ORIGINAL RESEARCH

Reversibility of Cardiac Function Predicts Outcome After Transcatheter Aortic Valve Replacement in Patients With Severe Aortic Stenosis

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***Background*—**Reversibility of left ventricular (LV) dysfunction in high-risk aortic stenosis patient and its impact on survival after transcatheter aortic valve replacement (TAVR) are unclear. We aimed to evaluate longitudinal changes of LV structure and function after TAVR and their impact on survival.

***Methods and Results*—**We studied 209 patients with aortic stenosis who underwent TAVR from May 2006 to December 2012. Echocardiograms were used to calculate LV end-diastolic volume index (LVEDVi), LV ejection fraction, LV mass index (LVMi), and global longitudinal strain before, immediately (<10 days), late (1–3 months), and yearly after TAVR. During a median follow-up of 1345 days, 118 patients died, with 26 dying within 1 year. Global longitudinal strain, LVEDVi, LV ejection fraction, and LVMi improved during follow-up. In patients who died during the first year, death was preceded by LVEDVi and LVMi increase. Multivariable longitudinal data analysis showed that aortic regurgitation at baseline, aortic regurgitation at 30 days, and initial LVEDVi were independent predictors of subsequent LVEDVi. In a joint analysis of longitudinal and survival data, baseline Society of Thoracic Surgeons score was predictive of survival, with no additive effect of longitudinal changes in LVEDVi, LVMi, global longitudinal strain, or LV ejection fraction. Presence of aortic regurgitation at 1 month after TAVR was the only predictor of 1-year survival.

***Conclusions*—**LV reverse remodeling was observed after TAVR, whereas lack of LVEDVi and LVMi improvement was observed in patients who died during the first year after TAVR. Post-TAVR, aortic regurgitation blocks reverse remodeling and is associated with poor 1-year survival after TAVR. **(*J Am Heart Assoc*. 2017;6:e005798. DOI: 10.1161/JAHA.117.005798.)**

Key Words: aortic valve stenosis • echocardiography • longitudinal strain • remodeling • transcatheter aortic valve implantation

Cardiac structures possess a quality of plasticity: an ability to change their size, shape, and wall thickness based on the development, or elimination, of chronic changes in hemodynamic conditions, such as preload increase, as in the presence of valvular regurgitation or afterload increase in the presence of aortic stenosis (AS).[1] In AS, pressure overload leads to a hypertrophic response in left ventricular (LV) walls, interstitial fibrosis, and eventually LV systolic dysfunction and death[2,3] In contrast, elimination of afterload (eg, by transcatheter aortic valve replacement [TAVR]) leads to immediate improvement of cardiac function, followed by delayed reverse remodeling in cardiac structures. Introduction of TAVR enabled AS patients who were older, sicker, and often with severely reduced LV function to receive potentially life-saving treatment.[4] In this population with aging hearts, it is unclear whether elimination of AS leads only to immediate improvement of LV systolic function or whether reverse remodeling also contributes to survival.

We aimed to evaluate longitudinal changes of LV function and structural parameters evaluated by echocardiography in severe AS patients undergoing TAVR, and to assess their impact on survival. We also aimed to identify the baseline echocardiographic parameters to predict reversibility of cardiac function in this population.

Methods

Study Sample

We retrospectively identified 237 consecutive symptomatic patients (New York Heart Association class II symptoms or

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/6/7/e005798/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- This study shows that elimination of pressure overload by transcatheter aortic valve replacement leads, in general, to improvement in left ventricular (LV) global longitudinal strain and reverse LV remodeling regardless of baseline characteristics.
- The absence of improvement, as evidenced by an increase of LV mass and LV volume, was observed in patients who eventually died during the first year after transcatheter aortic valve replacement.
- Significant post-transcatheter aortic valve replacement aortic regurgitation blocks reverse remodeling.
- The presence of aortic regurgitation post-transcatheter aortic valve replacement was the only independent predictor of survival during the first year of follow-up, whereas this effect is lost during a more-prolonged follow-up.

What Are the Clinical Implications?

- Our study shows that reversal of cardiac dysfunction is possible in patients with advanced age, depressed LV function, and advanced LV hypertrophy.
- Our findings also provide an additional mechanistic explanation of the worse prognosis associated with significant postprocedural aortic regurgitation.
- The diminished prognostic impact of cardiac dysfunction after the first year suggests that noncardiac comorbidities may have masked any beneficial effect of improved cardiac physiology on survival at long-term follow-up.

more) with severe AS who underwent transfemoral TAVR at Cleveland Clinic between May 2006 and December 2012. We defined severe AS as aortic valve area of <0.8 cm^2 with either a mean aortic pressure gradient ≥ 40 mm Hg or a peak aortic valve velocity ≥ 4.0 m/s.[5] Patients were included in this study if they had at least 1 follow-up echocardiographic study. All echocardiograms were acquired in a prospectively determined sequence at baseline, before discharge, 1 month, 6 months, and 1 year and annually thereafter. All strain measurements were performed by a single reader. All LV end-diastolic volume (LVEDV), LV ejection fraction (LVEF), and LV mass measurements were reviewed and, if necessary, reanalyzed by a single reader. To eliminate the confounding effects of planned staged interventions aimed to improve LV systolic function, we excluded patients who underwent biventricular pacing or revascularization after TAVR. Patients with inadequate image quality were also excluded. Clinical and demographic data were obtained by manual extraction from electronic medical records. The survival status of all patients after TAVR was also collected. All-cause mortality was considered to be the primary outcome. The study protocol was approved by the Cleveland Clinic Institutional Review Board, data were de-identified, and informed consent was waived.

