostheses. Da Silva et al. described an association between PPM and less LV mass regression post-TAVR[26] whereas Giannini et al. did not.[27] However, PPM post-TAVR has not been associated with mortality, major adverse valve-related and cardiovascular events, or poor functional class.[21,22,24] TAVR patients are characterized by older age, extensive comorbidities, frequent physical inactivity, frailty, and longer exposure to the hemodynamic effects of AS, which potentially contribute to a lower susceptibility to the adverse effects of PPM.[21,28] In the PARTNER A trial, Pibarot et al. demonstrated no impact of PPM on LV mass regression and survival in TAVR patients. Only in the TAVR nonrandomized continued access arm of this study was there higher mortality in patients with severe PPM, specifically in the absence of postprocedural AR.[5] In our study, PPM was not associated with all-cause mortality, but was associated with less post-TAVR AR.

PPM and Ventricular Function Post-TAVR

In the recent post-hoc analysis from the PARTNER A trial, PPM had no impact on the postprocedural change in LVEF in the TAVR group.[5] Conversely, Da Silva et al. reported an improvement in LVEF post-TAVR in the no-PPM subgroup only.[26] LVEF is not a sensitive marker to detect early recovery of LV systolic function post-TAVR, thus we have used myocardial strain instead. Our study demonstrates, for the first time, that PPM prevents recovery in myocardial function post-TAVR. Although not demonstrated in our study, a greater magnitude of change in GLS post-TAVR has been associated

Table 6. Reproducibility Analysis for Strain Parameters (n=10)

Variables	Interobserver Variability				Intraobserver Variability			
	Mean±SD	Mean Difference±2SD	ICC	COV (%)	Mean±SD	Mean Difference±2SD	ICC	COV (%)
Global longitudinal strain (%)	−13.9±3.8	0.9±4.8	0.90	7	−13.6±4.0	1.5±3.7	0.95	6
Global longitudinal SR, s^{-1}	−0.61±0.20	0.06±0.22	0.93	6	−0.60±0.20	0.08±0.26	0.89	6
Global circumferential strain (%)	−25.5±7.6	1.6±4.2	0.98	3	−25.7±7.7	1.2±3.9	0.98	3
Global circumferential SR, s^{-1}	−1.34±0.35	0.12±0.26	0.96	5	−1.36±0.35	0.10±0.19	0.98	3
Apical rotation (degrees)	8.4±4.2	−0.6±3.9	0.95	11	8.7±3.7	0.01±2.8	0.96	8
Peak twist angle (degrees)	12.6±6.3	−0.2±5.9	0.95	12	13.0±6.2	0.6±7.1	0.92	14

COV indicates coefficient of variation; ICC, intraclass correlation coefficient; SR, strain rate.

with lower mortality rate.[8] Longer-term follow-up and a larger sample size may be necessary to demonstrate the association of strain changes and long-term outcomes.

Interaction Between PPM and Aortic Regurgitation

In our study, the effect of PPM on the change in myocardial mechanics post-TAVR was adjusted for the presence of post-TAVR AR, because of the adverse impact of the latter on LV structural and functional remodeling post-TAVR as demonstrated in our previous work.[9] There was an interaction between PPM and post-TAVR AR, with significantly more AR in patients without PPM, potentially minimizing the expected benefit of the absence of PPM on LV recovery. It is possible that patients with larger aortic annuli (and, consequently, less PPM) have more prosthesis-annulus incongruence and worse prosthesis apposition contributing to post-TAVR AR.[29] Other groups have also reported more AR in the no-PPM subgroup.[5,21,22] The rate of moderate-to-severe paravalvular AR also tended to increase in accord with annulus size in the PARTNER trial and the FRANCE 2 registry.[20,30]

Limitations

There were a number of limitations to this study. We excluded significant proportion of patients. However, reasons such as poor echocardiographic tracking, image quality, and atrial fibrillation are not related to PPM and should not affect the validity of our findings. We have also shown that there are no important differences between the included and excluded patients with respect to their baseline characteristics, except for a lower prevalence of coronary artery disease in the latter. There was heterogeneity in the timing of the post-TAVR follow-up echocardiographic studies; however, the length of follow-up was not statistically different between the PPM and no-PPM subgroups. Our uniform methodology to derive the post-TAVR EOA based on the measurements taken underneath the apical margin of the valve stent recommended in the VARC II consensus document[16] has not been validated for the CoreValve prostheses.[23,31] However, because of the small magnitude of expected potential errors generated by this difference and the limited number of CoreValves included (n=12), this is unlikely to bias our findings. Although 3D imaging-based calculation of annular diameters either using the annular area or perimeter is more robust, these data were not available in all our patients. Similar to the majority of publications examining PPM,[5,22,23] we used 2D linear diameter from the long-axis views. Finally, this study was not powered to detect difference in survival or long-term outcomes.

Conclusion

PPM is relatively common in the TAVR era. High-risk patients with end-stage AS remain a vulnerable population to the adverse effects of PPM on recovery of LV longitudinal

Table 7. Reproducibility Analysis for LVOT Diameter (n=10)

Variables	Interobserver Variability				Intraobserver Variability			
	Mean±SD	Mean Difference±2SD	ICC	COV (%)	Mean±SD	Mean Difference±2SD	ICC	COV (%)
LVOT, mm	20.8±2.1	0.3±0.6	0.96	1.6	22.2±1.8	0.3±1.9	0.93	2

COV indicates coefficient of variation; ICC, intraclass correlation coefficient; LVOT, left ventricular outflow tract.

function. Even if the impact on clinical outcomes could not be demonstrated in the current study, our results provide a rationale to avoid PPM post-TAVR, which may assume greater importance if the indication for TAVR is expanded to include lower-risk and younger patients in the future. Optimal prosthesis selection and deployment using contemporary strategies should aim to avoid PPM in high-risk patients with severe AS.

Disclosures

None.

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