Prognostic Implications of Mitral Regurgitation in Patients With Severe Aortic Regurgitation

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**Background**—Mitral regurgitation (MR) is common in those with severe aortic regurgitation (AR) and can predispose to atrial fibrillation, heart failure, and a need for mitral valve surgery during aortic valve replacement (AVR). However, little data exist as to its clinical and prognostic implications.

**Methods and Results**—Search of our echocardiographic data base between 1993 and 2007 yielded 756 patients with severe AR. With comprehensive clinical data from chart review and mortality data from National Death Index. Mortality was analyzed as a function of MR severity. Effect of AVR and concomitant mitral valve repair were investigated. Patient characteristics were age, 61 ± 17 years; female sex, 41%; and ejection fraction, 54 ± 19%. MR grade ≥2+ was present in 343 (45%) patients: 2+ in 152 (20%), 3+ in 93 (12%), and 4+ in 98 (13%). There was a progressive decrease in survival with each grade of MR (P < 0.0001). Performance of AVR was associated with a better survival in those with 3 or 4+ MR (P = 0.02). In addition, concomitant mitral valve repair in these patients resulted in a better survival (hazard ratio, 0.29; P = 0.02).

**Conclusions**—MR is common in patients with severe AR, with 3 or 4+ MR occurring in a quarter of these patients. It is an independent predictor of reduced survival. Performance of AVR and concomitant mitral valve repair is associated with a better survival. Development of MR should serve as an indication for AVR even in asymptomatic patients. *(Circulation. 2010;122[suppl 1]:S43–S47.)*

**Key Words:** aortic regurgitation ■ aortic valve ■ aortic valve replacement ■ left ventricular dysfunction ■ survival

Mitral regurgitation (MR) is common in those with severe aortic regurgitation (AR). It can predispose to atrial fibrillation, heart failure, and a need for mitral valve (MV) surgery during aortic valve replacement (AVR). However, little data exist as to its clinical and prognostic implications. Hence, we investigated its impact on survival in a large cohort of patients with severe AR. In addition, we sought to determine the value of AVR as well as concomitant MV surgery in this population.

**Methods**

**Patient Population**

This is a retrospective cohort study from a large university medical center, and the patient cohort has been previously described. This study was approved by our institutional review board. Our echocardiographic database, which contains records from 1993 to 2007, was searched for patients with severe AR defined by a jet height to left ventricular (LV) outflow tract dimension ratio of ≥0.6 or a prominent holodiastolic flow reversal in the aortic arch or the abdominal aorta. Patients with prosthetic aortic valve were excluded. This yielded a total of 785 patients. Of these, 29 had no follow-up data and were excluded from the study, forming a final cohort of 756 patients. Detailed chart reviews were then performed on these patients (both alive and dead) by senior medical residents to extract clinical, pharmacological, and surgical data.

**Definition of Clinical Variables**

Hypertension was defined as blood pressure >140/90 mm Hg, a history of hypertension, or treatment with relevant medications. Diabetes was defined as having a history of diabetes or being treated with antidiabetic medications. Renal insufficiency was defined as serum creatinine >2 mg/dL, and coronary artery disease was defined as having a history of angina, myocardial infarction or coronary revascularization, ECG presence of Q waves, or a history of angiographic coronary artery disease.

**Pharmacological Data**

Pharmacotherapy at the time of echocardiography was recorded. This was categorized into aspirin, β-blockers, angiotensin-converting enzyme inhibitors, statins, loop diuretics, and thiazide diuretics.

**Echocardiographic Data**

All patients had standard 2-dimensional echocardiographic examinations. LV ejection fraction (EF) was assessed by a level-3 trained echocardiographer and entered into a data base at the time of the examination. Anatomic and Doppler measurements were performed according to the recommendations of the American Society of Echocardiography. Severe AR was defined as above. MR was graded 1 to 4+, based on the guidelines of the American Society of Echocardiography and interpreted by a level-3 trained echocardiographer as follows: 1+ was deemed to be 1+ if MR jet size was <20% of left atrial area, vena contracta diameter <3 mm, or effective regurgitant orifice area <20 mm²; 2+ if MR jet size was 20% to 29% of the left atrial area, vena contracta diameter 3 to 4.9 mm, or effective regurgitant orifice area 20 to 29 mm²; 3+ if MR jet size was 30% to 39% of left atrial area, vena contracta diameter 5 to 6.9 mm, or effective regurgitant orifice area 30 to 39 mm²; and 4+ if MR jet size was ≥40% of left atrial area, vena contracta...
diameter ≥7 mm, effective regurgitant orifice area ≥40 mm², or there was systolic flow reversal in pulmonary vein.

