Natural History and Predictors of Outcome in Patients With Concomitant Functional Mitral Regurgitation at the Time of Aortic Valve Replacement

Marc Ruel, MD, MPH; Varun Kapila, MD; Joel Price, MD; Alexander Kulik, MD; Ian G. Burwash, MD; Thierry G. Mesana, MD, PhD

Background—Concomitant functional mitral regurgitation (FMR) in patients undergoing aortic valve replacement (AVR) is frequently not corrected because it may improve after AVR; however, data supporting this assumption are sparse. We ascertained the impact of clinical and echocardiographic parameters on the outcome of patients with or without concomitant FMR at the time of AVR.

Methods and Results—Clinical and echocardiographic follow-up was performed on 848 patients who underwent AVR after 1990. Risk factors for mortality and a composite outcome of heart failure (CHF) symptoms, CHF death, or subsequent mitral repair or replacement, were examined with bootstrapped Cox proportional hazard models. Follow-up was 4591 patient-years (mean 5.4±3.4 years; maximum 14.2 years). FMR ≥2+ had no independent adverse effect on survival in patients with aortic stenosis (AS) or insufficiency (AI). However, AS patients with FMR ≥2+ and 1 additional risk factor (left atrial diameter >5 cm, preoperative peak aortic valve gradient <60 mm Hg, or atrial fibrillation) were at increased risk for the composite outcome (hazard ratio [HR]: 2.7; \( P = 0.004 \)). AI patients with FMR ≥2+ and a left ventricular end-systolic diameter <45 mm were also at risk (HR: 4.0; \( P = 0.02 \)). Clinical risk factors in the AS and AI subgroups were associated with an increased likelihood of mitral regurgitation ≥2+ at 18 months postoperatively.

Conclusions—AS patients with FMR ≥2+ and a left atrial diameter >5 cm, preoperative peak aortic valve gradient <60 mm Hg, or atrial fibrillation have a significantly higher risk of CHF and persistent mitral regurgitation after AVR than other AS patients. AI patients with FMR ≥2+ and a left ventricular end-systolic diameter <45 mm preoperatively are also at increased risk. Others fare well after AVR. (Circulation. 2006;114[suppl I]:I-541–I-546.)

Key Words: follow-up studies ■ heart failure ■ prosthesis ■ valves

Severe aortic valve disease may be associated with functional mitral regurgitation (FMR), defined as the failure of the mitral valve to prevent systolic backward flow in the absence of significant structural or intrinsic valvular disease.¹ Mitral valve competence requires the functional integrity of each component of the valvular apparatus; however, ventricular hypertrophy, ventricular dilatation, or annular dilatation commonly occur in patients with severe aortic stenosis or insufficiency and may result in FMR, without recognizable intrinsic disease of the mitral valve leaflets. FMR of varying degrees has been reported in up to 75% of patients undergoing AVR.²

Relatively few studies to date have examined the clinical impact of FMR in patients undergoing AVR.²⁻⁶ Most of these series were small, and none has focused on heart failure (CHF) outcomes and concomitant factors associated with FMR that might be predictive of a poor functional outcome.

In this study, we sought to examine whether AS and AI patients with significant FMR (≥2+) experienced an increase in adverse outcomes compared with patients without FMR (≤1+) at the time of AVR, and determine clinical predictors of prognosis in patients with concomitant FMR at the time of AVR.

Methods

Patient Population and Follow-Up

The study population consisted of 848 consecutive adult patients who underwent AVR after 1990 at the University of Ottawa Heart Institute and who were prospectively followed-up in a dedicated valve clinic after their operation. To examine the postoperative natural history of FMR at the time of AVR, we excluded patients with preoperative echocardiographic evidence of leaflet, annular, chordal, or papillary muscle pathology, patients who underwent concomitant mitral valve repair or replacement, and patients who did not survive the operation. Patients were also excluded if they...
received a prosthesis subsequently withdrawn from the North American market before January 2005 to limit their possible confounding effect.

