Effect of Transcatheter Aortic Valve Replacement on the Mitral Valve Apparatus and Mitral Regurgitation

Real-Time Three-Dimensional Transesophageal Echocardiography Study

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Background—The effect of transcatheter aortic valve replacement (TAVR) on the mitral valve apparatus and factors influencing the reduction of mitral regurgitation with or without mitral leaflet tethering after TAVR are poorly understood. The present 3-dimensional (3D) transesophageal echocardiography study aimed to elucidate early changes further in the structure and function of the mitral valve apparatus after TAVR.

Methods and Results—We analyzed 90 patients (nontenting group, 56 patients and tenting group, 34 patients) who underwent TAVR using the Edwards SAPIEN and had intraprocedural 3D transesophageal echocardiography evaluation of the mitral valve. Of all patients, mitral regurgitation improved in 54%, remained the same in 38%, and worsened in 8% 1 day after TAVR. There were no statistically significant differences in mitral annular 3D parameters before and after TAVR in both groups. In the tenting group, tenting area (P<0.01) and tenting height (P<0.01) were decreased, and coaptation length was increased (P<0.05) after TAVR. In a multivariable analysis, the predictors of improved mitral regurgitation were the decrease of tenting area (odds ratio, 8.15; 95% confidence interval, 1.31–50.7; P<0.05) and the decrease of valvuloarterial impedance (odds ratio, 7.57; 95% confidence interval, 1.15–49.9; P<0.05) in the tenting group and the decrease of valvuloarterial impedance (odds ratio, 6.96; 95% confidence interval, 1.24–39.2; P<0.05) in the nontenting group.

Conclusions—Mitral leaflet tethering was improved immediately by TAVR in patients with mitral leaflet tenting regardless of mitral annular geometry. Acute improvement in mitral regurgitation after TAVR is predominantly related to global left ventricular hemodynamics and mitral leaflet tethering change. (Circ Cardiovasc Imaging. 2014;7:344-351.)

Key Words: aortic valve stenosis  ■ echocardiography, three-dimensional  ■ hemodynamics  ■ mitral valve
surface area, peak E velocity of the transmitral inflow, pulmonary venous flow velocity data (S/D ratio), were incorporated. The MR jet area was measured as the maximum area among the apical 4-, 2-, and 3-chamber views. The MR jet area after TAVR was measured in the same view that showed the maximum MR jet area. Mitral leaflet tethering was defined as apical displacement of mitral leaflets by integrating TTE views. Tenting group was defined as the patients with ≥2 mm of tenting height, which is the vertical distance between the annulus and the leaflet coaptation point in the parasternal long-axis view.

The aortic valve area index and left ventricular (LV) mass index were calculated by dividing each by body surface area. Mitral annular calcification was classified as grade 0 to ≥3 according to an established grading method. To estimate the global LV hemodynamic load before and after prosthetic deployment, we calculated the valvular arterial impedance (Zva). The Zva theoretically accounts for the effects of both aortic stenosis and systemic arterial compliance, as the sum of the systemic arterial pressure and the mean transaortic gradient divided by the stroke volume index (stroke volume divided by body surface area), which were calculated as previously reported.

TAVR Procedure
All procedural records were reviewed to obtain information on the procedural access route, the type and size of aortic valve prosthesis, and the ballooning after prosthetic deployment.

Intraprocedural 3D Transesophageal Echocardiography and 3D Analysis
TEE was performed under general anesthesia using the iE33 ultrasound system equipped with an X7-2t TEE ultrasound probe providing a range frequency of 2.0 to 7.0 MHz and both two-dimensional and 3D matrix arrays (Philips Medical System). After morphological evaluation by two-dimensional and Doppler imaging, the live 3D data set, including that of the mitral valve apparatus, was mostly acquired before and after prosthetic deployment for later analysis; if the live 3D data could not obtain the mitral valve apparatus, we acquired a full-volume 3D data set.

