Improvement of mitral regurgitation after TAVI

Y Tayyareci and others

Objective: To assess the impact of mitral geometry, left ventricular (LV) remodelling and global LV afterload on mitral regurgitation (MR) after trans-catheter aortic valve implantation (TAVI).

Methods: In this study, 60 patients who underwent TAVI were evaluated by 3D echocardiography at baseline, 1 month and 6 months after procedure. The proportional change in MR following TAVI was determined by examining the percentage change in vena contracta (VC) at 6 months. Patients having a significant reduction of at least 30% in VC were defined as good responders (GR) and the remaining patients were defined as poor responders (PR).

Results: After 6 months of TAVI, 27 (45%) patients were GR and 33 (55%) were PR. There was a significant decrease in 3DE-derived mitral annular diameter and area (P=0.001), mitral valve tenting area (TA) (P=0.05), and mitral papillary muscle dyssynchrony index (DSI) (P=0.05) in the GR group. 3DE-derived LVESV (P=0.016), LV mass (P=0.001) and LV DSI (P=0.001) were also improved 6 months after TAVI. In addition, valvulo-arterial impedance (ZVA) was significantly higher at baseline in patients with PR (P=0.028).

3DE-derived mitral annular area (β: 0.47, P=0.04), mitral papillary DSI (β: −0.65, P=0.012) and ZVA (β: 0.45, P=0.028) were the strongest independent parameters that could predict the reduction of functional MR after TAVI.

Conclusion: GR patients demonstrate more regression in mitral annulus area and diameter after significant decrease in high LVEDP and trans-aortic gradients with TAVI. PR patients appear to have increased baseline ZVA, mitral valve tenting and restriction in mitral valve coaptation. These factors are important for predicting the impact of TAVI on pre-existing MR.

Introduction

Mitral regurgitation (MR) is present in up to two-third of patients with aortic stenosis (AS) (1). It may be secondary to AS (functional) or due to intrinsic pathology of the mitral apparatus itself (organic) (2).
The issue of how to address MR during a surgical or interventional procedure for AS continues to be a matter of debate. This is because limited data are currently available to support clinical decision-making. Residual MR in patients who undergo SAVR is important because it is clearly associated with a worse long-term prognosis. On the contrary, concurrent replacement of both valves is related to a two-fold or greater operative mortality than replacement of the aortic valve itself (3). Thus, it is important to predict MR improvement after SAVR.

The mechanisms underlying MR improvement after SAVR have not been well established. A decrease in left ventricular (LV) systolic pressure, which directly reduces MR, seems to be the strongest hypothesis. Moreover, LV structural changes and improvement in LV function have also been demonstrated to be factors that influence MR (4). Therefore, we hypothesized that remodelling of the LV as well as mitral annular geometry may play contributory roles in MR improvement following SAVR. With the recent advances in percutaneous aortic valve replacement (TAVI), the decision of the most suitable management strategy for patients with severe AS and significant functional MR has become even more challenging (3).

In this study, we aimed (i) to evaluate the role of mitral geometry, LV remodelling and LV global afterload in the genesis of functional MR in patients with chronic severe AS and (ii) to demonstrate pre-procedural echocardiographic predictors that may be useful to identify patients who would have improvement in MR after TAVI by using novel three-dimensional echocardiography (3DE) methods.

**Methods**

**Patients**

A total of 96 patients with severe symptomatic AS who were considered at high or prohibitive surgical risk and who underwent TAVI procedure (Edwards Sapien XT valve; Edwards Lifesciences, Irvine, CA, USA) between November 2009 and May 2012 at King’s College Hospital (London, UK) were included in this study. This was a retrospective study utilizing data and images clinically acquired as part of our routine TAVI protocol. Before the procedure, consensus on their treatment was achieved at a Heart Team multidisciplinary valve meeting. Briefly, patients were included if they had severe native valvular AS with an area <1 cm² or <0.6 cm²/m² and with aortic valve annulus >20 mm and <27 mm measured by 3DE. Patients who had more than mild-to-moderate degree of aortic regurgitation were excluded.

