Impact of Preoperative Symptoms on Survival After Surgical Correction of Organic Mitral Regurgitation
Rationale for Optimizing Surgical Indications

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Background—Surgical correction of mitral regurgitation in patients with no or mild symptoms remains controversial, particularly because the impact of preoperative symptoms on postoperative outcome is unknown.

Methods and Results—The long-term outcome of 478 patients with organic mitral regurgitation (199 in NYHA functional class I/II and 279 in class III/IV before surgery) operated on between 1984 and 1991 was analyzed. In patients in NYHA class I/II before surgery compared with those in class III/IV, postoperative long-term survival was higher (at 10 years, 7665% versus 4864%, \( P < 0.0001 \)), with lower operative mortality (0.5% versus 5.4%, \( P = 0.003 \)) and better late survival (\( P < 0.0001 \)). Comparison of observed and expected survival showed identical curves in patients in class I/II before surgery (\( P = 0.18 \)), whereas excess mortality was observed in patients in class III/IV before surgery (\( P < 0.0001 \)). Excess mortality associated with severe symptoms was also confirmed in all subgroups (all \( P < 0.003 \)) and in multivariate analysis (\( P = 0.0036 \); adjusted hazard ratio [95% CI], 1.81 [1.21 to 2.70]).

Conclusions—In patients with organic mitral regurgitation, preoperative functional class III/IV symptoms are associated with excess short- and long-term postoperative mortality independently of all baseline characteristics. These data should lead to consideration of surgical correction of severe organic mitral regurgitation when no or minimal symptoms are present in patients at low operative risk, especially if repair is feasible. (Circulation. 1999;99:400-405.)

Key Words: mitral valve ■ prognosis ■ regurgitation ■ surgery

The optimal timing for surgery for severe organic mitral regurgitation (MR) is not widely agreed on.1–5 Severe symptoms improve after surgery and remain the cornerstone of recommendations for surgery in MR.6 However, several facts have led to the suggestion that surgery should not be delayed until severe symptoms appear. First, left ventricular (LV) dysfunction progresses silently,7–9 and in patients operated on for severe symptoms, it frequently becomes overt after surgery10 and causes excess mortality.11–13 Second, LV dysfunction is only partly predictable14 and may occur unexpectedly,10,12 limiting the possibility of reliably monitoring patients with severe MR. Third, medically treated patients with severe MR, even with no or minimal symptoms, incur notable mortality and high morbidity.1 Fifth, valve repair, with its low operative mortality15 and good long-term outcome,16 is an incentive for early operation. Therefore, early surgery in patients with no or minimal symptoms has become a reasonable consideration1 and appears to improve the outcome of patients with MR.17

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However, clinicians are often hesitant to recommend surgery in patients with no or minimal symptoms, because it would expose these patients to operative mortality and morbidity.2 Also, despite a high rate of progression to severe symptoms, some patients may remain asymptomatic for years.1,4,18 The most important reason is that the excess postoperative risk imposed on patients who become severely symptomatic before surgery is unclear. In previous studies, the link between severe preoperative symptoms and excess operative11 or long-term mortality was not consistently observed,19,20 mainly because severe symptoms are not randomizable and usually not isolated. The demonstration of their specific impact on outcome is technically complex, but a significant and independent association of preoperative NYHA class I/II symptoms with improved postoperative outcome8 would be a strong incentive to offer surgical correction of severe MR in these patients. Accordingly, we examined the outcome of patients with pure and isolated organic MR operated on at our institution between 1984 and 1991 to verify this hypothesis.

Methods

The study was based on our experience with consecutive patients who underwent surgical correction of MR due to organic (nonische-
Survival was estimated by the Kaplan-Meier method. The comparisons between the 2 groups were performed overall and stratified in subgroups defined according to EF (with a 60% threshold), procedure performed (repair or replacement), and association of CABG and was based on the 2-sample log-rank test. Observed survival was compared with expected survival based on age- and sex-matched actuarial data from the 1980 US white population and tested with the 1-sample log-rank test. Multivariate analysis of overall long-term survival used Cox proportional hazards models. Secondary end points were operative mortality (by logistic regression), late survival of operative survivors, and postoperative congestive heart failure. Candidate independent variables included age, sex, atrial fibrillation, creatinine level, preoperative EF, method of correction (repair versus replacement), year of surgery, associated coronary artery disease, and CABG. Next, NYHA functional class was added to the models. To verify that the selected grouping of patients was the most appropriate, a backward stepwise model was applied with dummy variables, grouping patients in class I versus II, III, or IV; class I/II versus III/IV; and class I, II, or III versus IV. The analysis was repeated in 2 periods, 1984 to 1987 and 1988 to 1991, and for each period, the risk ratio associated with the NYHA class was calculated, adjusted for the independent determinants of outcome with and without an interaction term between the period and functional class. A value of $P<0.05$ was considered significant.

