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. 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. 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, in the absence of recognizable intrinsic leaflet, annular, chordal, or papillary muscle abnormality. 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. Left ventricular ejection fraction (LVEF) was quantified by the visual method, 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 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, (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. 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+ 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.

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Preoperative FMR grade</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>Bioprosthetic valve implant</td>
<td>341 (57.2%)</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.
Results

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 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
TABLE 2. Preoperative Risk Factors for Composite Heart Failure Outcome:* Aortic Stenosis Patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMR ≥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 fibrillation</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 ≥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 ≥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 peak aortic gradient <60 mm Hg, preoperative mean aortic gradient <40 mm Hg, or chronic atrial fibrillation.
FMR indicates functional mitral regurgitation.

In the AI subgroup, patients with FMR ≥2+ and a normal size left ventricle (<45 mm in end-systolic diameter) before AVR were more likely to experience both persistent MR ≥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 ≥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. 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. 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
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 3+/H11001 in the study, and thus our findings may not specifically apply to them.

**Conclusions**

The presence of FMR 3+/H11350 at the time of AVR does not constitute an independent risk factor for late postoperative death. However, AS patients with FMR 3+/H11350 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


Natural History and Predictors of Outcome in Patients With Concomitant Functional Mitral Regurgitation at the Time of Aortic Valve Replacement
Marc Ruel, Varun Kapila, Joel Price, Alexander Kulik, Ian G. Burwash and Thierry G. Mesana

Circulation. 2006;114:I-541-I-546
doi: 10.1161/CIRCULATIONAHA.105.000976
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/1_suppl/I-541

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/