All volumetric images were analyzed offline using commercial software (mitral valve quantification and 3D quantification in QLAB; Philips Ultrasound, Andover, MA). The cardiovascular mode was used for correct alignment. The 3D measurements of mitral annulus by mitral valve quantification were determined as follows (Figure 1): (1) in the midsystole frame, a long-axis view of the mitral apparatus was used to determine anterior, posterior, anterolateral, and posteromedial annular coordinates. (2) The annulus was manually outlined by defining annular points in multiple planes rotated around the axis perpendicular to the mitral annular plane. (3) The coaptation points in multiple parallel long-axis planes were determined. (4) The software automatically generated measurements of some parameters of the mitral annulus, such as anteroposterior diameter, commissure–commissure diameter, annular height, perimeter, and area. The 3D measurements of mitral leaflet coaptation by 3DQ, such as tenting height, tenting area (TA), coaptation length, and tethering angles, were determined in 3 anteroposterior planes (medial, middle, and lateral) perpendicular to the commissure–commissure plane in the midsystole frame (Figure 2).

Statistical Analysis
Data were presented as mean±SD for continuous variables, or as a number with a percentage for categorical variables. Differences between groups were analyzed by t tests or Mann–Whitney U test for continuous variables, and by χ² test or Fisher exact probability test for categorical variables, as appropriate. Differences between pre- and post-TAVR measurements were analyzed by Wilcoxon signed-rank test. Correlations between MR jet area and anatomic indices of mitral valve apparatus were analyzed by linear regression with Pearson correlation coefficients. To identify the predictors of reduced MR grade 1 day after TAVR, multiple logistic regression with the stepwise forward selection method was used to estimate the association between improved MR after TAVR and the following 7 variables: absence of atrial fibrillation, less mitral annular calcification, Δ ejection fraction (EF; pre-EF−post-EF), pulmonary arterial pressure <60 mm Hg, decrease of Zva, and less than mild postprocedural aortic regurgitation. Variables with P values <0.20 in individual analyses were included in the multivariable analysis. Intra- and interobserver variability for MR jet area by TTE and 3D measurements by TEE, such as mitral annular area and TA, were analyzed in 12 randomly selected patients.

Two-tailed P values <0.05 were considered statistically significant. Statistical analysis was performed using the SPSS 21.0 software (SPSS Inc, Chicago, IL).

Results
Clinical Characteristics, Procedure, and Postprocedural Data
The baseline data for the 90 patients are shown in Table 1. These patients were divided into 2 groups based on the presence of mitral leaflet tethering: nontenting group (n=56) andtenting group (n=34).

Figure 1. Three-dimensional (3D) transesophageal echocardiography analysis of mitral annulus: (1) 2 orthogonal long-axis views of the aortic valve were extracted from the 3D data sets. (2) Mitral annulus is manually initialized in 2 orthogonal planes and then repeated in multiple rotated planes and interpolated by mitral valve quantification. (3) The mitral leaflet coaptation is plotted (AO). (4) D, The 3D mitral annulus is displayed. A indicates anterior; AL, anterolateral; Ao, aortic annulus; P, posterior; and PM, posteromedial.

Figure 2. Schematics of geometric measurements of mitral annulus and 3 anteroposterior (AP) planes (left, A: medial; B: middle; and C: lateral). Tenting height, tenting area, coaptation length, and tethering angles of anterior (α) and posterior (β) were measured in AP angle. AML indicates anterior mitral leaflet; AV, aortic valve; CC, commissure–commissure; LA, left atrium; LV, left ventricle; and PML, posterior mitral leaflet.
When compared with the nontenting group, the tenting group had more male patients, larger body surface area, more patients with chronic kidney disease and moderate or severe MR, lower EF, larger LV diameters and mass, higher pulmonary arterial pressure, and lower mean transaortic gradient. There were no differences in TAVR procedure and Zva after TAVR between both groups (Table 2). The patients with moderate or severe MR had higher peak E velocity (P<0.01) and smaller S/D ratio (P<0.01) in comparison with the patients with mild MR or less both before and after TAVR.

At baseline, LVEF were 60±16%, 67±10%, and 50±17% in total, nontenting group, and tenting group, respectively. LV end-diastolic diameters were 49±8, 46±7, and 53±7 mm, respectively. LV end-systole diameters were 38±9, 34±7, and 43±9 mm, respectively (Table 1). After 1 month, LVEF were 62±12%, 64±10%, and 57±13% in total, nontenting group, and tenting group, respectively. LV end-diastolic diameters were 45±7, 43±7, and 49±7 mm, respectively. LV end-systole diameters were 31±8, 29±7, and 35±8 mm, respectively.