### Results

**Baseline Characteristics**

Before surgery, 75 patients were in NYHA class I, 124 in class II, 226 in class III, and 53 in class IV. Therefore, 199 were in class I/II (no or minimal symptoms), and 279 were in class III/IV (severe symptoms). The preoperative baseline characteristics of the 2 groups were summarized in Table 1. No differences were found between class I and class II patients ($P>0.05$). At baseline, class IV patients compared with class III patients had less atrial fibrillation (36% versus 52%, $P=0.05$) but were older (71 ± 10 versus 66 ± 12 years) and had a lower EF (56 ± 13% versus 61 ± 11%, $P=0.015$).

**Long-Term Postoperative Survival**

Overall postoperative survival for patients in class I/II before surgery (at 5 and 10 years, 90 ± 2% and 76 ± 5%, respectively)

### Table 1. Preoperative Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=478)</th>
<th>NYHA Class I/II (n=199)</th>
<th>NYHA Class III/IV (n=279)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65 ±13</td>
<td>61 ±13</td>
<td>67 ±12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male, %</td>
<td>61</td>
<td>66</td>
<td>57</td>
<td>0.061</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>0.29</td>
</tr>
<tr>
<td>History of MI, %</td>
<td>11</td>
<td>10</td>
<td>12</td>
<td>0.37</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>41</td>
<td>30</td>
<td>49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD, %</td>
<td>31</td>
<td>26</td>
<td>34</td>
<td>0.08</td>
</tr>
<tr>
<td>Creatinine level, mg</td>
<td>1.2 ±0.7</td>
<td>1.2 ±0.5</td>
<td>1.3 ±0.7</td>
<td>0.005</td>
</tr>
<tr>
<td>EF, %</td>
<td>61 ±11</td>
<td>62 ±9</td>
<td>60 ±12</td>
<td>0.13</td>
</tr>
<tr>
<td>LVDD, mm</td>
<td>61 ±9</td>
<td>62 ±9</td>
<td>60 ±9</td>
<td>0.26</td>
</tr>
<tr>
<td>LVSD, mm</td>
<td>38 ±9</td>
<td>38 ±8</td>
<td>38 ±9</td>
<td>0.87</td>
</tr>
<tr>
<td>Repair, %</td>
<td>68</td>
<td>79</td>
<td>60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABG, %</td>
<td>27</td>
<td>25</td>
<td>29</td>
<td>0.29</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; CAD, coronary artery disease; LVDD, left ventricular diastolic diameter; and LVSD, left ventricular systolic diameter. All continuous variables are presented as mean ± SD. $P$ values apply to the difference between NYHA class I/II and NYHA class III/IV.

### Preoperative and Surgical Procedures

The preoperative LV ejection fraction (EF) was calculated by echocardiography (398 patients) or LV angiography (258 patients) performed within 6 months before surgery. When values from both techniques were available, the EF was determined by the average of the 2 measurements. Therefore, preoperative EF (mean, 61 ±11%) was determined for 446 patients (93%). The degree of coronary artery disease was assessed by coronary angiography in 406 patients (85%), and obstructive coronary artery disease was defined as stenosis ≥70% of vessel diameter in any coronary artery or ≥50% stenosis of the left main coronary artery.

Valve replacement was performed in 155 patients, mitral repair in 323 patients, and corrected valve prolapse in 298 patients (of the posterior leaflet in 201, anterior leaflet in 38, and both leaflets in 59). Coronary artery bypass graft surgery (CABG) was performed in association with the valvular procedure in 130 patients (27%).

### Statistical Analysis

Descriptive results were expressed as mean ± SD. Comparison of groups of patients in NYHA class I/II (no or minimal symptoms) versus class III/IV (severe symptoms) used standard $t$ test or $\chi^2$ test. Survival was estimated by the Kaplan-Meier method. The comparison of survival between the 2 groups was performed overall and stratified in subgroups defined according to EF (with a 60% threshold), procedure performed (repair or replacement), and association of CABG and was based on the 2-sample log-rank test.
was significantly better than those in class III/IV (at 5 and 10 years, 73\% and 48\%, respectively, P < 0.0001) (Figure 1) and was related to lower operative mortality (0.5\% versus 5.4\%, P = 0.003) and better late survival (at 10 years, 76\% versus 50\%, P < 0.0001). Postoperative deaths, 65\% were of cardiac cause, 23\% were noncardiac, and 12\% were of unknown cause.

