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# Optimizing Timing of Surgical Correction in Patients With Severe Aortic Regurgitation: Role of Symptoms

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***Objectives.*** **We sought to determine the independent effect of preoperative symptoms on survival after surgical correction of aortic regurgitation (AR).**

***Background.*** **Aortic valve replacement for severe AR is recommended after New York Heart Association functional class III or IV symptoms develop. However, whether severe preoperative symptoms have a negative influence on postoperative survival remains controversial.**

***Methods.*** **Preoperative characteristics and postoperative survival in 161 patients with functional class I or II symptoms (group 1) were compared with those in 128 patients with class III or IV symptoms (group 2) undergoing surgical repair of severe isolated AR between 1980 and 1989.**

***Results.*** **Compared with group 1, group 2 patients were older ($p < 0.0001$), were more often female ($p = 0.001$) and more often had a history of hypertension ($p = 0.001$), diabetes mellitus ($p = 0.029$) or myocardial infarction ($p = 0.005$) and were more likely to require coronary artery bypass graft surgery ($p < 0.0001$). The operative mortality rate was higher in group 2 (7.8%) than in group 1 (1.2%, $p = 0.005$), and the 10-year postoperative survival rate was worse (45% ± 5% [group 2] vs. 78% ± 4% [group 1], $p < 0.0001$). Compared with age- and gender-matched control subjects, long-term postoperative survival was similar to that expected in group 1 ($p = 0.14$) but significantly worse in group 2 ($p < 0.0001$). On multivariate analysis, functional class III or IV symptoms were significant independent predictors of operative mortality (adjusted odds ratio 5.5, $p = 0.036$) and worse long-term postoperative survival (adjusted hazard ratio 1.81, $p = 0.0091$).**

***Conclusions.*** **In the setting of severe AR, preoperative functional class III or IV symptoms are independent risk factors for excess immediate and long-term postoperative mortality. The presence of class II symptoms should be a strong incentive to consider immediate surgical correction of severe AR.**

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Aortic regurgitation (AR) can be corrected successfully with aortic valve replacement (AVR) (1), but the timing of surgical repair is disputed. Because of the relatively high incidence of postoperative left ventricular (LV) dysfunction (2), objective indexes of LV size and function have been recommended to guide the timing of AVR (3–6), but this recommendation is not uniformly accepted (7). However, the presence of severe symptoms is overwhelmingly agreed on as an indication for AVR (4,8,9)—first, to relieve the symptoms (10–12) and, second, to avoid the grim prognosis of patients with such symptoms when treated medically. The management of patients with milder symptoms is less clear. Recent natural history studies have demonstrated that survival of patients with no or mild symptoms treated medically is good (4); consequently, it has been inferred that AVR for AR can safely be delayed until New York Heart Association functional class III or IV symptoms or LV dysfunction occurs. However, the natural history studies cannot provide information on the long-term postsurgical outcome, particularly that of patients operated on after severe (class III or IV) symptoms have occurred. Earlier studies provided some data suggesting that outcome of AVR for AR is mediocre when severe symptoms are present preoperatively (6,13–16), thus implying, contrary to the natural history studies, that surgical repair before the occurrence of severe symptoms is preferable. However, this inference is weakened by several problems. 1) These studies are usually small (6,15) and based on old data (13,14,16) and may not be applicable to current practice. 2) Severe symptoms are rarely isolated abnormalities (17), and the absence of adjustment for the other baseline characteristics leaves doubt as to the independent influence of preoperative symptoms on postoperative outcome and on the clinical management of severe AR.

To address this issue, the outcome of patients who had surgical correction of severe isolated AR between 1980 and 1989 was examined. We hypothesized that after adjustment for all baseline differences and predictors of outcome, severe symptoms represent independent predictors of worse postoperative survival.