We analyzed the mitral valve apparatus in the live 3D data (98%) and full-volume 3D data (2%). Table 3 shows 3D measurements of the mitral valve apparatus assessed in nontenting and tenting groups. At baseline, mitral annular diameters, height, perimeter, and area in the tenting group were significantly larger than those in the nontenting group. There were no statistically significant differences in mitral annular 3D parameters before and after prosthetic deployment in both groups. In the tenting group, tenting height, TA (Figure 3), and tethering angles decreased and coaptation length and nonplanar angle increased after TAVR.

### MR Grade

MR grade decreased in 49 patients (54%) and remained the same in 34 patients (38%) after TA VR. MR grade increased in 7 patients (8%) after TA VR (6 from trivial to mild and 1...
from none to trivial). In nontenting and tenting groups, MR improved in 26 and 23 patients (46% and 68%), respectively, including 8 and 15 patients with moderate or severe MR (14% and 44%). MR remained the same in 25 and 9 patients (45% and 26%) and worsened in 5 and 2 patients (9% and 6%) after TAVR, respectively. MR jet area decreased from 2.8 to 2.2 cm² in the nontenting group (P<0.01) and from 3.5 to 2.5 cm² in the tenting group (P<0.01). MR jet area decreased in 71 (79%) of all 90 patients and 32 (94%) of 34 patients with moderate or severe MR.

Of 24 follow-up patients with moderate or greater preprocedural MR (nontenting 13 and tenting 11), MR improved ≥1 grade in 14 patients (nontenting 6 and tenting 8) 1 day after TAVR. At 1-month follow-up, the MR improvement was sustained in 86% (nontenting 83% and tenting 88%) of the 14 patients.

Correlations Between MR Jet Area and Morphological Indexes
Both before and after TAVR, there were significant correlations between MR jet area by TTE and morphological parameters by 3D TEE, such as mitral annular area (r=0.24; P<0.01) and coaptation length (medial: r=-0.35, P<0.001; middle: r=-0.44, P<0.001; and lateral: r=-0.31, P<0.001). When patients with organic MR caused by prolapse and mitral valve calcification were excluded from the analysis, there were significant correlations between MR jet area by TTE and TA by 3D TEE (medial: r=0.24, P<0.01; middle: r=0.27, P<0.001; and lateral: r=0.22, P<0.01; Figure 5).

Predictors of Improved MR
Among the 7 parameters studied, individual analysis revealed ΔEF, decrease of TA, decrease of Zva, and less than mild postprocedural aortic regurgitation as predictors of improved MR (P<0.20) in the nontenting group. By stepwise multivariable analysis with these 4 parameters, only decrease of Zva (odds ratio, 6.96; 95% confidence interval [CI], 1.24–39.2; P<0.05) remained as a significant predictor of improved MR. Similarly, decrease of TA (odds ratio, 8.15; 95% CI, 1.31–50.7; P<0.05) and decrease of Zva (odds ratio, 7.57; 95% CI, 1.15–49.9; P<0.05) were significant predictors of improved MR after TAVR in the tenting group by stepwise multivariable analysis with 3 parameters (decrease of TA, pulmonary arterial pressure <60 mm Hg, and decrease of Zva). There was a significant correlation between ΔMR jet area (pre-MR jet...
area−post−MR jet area) and ΔZva (pre−Zva−post−Zva) in all patients (r=0.29; P<0.01; Figure 6).

**Intra- and Interobserver Variability**

For intraobserver variability, intraclass correlation coefficients of MR jet area, mitral annular area, and TA were 0.94 (P<0.001; 95% CI, 0.80−0.98), 0.96 (P<0.001; 95% CI, 0.86−0.99), and 0.95 (P<0.001; 95% CI, 0.86−0.99), respectively. For interobserver variability, intraclass correlation coefficient of these were 0.93 (P<0.001; 95% CI, 0.78−0.98), 0.94 (P<0.001; 95% CI, 0.62−0.99), and 0.92 (P<0.001; 95% CI, 0.75−0.98), respectively.