Basic Echocardiographic Measurement

Comprehensive echocardiographic measurements were performed using commercially available ultrasound systems (General Electric Medical Systems, Milwaukee, WI; Philips Medical Systems, NA, Bothell, WA; Siemens Medical Solutions USA, Inc, Malvern, PA). Baseline and subsequent echocardiographic measurements were systematically reviewed and measured by an experienced reader. Echocardiographic parameters included LVEDV, end-systolic volume, LVEF, LV mass index (LVMi), aortic valve area, and peak velocity of transaortic valve flow. The LVEDV, LVESV, and LVEF were measured by the biplane Simpson's method from apical views. The aortic valve area was estimated by the 2-dimensional Doppler method using the continuity equation.

Two-dimensional Strain Echocardiography

Two-dimensional speckle-tracking echocardiography measurements were performed offline using vender-independent software (Velocity Vector Imaging; Siemens Medical Solutions, Erlangen, Germany), and LV global longitudinal strain (GLS) was measured at each time point. Apical 4-chamber, 2-chamber, and long-axis views were acquired for strain analysis. The endocardial border was manually traced in the end-systolic frame; then, the software automatically performed speckle-tracking analysis throughout 1 cardiac cycle and calculated average strain value for 6 segments for each view. In segments with poor tracking, readjustment of the borders was performed until adequate tracking was achieved. Estimated peak systolic strain value from apical 4-chamber, 2-chamber, and long-axis views were averaged to obtain GLS. All strain measurements were performed by a single observer blinded to clinical, other echocardiographic data and outcome. To assess the intra- and interobserver variability of the strain measurements, we randomly selected 10 data sets. Two observers analyzed the same data sets on 2 different occasions separated by a 1-week interval, without knowledge of another observer's measurements. Variability was assessed by SE of the measurement. Intraobserver variability of GLS was 1.2%, whereas interobserver variability of GLS was 1.4%.

Statistical Analysis

Continuous data are expressed as mean$\pm$SD when normally distributed, or median (interquartile range). Categorical data are presented as an absolute number and percentages. The paired *t* test and Wilcoxon signed-rank test were used to

compare the data between, before, and after TAVR, as appropriate. Longitudinal data analysis of echocardiographic parameters was performed using a mixed-effect model under the assumptions of data missing at random. To assess the differences in the changes of LV function and geometry between groups over time, a linear mixed-effect model was applied with unstructured covariance for random effects.[6,7] The model was constructed using patient groups based on LVEF, LV hypertrophy (LVH), mortality, and time to examination. To account for early and late change in LV parameters, as appropriate, we also added to the model whether the assessment was pre-TAVR or post-TAVR. Model selection was accomplished using log likelihood ratio testing. Logarithmic transformation of time was used if shown to be superior to nontransformed data. Slopes of regression lines obtained by a mixed model are presented along with the corresponding SEs of the actual measurements to show change of echocardiographic parameters over time. Data were modeled as unbalanced longitudinal data. To assess relationships between aortic regurgitation (AR) and LVEDV index (LVEDVi), we modeled it as a multivariable longitudinal data analysis using a random coefficient mixed model, where regression coefficients were fit jointly for AR and LVEDVi for each subject. This was under the assumption that these regression coefficients represent a random sample from a population. In a next step, we used a longitudinal model to see how preceding AR severity impacts subsequent LVEDVi values. We assessed AR at baseline, AR at 30 days (defined as AR measured between 10 and 59 days), and AR at 60 days (defined as AR measured between 31 and 100 days) as potential predictors of the subsequent values of LVEDVi, as well as the change in AR from baseline. Initial LVEDVi was also included as a predictor in the model. A univariable Cox proportional hazards model was constructed to assess baseline or changes in echocardiographic parameter, which are associated with survival. Changes of echocardiographic parameter during the first 10 days after TAVR and during the first 100 days after TAVR were calculated by subtracting follow-up data by baseline value (negative value means improvement in GLS and LVEDVi). To adjust for potential bias that would stem from the longitudinal and survival analyses being conducted separately, we performed joint analysis of the echocardiographic longitudinal data and overall survival using the SAS software macro JMFIT.[8] A time trajectory shared parameter model was constructed where the trajectory function from the longitudinal data is treated like a time-varying covariate in the survival model. Model fit was assessed using decomposition of Akaike information criterion and Bayesian information criterion, as well as ΔAkaike information criterion and ΔBayesian information criterion. Multivariable linear regression analysis was performed to determine parameters associated with changes of GLS and LVEDVi. To find the determinants of LVEDVi changes, a multivariable linear regression model was constructed using forward step-wise selection with age, sex, baseline GLS (or LVEF), LVEDVi, LVMi, AR severity, and presence of coronary artery disease as covariates. A P value of <0.05 was considered statistically significant. All statistical analyses were performed with JMP (version 10.0; SAS Institute Inc, Cary, NC), SPSS software (version 23.0; SPSS Inc, Chicago, IL), and R software (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Population

Out of the initial group of 237, we excluded 27 patients because of inadequate image quality. In addition, 1 patient was excluded as he had cardiac resynchronization therapy defibrillator implantation immediately after TAVR, which left a final sample of 209 patients with interpretable baseline echocardiographic images and at least 1 follow-up echocardiographic study. There was no significant difference in patient demographics between included and excluded patients (Table S1). Table 1 shows patient demographics. Of those 209 patients, 145 (69%) were deemed to be inoperable, and the rest were considered intermediate- to high-risk surgical patients. Among the 183 patients who survived more than 1 year after TAVR, 155 (84%) had an echocardiogram obtained during the 6-month to 1-year interval of follow-up.