**Mortality Data**
The end point of the study was all-cause mortality. Mortality data were obtained from the National Death Index, using social security numbers as of August 9, 2007. The patients who were alive were censored as of this date. The reliability of the data were ensured by a match between the social security numbers, names, and date of birth.

**Statistical Analysis**
Analysis was performed using StatView 5.01 (SAS Institute Inc, Cary, NC). Characteristics of patients with and without 3 or 4+ MR were compared using the Student t test for continuous variables and χ² test for categorical variables. Statistical tools used for survival analysis included the Kaplan-Meier method, log rank statistic for probability value, Cox regression model, and propensity score analysis as described later. In all cases, time zero was defined as time of the earliest echocardiogram was performed in our institution. A probability value of ≥0.05 was considered statistically significant.

**Results**

**Patient Characteristics**
The patient characteristics are summarized in Table 1. Salient characteristics were age, 61±18 years; female sex, 41%; and LVEF, 54±19%. Comorbidities included diabetes mellitus in 14%, stroke in 18%, coronary artery disease in 34%, and renal insufficiency in 21%. Angina was present in 34% and...
a quarter of the patients had 3 or 4 MR in the entire population (A) and entire population stratified by AVR status (B). There was a progressive decrease in survival with each grade of MR in this population. Lower survival was associated with a larger LV size (P<0.0001), lower EF (P<0.0007), thicker LV wall, atrial fibrillation, hypertension, diabetes mellitus, coronary artery disease, renal insufficiency, EF, and performance of AVR; the other independent predictors of lower survival included higher age, lower EF, lack of AVR, and renal insufficiency.

AVR Rates and Survival in 3 or 4+ MR
AVR was performed in 288 (38%) patients during follow-up, with AVR rates being 34% (65/191) in those with 3 or 4+ MR compared with 36% in those with no AVR (Figure 1B, P<0.0001). Similarly, AVR was also associated with a better survival in lesser degrees of MR, 5-year survival being 85% in those undergoing AVR compared with 60% in those without AVR (Figure 1B, P<0.0001). MR was an independent predictor of lower survival after adjusting for other univariate predictors of survival listed in Table 2, which included age, sex, atrial fibrillation, hypertension, diabetes mellitus, coronary artery disease, renal insufficiency, EF, and performance of AVR; the other independent predictors of lower survival included higher age, lower EF, lack of AVR, and renal insufficiency.

**Table 2. Univariate Predictors of Survival in All Patients With Severe AR**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.04 (1.03–1.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.32 (1.06–1.64)</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.988 (0.982–0.994)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.43 (1.14–1.80)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.57 (1.23–2.01)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.80 (1.36–2.38)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.72 (1.37–2.14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1.38 (1.07–1.77)</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2.83 (2.26–3.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1.64 (1.23–2.17)</td>
<td>0.0007</td>
</tr>
<tr>
<td>3 or 4+ MR</td>
<td>1.90 (1.51–2.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AVR</td>
<td>0.42 (0.33–0.55)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

As shown in Figure 2, AVR was associated with a better survival in those with 3 or 4+ MR (P=0.02; relative risk, 0.61; 95% confidence interval, 0.40 to 0.93). It remained significant after adjusting for age, sex, and EF using the Cox regression model. Type of prosthetic aortic valve did not

**Effect of MR on Survival**

There was a progressive decrease in survival with each grade of MR in the whole cohort as well as the surgically and medically treated subsets (P<0.0001). Five-year survival rate in those with 3 or 4+ MR was 42% compared with 70% for those with lesser grades of MR in the whole cohort (Figure 1A, P<0.0001). In patients with severe AR and 3 or 4+ MR, AVR was associated with a 5-year survival of 70% compared with 36% in those with no AVR (Figure 1B, P<0.0001). Similarly, AVR was also associated with a better survival in lesser degrees of MR, 5-year survival being 85% in those undergoing AVR compared with 60% in those without AVR (Figure 1B, P<0.0001). MR was an independent predictor of lower survival after adjusting for other univariate predictors of survival listed in Table 2, which included age, sex, atrial fibrillation, hypertension, diabetes mellitus, coronary artery disease, renal insufficiency, EF, and performance of AVR; the other independent predictors of lower survival included higher age, lower EF, lack of AVR, and renal insufficiency.

**Frequency of Concomitant MR**

MR grade 2+ was present in 343 (45%) patients: 2+ in 152 (20%), 3+ in 93 (12%), and 4+ in 98 (13%). In other words, a quarter of the patients had 3 or 4+ MR.