![Figure 3. Three-dimensional measurements of tenting area in nontenting group (left, n=56) and tenting group (right, n=34) before and after transcatheter aortic valve replacement. NS indicates nonsignificant.](http://circimaging.ahajournals.org/content/full/3/3/348/F3.large.jpg)
Discussion

The main achievement of the present study was a successful 3D analysis of the mitral valve apparatus before and after prosthetic deployment. The main findings were as follows: (1) mitral leaflet tethering was significantly improved after TA VR in the tenting group, although there were no statistically significant differences in the mitral annular geometry before and after SAPIEN deployment. (2) Of all patients, MR improved in 54%, remained the same in 38%, and worsened in 8%. The predictors of improved MR 1 day after TA VR were the decrease of Zva (odds ratio, 6.96; 95% CI, 1.24–39.2; P <0.05) in the non-tenting group and the decrease of TA (odds ratio, 8.15; 95% CI, 1.31–50.7; P <0.05) and the decrease of Zva (odds ratio, 7.57; 95% CI, 1.15–49.9; P <0.05) in the tenting group.

Effect of TAVR on Mitral Valve Apparatus

Previous reports have described the relationship between TAVR by the Edwards SAPIEN and the mitral annulus.4–6 Tsang et al6 showed that postprocedural mitral annulus was more commissure–commissure oblong shape in comparison with preprocedural mitral annulus, although mitral annular area remained unchanged after TA VR. However, this previous report was limited by a study population that included CoreValve devices (n=8) and had only a small number of SAPIEN devices (n=19).6 Vergnat et al5 demonstrated by 3D TEE that the mitral annulus was preserved after TAVR using the SAPIEN. The report by Vergnat et al5 is consistent with the present study with the same prosthetic valve. However, this previous article also had a small sample size (n=10).5 More importantly, neither article evaluated the mitral leaflet anatomy, including tenting height, TA, and coaptation length. Thus, the mechanism of MR improvement after TAVR was not demonstrated in these previous articles. In contrast, the present study showed the effect of TAVR using the Edwards SAPIEN on mitral valve anatomy, including the mitral leaflet.

MR Reduction Before and After Prosthetic Deployment

In a few previous articles, decrease of MR degree in the short term has been reported after implantation of the Edwards SAPIEN.1,3–5 Hekimian et al4 showed that MR decreased in 28%, remained the same in 61%, and increased in 11% of 99 patients 7 days after the implantation of the Edwards SAPIEN. Toggweiler et al1 demonstrated that moderate MR improved in 62%, remained the same in 27%, and worsened in 5% of 89 patients, and severe MR improved in 60%, remained the same in 33%, and worsened in 7% of 43 patients 3 days after TA VR with the Edwards SAPIEN. The present study showed that the degree of MR improved in 54%, remained the same in 38%, and worsened in only 8% of all patients 1 day after TAVR with the Edwards SAPIEN, which is consistent with these previous articles.

Predictors of Short-Term MR Reduction After TAVR

Few previous studies have evaluated the predictors of reduction of MR in the short term. In addition, to the best of our knowledge, there have been no previous articles that have evaluated the relationship between MR and 3D structural changes of the mitral valve apparatus or hemodynamic changes in the LV. In our study, a decrease of leaflet tethering and a decrease of Zva were identified as predictors for MR reduction 1 day after TAVR. Zva provides an estimate of the global LV hemodynamic load that results from the summation of the valvular and vascular loads.10,11,19 Therefore, its concept is practical and useful
significant aortic valvular impedance against the LV is relieved by decreased Zva as a global LV hemodynamic index when significance or absence of mitral leaflet tethering is improved with a decrease predominantly explained by changes in hemodynamic because it accounts for not only valve stenosis severity but also volume flow rate, body size, and systemic vascular resistance. Giannini et al\(^1\) described that TAVR led to an acute improvement in Zva as global LV hemodynamic performance. However, the relationship between MR and Zva was not evaluated in this previous report. The present study is the first to demonstrate successfully that the mechanism of acute MR reduction results from global LV afterload or impedance, best represented by Zva.

