Management of moderate functional mitral regurgitation at the time of aortic valve replacement: Is concomitant mitral valve repair necessary?

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Objective: The optimal management of moderate functional mitral regurgitation at the time of aortic valve replacement remains undefined.

Methods: We retrospectively identified 686 consecutive patients undergoing aortic valve replacement between 1993 and 2006 with at least moderate (grade 2 or more) functional mitral regurgitation. Patients with structural valve abnormalities or significant coronary artery disease were excluded, leaving 190 in the study. Analyses for predictors of residual mitral regurgitation and survival were performed. The impact of mitral regurgitation on survival was further analyzed among 91 patients case matched for age, gender, and left ventricular ejection fraction to individuals without mitral regurgitation undergoing isolated aortic valve replacement.

Results: The mean age of the study group was 74 ± 11 years, 45% were male, and 78% had New York Heart Association III or IV Class classification. The mean preoperative ejection fraction was $48\% \pm 17\%$. Operative mortality was 5% ($n = 9$). Follow-up echocardiographic data were available for 88% of patients at discharge and 57% of patients at midterm. Mitral regurgitation was improved at discharge in 76% of patients and at mid-term follow-up in 67% of patients. Independent predictors of improved mitral regurgitation were lesser degrees of preoperative tricuspid regurgitation or prebypass mitral regurgitation, absence of cerebrovascular disease, and lower left ventricular ejection fraction. Postoperatively, 89% of patients were New York Heart Association Class I or II Symptom; No reoperations for mitral regurgitation were performed. Survival was 68% at 5 years and 42% at 10 years. Independent predictors of late mortality were increasing age, diabetes, dialysis-dependent renal failure, and increased tricuspid regurgitation severity. The survival of 91 patients from this cohort did not differ from case-matched patients without mitral regurgitation undergoing aortic valve replacement ($P = .33$).

Conclusion: Moderate functional mitral regurgitation improved in most patients after aortic valve replacement. Residual mitral regurgitation did not affect survival independently of left ventricular function.

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Some degree of functional mitral regurgitation (MR) in the absence of structural mitral valve disease¹ is present in up to 75% of patients undergoing aortic valve replacement (AVR).² Despite the frequency with which MR is seen, there remains controversy regarding its management. The majority of prior reports have involved relatively small sample

sizes and are confounded by the inclusion of patients with organic mitral valve disease or ischemic heart disease. Furthermore, although some reports have shown improvement in functional MR in up to half of patients undergoing AVR,²⁻⁸ no studies to date have clearly demonstrated whether improvement in functional MR affects survival.

We therefore sought to determine the 1) impact of AVR alone on functional MR of at least moderate degree, 2) predictors of change in MR, and 3) survival of patients with concomitant moderate functional MR undergoing AVR compared with a matched cohort without MR.

PATIENTS AND METHODS

Study Population

After obtaining approval from the institutional review board with a waiver of requirement for individual patient consent, we identified 5855 patients who underwent AVR or aortic root replacement between January 1993 and June 2006 through interrogation of the Society of Thoracic Surgeons compliant Mayo Clinic Rochester institutional database for cardiovascular surgery. Of these, 686 patients had concomitant MR of at least moderate degree (Figure 1). In the interest of examining most precisely the impact of AVR on functional MR secondary to the aortic valvular disease itself, we excluded those who underwent concomitant coronary artery bypass grafting; those with significant coronary artery disease, as defined by greater than 70% stenosis of the left anterior descending, circumflex, or right coronary artery, or greater than 50% stenosis of the left main coronary

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Abbreviations and Acronyms

AR	= aortic regurgitation
AS	= aortic stenosis
AVR	= aortic valve replacement
LV	= left ventricular
LVEDD	= left ventricular end-diastolic dimension
LVEF	= left ventricular ejection fraction
MR	= mitral regurgitation
NYHA	= New York Heart Association
TR	= tricuspid regurgitation

artery; and those with a history of myocardial infarction. We also excluded those with prior cardiac operation or mitral intervention, hypertrophic cardiomyopathy, infective endocarditis, connective tissue disease, and congenital or other organic causes of MR, including myxomatous or rheumatic causes. After excluding those in whom consent for research was not documented, 190 patients were included in the study cohort.