Table 1. Patient Clinical Characteristics

	All Patients (n=209)
Age, y	81±10
Male, n (%)	122 (58)
Body surface area, m^2	1.91±0.26
NYHA class	3 (3, 3)
NYHA ≥III, n (%)	196 (94)
Diabetes mellitus, n (%)	86 (41)
Dyslipidemia, n (%)	162 (78)
Hypertension, n (%)	175 (84)
Coronary artery disease, n (%)	176 (84)
STS score (risk of mortality)	9.6±5.2
Logistic Euro score	27.1±19.2
Creatinine, mg/dL	1.15±0.46
First generation valve, n (%)	193 (92)
Valve size 23 mm, n (%)	92 (44)
Valve size 26 mm, n (%)	117 (56)

Values are mean±SD, median (interquartile range), or n (%). NYHA indicates New York Heart Association; STS, Society of Thoracic Surgeons.

Among 161 patients who survived more than 2 years after TAVR, 132 (82%) had an echocardiogram obtained during the second year of follow-up. Finally, of 137 patients who survived more than 3 years, 99 (72%) had an echocardiogram during a third year of follow-up.

Echocardiographic Parameters at Baseline and After TAVR

At baseline, 114 (55%) patients had preserved LVEF (>50%) and 152 (75%) had significant LVH (Table 2). In total, 71 of our patients had a mean gradient across aortic valve ≤40 mm Hg, with 45 of these patients having also decreased systolic function. Dobutamine stress echocardiogram was done in 17 patients with decreased systolic function. Among the 209 patients with follow-up echocardiographic study, median range to the echocardiographic studies was 710 days (interquartile range, 212–1112) with 5 (interquartile range, 3–6) echocardiographic studies as median. Immediately after TAVR, there was expected improvement of peak aortic valve flow velocity (4.37±0.74 to 2.39±0.48 m/s; $P<0.001$), mean pressure gradient (47±15 to 12±5 mm Hg; $P<0.001$), and valvuloarterial impedance (6.9±2.6 to 5.6±2.7 mm Hg/mL per m^2; $P<0.001$), with no change in systolic blood pressure (128±21 to 128±22 mm Hg; $P=0.89$). Severity of post-TAVR AR was: none or trivial in 93 (44%) patients, mild in 93 (44%), and moderate or more in 23 (11%).

Table 2. Baseline Hemodynamic and Echocardiographic Parameters

	N=209
Systolic blood pressure, mm Hg	128±21
Indexed AVA, cm^2/m^2	0.33±0.08
AV peak velocity, m/s	4.37±0.74
AV mean PG, mm Hg	47±15
AR (≥moderate), n (%)	40 (19)
LVEDVi, mL	59±25
LVESVi, mL	30±21
LVEF, %	50±14
LV stroke volume index, mL/m^{2*}	35±10
LVMi, g/m^2	133±37
GLS, %	−12.0±3.7
AR post-TAVR (≥moderate), n (%)	23 (11)
Early after TAVR (<10 d)	
LVEDVi, mL	57±23
LVESVi, mL	28±20
LVEF, %	53±13
GLS, %	−12.8±3.4
Late after TAVR (10–100 d)	
LVEDVi, mL	60±25
LVESVi, mL	30±22
LVEF, %	53±13
GLS, %	−13.0±3.6

Values are mean±SD or n (%). AR indicates aortic regurgitation; AV, aortic valve; AVA indicates aortic valve area; GLS, global longitudinal strain; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVMi, left ventricular mass index; PG, pressure gradient; TAVR, transcatheter aortic valve replacement.

*Left ventricular stroke volume index was calculated as a product of the time-velocity integral of the pulse wave Doppler signal obtained at the left ventricular outflow tract and its corresponding cross-sectional area.

Immediate and Long-Term Changes in LV Systolic Function and Structure After TAVR

We used GLS and LVEF as parameters of systolic function and LVEDVi and LVMi as a parameter of LV structure. TAVR led to immediate improvement in GLS (from −12.0±3.7% to −12.8±3.4%; $P=0.008$), reflective of immediate reduction of afterload and subsequent further improvement during follow-up ($P<0.001$; Figure 1A). Similar to its effect on GLS, TAVR also led to immediate improvement in LVEF (from 50±14% to 53±13%; $P<0.001$), reflective of immediate release of afterload. This was followed by a trend toward further improvement over time ($P=0.07$). LVEDVi showed a small, but steady, rate of decrease after TAVR ($P<0.001$), without the abrupt early change that was characteristic of systolic function parameters (Figure 1B). LVMi also showed a small, but steady, rate of decrease during follow-up after TAVR ($P<0.001$), again without an abrupt early change.

