Management of concomitant mild to moderate functional mitral regurgitation during aortic valve surgery for severe aortic insufficiency

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Objectives: The optimal management of mild to moderate functional mitral regurgitation (FMR) during aortic valve replacement (AVR) for severe aortic insufficiency (AI) is poorly defined. We aimed to investigate the fate of FMR after AVR with or without concomitant mitral annuloplasty (MAP) and to identify the risk factors and clinical implications of persistent FMR.

Methods: Between June 1996 and August 2011, 155 patients with mild to moderate FMR undergoing AVR for severe AI were reviewed. The preoperative MR grade was mild in 101 patients (65%) and moderate in 54 patients (35%). Persistent FMR was defined as MR grade remaining the same or increased on the last follow-up echocardiogram.

Results: The mean follow-up duration was 4.5 ± 3.9 years. FMR improved in 88% of the patients. On multivariate analysis, left ventricular end-diastolic dimension (LVEDD) reduction after AVR was identified as the only predictor for FMR improvement ($P = .004$; hazard ratio, 0.927; confidence interval, 0.881 to 0.977). Concomitant MAP did not show additional benefit in preventing persistent FMR ($P = .35$). Although no survival difference was observed between the patients with and without persistent FMR ($P = .78$), persistent FMR was associated with greater heart failure events ($P < .001$).

Conclusions: Mild to moderate FMR as a result of severe AI improved with AVR in most patients with or without concomitant MAP. Poor postoperative LVEDD reduction was the only risk factor for persistent FMR. Because persistent FMR tended to be associated with heart failure events, close echocardiographic monitoring and proactive medical management are recommended in patients showing poor LVEDD reduction after AVR. (J Thorac Cardiovasc Surg 2014;148:441-6)

Functional mitral regurgitation (FMR) is a common finding in aortic valve disease patients.^{1,2} However, adequate guidelines for its management during aortic valve surgery are lacking.³ Although previous studies have investigated the fate and clinical impact of mild to moderate FMR in patients undergoing aortic valve replacement (AVR), they were mostly conducted mostly in patients with aortic valve stenosis⁴⁻⁸ and the literature addressing the fate of FMR specifically in the setting of severe aortic insufficiency (AI) has been limited. Even less is known about the outcome and the potential benefits of concomitant mitral annuloplasty.⁹ Therefore, we sought to investigate the following: (1) the fate of mild to moderate FMR after

AVR for severe AI, (2) the effect of concomitant mitral annuloplasty (MAP) in the management of mild to moderate FMR, and (3) the risk factors and clinical implications of persistent FMR.

PATIENTS AND METHODS

Patients

Between June 1996 and August 2011, 779 patients underwent AVR for predominantly severe AI. Patients who had trivial (1+) or severe (4+) FMR, MR caused by structurally abnormal mitral valve and subvalvular apparatus such as rheumatic or degenerative pathology, and ischemic MR with regional wall motion abnormality were excluded. Based on this criteria, a total of 155 patients with predominantly severe AI with mild to moderate functional MR constituted the subject of the present study. Clinical characteristics and echocardiographic and surgical data were obtained retrospectively by reviewing the patients' medical records. The present study was approved by the Asan Institutional Review Board with waiver of individual patient consent.

Echocardiographic FMR Grading and Follow-up Evaluation

Transthoracic and transesophageal echocardiography were performed preoperatively in all of the patients to assess the etiology and severity of the MR. FMR was defined as central MR caused by tethering and fluttering in the absence of morphologic abnormalities of the mitral leaflets such as thickening or calcification. Any MR with regional left ventricular wall motion abnormality, suggesting an ischemic etiology, also was excluded. MR

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Disclosures: Authors have nothing to disclose with regard to commercial support. Received for publication Jan 3, 2013; revisions received Aug 14, 2013; accepted for publication Sept 10, 2013; available ahead of print Nov 6, 2013.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2013.09.030>

