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The Structural Impact of Aortic Valve Replacement on Mitral Regurgitation

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Abstract

Background: Structural changes to the mitral annulus occur following aortic valve replacement (AVR) for severe aortic stenosis which may influence functional mitral regurgitation (MR). Methods: A retrospective review of 44 patients who underwent open AVR for aortic stenosis at a single center from 2010-2013 was performed. Patients undergoing concomitant aortic root surgery or with severe MR were excluded. MR was evaluated with preoperative and postoperative transthoracic echocardiograms. Univariate and multivariable analyses were performed to assess for factors associated with postoperative MR improvement and worsening. Results: Prior to AVR, none had severe MR, 5% (2 patients) had moderate, 9% (4 patients) mild-to-moderate, 46% (20 patients) mild, and 23% (9 patients) trace MR. Of patients with pre-operative MR, 44% (16 patients) experienced improvement of MR. Six patients had worsening of MR and the remaining 22 patients had no change. Cases of more severe MR were more likely to improve compared with mild or trace MR (P = 0.04). MR worsening was significantly more likely in patients with bicuspid aortic valves (83% vs. 24%; P = 0.004), and with larger aortic annulus diameters (P = 0.03). MR worsening was less frequent in cases of mitral annular calcification (0% vs 42%; P = 0.04) and left atrial enlargement (17% vs 65%; P = 0.03). Logistic regression analysis revealed negative predictors for MR improvement were mitral annular calcification (P = 0.04) and larger aortic annulus diastolic diameter (P = 0.05). Conclusion: Structural factors such as aortic annular size, mitral annular calcification and valve morphology may impact MR following AVR and should be investigated further as potential targets of surgical therapy.

Keywords

Aortic Valve, Replacement, Cardiac Anatomy/Pathologic Anatomy, Mitral Regurgitation

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1. Introduction

The presence of mitral regurgitation (MR) is common in patients undergoing surgical aortic valve replacement (AVR) for aortic stenosis (AS), with reported incidence ranging from 10% to as high as 70% [1]. After AVR, approximately 55% - 65% of patients with less-than-severe MR experience improvement in MR severity, while others remain stable, and 8% become more severe [2] [3]. In cases of functional MR, the repair of AS contributes to MR improvement by reduction of left ventricular end-diastolic volume (LVEDV), trans-mitral gradient and reverse remodeling [3]. However, aortic-mitral coupling via anatomic continuity and physiologic reciprocal dynamic behavior suggests a structural impact on the mitral valve (MV) could result from AVR. In fact, several studies have reported anatomic changes in the MV following AVR, including decreased mitral annulus (MA) diameters, perimeter, area, displacement and height, as well as changes in the aorto-mitral angle [4]-[7]. MA changes after AVR may be due to restricted mobility due to anchoring sutures of the AVR stent [6] or displacement of aortic annular calcification into the aortic-mitral curtain. We hypothesize that structural changes to the fibrous trigones account for the variegated influence of AVR on MR, and that identifiable patient characteristics can predict outcomes.

2. Materials and Methods

A retrospective review of patients undergoing AVR for AS at a single center from August 2010 to November 2013 was performed. Patients were evaluated by the heart team in a multidisciplinary valve clinic. Exclusion criteria were cases of degenerative MR or severe functional MR, as well as those undergoing concomitant aortic root reconstruction or AVR for aortic insufficiency. The in-house Institutional Review Board approved the review and informed consent was waived.

Carpentier-Edwards Magna Ease pericardial valves (Edwards Lifesciences, Irvine, CA) were implanted in all cases with pledgeted horizontal mattress suture technique. All patients received pre-operative and post-operative trans-thoracic echocardiographic (TTE) evaluations of MR by either of two attending cardiologists. Preoperative cardiac magnetic resonance imaging (CMR) was used to measure the aortic valve annulus in all patients.

Univariate analyses of factors associated with MR were performed. Continuous variables were normally distributed and therefore student t test was applied. Proportions were analyzed using x^2 tests. Evaluation of MR improvement included only patients with preoperative MR. Evaluation of MR worsening included all patients in the cohort. Multivariable logistic regression analyses were applied using MR improvement and MR worsening as dependent variables.

3. Results

Forty-four patients underwent AVR during the 3-year period, and met criteria for inclusion. Of these, 36 (81.8%) had some degree of pre-operative MR. Moderate MR was found in 2 cases (4.5%), mild-to-moderate in 4 (9.1%), mild in 20 (45.5%) and trace in 10 (22.7%) (**Table 1**). Post-operative TTE found zero cases of moderate MR, mild-to-moderate in 2 cases (4.5%), mild in 14 (31.8%) and trace in 24 cases (54.5%). Median time to post-operative TTE was 6 days (interquartile range: 5 - 8 days). Overall, 16 cases (44.4% of the 36 pre-operative MR) were improved post-operatively, 22 remained stable in severity and 6 developed more severe MR.