Definition and Grading of Functional Mitral Regurgitation

All patients underwent preoperative 2-dimensional echocardiography. The diagnosis of functional MR was made only after elimination of structural causes of MR. Although quantitative assessment of the degree of MR has become part of our standard clinical practice recently, over the course of the entire study period the degree of MR was determined semi-quantitatively. In most cases this was determined by examining parameters such as regurgitant jet area, vena contracta, and flow-convergence (proximal isovelocity surface area) on color-flow Doppler; jet profile in continuous-wave Doppler; and flow quantitation with pulse Doppler.⁹ Preoperative proximal isovelocity surface area measurements were available in 34% of the study group. Intraoperative transesophageal echocardiography is routine in our practice and was performed in all patients in the study group.

Surgical Data

All patients had severe aortic stenosis (AS), aortic regurgitation (AR), or a combination of these pathologies. Aortic valve or aortic root replacement with or without other associated procedures were performed using cardiopulmonary bypass ($2.4 \text{ L/min}^{-1}/\text{m}^2$) at normothermia or mild (32°C) hypothermia. In the majority of patients, antegrade cold blood cardioplegia was used for myocardial protection. In 3 patients, hypothermic circulatory arrest was required for hemiarch replacement of the aorta.

Follow-up

Survival data were obtained through review of patient medical records and the Social Security database, as well as through postal surveys administered by the Mayo Survey Research Center. Late follow-up of functional status and echocardiographic parameters, obtained through patient chart review, was available in 53% and 57% of survivors at 3.5 ± 2.8 years and 3.0 ± 2.6 years, respectively. Although this represents only a fraction of the whole study population, those for whom echocardiographic follow-up are available have baseline characteristics similar to the overall cohort (data not shown). Echocardiographic assessment was available in 159 patients (88%) at the time of discharge, however. Survival data were available in 94% of patients ($n = 179$) at a mean of 3.8 ± 3.6 years. Early mortality was defined as in-hospital or within 30 days of discharge. Late mortality was death occurring beyond this period.

Survival was further examined by case-matched comparison of patients with and without MR at the time of AVR. Cases and control patients were matched with respect to age (± 5 years), gender (exact match), and left ventricular ejection fraction (LVEF) ($\pm 10\%$). Matches were available for 119 patients, of whom survival information was available in 91.

Statistical Analysis

All group data were expressed as mean $\pm$ standard deviation or frequency and percentage. Continuous variables were compared using analysis of variance or rank-sum test as appropriate. Categorical variables were compared using chi-square tests. Survival end points were estimated using the Kaplan-Meier method. Multivariate analysis to identify risk factors for

FIGURE 1. Current study cohort of 190 patients with moderate functional MR at the time of aortic valve or root replacement. Flowchart represents application of inclusion and exclusion criteria. *MR*, Mitral regurgitation; *MS*, mitral stenosis; *CAD*, coronary artery disease.