In patients without mitral leaflet tethering, mitral leaflet coaptation and other valve geometric parameters did not statistically change after TAVR in our detailed 3D analysis. Thus, the improvement of MR after TAVR in those patients should be predominantly explained by changes in hemodynamic parameters. It seems natural that MR regardless of the presence or absence of mitral leaflet tethering is improved with a decrease of Zva as a global LV hemodynamic index when significant aortic valvular impedance against the LV is relieved by TAVR.

Effect of TAVR on MR Caused by Mitral Leaflet Tethering

The previous study by Toggweiler et al\(^1\) demonstrated that functional MR was 1 predictor of improved MR. Our study by 3D TEE demonstrated that the decrease of Zva and the TA change were identified as predictors for the improvement of MR in the tenting group, which is consistent with the previous article.\(^1\) In patients with aortic stenosis, it is known that concomitant functional MR frequently decreases after surgical aortic valve replacement because of the decrease in mitral leaflet tethering.\(^16,23\) Acute MR reduction with a decrease in leaflet tethering may occur when LV hemodynamics improve with TAVR, as functional or ischemic MR in general improves when LV dysfunction improves.\(^22,23\)

Limitations

There are some limitations in the present article. First, this was a single-center study with potential referral bias. Second, we did not analyze the comparison between the SAPIEN and the CoreValve in the mitral valve apparatus by 3D TEE. Third, this report is not a technical validation of the accuracy of 3D TEE for analysis of the mitral valve annulus. However, this commercial software by 3D TEE has been established to analyze morphological anatomy of the mitral valve annulus in previous reports.\(^12\) Fourth, the 3D assessment of mitral valve morphology was performed immediately before and after TAVR; however, MR grade assessment after TAVR was done 1 day after the procedure.

Particularly, MR severity was graded primarily using the MR jet area in TTE alone in most of the study subjects. However, other echocardiographic methods, such as vena contracta, proximal isovelocity surface area, peak E velocity, and pulmonary venous flow information, were incorporated to determine the MR severity and its change after TAVR. In addition, the assessment of MR grade used in this study was based on the read made as part of study-specific repeat evaluation.

Conclusions

MR improved in 54%, remained the same in 38%, and worsened in 8% of all patients 1 day after TAVR. Short-term improvement of MR was because of a decrease of Zva and an improvement of mitral leaflet tethering, which was revealed by 3D TEE.

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Disclosures

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References


**CLINICAL PERSPECTIVE**

Mitral regurgitation (MR), particularly functional MR, is present in most patients who undergo transcatheter aortic valve replacement (TAVR) for severe aortic stenosis. After TAVR with the Edwards SAPIEN, short-term reduction of MR has been observed in previous reports. However, few articles demonstrate the effect of TAVR on mitral valve apparatus, including mitral leaflet, with the use of three-dimensional (3D) transesophageal echocardiography and on valvuloarterial impedance (Zva) to identify the cause of the short-term MR reduction. Therefore, using conventional 2D echocardiography and 3D transesophageal echocardiography, we analyzed 90 patients, consisting of 34 patients in the tenting group, which was defined as patients with ≥2 mm of tenting height, and 56 patients in the nontenting group. MR improved in 54%, remained the same in 38%, and worsened in 8% 1 day after TAVR. In a multivariable analysis, the predictors of improved MR were the decrease of both 3D transesophageal echocardiography–derived tenting area (odds ratio, 8.15; 95% confidence interval, 1.31–50.7; P<0.05) and the decrease of Zva (odds ratio, 7.57; 95% confidence interval, 1.15–49.9; P<0.05) in the tenting group and the decrease of Zva (odds ratio, 6.96; 95% confidence interval, 1.24–39.2; P<0.05) in the nontenting group. In conclusion, acute improvement in MR after TAVR is predominantly related to the improvement of global left ventricular hemodynamics and mitral leaflet tenting. Our analysis with 3D transesophageal echocardiography and Zva presented in this article may provide new insight into the mechanisms of functional MR in patients with severe aortic stenosis.
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