Patients with pre-operative MR were somewhat older (69.9 years ± 10 versus 61.0 ± 8; P = 0.02). Aortic annula measured by preoperative CMR during diastole were significantly smaller (22.8 mm ± 2 versus 24.6 ± 3;

Table 1. Stratification by mitral regurgitation severity.

MR severity	Pre-AVR (N = 44)	Post-AVR (N = 44)	% Improved	% Worsened
Moderate	4.5% (2)	0%	100%	0%
Mild-moderate	9.1% (4)	4.5% (2)	50%	0%
Mild	45.5% (20)	31.8% (14)	30%	0%
Trace	22.7% (10)	54.5% (24)	0%	10%
None	18.2% (8)	2.3% (1)	-	62.5%
Total MR	81.8% (36)	90.9% (40)	44.4%	2.8%

MR: mitral regurgitation; AVR: aortic valve replacement.

P = 0.05) than those without MR, and this was nearly significant by systolic measurements (24.1 ± 2 versus 25.8 ± 3; P = 0.07). Incidence of mitral annular calcification (MAC) and left atrial enlargement (LAE) were much greater in patients with MR (P = 0.005 and 0.002, respectively) (**Table 2**). Bicuspid aortic valve morphology was more prevalent in the non-MR patients (75% versus 22.2%; P = 0.004).

Among patients with pre-operative MR, cases of moderate and mild-to-moderate severity were more likely to improve compared with mild and trace (31.2% versus 5%; P = 0.04) (**Table 3**). Pre-operative mean AV gradient was greater in cases of MR improvement, approaching statistical significance (48.8 ± 15 versus 40.8 ± 10; P = 0.07). Atrial fibrillation was found to be more prevalent in cases of MR improvement, while MAC and bicuspid aortic valve morphology were less prevalent; however, statistical significance was not reached for these.

Worsening of MR on post-operative TTE was found in 13.6% of the total 44 AVR cases, of which 5 had no MR identified pre-operatively. These patients had significantly more cases of bicuspid aortic valves (83.3% versus 23.7%; P = 0.004) and significantly larger average aortic annulus diameters as measured by CMR in systole (26.7 ± 3 versus 24.1 ± 2; P = 0.007), in diastole (25.6 ± 2 versus 22.8 ± 2; P = 0.003) and corroborated by larger average intra-operative valve sizing (24.0 ± 1 versus 22.8 ± 1; P = 0.03) (**Table 4**). MAC was significantly less prevalent in cases of worsened MR (0% versus 42.1%; P = 0.04), as was LAE (16.7% versus 64.9%; P = 0.03). Pre-operative aortic valve mean gradients were higher in cases of worsened MR (58.1 ± 26 versus 44.0 ± 13; P = 0.04) compared to those without worsening, mimicking the aforementioned trend among cases of MR improvement. Patients who developed worse MR were also approximately 10 years younger (60.7 ± 6 versus 69.5 ± 10; P = 0.04). None of the patients with atrial fibrillation had MR worsening, and 4 out of the 5 underwent concomitant Maze procedures (specifically, epicardial radiofrequency ablations with left atrial appendage ligations).

Multivariable logistic regression analysis of MR improvement found the presence of MAC to be a negative predictor (P = 0.04) when controlling for aortic valve morphology, atrial fibrillation, or preoperative MR severity. In addition, for each millimeter increase in aortic annulus diameter during diastole, the likelihood of MR improvement decreased by 52% (P = 0.05). Logistic regression analysis did not identify independent predictors of MR worsening after controlling for the same variables.

Table 2. Total mitral regurgitation characteristics.