TABLE 1. Baseline characteristics

	All patients n = 190	AS n = 158	AR n = 25	Mixed AS/AR n = 7	P value
Age	74 ± 11	75 ± 11	67 ± 10	69 ± 10	<.01
Male	85 (45%)	64 (41%)	17 (68%)	4 (57%)	.60
Diabetes	31 (16%)	24 (15%)	5 (20%)	2 (29%)	.56
Preoperative renal insufficiency	24 (13%)	19 (12%)	4 (16%)	1 (14%)	.85
Dialysis	8 (4%)	7 (4%)	1 (4%)	0 (0%)	.85
Hypertension	116 (61%)	94 (59%)	16 (64%)	6 (86%)	.36
Cerebrovascular disease	17 (9%)	16 (10%)	1 (4%)	0 (0%)	.60
Chronic lung disease	34 (18%)	26 (16%)	4 (16%)	4 (57%)	.02
Peripheral vascular disease	26 (14%)	22 (14%)	3 (12%)	1 (14%)	.96
NYHA 1	4 (2%)	2 (1%)	1 (4%)	1 (14%)	.22
NYHA 2	38 (20%)	30 (19%)	6 (24%)	2 (29%)	
NYHA 3	107 (56%)	90 (57%)	13 (52%)	4 (57%)	
NYHA 4	41 (22%)	36 (23%)	5 (20%)	0 (0%)	
Syncope	14 (8%)	13 (8%)	1 (4%)	0 (0%)	.85
CHF	103 (54%)	83 (53%)	18 (72%)	2 (29%)	.08
Atrial fibrillation/flutter	46 (24%)	37 (23%)	7 (28%)	2 (29%)	.85
LVH on ECG	74 (39%)	61 (39%)	9 (36%)	4 (57%)	.89
LVEF	48% ± 17%	49% ± 17%	43% ± 16%	55% ± 11%	.13
Peak gradient		90 ± 27 mm Hg		93 ± 26 mm Hg	
Mean gradient		54 ± 18 mm Hg		56 ± 14 mm Hg	
MR					.55
Grade 2	170 (89%)	142 (90%)	23 (92%)	5 (71%)	
Grade 3	19 (10%)	15 (9%)	2 (8%)	2 (29%)	
Grade 4	1 (1%)	1 (1%)	0 (0%)	0 (0%)	
LVEDD	55 ± 10	53 ± 8	66 ± 10	65 ± 9	<.01
LVESD	44 ± 12	38 ± 11	53 ± 13	44 ± 8	<.01
LV mass	294 ± 107	273 ± 90	371 ± 131	390 ± 145	<.01
LV mass index	157 ± 49	149 ± 42	184 ± 65	199 ± 39	<.01

AS, Aortic stenosis; AR, aortic regurgitation; NYHA, New York Heart Association; CHF, congestive heart failure; ECG, electrocardiogram; MR, mitral regurgitation; LV, left ventricular; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end systolic dimension.

survival was performed using Cox regression models. Univariate and multivariate predictors for residual MR were identified using logistic regression models. The multivariable model considered univariately significant variables ($P < .05$) with model selection using the stepwise method (backward and forward methods resulted in the same model). All statistical tests were 2-sided with the alpha level set at .05 for statistical significance.

RESULTS

Patient Characteristics

As shown in Table 1, the predominant aortic valve pathology was AS in 83% of patients (158), whereas AR was dominant in 25 patients. Only 7 patients had mixed AS and AR of significant degree. Those with AS were almost a decade older than those with predominant AR (75 vs 67 years, $P < .01$). Compared with patients with AS, those with AR had significantly larger left ventricular end-diastolic dimension (LVEDD), left ventricular (LV) end-systolic dimension, LV mass, and LV mass index. Similarly, patients with mixed AS and AR had a larger LVEDD and LV mass index.

The degree of MR was grade 2 in the majority of patients (89%), with grade 4 present in only 1 patient. This is likely

a reflection of our collective inclination to intervene on severe MR at the time of AVR. This is also likely responsible for the underrepresentation of individuals with grade 3 MR.

Operative Characteristics

There were 9 aortic root replacements. Of the 181 AVR procedures performed, 137 prostheses were biological and 44 prostheses were mechanical, as might be expected given the age distribution (Table 2). Of these, AVR was performed as an isolated procedure in 139 patients, with the others undergoing concomitant procedures such as ascending aortic replacement, tricuspid valve repair or replacement, and the Maze procedure. A small number of other miscellaneous procedures were performed: ligation of the left atrial appendage, limited septal myectomy, right atrial thrombectomy, and ascending aortic reduction plasty.