Aortic prostheses were implanted and oriented according to the manufacturer’s instructions, and their model and size were recorded for all patients. Postoperative clinic visits occurred on an annual basis, and all patients were followed-up for at least 1 visit. At each visit, a physician documented the patient’s medical history with a focus on determining functional status and the occurrence of valve-related complications.7 A physical examination was also performed, and patients had an ECG, chest radiograph, complete blood count, serum chemistries, and international normalized ratio determinations when applicable. Patients were anticoagulated according to guidelines, as previously described.8 Total follow-up was 4591 patient-years, with a mean duration of 5.4±3.2 years (range, 60 days to 14.2 years).

All patients underwent complete M-mode, 2-dimensional, and Doppler transthoracic echocardiograms before AVR. Echocardiograms were performed on a biannual basis or as clinically indicated after AVR. Significant FMR at the time of AVR was defined as mitral regurgitation (MR) ≥2+ on the preoperative transthoracic echocardiogram,9 in the absence of recognizable intrinsic leaflet, annular, chordal, or papillary muscle abnormality.10 For within-group comparison purposes, patients were defined as having predominant aortic stenosis (AS) if they had aortic stenosis and ≥2+ aortic insufficiency before AVR, and as predominant aortic insufficiency (AI) if they had ≥3+ aortic insufficiency.9 Left ventricular ejection fraction (LVEF) was quantified by the visual method,11 and overall systolic function was graded as follows: 1, normal (LVEF ≥50%); 2, mildly impaired (LVEF 40% to 49%); 3, moderately impaired (LVEF 30% to 39%); and 4, severely impaired (LVEF <30%). The echocardiogram closest to 18 months postoperatively was used to assess postoperative MR to allow for left ventricular remodeling and left ventricular hypertrophy regression, while minimizing the effects of heart disease progression and/or prosthesis deterioration.12,13

**Outcomes and Statistical Analyses**

Data were imported and analyzed in Intercooled Stata 9 (College Station, Tex). Patients with or without significant FMR were compared with respect to: (1) preoperative clinical and echocardiographic characteristics; (2) all-cause mortality; (3) a composite CHF outcome a priori defined as the occurrence, >60 days after AVR, of (a) New York Heart Association (NYHA) functional class 3 or 4 for >4 consecutive weeks,14 (b) death in which the primary or contributing diagnosis was CHF, or (c) subsequent mitral valve repair or replacement for any reason other than endocarditis; and (4) postoperative MR severity after AVR.

**Preoperative Characteristics**

Preoperative characteristics were compared between patients with or without significant FMR with a Student t test or Fisher exact test as appropriate. Characteristics that differed between groups were incorporated and retained in the multivariate models examining predictors of all-cause mortality and the composite CHF outcome. The presence or absence of coronary artery disease (CAD) was also incorporated and retained as a covariate in each model because of its potential confounding effect, regardless of whether a significant difference in the baseline prevalence of CAD existed.

**All-Cause Mortality, Composite Heart Failure Outcome**

Possible predictors of all-cause mortality and of the composite CHF outcome were tested for equality with a log-rank test. For multivariate models, the proportional hazard assumption was verified with generalized Cox-Snell residuals. If the assumption was met, Cox proportional hazards models were separately developed for AS and AI subgroups by incorporating into each model: (1) variables that had P≤0.05 on log-rank testing; and (2) the presence of CAD and of baseline characteristics that differed between the groups with or without significant FMR. No automated model selection procedure was used and all covariates were used simultaneously. Proportional hazards models were subjected to 1000 bootstrap replications, as described previously;15 95% confidence intervals and P values were derived from the 1000 replications by using a bias-corrected method.

**Postoperative MR**

The presence of MR ≥2+18 months postoperatively was compared between patient subgroups by using logistic regression. Bonferroni corrections for multiple tests were applied as appropriate.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