	MR (N = 36)	**No MR (N = 8)**	**P-value**
Age (years)	69.9 ± 10	61.0 ± 8	**0.02**
Diabetes	61.1% (22)	25.0% (2)	0.06
BMI	30.4 ± 6	32.8 ± 8	0.37
Hypertension	86.1% (31)	100% (8)	0.26
ESRD	2.8% (1)	0%	0.63
LVEF < 55%	12.5% (1)	27.8% (10)	0.38
Current smoking	37.5 (3)	13.9% (5)	0.11
MAC	44.4% (16)	0%	**0.005**
Bicuspid	22.2% (8)	75.0% (6)	**0.004**
AVA	0.74 ± 0.1	0.75 ± 0.1	0.77
AV mean gradient	44.2 ± 13	53.6 ± 24	0.13
AoA systolic diameter	24.1 ± 2	25.8 ± 3	0.07
AoA diastolic diameter	22.8 ± 2	24.6 ± 3	**0.05**
AVR prosthetic size	22.9 ± 1	23.5 ± 1	0.20
LAE	66.7% (24)	10% (1)	**0.002**
Atrial fibrillation	14.3% (5)	0%	0.26
Maze procedure	11.1% (4)	0%	0.32
CABG	36.1% (13)	50.0%	0.47

Proportions expressed as %. Continuous variables expressed and mean ± stdev.
MR: mitral regurgitation; BMI: body mass index; ESRD: end stage renal disease; LVEF: left ventricular ejection fraction; MAC: mitral annular calcification; AVA: aortic valve area; AV: aortic valve; AoA: aortic valve annulus; AVR: aortic valve replacement; LAE: left atrial enlargement; CABG: coronary artery bypass grafting.

Table 3. Mitral regurgitation improvement.

	MR Improvement (N = 16)	No MR Improvement (N = 20)	P-value
Age (years)	68.8 ± 9	70.7 ± 10	0.56
Diabetes	62.5% (10)	60.0% (12)	0.88
BMI	30.4 ± 6	30.4 ± 7	1.00
Hypertension	87.5% (14)	85.0% (17)	0.83
ESRD	0%	5.0% (1)	0.36
LVEF < 55%	32.1% (5)	25.0% (5)	0.68
Current smoking	12.5% (2)	15.0% (3)	0.83
MR worse than mild	31.2% (5)	5.0% (1)	**0.04**
MAC	31.2% (5)	55.0% (11)	0.20
Bicuspid	18.8% (3)	25.0% (5)	0.65
AVA	0.73 ± 0.1	0.75 ± 0.2	0.67
AV mean gradient	48.8 ± 15	40.8 ± 10	0.07
AoA systolic diameter	23.6 ± 2	23.1 ± 1	0.14
AoA diastolic diameter	23.6 ± 2	23.3 ± 2	0.07
AVR prosthetic size	22.6 ± 1	23.1 ± 1	0.23
LAE	68.8% (11)	65.0% (13)	0.60
Atrial fibrillation	18.8% (3)	10.0% (2)	0.40
Maze procedure	12.5% (2)	10.0% (2)	0.81
CABG	43.8% (7)	30.0% (6)	0.39

Proportions expressed as %. Continuous variables expressed and mean ± stdev.
MR: mitral regurgitation; BMI: body mass index; ESRD: end stage renal disease; LVEF: left ventricular ejection fraction; MAC: mitral annular calcification; AVA: aortic valve area; AV: aortic valve; AoA: aortic valve annulus; AVR: aortic valve replacement; LAE: left atrial enlargement; CABG: coronary artery bypass grafting.

Table 4. Mitral regurgitation worsening.

	MR Worsening (N = 6)	No MR Worsening (N = 38)	P-value
Age (years)	60.7 ± 6	69.5 ± 10	**0.04**
Diabetes	33.3% (2)	57.9% (22)	0.26
BMI	32.0 ± 5	30.6 ± 7	0.64
Hypertension	100% (6)	86.8% (33)	0.35
ESRD	0%	2.6% (1)	0.69
LVEF < 55%	33.3% (2)	23.7% (9)	0.61
Current smoking	33.3% (2)	15.8% (6)	0.30
MR worse than mild	0%	15.8% (6)	0.30
MAC	0%	42.1% (16)	**0.04**
Bicuspid AV	83.3% (5)	23.7% (9)	**0.004**
AVA	0.78 ± 0.1	0.74 ± 0.1	0.51
AV mean gradient	58.1 ± 26	44.0 ± 13	**0.04**
AoA systolic diameter	26.7 ± 3	24.1 ± 2	**0.007**
AoA diastolic diameter	25.6 ± 2	22.8 ± 2	**0.003**
AVR prosthetic size	24.0 ± 1	22.8 ± 1	**0.03**
LAE	16.7% (1)	64.9% (24)	**0.03**
Atrial fibrillation	0%	13.2% (5)	0.34
Maze procedure	0%	10.5% (4)	0.41
CABG	50.0% (3)	36.8% (14)	0.54

Proportions expressed as %. Continuous variables expressed and mean ± stdev.
MR: mitral regurgitation; BMI: body mass index; ESRD: end stage renal disease; LVEF: left ventricular ejection fraction; MAC: mitral annular calcification; AVA: aortic valve area; AV: aortic valve; AoA: aortic valve annulus; AVR: aortic valve replacement; LAE: left atrial enlargement; CABG: coronary artery bypass grafting.