Abbreviations and Acronyms

AI	= aortic insufficiency
AVR	= aortic valve replacement
CHF	= congestive heart failure
FMR	= functional mitral regurgitation
LVEDD	= left ventricular end-diastolic dimension
LVESD	= left ventricular end-systolic dimension
MAP	= mitral annuloplasty

grade was assessed by measuring the maximum color flow Doppler regurgitant jet area from the left ventricle to the left atrium during the systolic phase on a 4-chamber or 2-chamber view. The FMR was graded as none (0), trivial (1+), mild (2+), moderate (3+), or severe (4+) on an ordinal scale. All of the patients had a postoperative transthoracic echocardiogram before being discharged. Follow-up echocardiography was performed 6 months or 1 year after surgery in 88% of the patients. Biannual echocardiographic follow-up evaluation was recommended after the first year.

Surgical Techniques

Aortic valve replacement was performed by any 1 of 4 surgeons. Aortobicaval cannulation was used in a routine manner, with institution of antegrade and retrograde cardioplegia under mild hypothermia. All of the patients underwent AVR with either a mechanical or bioprosthetic valve as appropriate for the patient's age and clinical condition. Valve size was determined by intraoperative visual inspection of the aortic annulus and sizing of the left ventricular outflow tract. During this study period, there were no specific guidelines available for MAP. As a result, the decision to perform a concomitant MAP as well as choosing the type of mitral annuloplasty ring was left to the surgeon's discretion. The determination of ring size was based on the intercommissural distance and the anterior mitral valve leaflet height.

Follow-up Evaluation

Data collection was performed until October 2011 through interviews during regular outpatient clinic visits or by telephone inquiry. Follow-up evaluation was complete in 92% of the patients. Early mortality was defined as in-hospital death or death within 30 days of surgery. Mortality was categorized as cardiac or noncardiac based on the contents of the medical records. All deaths were considered to be of cardiac origin unless a noncardiac origin was established.

The primary study end point was cardiac death. The secondary end points included changes in the FMR grade after AVR and new-onset congestive heart failure (CHF) events (death or readmission caused by CHF) during the follow-up period. FMR was documented as either improved or persistent. Persistent FMR was defined as an MR grade that either remained the same or was aggravated in the last echocardiographic follow-up evaluation from the preoperative finding.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are expressed as the mean $\pm$ standard deviation. Cumulative incidence rates of individual and composite outcomes were estimated by the Kaplan-Meier method and compared by the log-rank test. To reduce the impact of treatment selection bias and confounding potential in this observational study, we performed a rigorous adjustment for significant differences in patient characteristics by using Cox proportional-hazards regression models. Results were expressed as hazard ratios with 95% confidence intervals. All reported *P* values are 2-sided,

and *P* values less than .05 were considered statistically significant. SAS software version 9.1 (SAS Institute, Inc, Cary, NC) was used for statistical analysis.

RESULTS**Preoperative Characteristics and Surgical Data**

The preoperative clinical characteristics are shown in [Table 1](#). The mean age of the patients was 56 ± 14 years. Severe AI was the predominant aortic valve pathology in all of the patients, with only 2 patients showing mixed aortic valve disease. Grade 2+ FMR was observed in 101 patients (65%) and grade 3+ FMR was observed in 54 patients (35%). The mean left ventricular end-systolic dimension (LVESD) and left ventricular end-diastolic dimension (LVEDD) were 50.5 ± 11.0 mm and 69.5 ± 9.4 mm, respectively. MAP was performed in 22 patients ([Table 2](#)); preoperative FMR grade was 3+ in 19 patients (86%). The mean MAP ring size was 30.6 ± 2.9 mm.

Clinical Outcomes

There were 4 early deaths (2.6%). Two of them occurred in patients who had received concomitant MAP for preoperative FMR grade 3+. The mean follow-up duration was 53.5 ± 47 months. There were 22 late mortalities (14.2%), of which 3 were caused by cancer-related complications (1 advanced gastric cancer and 2 lung cancers). Therefore, the overall cardiac-related mortality rate was 12.5%. CHF events occurred in 4 patients. Two of the patients were rehospitalized with aggravated dyspnea and showed symptomatic improvement with medical management, but the other 2 patients who had very low postoperative left ventricular ejection fraction (ejection fraction, 16%) died of CHF 4 and 9 years after AVR. There were 7 reoperations during the follow-up period. Most of the reoperations were for aortic valve-related problems such as endocarditis or paravalvular leakage.