Impact of Baseline LV Function on Recovery After TAVR

When we stratified patients according to their baseline LVEF, patients with decreased baseline ejection fraction (EF) showed a larger immediate improvement in GLS (reduced EF, −1.0%; preserved EF, −0.3% change; $P=0.04$). Both groups showed similar GLS improvement during the late phase (P=NS between groups). As expected, immediately after TAVR, LVEF improved only in patients with reduced baseline LVEF (reduced EF,, +6%; preserved EF, +0.3% change; $P<0.001$); LVEF continued to improve during follow-up only in patients with initially reduced EF (reduced EF, +9% change at first year; preserved EF, −0.1% change at first year; $P=0.01$). Similarly, LVEDVi decrease was only observed in reduced EF patients (reduced EF, −7 mL/m^2 change at first year; preserved EF, +1 mL/m^2 change at first year; $P<0.001$). Baseline LVEF did not influence the rate of LVMi decrease (reduced EF, −17 g/m^2; preserved EF, −14 g/m^2 change at first year; $P=0.43$). In addition, we also compared GLS

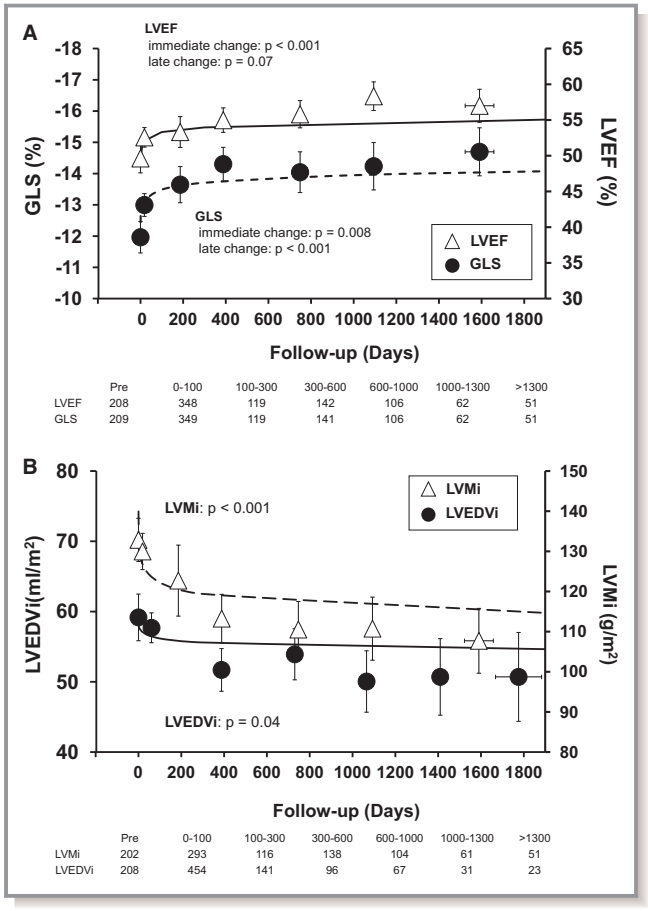

Figure 1. Changes of (A) GLS and LVEF and (B) LVEDVi and LVMi. Markers represent the average of the observed data obtained before TAVR (time zero) over the intervals of 0 to 100, 101 to 300, 301 to 600, 601 to 1000, 1001 to 1300, and >1300 days. Error bars represent 95% CIs. The regression line is obtained by the mixed-model approach. In GLS and LVEF, immediate change and late change were analyzed separately. *P* values for time after TAVR are shown. GLS indicates global longitudinal strain; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; TAVR, transcatheter aortic valve replacement.

improvement in patients with and without LVH.[9] Patients with LVH had worse baseline GLS (LVH, −11.6±3.8%; no LVH, −12.9±3.3%; *P*=0.01), but greater GLS improvement during the follow-up period (LVH, −2.0% change at the first year; no LVH, −1.1% change at the first year; *P*=0.04) compared with no LVH patients. When we subdivided patients according to the presence or absence of coronary artery disease, changes in LVEF, GLS, LVEDVi, and LVMi over time were not different between the 2 groups (*P*>0.10 for all comparisons).

Impact of Post-TAVR Aortic Regurgitation on LVEDVi

Figure 2A shows LVEDVi over time with patients stratified according to severity of AR occurring immediately after TAVR, whereas Figure 2B shows relative change in LVEDVi when referenced to baseline LVEDVi. Of note changes in LVESVi, LVEF, LVMi, and GLS were similar between these 2 groups of AR severity. Interestingly, patients with moderate-to-severe AR had slightly higher initial LVEDVi (*P*=0.044). As can be seen, patients with moderate and severe postprocedural AR showed a lack of LVEDVi decrease.

Multivariable longitudinal data showed an overall trend of LVEDVi decrease over time (*P*=0.019), whereas the change in AR over time was more variable between patients (*P*=0.965). However, the correlation between the regression coefficients of AR and LVEDVi was quite high with *r*=0.89. Assessment of the way AR impacts subsequent LVEDVi values showed that AR at baseline (*P*=0.004), AR at 30 days (*P*=0.015), and initial LVEDVi (*P*<0.001) were simultaneously significant predictors of subsequent LVEDVi. The change in AR from baseline to 1 month, regardless of the actual AR value at baseline, was also a significant predictor (*P*=0.002). Similarly, in a model with AR at 60 days, AR at baseline (*P*=0.007), AR at 60 days (*P*=0.001), and initial LVEDVi (*P*<0.001) were simultaneously significant predictors of LVEDVi, as well as the change from baseline to 2 months (*P*=0.001).