Fate of Functional Mitral Regurgitation

At the time of discharge, MR was mild or less in 114 patients (72%) (Table 3). MR was grade 2 in 42 patients

TABLE 2. Concomitant cardiac procedures

All patients n = 190	
Aortic valve replacement	181
Mechanical prosthesis	44
Bioprosthesis	137
Aortic root replacement	9
Aortic root augmentation	14
Tricuspid annuloplasty/replacement	9
Ascending aortic replacement	13
Hemiarch replacement	3
Maze/modified Maze	5
Other	9

(26%) and grade 3 in 3 patients (2%). The spectrum of MR severity appeared stable at midterm follow-up. Improvement in MR severity was similar regardless of the functional nature of the aortic valve disease (Table 4). This too appeared stable at follow-up (mean = 3.0 years). Of particular note, although 25% and 17% of patients with AS and AR, respectively, had unchanged MR grade, only 1% and 4% of patients with AS and AR, respectively, had worsened MR grade at time of discharge. Worsened MR was present at mid-term in 3 patients with AS (3%) and in zero patients with AR. There were no reoperations for postoperative MR identified among the study patients. At a mean follow-up duration of 3.5 years, 25 patients (27%) had New York Heart Association (NYHA) I classification, 56 patients (62%) had NYHA II classification, and 10 patients (11%) had NYHA III classification.

Predictors of Postoperative Improvement in Mitral Regurgitation

Univariate predictors of improvement in MR at the time of discharge included younger age, male gender, higher mean aortic valve gradient, higher body surface area, lower preoperative tricuspid regurgitation (TR) grade, larger aortic prosthesis, and lower preoperative MR grade under anesthesia. By multivariate analysis, only TR grade and lower preoperative MR grade under anesthesia remained significant.

Predictors of improved MR at the time of midterm follow-up by univariate analysis included absence of cerebrovascu-

TABLE 3. Mitral regurgitation grades at discharge and follow-up

MR grade		
Discharge	<1	23 (14%)
	1	91 (57%)
	2	42 (26%)
	3	3 (2%)
	4	0
Follow-up	<1	16 (16%)
	1	47 (47%)
	2	34 (34%)
	3	4 (4%)
	4	0

MR, Mitral regurgitation.

TABLE 4. Change in mitral regurgitation severity at discharge and follow-up

		All patients	AS	AR
Discharge	Improved	120 (76%)*	96 (74%)*	18 (78%)*
	Unchanged	36 (23%)	32 (25%)	4 (17%)
	Worsened	2 (1%)	1 (1%)	1 (4%)
Follow-up	Improved	68 (67%)*	60 (69%)*	6 (67%)
	Unchanged	30 (30%)	24 (28%)	3 (33%)
	Worsened	3 (3%)	3 (3%)	0

AS, Aortic stenosis; AR, aortic regurgitation. * $P < .0001$ versus preoperative MR.

lar disease, congestive heart failure at presentation, lower LVEF, lower preoperative systolic blood pressure, decreased MR severity at discharge, increased LVEDD, and decreased septal thickness. In multivariate analysis, however, only absence of cerebrovascular disease and lower preoperative LVEF remained (Table 5).

Survival

Early mortality was observed in 9 patients (4.7%). Survival of the whole cohort was 68% at 5 years and 42% at 10 years (Figure 2, A). When compared with an age- and gender-matched white population in Minnesota, long-term survival was significantly lower among the study group ($P < .001$). This was true irrespective of the degree of residual MR postoperatively (Figure 2, B).

Univariate predictors of mortality included increasing age, severity of diabetes (defined by insulin dependence vs oral hypoglycemic vs diet controlled), dialysis dependence, higher NYHA functional class, history of syncope, atrial arrhythmias and absence of sinus rhythm, higher degree of TR, mitral annular calcification, smaller aortic prosthesis size, and pre-discharge MR grade of 1 or higher. By multivariate analysis, however, only increasing age, severity of diabetes, dialysis dependence, and greater degree of preoperative TR were independent predictors for overall mortality (Table 6).