Changes in Echocardiographic Data After AVR

Postoperative echocardiographic follow-up evaluation was performed over a mean follow-up duration of 24.3 ± 11.8 months. The changes in the FMR during the follow-up period are shown in [Figure 1](#). FMR improved after aortic valve surgery in 88% (133 of 151) of the patients and persisted in 12% (18 of 151). When comparing the FMR from the preoperative state, 84% (83 of 99) of the patients with grade 2+ FMR and 96% (50 of 52) of the patients with grade 3+ FMR showed improvement. The mean LVESD and LVEDD also improved from 50.5 ± 11.0 mm and 69.5 ± 9.4 mm to 36.3 ± 10.4 mm and 52.4 ± 8.6 mm, respectively. Among the 20 surviving patients who underwent concomitant MAP, FMR persisted in 1 patient.

TABLE 1. Patient characteristics

Variables	Patients (n = 155)	%
Age (y)	56 ± 14	
Female sex	50	32
Hypertension	54	35
Diabetes	7	4.5
Coronary artery disease	17	11
Chronic renal failure	3	2
Atrial fibrillation	20	12.9
NYHA functional class		
I	40	25.8
II	54	34.8
III	45	29
IV	16	10.3
LVEF (%)	50.2 ± 12.5	
LVEDS (mm)	50.5 ± 11.0	
LVEDD (mm)	69.5 ± 9.4	
LA size (mm)	47.3 ± 5.1	
RV systolic pressure (mm Hg)	36.5 ± 16.9	
Etiology of AI		
Degenerative	41	26.4
Root dilatation	34	21.9
Endocarditis	34	21.9
Rheumatic	3	1.9
Others	43	27.7
TR grade		
I	75	48.4
II	17	11
III	12	7.7
IV	1	0.6
FMR grade		
II	101	65.1
III	54	34.8

NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; LA, left atrium; RV, right ventricle; TR, tricuspid regurgitation; LVEDS, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; AI, aortic insufficiency; FMR, functional mitral regurgitation.

Risk Analysis for Persistent FMR and Its Clinical Impact

The patients were divided into 2 groups after AVR based on the FMR status of their last transthoracic echocardiography (ie, improved [n = 133] and persistent

TABLE 2. Surgical data

Concomitant surgery	N (%)
Mitral valve repair	22 (14)
Medtronic Duran*	3
St Jude Tailor†	4
Carpentier-Edwards Physio‡	11
Cosgrove-Edwards‡	4
Tricuspid valve repair	12 (8)
Maze surgery	7 (5)
Ascending aorta replacement	10 (6)
Coronary artery bypass surgery	10 (6)

*Medtronic, Inc, Minneapolis, Minn. †St Jude Medical, Inc, St Paul, Minn.

‡Edwards Lifesciences, Irvine, Calif.

FMR [n = 18]). Preoperative left ventricular ejection fraction was 50.56 ± 12.8 in the improved group and 49.17 ± 9.3 in the persistent FMR group ($P = .58$). On univariate analysis, poor reduction in LVEDS, LVEDD, and the preoperative left atrium size; presence of chronic renal disease; and coronary artery disease were risk factors for persistent postoperative FMR. However, on multivariate analysis, only poor LVEDD reduction ($P = .004$; hazard ratio, 0.927; confidence interval [CI], 0.881 to 0.977) and preoperative left atrium size ($P = .017$) were significant risk factors for persistent FMR (Table 3). The FMR type in 71% of the patients (n = 107) was type IIb, and was type I in the remaining patients. No significant differences were observed in the incidence of persistent FMR between the 2 types of FMR. Concomitant MAP was not found to be of additional benefit in preventing persistent FMR. To exclude the influence of MAP from the evaluation, univariate and multivariate analyses were performed in the patients without MAP, but the results remained similar to that of the total patient cohort (Table 4).