Compared with their respective expected survivals, survival of patients in class I/II before surgery was identical to expected (at 10 years, 104\% of expected, P = 0.18), whereas for those in class III/IV before surgery, excess mortality was noted (observed survival was only 74\% of expected at 10 years, P < 0.0001) (Figure 2).

With multivariate analysis, NYHA functional class III/IV was a strong independent predictor of overall postoperative mortality (P = 0.0036; adjusted risk ratio, 1.81; 95\% CI, 1.21 to 2.70). Age (P = 0.0001), atrial fibrillation (P = 0.0068), valve repair (P = 0.0023), EF (P = 0.02), and associated coronary artery disease (P = 0.0001) were also independent predictors of overall survival. Multivariate analysis also showed that NYHA functional class was an independent predictor of operative mortality (P = 0.016).

Survival of patients in class I before surgery tended to be slightly higher than that of patients in class II, but the difference did not reach statistical significance (P = 0.19) and at 10 years represented the same percentage of the expected survival (103\% and 104\%, respectively). Excess mortality was higher in class IV than in class III (at 10 years, survival represented 55\% and 78\% of expected, respectively; both P < 0.0001), but in multivariate backward analysis, the best separation between NYHA classes was between class I/II (without excess mortality) and class III/IV (with excess mortality) (P < 0.0001).

Subgroup Analysis
Excess mortality of class III/IV patients was observed in all subgroups examined. The 10-year survival rate was higher for patients in NYHA class I/II than for those in class III/IV before surgery, whether they had an EF \( \geq 60\% \) (79\% versus 49\%, respectively; P = 0.0003) or \( \leq 60\% \) (75\% versus 41\%, respectively; P = 0.0001) (Figure 3), whether they had valve repair (80\% versus 55\%, respectively; P = 0.0002) or valve replacement (66\% versus 39\%, respectively; P = 0.0025) (Figure 4), and whether they had associated CABG (82\% versus 29\%, respectively; P = 0.0001) or no CABG (74\% versus 56\%, respectively; P = 0.0011) (Figure 5). Of note, the benefit (risk ratio) of surgery in class I/II compared with class III/IV was similar in patients receiving valve repair or replacement (0.41 versus 0.39) even after adjustment for other predictors of survival (P = 0.67).

**Subgroup Analysis**
Excess mortality of class III/IV patients was observed in all subgroups examined. The 10-year survival rate was higher for patients in NYHA class I/II than for those in class III/IV before surgery, whether they had an EF $\geq 60\%$ (79\% versus 49\%, respectively; $P=0.0003$) or $\leq 60\%$ (75\% versus 41\%, respectively; $P=0.0001$) (Figure 3), whether they had valve repair (80\% versus 55\%, respectively; $P=0.0002$) or valve replacement (66\% versus 39\%, respectively; $P=0.0025$) (Figure 4), and whether they had associated CABG (82\% versus 29\%, respectively; $P=0.0001$) or no CABG (74\% versus 56\%, respectively; $P=0.0011$) (Figure 5). Of note, the benefit (risk ratio) of surgery in class I/II compared with class III/IV was similar in patients receiving valve repair or replacement (0.41 versus 0.39) even after adjustment for other predictors of survival ($P=0.67$).
Remarkably, operative mortality in class I/II was extremely low for patients who had valve repair (0.6%) or were <75 years (0%) or did not require CABG (0%) whether valve repair or replacement was performed. It was also much lower than in similar subgroups in class III/IV (3.6%, 2.5%, and 2.5%, respectively; all P<0.07).

The 8 years covered by the present study were divided into two 4-year periods. Comparison of the 2 periods (Table 2) showed that the practice progressively changed, with more patients in class I/II and more valve repairs in the later period. In each period, patients with severe symptoms displayed higher mortality (P=0.003 in the period 1984 to 1987 and P=0.0001 in the period 1988 to 1991). However, 6-year mortality for patients in class I/II decreased from 15±5% for those operated on in 1984 to 1987 to 11±3% for those operated on in 1988 to 1991, and in multivariate analysis, the survival benefit associated with preoperative class I/II symptoms (Table 2) improved significantly (P=0.029).

