Prognostic Importance of Exercise-Induced Changes in Mitral Regurgitation in Patients With Chronic Ischemic Left Ventricular Dysfunction

Patrizio Lancellotti, MD; Pierre Troisfontaines, MD; Anne-Christine Toussaint, MD; Luc A. Pierard, MD, FESC

Background—In the post–myocardial infarction phase, mortality risk is related to the severity of mitral regurgitation (MR). Ischemic MR is a dynamic condition that can be studied during exercise. Whether the assessment of exercise-induced changes in the degree of MR provides prognostic information is unknown.

Methods and Results—Ninety-eight consecutive patients with chronic ischemic left ventricular dysfunction and at least mild MR who prospectively underwent quantitative measurement of the regurgitant volume and the effective regurgitant orifice (ERO) of MR at rest and during semisupine exercise test were followed up for 19±8 months. The 16 patients who underwent surgery were censored at the time of operation. Of the 82 patients who were medically treated, 9 (11%) died. No clinical data demonstrated a distinction between survivors and nonsurvivors. By multivariate Cox regression analysis, independent predictors of cardiac death were an increase in ERO by ≥13 mm² (P=0.0045) during exercise, an ERO >20 mm² at rest (P=0.01), and a shorter mitral deceleration time (P=0.044). Half of the patients with exercise-induced significant increases in MR who died had moderate MR at rest. In contrast, none of the 14 patients with a decrease in MR at exercise displayed cardiac death.

Conclusions—In patients with ischemic MR and left ventricular dysfunction, quantitative assessment of exercise-induced changes in the degree of MR provides independent prognostic information. Significant exercise-induced increases in MR unmask patients at high risk of poor outcome. (Circulation. 2003;108:1713-1717.)

Key Words: echocardiography ■ heart failure ■ mitral valve ■ exercise ■ myocardial infarction

Mitral regurgitation (MR) is a common complication of ischemic heart disease and carries an adverse prognosis. The increased mortality risk is independent of the severity of left ventricular (LV) dysfunction but relates to the quantified degree of MR. Ischemic MR is a dynamic condition. Many patients probably have episodes of increased regurgitant volume (R Vol) and effective regurgitant orifice (ERO) during various conditions that result in worsening of dyspnea and orthopnea. We recently reported the feasibility and reliability of quantifying MR during exercise by Doppler echocardiography. A wide range of exercise-induced changes in R Vol were observed and correlated well with changes in pulmonary pressures. The prognostic significance of exercise-induced changes in MR has never been investigated. Therefore, this study was undertaken to evaluate the independent prognostic significance of an increase or decrease in the severity of MR during exercise.

Methods

Population

Ninety-eight consecutive patients with chronic ischemic LV dysfunction (ejection fraction <45%) and at least mild MR who were able to perform a semisupine exercise echocardiographic test were followed up prospectively. All patients were stable for at least 2 months, and none had the following exclusion criteria: technically inadequate echocardiogram, organic mitral valve disease, more than trivial aortic regurgitation, intraventricular conduction abnormality, New York Heart Association (NYHA) functional class IV, history of myocardial infarction <6 months, or atrial fibrillation or flutter. During follow-up, 16 patients underwent cardiac surgery. Patients were in NYHA functional class I (n=10), II (n=63), or III (n=25). The site of myocardial infarction was anterior in 43 patients, inferior in 41, and both anterior and inferior in 14. Medications used included ACE inhibitors in 70 patients, diuretics in 60, β-blockers in 51, nitrates in 31, and spironolactone in 18. A history of arterial hypertension was noted in 43 patients, and 25 were diabetic. Twenty patients had previously had surgical revascularization. Twenty-two patients had a history of acute pulmonary edema. All patients gave their informed consent, and the protocol was approved by the local ethics committee.

Exercise Echocardiography

β-Blockers were stopped 24 hours before the test. A symptom-limited graded bicycle exercise test was performed with the patient in the semisupine position on a tilting exercise table. After an initial workload of 25 W had been maintained for 6 minutes, the workload was increased every 2 minutes by 25 W. Blood pressure and a 12-lead ECG were recorded every 2 minutes. 2D and Doppler echocardiographic recordings were available throughout the test.
Echocardiographic Measurements

Echocardiographic examinations were performed with a phased-array Acuson Sequoia imaging device. All echocardiographic and Doppler data were obtained in digital format and stored on optical disks for offline analysis. Quantification of MR was performed by both the quantitative Doppler method with mitral and aortic stroke volumes and the proximal isovelocity surface area (PISA) method as described previously. The results of these 2 methods were averaged to allow calculation of R Vol and ERO. LV end-diastolic volume (EDV) and end-systolic volume (ESV) and ejection fraction were measured by the biapical Simpson disk method.