Persistent FMR did not seem to affect the estimated long-term survival ($P = .709$) (Figure 2). However, it is remarkable that all of the CHF events (n = 4) occurred in the persistent postoperative FMR patients ($P < .001$).

DISCUSSION

The present study was focused on assessing the course of mild to moderate FMR and the clinical impact of persistent postoperative FMR in patients undergoing AVR for predominantly severe AI. The results showed FMR improvement in most of the patients with AVR only. However, some patients showed persistent FMR, which had an adverse impact on the clinical outcomes, especially with respect to a greater incidence of CHF-related events. The most important factor relating to persistent FMR after AVR was poorly reduced LVEDD. Concomitant MAP was not necessarily found to be of greater benefit in preventing persistent FMR.

Although FMR associated with aortic valve disease is relatively common, its course may vary depending on the predominant aortic valve pathology (ie, stenosis or regurgitation). Although numerous studies were conducted to define the relationship between FMR and aortic valve disease, the predominant aortic valve pathology in most of these studies was aortic stenosis,^{6,8,10,11} with only a few of them dealing with predominantly severe AI. Even in the studies that purportedly investigated mixed aortic pathologies, the proportion of AI patients was small and the distinction between the 2 pathologies was unclear.^{7,12} It is our contention that distinguishing the FMR in relation to the type of aortic valve pathology is important because the underlying left ventricular remodeling behavior may differ accordingly, and thereby affect the course of the FMR and consequently the overall clinical

() – number of patients who had concomitant mitral annuloplasty

FIGURE 1. The changes in the degree of FMR after AVR. FMR, Functional mitral regurgitation; AVR, aortic valve replacement.

outcome. The left ventricular remodeling in aortic stenosis is characterized by ventricular hypertrophy followed by dilatation as a delayed response to disease progression. On the other hand, the left ventricular remodeling response to severe AI is usually dilatation and increase in

TABLE 3. Cox proportional hazards model analyzing predictors for persistent FMR in all patients (n = 151)

Variables	Hazard ratio	95% confidence interval	P value
Univariate analysis			
Age	1.003	0.969	1.038
Sex	1.531	0.588	3.987
Hypertension	0.455	0.100	2.068
Diabetes	2.699	0.339	21.467
NYHA	0.981	0.365	2.636
Coronary artery disease	3.352	1.178	9.543
Dialysis	10.703	1.237	92.623
Atrial fibrillation	2.333	0.748	7.275
LVEDS difference	0.944	0.897	0.993
LVEDD difference	0.923	0.877	0.972
LA size	1.074	1.000	1.153
RV pressure	0.977	0.943	1.012
Tricuspid regurgitation	1.870	0.525	6.660
Mitral annuloplasty	0.381	0.050	2.884
LVEF	0.974	0.938	1.011
Multivariate analysis			
LVEDD difference	0.927	0.881	0.977

NYHA, New York Heart Association; LVEDS difference, preoperative LVEDS value - postoperative LVEDS value; LVEDD difference, preoperative LVEDD value - postoperative LVEDD value; LVEDS, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LA, left atrium; RV, right ventricle; LVEF, left ventricle ejection fraction. *P < .05.

TABLE 4. Cox proportional hazards model for predictors of persistent FMR in patients without concomitant mitral annuloplasty (n = 131)

Variables	Hazard ratio	95% confidence interval	P value
Univariate analysis			
Age	1.004	0.969	1.041
Sex	1.466	0.544	3.945
Hypertension	0.221	0.028	1.717
Diabetes	2.329	0.293	18.521
NYHA	1.239	0.452	3.397
Coronary artery disease	3.963	1.249	12.578
Dialysis	9.291	1.074	80.385
Atrial fibrillation	2.240	0.630	7.964
LVEDS difference	0.953	0.903	1.006
LVEDD difference	0.928	0.875	0.984
LA size	1.136	1.041	1.239
RV pressure	0.983	0.950	1.017
Tricuspid regurgitation	2.407	0.654	8.857
LVEF	0.968	0.930	1.007
Multivariate analysis			
LVEDD difference	0.927	0.749	0.977
LA size	1.121	1.020	1.231

NYHA, New York Heart Association; LVEDS difference, preoperative LVEDS value - postoperative LVEDS value; LVEDD difference, preoperative LVEDD value - postoperative LVEDD value; LA, left atrium; RV, right ventricle; LVEF, left ventricle ejection fraction; LVEDS, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension. *P < .05.