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**TABLE 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>FMR ≤1+ (n=741)</th>
<th>FMR ≥2+ (n=107)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>239 (32.3%)</td>
<td>39 (36.5%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Age at surgery, y</td>
<td>63.3±13.8</td>
<td>69.6±11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.87±0.25</td>
<td>1.88±0.22</td>
<td>0.6</td>
</tr>
<tr>
<td>NYHA class 4</td>
<td>114 (15.4%)</td>
<td>20 (18.7%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Decreased left ventricular systolic function*</td>
<td>176 (23.8%)</td>
<td>53 (49.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>245 (33.1%)</td>
<td>44 (41.1%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Chronic atrial fibrillation</td>
<td>74 (10.0%)</td>
<td>20 (18.7%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Operative indication for aortic stenosis</td>
<td>630 (85.0%)</td>
<td>76 (71.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Preoperative FMR grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>317 (42.8%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>424 (57.2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>0</td>
<td>95 (88.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3+</td>
<td>0</td>
<td>12 (11.2%)</td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bioprosthetic valve implant</td>
<td>341 (46.0%)</td>
<td>63 (58.9%)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*Left ventricular ejection fraction<50%.

FMR indicates functional mitral regurgitation; NYHA, New York Heart Association.
valve replacement; CI, confidence interval; FMR, functional cal prosthesis, and coronary artery disease. AVR indicates aortic systolic function, atrial fibrillation, use of tissue versus mechani-

comorbid factors. No significant effect of FMR

experienced significantly increased crude all-cause mortality if

and AI patient subgroups, according to the presence or

Figure 1 displays the crude and adjusted mortality in the AS

All-Cause Mortality

Patient Characteristics

Preoperative characteristics of the study cohort are shown in

Table 1. Patients with FMR ≥2+ were significantly older, had a greater prevalence of atrial fibrillation and decreased left ventricular systolic function, and were more likely to receive a bioprosthesis, compared with patients with ≤1+ FMR. Patients with FMR ≥2+ also had a trend toward a higher co-prevalence of CAD.

All-Cause Mortality

Figure 1 displays the crude and adjusted mortality in the AS and AI patient subgroups, according to the presence or absence of FMR ≥2+ at the time of AVR. Increased age, atrial fibrillation, decreased ventricular function, and concomitant CAD all had independent adverse effects on mortality (all \( P < 0.05 \); data not shown). These comorbidities were more common in patients with FMR ≥2+; however, FMR ≥2+ in itself had no independent adverse effect after adjustment for baseline differences in either AS or AI patient subgroup.

Composite Heart Failure Outcome

In AS patients, FMR ≥2+ at the time of AVR was overall associated with an increased risk of the composite CHF outcome. Left atrial size >5 cm, preoperative peak aortic gradient <60 mm Hg, preoperative mean aortic gradient <40 mm Hg, and chronic atrial fibrillation were also significant risk factors for the composite outcome (Table 2). However, when only AS patients with FMR ≥2+ and none of these additional risk factors were studied, these patients showed no increased risk of the composite CHF outcome (hazard ratio [HR]: 1.2; \( P = 0.9 \)). Conversely, patients with FMR ≥2+ in combination with any one of these additional risk factors were at significantly increased risk of the composite CHF outcome (HR, 2.7; \( P = 0.004 \) ) (Figure 2).

In AI patients, FMR ≥2+ at the time of AVR was not associated with an increased risk of the composite CHF outcome. However, preoperative left ventricular end-systolic diameter was an effect modifier, and AI patients with both FMR ≥2+ and a left ventricular end-systolic diameter <45 mm were at significantly increased risk for CHF (Figure 2).

Postoperative Mitral Regurgitation

Postoperative echocardiographic data from our institution were available in 758 (89.4%) patients. The majority of AS patients with FMR ≥2+ experienced an improvement in MR severity after AVR (Figure 3). However, these patients were at a greater risk of having persistent MR ≥2+ postoperatively, and this risk increased with the number of preoperative risk factors for the composite CHF outcome, as identified in Table 2. Postoperative MR ≥2+ was observed in 31.6% of AS patients with FMR ≥2+ and no preoperative risk factors for the composite CHF outcome, compared with 10.7% of AS patients with FMR ≤1+ preoperatively (\( P = 0.01 \)). The proportion of AS patients with MR ≥2+18 months after AVR increased to 36.5% and 55.6% in the presence, respectively, of 1 and 2 preoperative risk factors for the composite CHF outcome.