Of the 96 patients, we retrospectively analysed 60 patients who had at least mild degree of functional MR on the pre-procedural echocardiography. Functional MR was defined as MR without morphological abnormalities of the mitral apparatus such as valve prolapse, significant calcification of leaflet or annulus, or ruptured chordae. Patients with any degree of mitral stenosis were excluded.

**Ethics**

This study is not classified as a research under NHS Health Research Authority Guidance, so we did not need to apply for ethical approval.

**Echocardiographic evaluation**

All patients were examined by two-dimensional (2D) and 3DE (Philips iE33, Bothell, WA, USA) equipped with SS-1 (2D) and XS-1 (3D-matrix array) transducers and subsequently analysed blindly offline by two independent echocardiographers (Y T and P K) using version 7 of QLab software (Philips Medical Systems, Andover, MA, USA). Aortic valve area was calculated by the continuity equation (5). Medial and lateral as well as E/E′ were calculated to provide estimates of LV filling pressures, and systolic function/contractility was measured with dP/dt max (calculated from the MR Doppler trace) and the early peak systolic velocity (S').

Patients were classified as having no, mild, moderate and severe MR by a qualitative evaluation according to the American Society of Echocardiography Guidelines for MR evaluation (6). Vena contracta (VC) method was then applied as a quantitative measure of MR severity. The VC measured as the width of the narrowest portion of the regurgitant jet on the parasternal long-axis view. A jet width <0.3 cm was defined as mild, between 0.3 and 0.7 cm as moderate, and >0.7 cm as severe (6). The proportional change in MR following TAVI was determined by examining the percentage change in VC at 6 months; the patients were then allocated to two groups based on this change. Patients having a reduction of at least 30% in VC were defined as good responders (GRs) and the remaining patients were defined as poor responders (PRs) (7).
The multiplanar reconstruction (MPR) mode of 3D software (QLab Advanced) was used to define the planes for the geometric measurements for both LV volumes and MV geometry. For evaluation of MV geometry, we first defined the mid-systole of the cardiac cycle, and then a cross-sectional plane of the MV that clearly visualized both mitral commissures was used to define the commissure–commissure (CC) plane – a plane that passes through both commissures and the LV apex. Finally, anteroposterior (AP) planes perpendicular to the centre of the CC axis was defined for imaging of the geometry of the central side of the MV. Mitral annular area (MAA) was calculated with the simplified equation: 

\[ \text{MAA} = \frac{3.14 \times \text{CC dimension} \times \text{AP dimension}}{4}. \]

MV tenting area (MVTa), the area enclosed by the annular plane and two leaflets, was also measured on AP planes (Fig. 1). The tenting height (TH) was measured in the apical four-chamber view at mid-systole and defined as the distance between the mitral valve annular line and the mitral leaflets’ coaptation point (7).

We also evaluated mitral papillary dyssynchrony index by 2D speckle tracking in apical four-chamber view for the anterolateral papillary muscle and the apical long-axis view for the posteromedial papillary muscle. For the measurement of timing, the beginning of the QRS complex to the time of peak systolic (TS) velocities was quantified. The maximal difference in TS between anterolateral and posteromedial papillary muscles was calculated. Interpapillary dyssynchrony was defined as >60ms difference (8).

**Systemic arterial haemodynamics and global left ventricular afterload**

Baseline systemic arterial pressure was measured using an arm-cuff sphygmomanometer at the time of the

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**Figure 1**

(A) The 3DE-derived anteroposterior mitral annulus diameter. (B) 3DE-derived mitral annulus area. (C) Tenting height. (D) Tenting area.
Doppler echocardiographic examination. The ratio of the stroke volume index to the brachial pulse pressure (the difference between the systolic and the diastolic blood pressure) was used as an indirect measure of the total systemic arterial compliance. To estimate the global LV afterload, we calculated the 3DE-derived valvulo-arterial impedance (ZVA) as the sum of the systolic arterial pressure and the mean transvalvular pressure gradient divided by the 3DE-derived stroke volume index, as appropriate (9).