LV mass. Therefore, the onset and LV dysfunctional state secondary to myocardial remodeling in patients with predominantly severe AI may be qualitatively different from aortic stenosis. From this perspective, the present

FIGURE 2. Freedom from cardiac mortality. FMR, Functional mitral regurgitation.

study was remarkable in having focused specifically on LV remodeling and FMR in AVR patients with predominantly severe AI. The reversal of FMR after AVR in these patients was rapid with significant reverse remodeling that was characterized by decreased LVEDD and FMR improvement within the first few months of surgery. Although the findings of this study may guide proactive postoperative medical treatment in those patients showing poor LVEDD reduction, the surgical utility remains limited because significant preoperative factors predicting persistent postoperative FMR were not identified.

Until recently, most studies on FMR involved patients with MR ranging between 1+ or 2+. ^{7,9,12,13} In this study, we chose to limit our patients to those with MR grade 2+ or 3+ MR because the treatment of FMR in this group of patients remains the most controversial. A total of 35% of the patients had grade 3+ FMR and, remarkably, most of them (96%) showed improvement in their MR after AVR alone without concomitant MAP. Therefore, the results seemed to suggest that AVR alone may be sufficient to induce the necessary reverse remodeling for correcting the mild to moderate FMR, but the relatively small population of 155 patients in the present study warrants further investigation over a larger cohort and longer duration to adequately assess the clinical implications.

Although it is intuitive to expect a greater preventive effect on persistent postoperative FMR by concomitant MAP, multivariate analysis showed no additional benefit with MAP, even in patients with preoperative grade 3+ MR. These findings corroborate the views argued by Wan et al ⁹ that AVR alone in most cases is highly effective in resolving mild to moderate FMR at the time of AVR. In a review by Abdullah et al, ⁵ the cause of MR worsening after AVR was suggested to be multifactorial. ^{10,12,14-16} In the present study, poor reduction in LVEDD was the only significant risk factor identified for persistent FMR after AVR ($P = .004$). Joo et al ⁷ also suggested LVEDD increase to be predictive of persistent FMR on univariate analysis. These findings stress the significant role of adverse LV remodeling in contributing to persistent FMR after AVR. Although the size of the preoperative LVEDD was not a significant predictor of persistent FMR, changes in LVEDD (ie, poorly reduced LVEDD after AVR) were identified as having an adverse influence on the clinical outcomes, verifying the importance of the postoperative LV remodeling behavior. The clinical impact of persistent FMR was most readily apparent through its greater association with increased CHF events during the follow-up period. This was consistent with the reported long-term outcomes of previous studies that showed an increased incidence of CHF-related events in patients with persistent FMR. ^{6,12} The tendency for a decrease in the LVEDD to be associated with greater FMR improvement as observed in the present

study is consistent with the outcomes reported by Ruel et al. ¹²

Study Limitations

Limitations include the retrospective nature of the present study and the possibility of treatment bias by the attending surgeons. The relatively short follow-up duration and the small number of CHF events are further limitations. Although the relatively homogenous study population consisting of patients with predominantly severe AI adds support to the arguments advocated in the present study, further long-term studies in a larger study cohort are warranted to identify the preoperative risk factors of persistent postoperative FMR and the surgical utility of the present study findings.

CONCLUSIONS

Mild to moderate FMR associated with severe AI showed improvement after aortic valve surgery alone in most patients. Concomitant MAP did not result in an additional beneficial effect in preventing persistent FMR. The only risk factor for persistent FMR after AVR was poor LVEDD reduction on follow-up echocardiography. Although persistent FMR did not affect the overall survival rate, it tended to be associated with a higher incidence of congestive heart failure events during the follow-up period. Therefore, proactive medical management is recommended in patients with poor LVEDD reduction after AVR.

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