Because of this finding of reduced survival below expected, we further investigated the impact of MR on survival using a case-matched comparison with individuals undergoing AVR who did not have preoperative MR. In the interest of distinguishing between the effects of age and ventricular function, cases were matched for age, gender, and LVEF with individuals undergoing surgery during the same time

TABLE 5. Independent predictors for postoperative improvement in mitral regurgitation at discharge and follow-up

Variable	OR	95% CI	P value
At discharge			
Lower TR severity	2.05	1.11–3.79	.02
Lower preoperative MR under anesthesia	3.07	1.30–7.21	.01
At follow-up			
Absence of cerebrovascular disease	6.37	1.49–27.22	.01
Lower LVEF	1.04	1.01–1.07	.01

OR, Odds ratio; CI, confidence interval; TR, tricuspid regurgitation; MR, mitral regurgitation; LVEF, left ventricular ejection fraction.

FIGURE 2. Probability of survival of patients with moderate functional MR versus age- and gender-matched Minnesota white population (A), residual MR mild or less than mild at dismissal from hospital versus age- and gender-matched Minnesota white population (B), and moderate functional MR (MR+) at the time of aortic valve or root replacement versus matched patients undergoing isolated AVR without MR (MR-) (C). Patients are matched to age, gender, and LVEF. MR, Mitral regurgitation.

interval as those undergoing isolated AVR who did not have MR. In 91 such pairs, late survival data were available. The baseline characteristics of both groups were similar, except that patients with MR from the current cohort of interest had a higher incidence of chronic renal failure and peripheral vascular disease than controls. Kaplan–Meier survival curves of these 2 groups were not significantly different (Figure 2, C). By multivariate analysis, chronic renal failure was an independent predictor of mortality ($P < .01$).

DISCUSSION

The results of our study demonstrate that moderate (grade 2 to 3) functional MR improves in approximately 75% of patients undergoing AVR for AS or AR and remains stable in the remainder. Furthermore, progression of MR in this population seems to be uncommon, as is reoperation for mitral regurgitation. Furthermore, improvement in the degree of MR intraoperatively may predict improvement after aortic valve surgery. Functional status is improved in the majority of patients after AVR alone. Unfortunately, long-term sur-

vival remains below predicted despite successful AVR; this was independent of persistent MR. Furthermore, we were unable to demonstrate an impact of MR itself on survival in comparison with case-matched control patients free of MR undergoing AVR alone. This exercise may have been complicated by our effort to control for ventricular function as LVEF is an imperfect measure of ventricular function in the presence of MR. The effect, however, should have been to bias survival against those with MR, since they would be expected to have artificially high LVEF biasing the results against those individuals if at all. Taken together, these data support a highly selective approach to intervention on the mitral valve at the time of AVR when MR is mild to moderate in the absence of a structural abnormality or ischemic disease. In the presence of organic mitral disease, it is our practice to repair or replace the valve. The management of ischemic disease remains in our view an issue of controversy.

Although MR improved in most, it persisted in what was still a significant percentage of patients. The independent predictors of immediate improvement included lesser degree of TR and improvement in MR with anesthesia. Qualitative echocardiographic estimates notwithstanding, greater degrees of TR may reflect more physiologically substantial MR. Such may be less likely to improve with AVR alone. A reduction in MR with anesthesia is easy to appreciate as a predictor of postoperative improvement in the presence of aortic valve disease, although we recognize that this same sign is imperfect in the setting of ischemic causes. Both of these observations may be useful to the clinician insofar as they suggest a lower threshold for intervention on the valve may be appropriate in the presence of TR, whereas one may be reassured if the MR improves in the operating room.

TABLE 6. Independent predictors for overall and late mortality

Variable	HR	95% CI	P value
Overall mortality			
Age	1.08	1.04–1.11	<.001
Severity of diabetes	1.45	1.06–1.99	.020
Dialysis	12.42	3.31–46.66	<.001
Late mortality			
Age	1.10	1.06–1.14	<.001
Severity of diabetes	1.70	1.17–2.47	.005
Dialysis	16.40	4.03–66.77	<.001
Increased TR severity	1.51	1.05–2.16	.024

HR, Hazard ratio; CI, confidence interval; TR, tricuspid regurgitation.