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**Abbreviations and Acronyms**

AR = aortic regurgitation
AVR = aortic valve replacement
CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
CI = confidence interval
LV = left ventricular
LVEF = ejection fraction

## Methods

**Patient selection.** The inclusion criteria were 1) surgical correction (repair [n = 9] or replacement [n = 280]) of AR between 1980 and 1989; 2) severe AR as diagnosed by clinical assessment in all patients and confirmed by grade III or IV regurgitation by aortography (n = 203) (18) or color flow imaging (19), or both; and 3) isolated, pure, chronic AR, as documented by echocardiography or cardiac catheterization, or both, and by surgical assessment. Excluded were patients with associated aortic stenosis or concomitant mitral or tricuspid valve repair or replacement. Patients undergoing coronary artery bypass graft surgery (CABG) or aortic root replacement at the time of the operation were not excluded. The baseline characteristics of the 289 patients included are summarized in Table 1. The preoperative (within 1 month before operation) symptoms analyzed were dyspnea (ranked using the New York Heart Association functional classification) and angina (ranked using the Canadian Cardiovascular Society classification). Dyspnea was absent in 94 patients (class I), minimal in 80 (class II), marked in 93 (class III) and permanent in 22 (class IV). Angina was absent in 242 patients (class 0), minimal in 21 (class II), marked in 19 (class III) and occurred with any activity or at rest in 7 (class IV). The combined consideration of dyspnea and angina showed that 80 patients were asymptomatic (class I), 81 had minimal symptoms (class II), 101 had marked exertional symptoms (class III) and 27 had rest symptoms (class IV). Therefore, 161 patients (group 1) had no or minimal symptoms (class I or II), and 128 patients (group 2) had advanced symptoms (class III or IV).

**Table 1.** Preoperative Patient Characteristics

| Variable | Functional Class I/II (n = 161) | Functional Class III/IV (n = 128) | p Value |
|---|---|---|---|
| Age | 50 ± 16 | 61 ± 14 | <0.0001 |
| Men | 139 (86) | 90 (70) | 0.001 |
| Creatinine level (mg/dl) | 1.14 ± 0.38 | 1.25 ± 0.52 | 0.048 |
| Hypertension | 29 (18) | 46 (36) | 0.001 |
| Diabetes mellitus | 3 (2) | 9 (7) | 0.029 |
| History of smoking | 70 (44) | 65 (51) | 0.22 |
| History of MI | 2 (1) | 10 (8) | 0.005 |
| Atrial fibrillation | 23 (14) | 24 (19) | 0.31 |
| Presence of aneurysm | 49 (30) | 37 (29) | 0.78 |
| Presence of CAD | 18 (11) | 45 (35) | <0.0001 |
| Echo LVEF (n = 249) | 53 ± 11 | 49 ± 14 | 0.013 |
| Angio LVEF (n = 137) | 51 ± 12 | 48 ± 14 | 0.18 |
| Aortic root replacement | 49 (30) | 34 (27) | 0.47 |
| CABG | 13 (8) | 41 (32) | <0.0001 |

Data presented are mean value ± SD or number (%) of patients. Angio = angiographic; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; Echo = echocardiographic; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

The assessment of preoperative LV function was performed within 6 months before valve replacement by echocardiography (20,21) in 249 patients and by angiography in 137. Follow-up was complete in 98% of patients up to 1994 or until death. Heart transplantation for heart failure was performed in two patients during follow-up and was combined with death as an equivalent end point. Results obtained in a subgroup of the present series have been previously reported (22,23).

**Statistical methods.** Group statistics were expressed as mean value ± SD. Group comparisons (group 1 vs. group 2) were performed with a standard *t* test or chi-square test. End points were operative mortality (death occurring within 30 days after the operation or within the same hospital period) and long-term postoperative survival. Long-term survival analysis was carried out using the Kaplan-Meier method, and groups were compared using the two-tailed log-rank test. Comparison between observed and expected survival of age- and gender-matched populations was performed using the one-tailed log-rank test. The determinants of operative mortality and long-term survival were analyzed using logistic regressions and proportional hazards analysis, respectively. To determine the most appropriate prognostic separation between the four functional classes for prognostic purposes, group variables representing class I, class I and II and class I, II and III were used, and backward stepwise logistic and proportional hazards analysis was performed. The independent influence of preoperative symptoms on survival was assessed by adjusting for baseline characteristics (Table 1) using multivariate analysis, first with only clinical and surgical variables (clinical model) and, second, by including separately the echocardiographic (echocardiographic model) and angiographic (angiographic model) LV ejection fraction (LVEF) in two separate models. The value $p < 0.15$ was used for variable entry in all models for adjustment purposes, and $p < 0.05$ was considered statistically significant.