Cardiac Function and Survival After TAVR

During a median follow-up period of 1345 days (interquartile range, 822–1674), 118 (56%) patients died. Twenty-six deaths occurred during the first year. To assess whether LV function and structure affected survivorship, we divided the patients based on whether or not they survived the first year of follow-up. LVEDVi increased throughout the first year in patients who died during the first year, whereas the opposite was true in survivors (*P*=0.02 for first-year change; Figure 3A). Similarly, LVMi increased in patients who died during the first year, whereas LVMi decreased continuously in survivors (*P*=0.02 for first-year change; Figure 3B). GLS and LVEF showed similar changes in first-year survivors and nonsurvivors.

In the next step, we analyzed the impact of systolic function and cardiac reversibility on survival.

In univariable survival analysis, higher baseline Society of Thoracic Surgeons (STS) score (*P*=0.003) and baseline GLS (*P*=0.040) were associated with poor survival, with baseline LVMi (*P*=0.08) showing a trend toward significance (Table S2). In a multivariable nonparsimonious analysis that included baseline STS score, GLS, and AR at 1 month of follow-up, baseline STS score (*P*=0.009) was predictive of survival, with GLS (*P*=0.114) and AR 1 month post-TAVR (*P*=0.222) showing only a weak trend toward significance. A joint analysis of the longitudinal data and overall survival showed a weak trend of LV mass change (*P*=0.127) having impact of survival, with LVEDVi change, GLS change, and EF change having no impact (*P*>0.50 for all). Interestingly, when we examined survival at

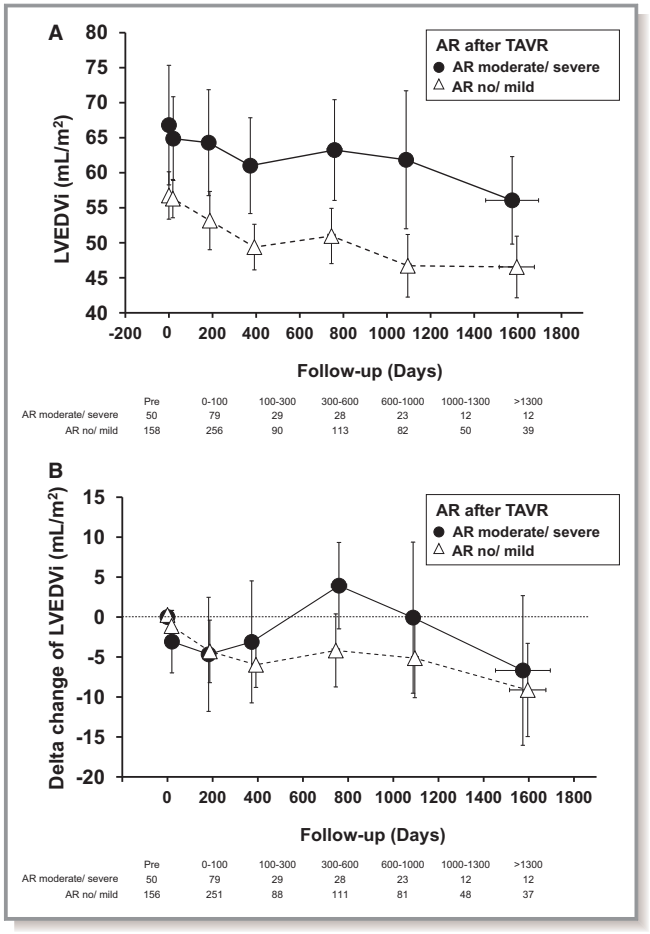

Figure 2. Changes of (A) LVEDVi and (B) delta change of LVEDVi when we stratified patients according to postprocedural aortic regurgitation severity at 1 month after TAVR. Patients with postprocedural aortic regurgitation detected during the first 30 days after TAVR had higher initial LVEDVi. They did not show decrease in LVEDVi during long-term follow-up. Markers represent the average of the observed data obtained before TAVR (time zero) over the intervals of 0 to 100, 101 to 300, 301 to 600, 601 to 1000, 1001 to 1300, and >1300 days. Error bars represent 95% CIs. Delta change of LVEDVi was calculated by subtracting follow-up data by baseline value (negative value means improvement in LVEDVi). AR indicates aortic regurgitation; LVEDVI, left ventricular end-diastolic volume index; TAVR, transcatheter aortic valve replacement.