**Predictors of 3 or 4+ MR**

As summarized in Table 1, presence of 3 and 4+ MR was associated with a larger LV size (P<0.0001), thinner LV walls (P=0.0002), lower EF (P<0.0001), greater age (P=0.0001), female sex (P=0.0007), coronary artery disease (P<0.0001), renal insufficiency (P=0.0002), greater degrees of tricuspid regurgitation (P<0.0001), and atrial fibrillation (P<0.0001). Both groups had similar prevalence of hypertension and diabetes mellitus. There was a higher stroke risk in those with 3 or 4+ MR, which could be explained by greater age, lower EF, and higher rates of atrial fibrillation. Logistic regression analysis identified lower EF, thinner LV wall, female sex, greater age, atrial fibrillation, coronary artery disease, and renal insufficiency to be the independent risk factors for 3 or 4+ MR in this population.

**Figure 1. Effect of 3 or 4+ MR on survival in 756 patients with severe AR in the entire population (A) and entire population stratified by AVR status (B).**

Dyspnea in 70%; 26% were in atrial fibrillation. Concomitant pharmacotherapy is listed in Table 1.
affect the outcome. It can also be seen from Figure 1B that though AVR resulted in a better survival in both MR and non-MR groups, the size of the benefit appears to greater in the 3 to 4+ MR group.

We also used the propensity score analysis to balance the differences in pretreatment covariates to reduce the impact of bias in performing AVR in those with 3 or 4+ MR. A propensity score for receiving AVR was calculated using logistic regression analysis based on the following variables: age, sex, EF, hypertension, diabetes mellitus, coronary artery disease, renal insufficiency, and atrial fibrillation. After adjusting for the propensity score using the Cox regression model, AVR was associated with a mortality hazard of 0.46 in patients with severe AR with 3 or 4+ MR (P=0.03).

In patients with severe AR and 3 or 4+ MR undergoing AVR (n=65), 17 had concomitant MV repair, 22 had MV replacement, and 26 had no MV surgery. As shown in Figure 3, MV repair was associated with a better survival adjusted for age, sex, and EF (P=0.02; relative risk, 0.29; 95% confidence interval, 0.09 to 0.94). No survival advantage was seen with MV replacement compared with no MV surgery.

**Discussion**

There are several novel findings from our study with important implications. The results show that 3 or 4+ MR is present in a quarter of the patients with severe AR and its presence increases mortality. It appears to be mechanistically...
related to a larger LV with thinner walls and lower EF. It also predisposes to atrial fibrillation, pulmonary hypertension, and possibly stroke. AVR in these patients confers a mortality benefit, and a concomitant MV repair appears to be additionally beneficial in terms of better survival. Though the issue of MR is extensively studied in severe aortic stenosis, we did not come across systematic studies of MR in a severe AR population. It is difficult to apply the findings from aortic stenosis to an AR population because LV in AR has both pressure and volume overload, LV is larger, patients tend to be younger than aortic stenosis by about a decade, and response of the LV to AVR is both qualitatively and quantitatively different. Hence, we think that the findings of our study are important and give valuable insights into MR mechanisms and outcomes in severe AR.

In view of the deleterious consequences of MR in those with AR, we think that LV size and mitral anatomy must be closely monitored in those with severe AR for the early signs of genesis of functional MR. The mean LV end-systolic dimension in those with 3 or 4+ MR was only 4.3 cm, and risk should be much higher with larger LV. The current American College of Cardiology/American Heart Association guidelines do not address MR as a marker of risk in AR. In addition, AVR is proscribed in severe AR patients with normal EF and LV end-systolic dimension <50 mm. One is likely to come across significant amounts of MR at this LV size. Because MR can cause heart failure, atrial fibrillation, and pulmonary hypertension, it may be prudent to consider AVR when significant MR occurs, though this is not a recommendation by the current valve guidelines. Concomitant MV repair should be strongly considered if 3 or 4+ MR exists, though there is a greater potential for reverse LV remodeling in AR compared with aortic stenosis. It is also noteworthy that AVR benefit in those with 3 to 4+ MR is smaller compared with those with lesser degrees of MR. Additionally, with or without AVR survival is poorer in those with 3 to 4+ MR. This finding supports performance of AVR before significant functional MR occurs in patients with severe AR.

The main limitations of our study include observational and retrospective study nature. The strengths are that it includes the entire denominator of severe AR population presenting to the institution instead of selected subsets seen by certain practitioners or clinics. In addition, it is a large study, and the patients are well characterized in terms of comorbidities, pharmacotherapy, and echocardiographic details.

Conclusions

MR is common in patients with severe AR, with 3 or 4+ MR occurring in a quarter of these patients. It is an independent predictor of reduced survival. Despite a lower AVR rate, AVR is associated with a better survival in those with significant MR. Concomitant MV repair may confer a survival benefit as well. Development of MR should serve as an indication for AVR even in asymptomatic patients.

Disclosures

None.

References

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