TABLE 2. Trends of Risk

<table>
<thead>
<tr>
<th></th>
<th>Period</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>201</td>
<td>277</td>
<td></td>
</tr>
<tr>
<td>% in class III/IV</td>
<td>71</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>% Repair</td>
<td>45</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Mortality risk ratio for class I/II vs III/IV (P)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>0.65 (0.001)</td>
<td>0.41 (0.0001)</td>
<td></td>
</tr>
<tr>
<td>Multivariate without repair</td>
<td>0.78 (0.08)</td>
<td>0.53 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Multivariate with repair</td>
<td>0.77 (0.07)</td>
<td>0.54 (0.0002)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The present study shows that in patients undergoing surgical correction of organic MR, those who have no or minimal symptoms before surgery (class I/II), compared with those with preoperative severe symptoms (class III/IV), incur lower mortality and morbidity after surgery. This advantage was confirmed in multivariate analysis, adjusting for all independent predictors of outcome. Remarkably, this advantage was confirmed in comparison with expected survival, showing no excess postoperative mortality for patients in class I/II, in contrast to excess mortality in class III/IV. This advantage was confirmed in all subgroups and increased in the most recent period. Therefore, performance of surgical correction of MR when no or minimal symptoms are present is an independent determinant of improved postoperative outcome, suggesting that this asymptomatic or minimally symptomatic stage should be the preferred period for timing surgical correction of organic, severe MR.

Rationale for Early Surgical Correction of MR

The optimal timing for surgical correction of severe MR is not widely agreed on.1–5 The major rationale for early surgery (ie, before severe symptoms or LV dysfunction) is the high frequency in symptomatic patients of postoperative LV dysfunction,10,12,13 which is associated with poor survival11 and a high rate of postoperative heart failure.21 The detection of LV dysfunction on the basis of alterations of indices of LV function is possible10,12,13 but is imperfect, as shown by the inconsistencies of reported results.20,23 and the relative frequency of unexpected LV dysfunction.10 Importantly, early suppression of volume overload due to MR has been shown experimentally to result in restoration of normal postoperative LV function,24,25 suggesting that early surgery for MR may decrease postoperative complications. This approach is supported by (1) the excess mortality and high morbidity observed in medically treated severe MR,1,4 (2) the low operative mortality and high feasibility of valve repair,15,16,26 and (3) the improved survival provided by surgery performed immediately after diagnosis.17

All these arguments are a strong incentive for early surgery, but without a randomized trial, this concept is not unanimously accepted.2,4,27 Recent authoritative recommendations have been that surgery should be performed after class III/IV symptoms occur, especially without signs of LV dysfunction.2 Furthermore, in patients with no or minimal symptoms, symptomatic improvement cannot be expected. Therefore, the risk/benefit ratio of early surgery is unclear without knowledge of the risk imposed by severe preoperative symptoms on postoperative outcome of patients after surgical correction of isolated organic MR.

Effect of Preoperative Symptoms on Postoperative Outcome

Postoperative implications of preoperative symptoms are difficult to ascertain, because the occurrence of severe symptoms cannot be randomized and is associated with other
baseline differences, particularly age.\textsuperscript{30} To analyze the specific effect of preoperative symptoms on postoperative outcome, adjustment for these complex interactions requires large populations\textsuperscript{8} with extensive data to obtain sufficient statistical power, a requirement that probably explains the inconsistent results reported.\textsuperscript{11,19–21}

The present results show that waiting for class III/IV symptoms to appear before recommending surgery is associated with excess postoperative mortality and morbidity. This excess risk was observed directly and in multivariate analysis independently of age, LV function, or associated coronary artery disease and was confirmed in all subgroups examined. Most importantly, by comparison with the specific expected survival, the excess postoperative mortality in patients in class III/IV before surgery was also confirmed. This novel result is an essential observation for the clinical decision-making process in MR and strongly supports the early surgical approach to this disease.

Some facts are important for clinical decision-making. First, the operative risk for patients in class I/II is remarkably low, 0.5% for all ages\textsuperscript{8} and 0% for patients <75 years old. These extremely low operative risks are essential to make early surgery a reasonable option\textsuperscript{31} and should be carefully reviewed in each institution in which surgery is considered for class I/II patients. In patients >75 years old, the operative risk is higher, 3.6% for those in class I/II and 12.7% for those with severe symptoms. Although early surgery is a complex issue in elderly patients, these figures suggest that it deserves serious consideration in elderly patients with mild symptoms. Second, postoperative survival of class I/II patients is not only better than for class III/IV patients but is also equivalent to expected survival, even with operative mortality taken into account. This excellent result is an incentive for early surgery for organic MR. The third important fact is related to the surgical procedure performed. Mitral valve repair has considerable advantage over valve replacement\textsuperscript{15,28,29,32} and is the preferred mode of correction of MR.\textsuperscript{16} Remarkably, valve repair, although not feasible in all patients,\textsuperscript{16} has been achieved most recently in 84% of patients. Therefore, the risk of having to resort to valve replacement has recently decreased considerably. However, even in patients who, despite this progress, ultimately undergo valve replacement, a post-operative outcome benefit is observed when patients are operated on when in class I/II instead of class III/IV.