4. Discussion

A growing body of literature has identified reproducible structural changes in the MA following AVR. Improved imaging modalities, particularly 3-D trans-esophageal echocardiography (TEE), have enhanced our understanding of mitral-aortic coupling in this setting [4]-[8]. Consistent findings include reduction of several different MA diameter metrics (intercommissural distance, anterolateral distance, systolic and diastolic diameters and others), reduced circumference, loss of saddle shape conformation, and reduced mobility identified by a decrease in vertical displacement throughout the cardiac cycle [4]-[6]. By contrast, MA area, diameter and height have not been found to change significantly after transcatheter aortic valve replacement, in which the valves are not sutured and the sewing ring is absent [5] [9].

The implications of the MA parameter effects are often unclear, representing limitations in our understanding of the anatomic relationships. A review by Waisbren *et al*. of 227 patients undergoing AVR for AS found a greater improvement in MR when it was more severe pre-operatively [2], consistent with the findings in our cohort. However, Ruel *et al*. observed greater degree of improvement in MR postoperatively when preoperative MR was milder [10], when considering functional MR, specifically. The aorto-mitral angle was reported to increase after AVR by Warriach *et al*., but found was unchanged in a report by Tsang and colleagues.

Some have labelled the improvement of MR following AVR a "functional mitral annuloplasty" [4], recognizing this as a beneficial effect. However, it must be clarified which patients will achieve this result pre-operatively because many do not, and some deteriorate. A meta-analysis that included 10 studies reporting pre-operative MR severity established the rate of MR cases that worsen after AVR to be approximately 8%, slightly lower than the rate in our patients. Moreover, milder pre-operative MR conferred better survival at 3, 5 and 10 years after AVR [3]. If more severe cases of MR do acquire greater immediate improvement following AVR, but milder MR cases have better long-term survival, then there is a need for better understanding of the mechanism to address this disparity.

The finding of worse MR after AVR in our patients with bicuspid aortic valves suggests that variation in flexibility of the aortic annulus affects the mitral valve by altering tension across the aortic-mitral curtain. The absence of MAC in patients with MR worsening adds to previous discussions in the literature about AVR prosthesis compression of the mitral annulus. Although an inflexible prosthetic AV stent may reduce anterolateral dimension of the mitral annulus to increase mitral coaptation in some patients, it is conceivable that MAC shields the mitral annulus against this compression through its own rigidity. Interestingly, MAC was also a negative predictor of MR improvement, reinforcing the hypothesis that MAC stabilizes the mitral annulus.

That fact that larger aortic annula in our patients conferred greater risk of MR worsening is also congruent with the understanding that forces acting across the aortic-mitral curtain can affect mitral valve coaptation. Distortion conferred on the MA from the AV prosthesis may enhance alignment at some optimal distance, but when delivered to a larger extent could surpass that point of equilibrium creating worsening of MR.

Although not statistically significant, the percentage of patients with atrial fibrillation that experienced MR improvement was greater than those without improvement, and none had MR worsening. Of the 5 patients with pre-operative atrial fibrillation, 4 underwent Maze procedures via epicardial radiofrequency ablation. Atrial functional MR has been supported as a mechanism of MR improvement in other settings and may have contributed in some of our patients [11].

Several important aspects of our study limit its interpretation. Small sample size decreases statistical power, and indeed numerical trends in valve sizes and atrial fibrillation remained indeterminate. The cohort of preoperative MR patient also consisted of a large proportion of mild and trace MR. Although moderate MR carries more clinical influence pertaining to questions of survival and operative decision-making, milder cases of MR likely hold value in defining immediate structural effects on aortic-mitral coupling. Ultimately a prospective study that includes medium and long-term outcomes of MR and survival would elucidate the importance of early post-operative echocardiographic findings and their impact on ventricular remodeling.

5. Conclusion

The structural coupling of the aortic and mitral valve is a relationship that undergoes measurable changes following AVR for AS. Though this issue is made complex by functional changes due to decrease in trans-aortic pressure gradient and subsequent ventricular remodeling, the structural effects must be clearly defined in order to understand the impact on mitral valve function. Enhanced understanding has great potential to usher valve design innovation and individualized surgical decision-making that will improve clinical outcomes.

Conflict of Interests

The authors have not received financial support for this research, and have no conflicts of interest.

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