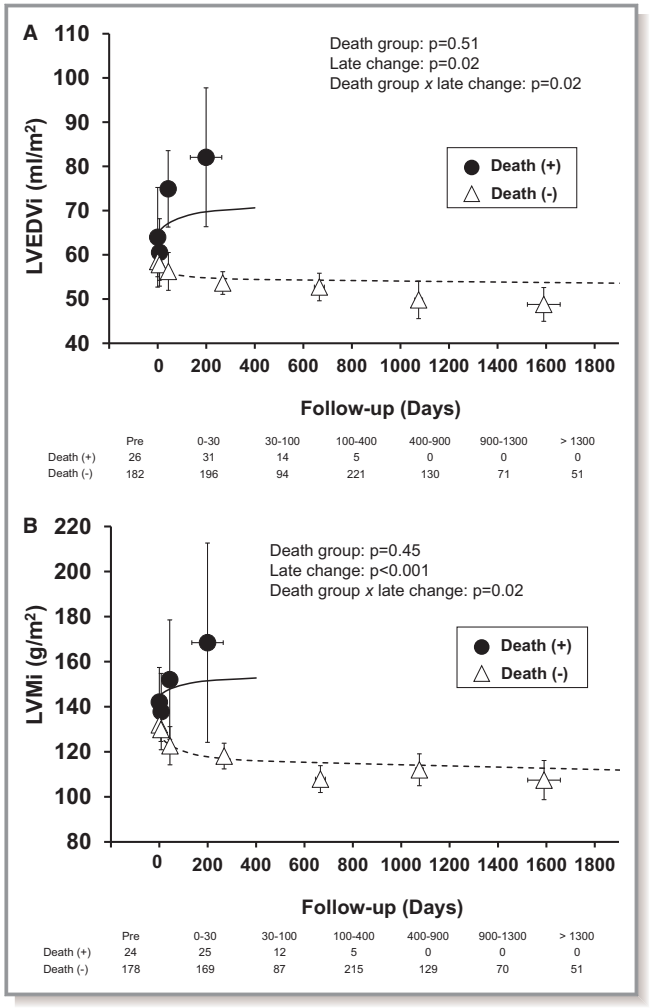

Figure 3. Changes of (A) LVEDVi and (B) LVMi when we stratified patients according to 1-year mortality. Markers represent the average of the observed data obtained before TAVR (time zero) over the intervals of 0 to 30, 31 to 100, 101 to 400, 401 to 900, 901 to 1300, and >1300 days. Error bars represent 95% CIs. The regression line is obtained by the mixed-model approach. The model was constructed with patients' groups, change over time, and interaction between groups and change (showing if magnitude of changes are different between groups). Significant *P* values for comparison between groups, change over time, and interaction between group and change (Group × change over time) are shown. GLS indicates global longitudinal strain; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVMi, left ventricular mass index.

1 year, presence of AR 1 month post-TAVR was a significant predictor of survival (P=0.002), with GLS showing a weak trend (P=0.14) and STS score having no impact on survival. There was no additive effect of longitudinal changes in either LV mass, LVEDVi, GLS, or EF (P>0.50 for all).

Discussion

In this article, we show that removal of afterload improves cardiac structure and function even in patients with advanced cardiac dysfunction. The subsequent reduction in LVEDVi was associated with less postprocedural AR after TAVR, suggesting that residual AR blocks reverse remodeling after TAVR. In addition, we show that patients who died during the first year after TAVR had an increase in LVEDVi and LVMi. The presence of AR post-TAVR was the only independent predictor of survival during a first year of follow-up, whereas this effect appears to be lost during a more-prolonged follow-up as STS score becomes a dominant predictor of all over survival. This

suggests that, in the long run, noncardiac comorbidities could mask any beneficial effect of improved cardiac physiology on survival.

Reversibility of Cardiac Function After TAVR

Whereas several previous studies assessed LV structural and functional changes after AVR,[10–16] their focus was on pair-wise comparisons between baseline, and values at a discrete point of follow-up that occurred either early or late after procedure. In contrast, we designed our study to define a pattern of longitudinal changes of LV parameters over time. We confirm findings of previous studies (Figure 4)[11–15] that GLS improved at 3 months to a 1-year follow-up time point. The novel finding of the present study shows the dynamic of GLS change, with its immediate improvement followed by a late gradual nonlinear improvement with a rate diminishing over time. This dynamic is in line of expected immediate improvement after removal of afterload, followed by delayed structural changes that further improve cardiac function.[10] EF improved immediately after TAVR without further change over time, which confirms findings of a previous report.[14] However, when patients were stratified according to initial EF, patients with decreased EF did show a late improvement that followed the similar pattern as was shown for GLS. We also show a small, but significant, continued reduction in LVEDVi over time. This is different from previous findings, which reported absence of LVEDVi change.[11–16] This difference may be the result of a different statistical approach. Another possible explanation is difference of patient population. Among the patients who were included in our study, the majority were considered inoperable, which suggests that our patient population was sicker than previous studies that assessed high-risk surgical patients.[14] Also, the fact that we show that recovery of LVEDVi was more prominent in the reduced EF population supports this hypothesis. Finally, we demonstrate that LVMi after TAVR showed slow continuous nonlinear decrease, which was consistent with previous studies.[11,12,14–16]

Systolic Function After TAVR in AS Patients

Although, in line with previous studies, higher baseline GLS was associated with lower mortality after TAVR,[17,18] the improvement in GLS post-TAVR was not. The likely reason for this is that afterload unloading by TAVR improves LV systolic function in 2 phases: immediate and delayed (ie, occurring over the months and years following the TAVR). Given that LVEF and GLS are inversely related to afterload,[19–21] their immediate improvement is expected after TAVR.[22,23] The immediate improvement was more pronounced in patients with more signs of pressure overload, such as reduced EF or more-pronounced LVH at baseline. This can be predicted from pressure-volume loop analysis[22] and is in line with previously published studies.[13,24–26] Hence, change in GLS immediately after TAVR does not reflect the magnitude of recovery in LV systolic function. On the other hand, the second phase of improvement in systolic function reflects the ability of cardiac muscle to recover by decreasing LV hypertrophy, reducing myocyte size and decreasing fibrosis,[10] given that it occurs over months and years after initial intervention. In the present study, delayed effects of TAVR affected systolic function similarly in patients with and without initial LVEF decrease and were not normalized at 5 years after TAVR. This delayed change in the second phase likely reflects ongoing improvement of pathological hypertrophy and myocardial fibrosis of LV,[10,19,25,27] but the impact of this late change might be masked by noncardiac comorbidities.