The majority of AI patients with FMR ≥2+ had an improvement in MR severity after AVR. Only 20% of AI patients with FMR ≥2+ and an enlarged left ventricle (defined as an end-systolic diameter ≥45 mm) had MR ≥2+18 months after AVR. This was not statistically different from the 10.6% of AI patients with preoperative FMR ≤1+ who demonstrated MR ≥2+18 months after AVR. However, 42.1% of AI patients with preoperative FMR ≥2+ and a left ventricular end-systolic diameter <45 mm had MR ≥2+18 months after AVR (\( P < 0.001 \)).

Discussion

The main finding of this study is the identification of factors associated with a suboptimal outcome in patients with aortic
valve disease who undergo AVR and also have concomitant FMR $\geq 2+$. We have shown that FMR $\geq 2+$ is not an independent predictor of late mortality in AS and AI patients undergoing AVR. However, FMR $\geq 2+$ results in a higher risk of a composite CHF outcome (CHF symptoms, CHF death, or mitral valve repair/replacement) in AS patients if it is associated with a left atrial size $>5$ cm, a preoperative peak aortic valve gradient $<60$ mm Hg or preoperative mean aortic valve gradient $<40$ mm Hg, or chronic atrial fibillation. In AI patients, a higher risk of CHF is seen if the preoperative left ventricular end-systolic diameter is $<45$ mm.

FMR $\geq 2+$ at the time of AVR is a relatively common clinical situation; however, paradoxically, little published outcome data exist. Thus, these criteria provide valuable prognostic information for the patient, cardiologist, and surgeon faced with the presence of FMR at the time of AVR. Importantly, these criteria do not constitute indications for mitral valve repair or replacement at the time of AVR, but rather identify the target population for whom a concomitant mitral valve procedure could be of benefit, and perhaps even more importantly, the subpopulation of AVR patients with FMR $\geq 2+$ for whom mitral valve repair does not appear necessary. Patients undergoing AVR with FMR $\geq 2+$ and no associated risk factor appear to have an outcome as good as that of patients with FMR $\leq 1+$.

In AS patients with FMR $\geq 2+$ undergoing AVR, additional risk factors predictive of the composite CHF outcome were also associated with persistent MR $\geq 2+18$ months postoperatively and with a higher risk of a subsequent mitral valve procedure. However, the correlation between CHF symptoms and persistent MR was not absolute, and a number of AS patients with FMR $\geq 2+$ and no associated risk factors remained asymptomatic postoperatively despite the persistence of MR $\geq 2+$. It is therefore possible that the identified risk factors for the composite CHF outcome in AS patients may have reflected more advanced cardiac disease. In this regard, lower gradient AS, atrial fibillation, and a larger atrial diameter (suggestive of more longstanding FMR or more advanced diastolic dysfunction) constitute risk factors for CHF after AVR that have previously been identified by our group,$^{14,15}$ and that may have impacted beyond the relationship between FMR and symptoms. For these reasons, the present study does not establish the indications for mitral valve repair at the time of AVR in AS patients with FMR, but instead provides insight into which AS patients with FMR $\geq 2+$ constitute those for whom mitral repair does not appear to be necessary, ie, patients with FMR $\geq 2+$ and no associated risk factor for the composite CHF outcome.

In the AI subgroup, patients with FMR $\geq 2+$ and a normal size left ventricle ($<45$ mm in end-systolic diameter) before AVR were more likely to experience both persistent MR $\geq 2+$ and the composite CHF outcome. This suggests that LV size remodeling is an important mechanism by which FMR occurs and can improve in these patients postoperatively. FMR $\geq 2+$ in an AI patient without LV dilatation (ie, with a low potential for LV size reduction) may thus persist after AVR and may constitute an indication for concomitant mitral valve repair.