### Statistical analysis

Statistical data were processed with the Statistical Package for the Social Sciences (16.0 SPSS 16.0) programme. The results were expressed as means and standard deviations. The results were expressed as mean and standard deviation together with one-way ANOVA that was used for comparisons of the groups. Tukey’s multiple comparison test was used for comparison in subgroups. Test and control groups were compared using unpaired t-test. Correlation analyses were derived by using Pearson’s analysis. Regression analysis was used to define the independent predictors that affect the MR response to TAVI. The results were considered significant when P value was less than 0.05.

### Results

Of the total number of patients, 60 (mean age 84.4 ± 5.97 years and 41.6% patients were women (mean ± range)) who had at least a mild degree of MR at baseline echocardiography were included in the study. The patient’s logistic Euroscore was 21.36 ± 7.7 and STS score was 4.3. Transfemoral access was used in 63.3% patients (n: 38) whereas 36.7% patients (n: 22) had transapical access. Table 1 presents the baseline echocardiographic parameters of the 60 patients who completed 6 months of follow-up. According to VC diameter, severe MR was detected in five (8.3%) patients, moderate in 38 (63.3%) patients and mild MR in 17 (28.3%) patients; 37 (61.6%) patients had normal LVEF and/or mild-degree LV dysfunction, 12 (20%) had moderate and 11 (18.3%) patients presented with severe LV dysfunction before the TAVI procedure.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline and follow-up conventional echocardiographic parameters in TAVI patients.</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
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<tr>
<td>AV peak</td>
<td>76.4 ± 22.6</td>
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<tr>
<td>AV mean</td>
<td>44.8 ± 16.9</td>
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<tr>
<td>AVA</td>
<td>0.69 ± 0.15</td>
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<tr>
<td>VC</td>
<td>0.37 ± 0.11</td>
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<td>LVDD</td>
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<td>LVSD</td>
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<tr>
<td>LVEF</td>
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<tr>
<td>LVEDV</td>
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<td>LVESV</td>
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<tr>
<td>SV</td>
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<tr>
<td>IVS</td>
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<tr>
<td>PW</td>
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<tr>
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<tr>
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<tr>
<td>E/A</td>
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<td>E/E</td>
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<tr>
<td>DT</td>
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<tr>
<td>Dp/Dt</td>
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<tr>
<td>PAP</td>
<td>40.36 ± 13.57</td>
</tr>
<tr>
<td>LAA</td>
<td>27.7 ± 8.2</td>
</tr>
</tbody>
</table>

A, late diastolic filling velocity; AV, aortic valve; DT, deceleration time; E, early diastolic filling velocity; E', early diastolic filling velocity by TDI; IVS, interventricular septum thickness; LAA, left atrial area; LVDD, left ventricle end-diastolic diameter; LVDS, left ventricle end-systolic diameter; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; PAP, pulmonary artery pressure; PW, posterior wall thickness; SV, stroke volume; VC, vena contracta (MR). P < 0.05 was considered statistically significant.

### Conventional echocardiographic follow-up

We performed follow-up echocardiography at 1 and 6 months after TAVI as per our clinical protocol. There was a significant decrease in the peak and mean trans-aortic gradients (from 76.4 ± 22.6 to 16.5 ± 6.8 mmHg and 44.8 ± 16.9 to 8.3 ± 3.6 mmHg; P = 0.0001, respectively) and a marked increase in AVA (0.69 ± 0.15 to 1.72 ± 0.28 cm²; P = 0.0001) at 1 month. The decrease in peak gradient and AVA was continued at 6 months but was not statistically significant. Vena contracta diameter was markedly improved at 1 month (0.37 ± 0.11 to 0.30 ± 0.11 cm; P = 0.001). Improvement in VC was also significant at 6 months. Patients with a significant improvement in MR (defined as at least 30% reduction at 6 months) were grouped as GRs (n: 27) (0.40 ± 0.13 to 0.21 ± 0.08 cm; P = 0.0001) and the remaining 33 (55%) patients were grouped as PRs. The reduction in VC diameter was most obvious in patients with severe MR at baseline, whereas the patients with mild baseline MR had the least reduction in MR at 6 months after TAVI (Fig. 2).
By 2DE, there was no statistical difference between the baseline and follow-up echocardiographic parameters of LV geometry and LV systolic and diastolic function. E/E′ was the only parameter that showed improvement after TAVI (Table 1).