## Results

The preoperative data of the patients are shown in Table 1. Compared with patients with mild symptoms, those with advanced symptoms were older and more likely to be women, to have a higher creatinine level and to have a history of hypertension, diabetes mellitus, myocardial infarction and known significant coronary artery disease (CAD). Furthermore, they were more likely to require concomitant CABG at the time of AVR, and they tended to display a lower preoperative LVEF (by echocardiography, $p = 0.013$; by angiography, $p = 0.18$).

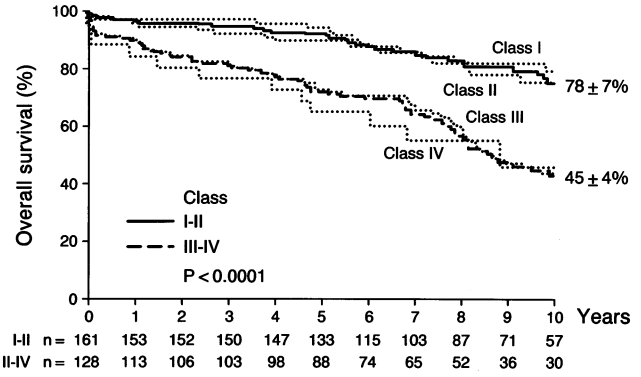


**Figure 1.** Long-term postoperative survival stratified according to preoperative symptoms. Patients with functional class III or IV symptoms experienced significantly worse survival than patients with class I or II symptoms.

**Operative mortality.** The overall operative mortality rate was 4.2% (12 of 289 patients): 1.2% (2 of 161 patients) for group 1 and 7.8% (10 of 128 patients) for group 2 ($p = 0.005$). On multivariate analysis, in all models, the only significant independent predictor of operative mortality was preoperative symptomatic status of the patient (all $p < 0.015$). In a model including age, the only separation among the four functional classes that was significant was between class I/II and class III/IV in the backward logistic regression ($p = 0.04$, adjusted odds ratio 5.5, 95% confidence interval [CI] 1.08 to 28.2).

In patients without CAD, preoperative symptomatic status was also the only significant independent predictor of operative mortality in all models (all $p < 0.03$). The operative mortality rate was 0.7% (1 of 140) for patients in functional class I/II and 7.3% (6 of 82) for those in class III/IV ($p = 0.007$).

**Long-term postoperative survival.** Long-term postoperative survival rate at 5 and 10 years was 92 ± 2% and 78 ± 7%, respectively, for group 1 and 72 ± 4% and 45 ± 4%, respectively, for group 2 ($p < 0.0001$) (Fig. 1). This difference was not due only to the difference in operative mortality, because comparison of survival between groups 1 and 2 after excluding the operative deaths showed a highly significant difference ($p < 0.0001$). Although 10 of 31 deaths in group 1 were due to LV failure or sudden death compared with 26 of 61 deaths in patients with advanced symptoms, no significant difference between groups existed in the distribution of the causes of death ($p = 0.67$). Compared with the survival of age- and gender-matched general groups, long-term postoperative survival was similar to that expected in group 1 (representing 100% and 94% of expected survival at 5 and 10 years, respectively, $p = 0.14$), but markedly diminished in group 2 (representing 84% and 64% of expected survival at 5 and 10 years, respectively, $p < 0.0001$) (Fig. 2). In all models (including those adjusting for LVEF), only age ($p = 0.0001$) and preoperative symptomatic status ($p < 0.009$) were independent predictors of postoperative survival. The adjusted hazards ratio for patients in class III/IV compared with those in class I/II was 1.81 (95% CI 1.16 to 2.82). In the backward proportional hazard analysis, the only separation among the four functional classes that was significantly associated with excess mortality was between class III/IV and class I/II. The univariate comparison of survival showed no difference between classes I and II (at 10 years, 80 ± 5% and 77 ± 6%, respectively, $p = 0.79$) or between classes III and IV (at 10 years, 45 ± 6% and 47 ± 12%, respectively, $p = 0.79$).