At midterm, predictors of improved MR included absence of cerebrovascular disease and lower preoperative LVEF. The relationship between the former and MR is not obvious, although the cerebrovascular disease may in fact be a surrogate for hypertension and subclinical atherosclerotic disease in other beds, such as the coronary vasculature. This may in turn correlate with continued ventricular dysfunction and persistent hypertension.¹⁰ With regard to lower LVEF as a predictor of MR improvement, it is known that ventricular function improves after AVR even in the presence of preoperative ventricular dilatation.¹¹⁻¹⁴ The dilated left ventricle with lower preoperative LVEF may therefore undergo the greatest favorable reverse remodeling, thereby reducing preoperative functional MR to the greatest degree. Similar findings have been found in another study.⁵

Our findings are consistent with those of Absil and colleagues,¹⁵ who reported improvement in MR severity among the majority of patients with moderate functional MR and no difference in survival in a case-matched comparison of patients with mild versus moderate MR at the time of isolated AVR.¹⁵ Among elderly patients (≥ 70 years of age), Barreiro and associates⁶ found moderate MR to be an independent predictor of late mortality; however, their study group included individuals with organic or ischemic mitral valve disease (48%) of patients with moderate MR undergoing AVR.⁶ Among those with functional MR, the degree of MR improved in more than 80%. In a smaller study, Brasch and coauthors⁴ also found improvement in a substantial percentage among patients with AS undergoing AVR alone.

The principle limitation of our study is incomplete echocardiographic follow-up. Although the patients who underwent echocardiography were demographically similar to those who did not, there is significant potential for sampling bias in the assessment of recurrent MR at the mid-to-late term. Symptomatic patients may be less likely to return for follow-up. Echocardiographic follow-up before discharge was available in the majority of patients, and selection bias was less likely. As a retrospective study, it is also subject to the biases inherent in such a design, including information bias, recall bias, and treatment selection bias.¹⁶ Despite these weaknesses, this is a relatively large study that provided power to determine predictors of survival and improvement in MR over time.¹⁷ A matched comparison of patients undergoing AVR without MR to a subgroup from our cohort was also possible.

CONCLUSIONS

Improvement in functional MR can be expected in the majority of patients with significant aortic valve pathology after AVR. Diminished degrees of MR severity under anesthesia predicts improvement in MR grade by the time of discharge

from hospital. Although moderate functional MR in association with aortic valve pathology is associated with lower than predicted survival for age-matched controls, this effect seems unrelated to the degree of residual MR, suggesting that surgical correction of coexistent moderate functional MR at the time of AVR is unlikely to affect survival; its impact on symptomatology remains unclear. A more complete assessment of long-term functional status is an important area of further study. Lacking such information thus far, a highly selective approach to moderate MR at the time of AVR would be appropriate.

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TABLE E1. Baseline characteristics of case-matched patients undergoing lone AVR without MR vs. patients in the current cohort

	Control (MR-) n = 91	Case (MR+) n = 91	P-value
Male	48 (47%)	48 (47%)	1.00
Age	71.6	71.8	0.55
Body surface area	1.93	1.91	0.52
Preop LVEF	54.8%	53.1%	0.47
Aortic prosthesis size	23.4 mm	23.0 mm	0.15
History of smoking	47 (52%)	47 (52%)	1.00
Diabetes	13 (14%)	14 (15%)	0.83
Chronic renal failure	3 (3%)	10 (11%)	0.04
Dialysis-dependence	1 (1%)	2 (2%)	1.00
Hypertension	46 (51%)	56 (62%)	0.14
Pulmonary hypertension	9 (15%)	9 (24%)	0.28
Cerebrovascular accident	3 (3%)	5 (5%)	0.72
Chronic obstructive pulmonary disease	7 (12%)	10 (26%)	0.07
Peripheral vascular disease	3 (3%)	11 (12%)	0.03
Cerebrovascular disease	6 (7%)	11 (12%)	0.20
NYHA 1	4 (4%)	4 (4%)	0.99
NYHA 2	24 (26%)	22 (24%)	
NYHA 3	46 (51%)	48 (53%)	
NYHA 4	17 (19%)	17 (19%)	