**Previous Related Work**

To our knowledge, no study to date has simultaneously examined the survival, functional outcome, and postoperative severity of MR in closely followed AS patients who have concomitant FMR and undergo AVR. With respect to AI patients, even less data exist. Barreiro et al examined quality of life and long-term survival in a mixed cohort that included structural as well as functional MR patients.$^5$ The authors demonstrated decreased long-term survival in patients with moderate preoperative MR. The study, however, did not identify associated risk factors that may help differentiate AVR patients with FMR who do well postoperatively from those who do not, and echocardiographic follow-up was only available in half of the patients. Several groups using echocardiography to evaluate the severity of MR after isolated AVR for AS demonstrated, like in the present study, that MR decreased in majority of patients postoperatively.$^2-4,6,16,17$ This finding was most prevalent in patients with mild to moderate MR preoperatively, but the functional and echocardiographic impact of associated conditions was not examined. One study, which used routine preoperative and postoperative

<table>
<thead>
<tr>
<th>TABLE 2. Preoperative Risk Factors for Composite Heart Failure Outcome:* Aortic Stenosis Patients</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMR $\geq 2+$, all patients</td>
<td>2.2</td>
<td>1.0, 5.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Left atrial size $&gt;5$ cm</td>
<td>3.8</td>
<td>1.6, 8.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Preoperative peak aortic gradient $&lt;60$ mm Hg†</td>
<td>2.2</td>
<td>1.2, 4.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Preoperative mean aortic gradient $&lt;40$ mm Hg†</td>
<td>2.0</td>
<td>1.1, 3.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Chronic atrial fibillation</td>
<td>4.1</td>
<td>1.4, 11.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Left ventricular ejection fraction over 55%</td>
<td>2.1</td>
<td>0.8, 5.5$</td>
<td>0.1$</td>
</tr>
<tr>
<td>FMR $\geq 2+$, without any additional risk factor above§</td>
<td>1.2</td>
<td>0.2, 8.5</td>
<td>0.9</td>
</tr>
<tr>
<td>FMR $\geq 2+$, with any single additional risk factor above§</td>
<td>2.7</td>
<td>1.4, 5.4</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Heart failure symptoms, heart failure death, mitral valve repair or replacement.
†Collinear terms successively but not simultaneously entered in the model.
‡Was statistically significant (95% CI: 1.1, 6.1; $P=0.01$) before 1000 bootstrap replications.
§Any of: left atrial size $>5$ cm, preoperative mean aortic gradient $<40$ mm Hg, preoperative mean aortic gradient $<40$ mm Hg, or chronic atrial fibillation.
FMR indicates functional mitral regurgitation.
echocardiography, found preoperative left atrial diameter and pulmonary artery pressure to be related to postoperative MR severity. However, this study did not link echocardiographic data to functional outcomes and included patients with functional and structural MR.

Limitations

This study examined the outcomes of patients who survived AVR, and did not focus on early perioperative outcomes, to evaluate CHF symptoms, subsequent need for mitral valve surgery, and echocardiographic changes in MR severity, all of which cannot be adequately evaluated in the perioperative period. The study was not of randomized design and it is possible, despite the use of a priori specified end points and covariates and bootstrapped methods, that selection bias or unidentified confounders may have influenced the results. Furthermore, the findings of this study, as with any observational cohort, may not necessarily be generalizable to all patients with concomitant FMR at the time of AVR; for instance, there were relatively few patients with FMR ≥2+ in the study, and thus our findings may not specifically apply to them.

Conclusions

The presence of FMR ≥2+ at the time of AVR does not constitute an independent risk factor for late postoperative death. However, AS patients with FMR ≥2+ who undergo
AVR have a higher risk of a composite CHF outcome when they also have a left atrial size >5 cm, a preoperative peak aortic valve gradient <60 mm Hg or preoperative mean aortic valve gradient <40 mm Hg, or chronic atrial fibrillation. AS patients with FMR ≥2+ and no associated risk factors fare as well as FMR ≤1+ patients. In AI patients, FMR ≥2+ has a higher risk of a composite CHF outcome only if associated with a left ventricular end-systolic diameter <45 mm before AVR. AI patients with FMR ≥2+ and a left ventricular end-systolic diameter ≥45 mm fare as well as AI patients with FMR ≤1+. The majority of patients with FMR ≥2+ undergoing AVR experience an improvement in MR severity postoperatively, but AS patients with preoperative FMR ≥2+ and associated risk factors for the composite CHF outcome are at significantly higher risk of persistent MR ≥2+ postoperatively, as are AI patients with FMR ≥2+ and a left ventricular end-systolic diameter <45 mm preoperatively.

Disclosures

None.

References

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