Relationship Between AR, End-Diastolic Volumes, and Survival

We demonstrate expected interplay of AR and LVEDV. It appears that residual AR (most often caused by perivalvular leak) blocks a decrease in LVEDV post-TAVR. Postprocedural AR is known as a significant prognostic factor after TAVR.[28] Several studies conducted with early generation valves showed that even mild AR has an adverse impact on survival.[29] Poulin et al[16] reported absence of LV GLS improvement or favorable remodeling in patients with significant post-TAVR AR. Our results provide a mechanistic link by showing that the presence of post-TAVR AR leads to subsequently higher LV diastolic volumes. Of note, we have also shown that post-TAVR AR is associated with larger initial LV diastolic volumes. Although this finding may seem surprising, it is consistent with previous findings of larger LV volumes and lower EF being associated with post-TAVR AR.[29]

Interestingly, we show that patients who die during the first year after TAVR have an increase in LVEDV, and that presence of AR post-TAVR is the only independent predictor of survival during a first year of follow-up. This effect appears to be lost during a more-prolonged follow-up, when STS score becomes a dominant predictor. In other words, these associations suggest that a less-than-optimal TAVR procedure that results in post-TAVR AR induces cardiac dysfunction and subsequently leads to higher mortality during first year of follow-up. The loss of importance of cardiac dysfunction after the first year probably results from the fact that competing noncardiac risk factors (as evidenced by impact of STS score), become a major cause of death.

Limitations

This study was a retrospective, observational study conducted at a large tertiary referral center and thus might suffer from selection bias, although all echocardiograms were acquired in

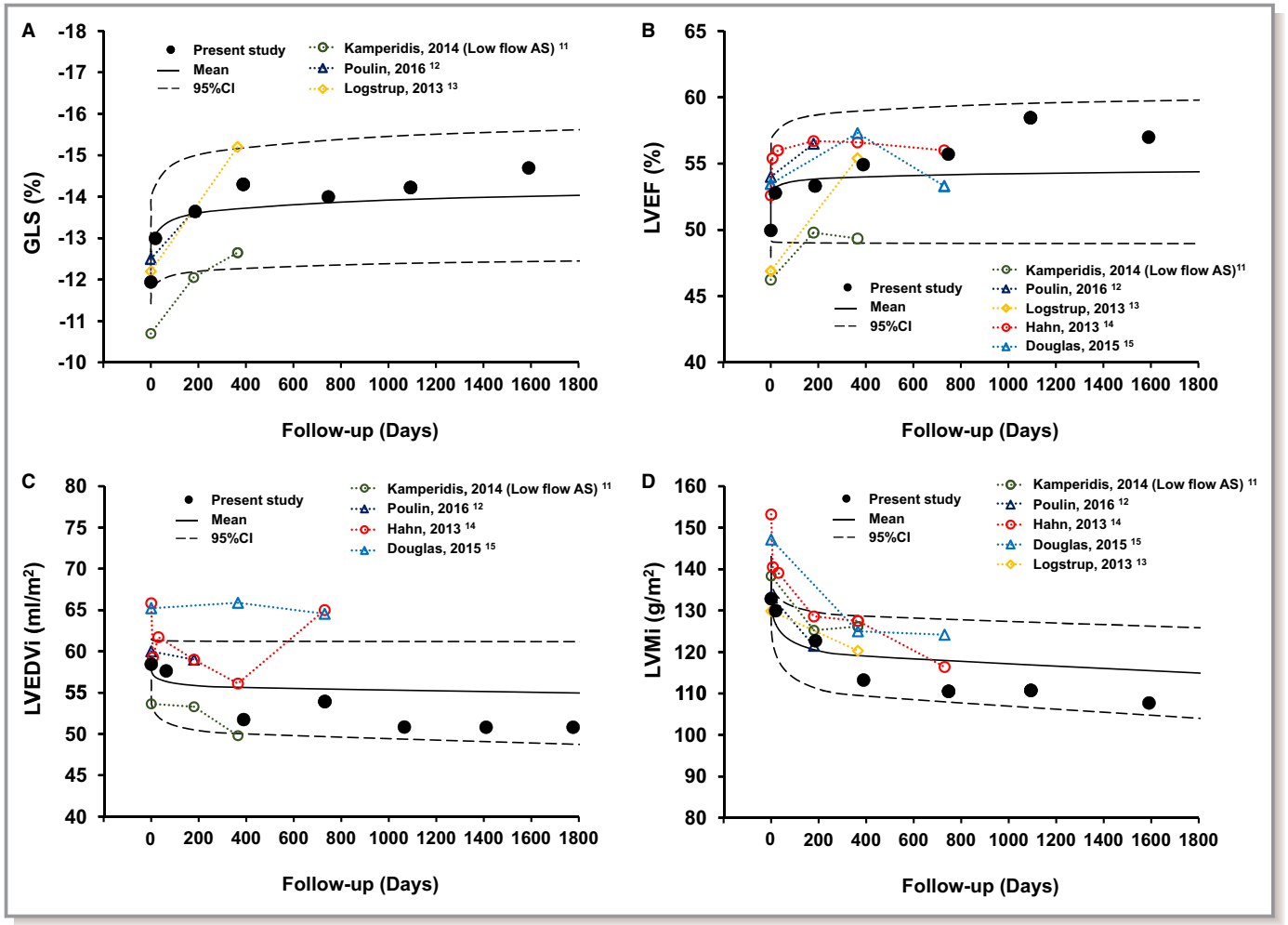

Figure 4. Comparison of changes of (A) GLS, (B) LVEF, (C) LVEDVi, and (D) LVMi in present study with previous studies. Markers (black circle) represent the average of the observed data obtained each time point as described in Figure 1. The solid line showed regression line which was obtained by a mixed-model approach in the present study, and the dashed line shows 95% CIs of regression line. Average of the reported values in previous studies at baseline and follow-up are also plotted. GLS indicates global longitudinal strain; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; TAVR, transcatheter aortic valve replacement.