**Subgroup analysis.** To further assess the effect on long-term survival of preoperative symptoms, the comparison between group 1 and group 2 was performed in subsets of patients defined according to clinically important variables.

*Coronary artery disease.* In patients with significant CAD (stenoses ≥70%) or CABG, or both, overall survival at 10 years was 76 ± 11% and 39 ± 8% in groups 1 and 2, respectively ($p = 0.028$) (Fig. 3). In patients without CAD, 10-year survival was 79 ± 4% and 48 ± 7% in groups 1 and 2, respectively ($p < 0.0001$). Multivariate analysis repeated in patients without CAD showed an independent effect of preoperative symptoms on survival, similar to the overall group (adjusted hazard ratio 1.76, 95% CI 1.03 to 3.03, $p = 0.04$) in association with age ($p = 0.0002$), diabetes mellitus ($p = 0.01$), aortic aneurysm ($p = 0.02$), atrial fibrillation ($p = 0.028$) and female gender ($p = 0.02$).

*Gender.* In men, overall survival at 10 years was 80 ± 4% and 55 ± 6% in groups 1 and 2, respectively ($p = 0.0004$), whereas the corresponding survival rates for women were 73 ± 11% and 21 ± 9% ($p = 0.004$) (Fig. 4). Compared with the expected survival, there was no significant difference for group 1, representing 95% of that expected in men ($p = 0.30$) and 88% of that expected in women ($p = 0.14$) at 10 years. There

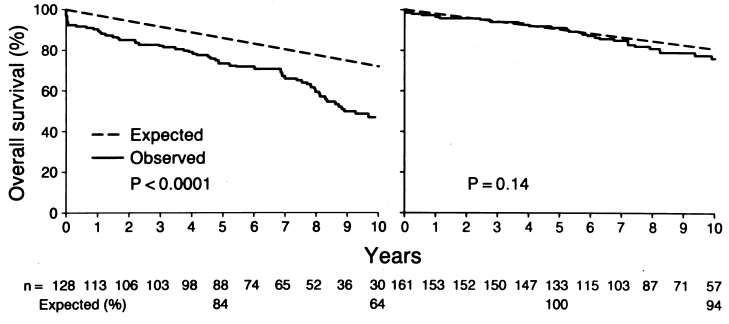


**Figure 2.** Long-term postoperative survival compared with age- and gender-matched populations. Overall survival was similar to that expected in patients with functional class I or II symptoms (**right**) but was markedly worse than that expected in patients with class III or IV symptoms (**left**).

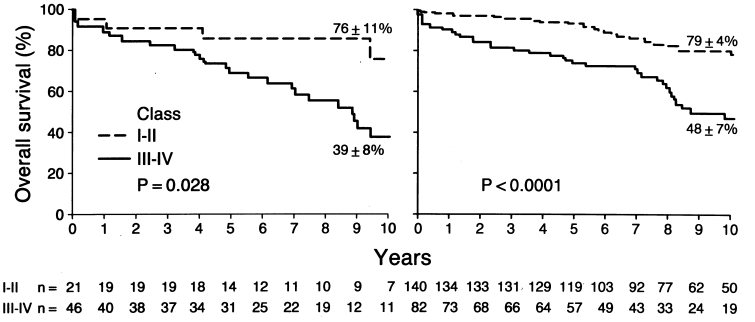


**Figure 3.** Long-term postoperative survival stratified according to preoperative symptoms in subgroups defined according to the presence of CAD. Patients with functional class III or IV symptoms experienced significantly worse survival than those with class I or II symptoms whether CAD was present (**left**) or absent (**right**).

was a significantly reduced survival rate in group 2, representing 78% of that expected in men ($p = 0.001$) and 31% of that expected in women ($p = 0.0001$) at 10 years.