Statistical Analysis

Continuous variables are expressed as mean±SD. Student’s t test was used to assess differences between mean values, and categorical variables were compared with the χ² test. The end point was cardiac mortality. Analysis was performed by censoring follow-up at the time of cardiac surgery if eventually performed. The individual effects of the importance of exercise-induced changes in MR on event-free survival were evaluated with the Cox regression model. To detect independent predictors of cardiac death, we performed a multivariate Cox regression procedure according to the unmodified forward-selection stepwise analysis (Statistica version 5). The variable that had the most significant relation with dependent outcome was included first in the model. At the second and subsequent steps, the set of remaining variables was evaluated, and the most significant variable was included if it significantly improved the prediction of outcome. The algorithm ceased to select variables when there was no further significant improvement in the prediction of the whole model. MR was used in the model as a continuous or categorical variable. The Kaplan-Meier method was used for cumulative survival analysis, with the log-rank test for assessment of statistical differences between curves. P<0.05 was considered significant. Receiver-operator characteristic curve analysis was performed to determine the cutoff value of change in ERO that best distinguished the issue.

Results

Baseline and Exercise Characteristics

During testing, heart rate and systolic blood pressure increased significantly from rest to peak exercise (75±12 versus 113±13 bpm and 128±14 versus 152±19 mm Hg, respectively; P<0.0001). LV EDV remained unchanged during exercise (143±30 versus 141±32 mL/m²), whereas ESV decreased (92±25 versus 79±27 mL/m²; P<0.0001) and ejection fraction increased (36±7% versus 45±9%; P<0.0001). MR was measured by quantitative Doppler in all patients and by the PISA method in 77 patients (78%) at rest and in 89 (91%) at exercise. As calculated by the average of both methods in patients who had PISA measurements at rest and during exercise, R Vol and ERO increased from 21±13 mL (range 4.5 to 66 mL) to 30±21 mL (range 3 to 85 mL) and from 15±9 mm² (range 4 to 50 mm²) to 22±14 mm² (range 0.6 to 54 mm²), respectively (all P<0.0001). ERO increased by ≥13 mm² in 24 patients. Of the 27 patients with severe MR (ERO ≥20 mm²) at rest, ERO increased by ≥13 mm² in only 10 (37%). Of the 24 patients with increases in ERO ≥13 mm², 14 (58%) had mild MR at rest. ERO decreased in 14 patients (−8.6±5.7 mm², range −3.6 to −23.2 mm²).

Predictors of Cardiac Death

Patients were followed up for 19±8 months. During this period, 9 patients (9%) died, 3 of sudden cardiac death, 4 of refractory heart failure, and 2 of fatal myocardial infarction. The clinical and echocardiographic characteristics of survivors and nonsurvivors are listed in Tables 1 and 2. No clinical data enabled a distinction to be made between the 2 groups. Ejection fraction, transtricuspid pressure gradient, EDV, and ESV obtained at rest and at peak exercise were also similar between survivors and nonsurvivors. Patients who died had shorter mitral deceleration time and higher R Vol and ERO in baseline conditions. Patients with ERO ≥20 mm² at rest displayed a higher mortality rate (P=0.0096). During exercise, the increase in ERO was larger in patients who died. Patients with exercise-induced increases in ERO of ≥13 mm² and increases in transtricuspid pressure gradient demonstrated higher mortality. None of the 14 patients with a decrease in ERO during exercise died during follow-up. Exercise-induced decreases in EDV were higher in survivors. In multivariate analysis, ERO (P=0.016) and change in ERO (P<0.0025) emerged as independent predictors of cardiac death. With MR as a categorical variable, 3 independent predictors of cardiac death were selected in the multivariate model: an increase in ERO by ≥13 mm² (P=0.0045) during exercise, an ERO ≥20 mm² at rest (P=0.01), and a shorter mitral deceleration time (P=0.044; Table 3). Patients with either severe MR at rest (ERO ≥20 mm²) or significant increases in MR at peak exercise (changes in ERO of ≥13 mm²) had significantly lower survival estimates (59% and 66%) than those with mild MR or small changes in MR (93% and 88%; Figure).

Characteristics of the Surgical Population

The decision to perform surgery was made by the physician in charge of the patient, who knew the results of stress testing. The surgical approach was taken mainly in patients with recurrent angina or with an episode of acute pulmonary edema during follow-up (Table 4). The severity of MR at rest was similar in the surgical and nonsurgical groups, whereas significant increases of MR at peak exercise were more
also experienced excess cardiac mortality. In contrast, all conditions but with a severe exercise-induced increase in MR ventricular dysfunction. Patients with mild MR in basal

tion. These results confirm and extend recent data suggesting that ERO ≥20 mm² defines severe MR in the setting of ischemic heart disease. A higher degree of MR is associated with more severe symptoms, pulmonary hypertension, an increase in LV filling pressures, volume overload, and LV remodeling. Symptoms, NYHA class, ejection fraction, transtricuspid pressure gradient, and volumes were similar between survivors and nonsurvivors in the present study, which included patients with mild or moderate heart failure. Patients who died and survivors had similar LV volumes, ejection fraction, and systolic pulmonary artery pressure, as estimated by transtricuspid velocity. Nonsurvivors had a shorter mitral deceleration time, which indicates higher filling pressures that can be caused not only by diastolic dysfunction but also by the MR itself.