### 3DE-derived mitral annular geometry

3DE-derived mitral AP diameter (Mad) was the only parameter that improved 6 months after TAVI in the entire group \((P=0.02)\), whereas changes in MAA, TH, TA and PMDI were not statistically different. In the subgroup analysis, we observed that impairment in baseline mitral geometry was more significant for the PR patients. In addition, improvement in Mad, MAA \((P=0.001)\) and TA \((P=0.05)\) was significant in the GR group compared with the PR group. Improvement in mitral geometry was also more obvious at 1-month follow-up compared with 6-month follow-up \((P=0.0001)\). Papillary muscle dyssynchrony was more significant at baseline in PRs and it was markedly improved after TAVI in GR group \((P=0.05)\) (Table 2).

### 3D-derived LV geometry

Using 3D volumetric analysis, we demonstrated a marked improvement in LVESV \((P=0.016)\) and LV mass \((P=0.001)\) 6 months after TAVI, whereas the 2D-derived LV geometry parameters did not improve. LVEF did not change significantly \((P=0.28)\) when using both 2D and 3D. LV 3D-derived dyssynchrony index was also improved at 6 months \((P=0.001)\). In the subgroup analysis, when GRs and PRs were analysed separately, no difference between the groups according to LV geometry and function was found (Table 3).

### Systemic arterial haemodynamics and global LV afterload

Valvulo-arterial impedance, which defines the sum of the valvular and vascular load on the valve, was higher at baseline in patients with poor MR reduction response \((5.1 \pm 0.98 \text{ to } 5.7 \pm 0.88 \text{ mmHg mL/m2}; P=0.028)\). Systemic arterial compliance did not differ between the two groups \((P=0.76)\). This finding suggests that PR patients have more significant afterload mismatch.
Subgroup analysis amongst baseline echocardiographic parameters

When baseline characteristics of the study subgroups at baseline were analysed, mitral valve geometry parameters did not differ significantly. Valvulo-arterial impedance was markedly increased in patients with poor MR reduction response at baseline. Papillary muscle dyssynchrony was also more significant in non-responder patients compared with the responders (Table 4).

Echocardiographic predictors associated with improvement in MR after TAVI

3DE-derived baseline MAA (β: 0.47, P=0.04), mitral PMDI (β: −0.65, P=0.012) and ZVA (β: 0.45, P=0.028) were the strongest independent parameters that could predict the improvement of functional MR after TAVI. Furthermore, we analysed the relationship between LV afterload and mitral geometry. Changes in 3DE-derived MAA were markedly correlated with the change in AV mean gradient (β: −0.27, P=0.018) and AVA (β: −0.39, P=0.001). Change in Mad was also correlated with the change in AVA (β: −0.26, P=0.02) but not with AV mean gradient (β: −0.06, P=0.57). There was no statistically significant correlation between the mitral annular geometry and ZVA. We also found a marked correlation between LVEF and TAA (β: −0.25, P=0.001). There was a decrease in LVEDP (E/E′) 6 months after TAVI, which was also markedly correlated with the decrease in MAA (β: 0.29, P=0.02).

### Discussion

In this study, we have demonstrated a significant improvement in functional MR and LV geometry after TAVI. Reduction of MR was strongly associated with the baseline mitral geometry and subsequent improvement in mitral geometry after TAVI. Persistence of MR after TAVI was more obvious in patients with increased baseline ZVA supporting the concept that LV global afterload has an important role in the pathogenesis of functional MR in severe AS.

There are three possible mechanisms, suggested in recent studies, which could explain the pathophysiological mechanism behind the presence of residual MR after AVR. First, MR associated with an increase in MV tenting and consequent restriction in MV coaptation would be caused by geometric distortion of the MV by LV dilatation and dysfunction (10). This is a result of changes in LVESV, ventricular shape and papillary muscle position. After AVR, the LV is expected to remodel with a reduction in the LV myocardial mass and volume over time. However, if there are accompanying factors such as coronary artery disease and previous MI, this does not happen and MR will not improve. These patients are probably amongst those whose MR does not improve after SAVR or TAVI. On the contrary, functional MR in the non-tenting group may be explained by dilatation of the mitral anulus and extremely high LV systolic pressure. Reduction in LV afterload and therefore trans-mitral systolic pressure will improve the MR in these patients. Meanwhile, such a large overall reduction in LV afterload could not be achieved in the patients with a high ZVA pre-TAVI, which explains why they tend to be PRs.