a prospectively determined manner. Because echocardiographic data were obtained using ultrasound machines from various vendors, we analyzed GLS by vendor independent software (velocity vector imaging) to overcome differences of vendor-specific strains.[30] In the present study, only first- and second-generation Edwards SAPIEN valves were used, and the majority of patients underwent TAVR with the first-generation valve. Hence, the generalizability of our results to other transcatheter valves might be limited. In addition, whereas our cohort included 47 patients who had low-flow, low-gradient AS and 17 of those received dobutamine stress echocardiographic assessment before TAVR, our results in low-flow, low-gradient AS, with or without reduced EF, might be limited. Moreover, although data were collected prospectively and analyzed by a mixed-effect model, half of patients (108) died during the first 5 years of follow-up. Also, missing data led to a decrease in the number of echocardiographic examinations available for analysis, and survival bias needs to be considered. The average change in studied parameters was seemingly small, with LVEF improving by ≈3%. On the other hand, improvement of LVEF observed during carvedilol treatment of patients with systolic heart failure is in a similar range.[31] Of note, concomitant and steady improvement in LV systolic function noted by EF and GLS, which occurs despite increase of arterial afterload after TAVR,[32] mechanistically supports improved survival in these patients, by showing immediate beneficial effects and subsequent cardiac plasticity in this very elderly population. Furthermore, longitudinal data analysis does not accurately adjust for missing data if the missing pattern is not random. In other words, earlier death of patients with initially worse systolic function (or with smaller improvement in it) could lead to a spuriously significant improvement in systolic function during follow-up. On the other hand, joint modeling of overall survival and longitudinal

data did not show a significant independent impact of LV mass, LVEDVi, GLS, or EF on survival, indicative that, in this patient population, deaths frequently occurred independent of their cardiac function.

Conclusions

In this article, we show that, in AS patients, the removal of afterload by TAVR improves cardiac structure and function even in patients of advanced age and with cardiac dysfunction. The absence of improvement, as evidenced by an increase of LV mass and LV volume, was observed in patients who eventually died during the first year after TAVR. Significant post-TAVR AR blocks reverse remodeling and is associated with worse survival at 1 year after TAVR.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of Patient Characteristics of the Study Cohort and Excluded Patients

	Included patients (n = 209)	**Excluded patients (n = 28)**	**P value**
Age, years	81 ± 10	77 ±10	0.054
Male, n (%)	122 (58%)	18 (64%)	0.55
Body surface area, m^2	1.91 ± 0.26	2.06 ± 0.21	0.21
NYHA class	3 (3, 3)	3 (3, 3)	0.87
NYHA ≥ III, n (%)	196 (94%)	27 (96%)	0.83
Coronary artery disease, n (%)	176 (84%)	24 (86%)	0.84
STS score (risk of mortality)	9.6 ± 5.2	9.4 ± 5.4	0.83
Creatinine (mg/dl)	1.15 ± 0.46	1.26 ± 0.47	0.24
First generation valve, n (%)	193 (92%)	22 (88%)	0.47
Valve size 23mm, n (%)	92 (44%)	10 (40%)	0.95
Death, n (%)	118 (56%)	18 (64%)	0.43

NYHA indicates New York Heart Association; STS, Society of Thoracic Surgeons.

Table S2. Univariable Cox proportional hazards model to predict mortality after TAVR

	Hazards ratio (95% CI)	**P value**
Age	1.01 (0.99-1.03)	0.17
Male	0.85 (0.58-1.25)	0.41
NYHA	1.21 (0.77-1.90)	0.40
Coronary artery disease	0.84 (0.51-1.38)	0.49
STS score	1.05 (1.02-1.08)	0.003
Post-TAVR AR severity	1.21 (0.88-1.65)	0.25
Baseline GLS	1.05 (1.002-1.11)	0.040
Baseline EF	0.995 (0.98-1.01)	0.47
Baseline LVEDVi	1.002(0.99-1.01)	0.57
Baseline LVMi	1.004 (1.00-1.009)	0.076
GLS change during first 10 days	0.92 (0.86-0.99)	0.017
EDVi change during first 10 days	1.00(0.99-1.01)	0.98
GLS change during first 100 days	0.95 (0.88-1.04)	0.26
EDVi change during first 100days	1.01(0.99-1.02)	0.27

TAVR indicates transcatheter aortic valve replacement; CI, confidence interval; NYHA, New York Heart Association; STS = Society of Thoracic Surgeons; AR, aortic regurgitation; GLS = global longitudinal strain; EF, ejection fraction; LVEDVi = left ventricular end-diastolic volume index; LVMi, left ventricular mass index.