Analysis of the trends of risk shows that the excess mortality of patients in class III/IV is not related to inclusion of the “old” data. Instead, the benefit attached to performing surgical correction of MR in class I/II is a recent phenomenon. Patients in class I/II before surgery have benefited most from recent progress in surgery.\textsuperscript{26} These trends make the present results most applicable to current practice.

The mechanism by which preoperative symptoms affect postoperative outcome is unclear. Although severely symptomatic patients had an increased rate of death because of LV dysfunction, their excess risk occurred independently of preoperative LV function. Prolonged duration of volume overload may have contributed to higher frequencies of postoperative LV dysfunction,\textsuperscript{10} complications,\textsuperscript{4} left atrial alterations,\textsuperscript{20} and atrial fibrillation.\textsuperscript{17,33,34} Alterations of dias-tolic LV function\textsuperscript{15} or myocardial fibrosis\textsuperscript{36} may lead to the progression of symptoms and influence postoperative outcome unfavorably. Regardless of these mechanistic considerations, the negative impact of severe preoperative symptoms on postoperative survival should be recognized and integrated into the clinical decision-making process.

**Clinical Implications**

In view of our results, the preferred timing for surgical correction of severe organic MR is when patients are in NYHA class I/II, further supporting the concept of early surgery.\textsuperscript{17} However, this aggressive approach for patients with MR and no or minimal symptoms is defensible only under strict conditions. First, the diagnosis of severe MR should be well documented, possibly by quantitative methods.\textsuperscript{32} The spontaneous risk associated with MR of moderate or lesser degree does not appear to justify surgery. Second, there is no evidence that early surgery is beneficial in ischemic or functional MR; currently, only patients with MR of organic cause are candidates for early surgical correction. Third, the likelihood of valve repair should be high, on the basis of valve lesions and experience of the surgeon, and the quality of repair should be verified by intraoperative echocardiography. Fourth, the operative risk should be low, as determined by the patient’s age\textsuperscript{11} and condition and documented by the results in the medical center considered.\textsuperscript{8,11,15,26}

For patients who do not fulfill these strict criteria, important factors such as decreased LV function, hemodynamic alterations, and the preference of the patient must be taken into account and may lead to surgical correction of MR in patients with no or minimal symptoms.\textsuperscript{5} The alternative strategy of conservative follow-up for asymptomatic patients at high operative risk (eg, elderly patients) appears reasonable, with the goal of considering surgery with occurrence of class II symptoms. The limitation of this approach is the high rate of direct symptomatic progression to class III/IV, which is not accurately predictable.\textsuperscript{5} How long-term vasodilator therapy may modify these indications for surgery is questionable,\textsuperscript{27} because the beneficial effects of these medications on LV remodeling and on survival remain to be proved.\textsuperscript{38}

**Limitations of the Study**

The 2 groups of patients showed differences in baseline characteristics. It is not possible to randomize symptom occurrence, and multivariate analysis in a large study group, as performed in the present study, allows appropriate adjustment for these differences. Furthermore, because survival was adjusted not only for age but also compared with expected survival, the possibility of lead time bias is extremely low.

The poor postoperative outcome associated with severe preoperative symptoms does not prove that early surgery is superior to conservative management.\textsuperscript{17} The recent increased feasibility and success rate of valve repair make early surgery even more attractive,\textsuperscript{8,16} but randomized studies of early surgery are needed.

The NYHA functional classification is subjective, and although the uniformity of its criteria may not be perfect, it is widely used, is the basis for current recommendations for
surgery, and is predictive of survival with medical and surgical treatment. Therefore, the conclusion of the present study should be widely applicable to patients evaluated for MR.

Conclusions

Patients operated on for organic MR with NYHA functional class III/IV symptoms display excess mortality and morbidity after surgery compared with those with class I/II symptoms, independently of age, LV function, and other baseline characteristics. Therefore, in patients with organic MR of severe degree, at low operative risk, and with a high probability of valve repair, early surgery should be considered when no or minimal symptoms are present to benefit from the usually excellent postoperative outcome observed at that stage.

Acknowledgments

Dr Tribouilloy was supported by a grant from the Federation Française de Cardiologie. We appreciate the major statistical support of Sara Fett in the completion of this study.

References

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Circulation. 1999;99:400-405
doi: 10.1161/01.CIR.99.3.400

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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