**Prognostic Importance of Exercise-Induced Changes in MR**

The present study is the first to examine the prognostic significance of exercise-induced changes in MR. Our results indicate that patients with a large increase in the degree of MR during exercise have a worse outcome. An increase in
ERO by ≥13 mm², determined by receiver-operator characteristic curve analysis, was associated with excess mortality independent of the degree of MR at rest and independent of other baseline characteristics. Half of the patients with a large exercise-induced increase in MR who died had moderate MR at rest. In contrast, none of the 14 patients with a decrease in MR during exercise had cardiac death during follow-up. The link between a significant increase in MR during exercise and greater mortality could involve several mechanisms. Ischemic MR is a dynamic condition. Intermittent increases in ERO and in R Vol can contribute to symptoms, including flash pulmonary edema and larger ventricular volume overload. Patients with either moderate or severe MR at rest and an exercise-induced increase in MR can experience a more rapid progression of LV remodeling, leading in turn to more rapid end-stage heart failure. Chronic volume overload is also associated with a high incidence of ventricular tachyarrhythmias. In the present study, patients who had sudden cardiac death had moderate MR at rest but a large increase in MR during exercise. Thus, dynamic MR in the setting of ischemic heart disease may be a predisposing factor to lethal arrhythmias. These data are not consistent with previous studies assessing the natural history of organic MR, which suggested that mild MR tends to display low rates of sudden death. The cardiac mortality rate of medically treated patients with dynamic MR was 39% at 20 months, which represents excess mortality in patients in functional class II or III. The overall mortality rate in the surgical group was lower, at 19% (3 of 16). The potential benefit of surgical revascularization and valve repair was not assessable in this nonrandomized small population. However, only 1 of the survivors who underwent surgery experienced pulmonary edema after operation as a possible result of dynamic MR.

Clinical Implications
The present study underlines the clinical importance of quantifying MR, both at rest and during exercise, in patients with coronary artery disease and LV dysfunction. In contrast to organic MR, ERO ≥20 mm² in the context of ischemic heart disease should be considered severe. However, patients with severe MR at rest but a decrease in MR during exercise have a good medium-term prognosis. Whatever the severity of MR in basal conditions, a large exercise-induced increase in MR is associated with a worse outcome. Obviously, a large increase in MR overestimates ejection fraction. The high-risk patients cannot be identified by a small increase or a decrease in LV ejection fraction during exercise. The potential benefit of a specific approach for individual patients remains to be investigated. The validity of our observations needs to be confirmed in a larger series of patients.

Study Limitations
Our results pertain only to patients who are not in NYHA class IV and who are capable of exercising in a semisupine position. None of the patients developed exercise-induced angina or ECG ST-segment changes. For technical reasons, images were not recorded side by side to evaluate ischemia. Thus, exercise-induced ischemia cannot be excluded and could have been a contributor to our quantitative findings. The Doppler methods performed to quantify MR have some pitfalls. Nevertheless, the 2 quantitative methods used in the present study have been validated at rest and during exercise in our institution. Peak oxygen uptake was not obtained, but the prognostic value of intermediate ranges of peak oxygen uptake is controversial. Treatment was not standardized, and only 52% of the medically treated patients received β-blockers. There was, however, no difference in medications used between survivors and nonsurvivors. Specific manage-

**TABLE 4. Comparison Between Surgical and Nonsurgical Patients**

<table>
<thead>
<tr>
<th>Variables Before Surgery</th>
<th>Surgical Group (n=16)</th>
<th>Nonsurgical Group (n=82)</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent angina</td>
<td>5 (31)</td>
<td>8 (10)</td>
<td>5.4</td>
<td>0.026</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>8 (50)</td>
<td>11 (13)</td>
<td>9.2</td>
<td>0.0024</td>
</tr>
<tr>
<td>ERO ≥20 mm²</td>
<td>7 (44)</td>
<td>20 (24)</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>ERO difference ≥13 mm²</td>
<td>8 (50)</td>
<td>16 (20)</td>
<td>6.7</td>
<td>0.0095</td>
</tr>
</tbody>
</table>

*Values are n (%).
ment was dictated by individual cardiologists in charge of the patients. The number of cardiac deaths was low, but we excluded patients in class IV who could not perform an exercise test in the semisupine position. It should be tested whether the prognostic importance of MR at rest and during exercise is independent of more easily obtainable parameters, such as type B natriuretic peptide.

Conclusions
This study showed that in the chronic post–myocardial infarction phase, quantitative measurement of MR by Doppler echocardiography is important not only at rest but also during exercise. Further studies are warranted to assess the potential role of exercise Doppler echocardiography for selecting medical or surgical treatment in high-risk patients.

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References
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