We found that GR patients, who had at least 30% reduction in VC diameter 6 months after TAVI, had more regression in mitral annulus diameter and...
MAA and TA. This suggests that these patients were probably the ones with real functional MR, where the regression of MR correlates well with the decrease in trans-aortic gradients. Significant reduction in mitral annulus size soon after TAVI (1 month) also supports the concept that mitral annular dilatation and the reduction in trans-aortic gradient are the mechanisms in GR patients. Moreover, baseline MV geometry seemed more impaired in the PR group compared with the GR group. Mitral papillary muscle dyssynchrony based on 2D speckle tracking was also improved in the GR group. However, in PR patients, PMDSI was more abnormal at baseline and did not improve after the procedure.

Durst and coworkers (11) also analysed changes in mitral geometry after TAVI to define the echocardiographic predictors of MR improvement. As in our study, they assessed mitral valve tenting height and area but failed to show a significant difference between the GR and PR groups. This might be because they used 2DE to evaluate mitral valve geometry and they included some patients with mitral annular calcification (MAC). However, in this study we used 3DE to measure mitral valve annular geometry and this is more reliable than 2DE. We also excluded patients with moderate-to-severe MAC to remove the structural effects of this abnormality.

Positive LV remodelling is also expected to be associated with MR reduction after SAVR or TAVI (12). According to our results, 3DE-derived LVESV and LV mass reduction were significant 6 months after TAVI, which demonstrates an improvement in LV geometry. Conventional echocardiography failed to show positive LV remodelling, which supports the concept that 3DE volume analysis is more sensitive and reproducible. However, we did not observe a statistical difference between 3DE LV remodelling responses in the GR and PR groups. This suggests that improvement in LV remodelling is not the only mechanism for reduction in MR. Left ventricular afterload and mitral annular geometry also play contributory roles.

A few studies in the literature have examined the echocardiographic predictors of residual functional MR after AVR. Ruel and coworkers (13) demonstrated that a larger left atrium, atrial fibrillation and lower preoperative trans-aortic gradients were significantly associated with persistent MR after SAVR, but they did not examine the effect of MV geometry. In another study, Unger and coworkers (14) reported a good correlation with the regression of functional MR and LV reverse remodelling. However, they failed to find any relationship with changes in MV geometry, but they included patients with both functional and organic MR. In a recent study, Matsumura and coworkers (15) demonstrated that preoperative MV tenting could predict persistent functional MR after AVR, which is similar to our results.

Significant LV afterload mismatch is the main mechanism of LV impairment in patients with severe AS. Valvulo-arterial impedance can estimate the global LV haemodynamic load, which is the sum of valvular and vascular loads. In this study, we found that ZVA was a strong independent predictor of improvement in MR after TAVI. We also demonstrated that baseline ZVA was higher in PR patients. This implies that not only the trans-aortic gradients but also the aortic wall changes, such as increased stiffness and a decrease in compliance, contribute in the pathogenesis of MR in patients with severe AS. In a recent study, Katsanos and coworkers (16) demonstrated that ZVA was an independent predictor of overall mortality at 2-year follow-up of patients who underwent TAVI.

In conclusion, our study demonstrates that TAVI has a positive effect on MR and LV function. Mitral valve geometric changes and LV afterload mismatch are also important in predicting MR improvement after TAVI. Thus, a detailed and careful echocardiographic examination by advanced imaging technologies such as 3DE and strain imaging are important to define patients who will respond to TAVI therapy in terms of an improvement in mitral regurgitation.

Limitations of the study

The main limitation of the study is the short follow-up period after TAVI. Although the 6-month follow-up data have highlighted the effectiveness of TAVI in improving MR, LV function and LV geometry, it would be interesting to verify whether this improvement would be sustained at longer follow-up periods.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
All TAVI patients have given permission for their data to be used for research and audit.

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