*LVEF.* In patients with an echocardiographic LVEF <50%, overall survival at 10 years was 73 ± 7% and 40 ± 9% in groups 1 and 2, respectively ($p = 0.023$) (Fig. 5). In patients with an LVEF ≥50%, overall survival at 10 years was 82 ± 5% and 40 ± 8% in groups 1 and 2, respectively ($p < 0.0001$).

## Discussion

The present study revealed that in patients undergoing AVR for severe AR, preoperative class III/IV symptoms were associated with a significantly higher operative mortality and worse postoperative survival in comparison with patients with class I/II symptoms, even after adjustment for baseline characteristics on multivariate analysis. Furthermore, in comparison with expected survival, patients who were in class III or IV preoperatively demonstrated an excess mortality after the operation. In contrast, patients with no or minimal symptoms (class I or II) had a remarkably low operative mortality and excellent long-term survival, not different from that expected.

**Symptoms of AR and outcome.** In patients with severe AR, symptoms are major determinants of outcome. Natural history studies have reported high mortality rates in patients with severe AR who experience symptoms of heart failure and remain without an operation (24,25). This dismal spontaneous survival rate and the marked symptomatic improvement provided by AVR (1) have led to the consensus that these symptomatic patients should be offered an operation without delay (13,26,27). However, with the exclusive use of this classic indication for surgical repair, irreversible LV dysfunction was frequent postoperatively (16) and was related to preoperative LV dysfunction (2,28), which had developed silently during the asymptomatic phase of the natural history of AR (10,29). Therefore, objective indices of LV size and function have been recommended for timing of AVR for AR in asymptomatic patients (3–6). Although some investigators do not recognize the validity of the LV predictors of outcome (7) and some contest the concept of surgical repair in asymptomatic patients (9), early operation in asymptomatic patients has been accepted and applied worldwide (22,26,30–32). Therefore, the current recommendations for surgical repair are class III or IV symptoms or, in asymptomatic patients, LV marked dilation or dysfunction (4,11). These recommendations have been used as end points in a randomized trial of vasodilators (33).

However, certain issues regarding the symptoms of AR and the indications for surgical repair deserve clarification. First, patients with mild symptoms (class II) have usually been grouped with truly asymptomatic patients (4) and followed as such. Second, the impact of preoperative class III or IV symptoms on long-term postoperative outcome is controversial. The observation in natural history studies that patients in class I or II have a low mortality with medical treatment (4,11) has been used to justify performing AVR for AR only when class III or IV symptoms develop. However, natural history studies cannot analyze the long-term outcome after AVR. Whether an excess mortality is observed after AVR for AR in patients operated on after marked symptoms have developed is critical in timing the operation before or when the severe symptomatic stage develops. The current published data does not provide definitive answers regarding that point. Indeed,

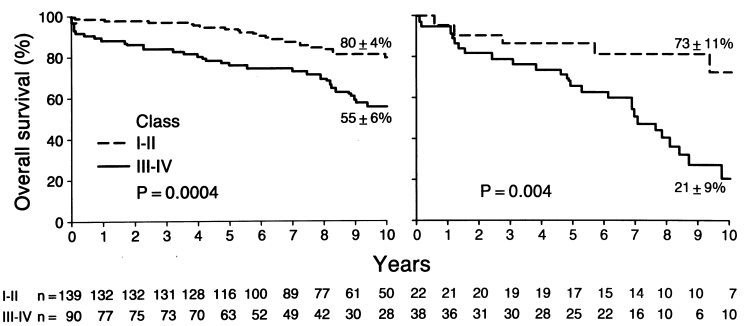


**Figure 4.** Long-term postoperative survival stratified according to preoperative symptoms in subgroups defined according to gender. Male (**left**) and female (**right**) patients with class III/IV symptoms experienced significantly worse survival than those with class I or II symptoms.

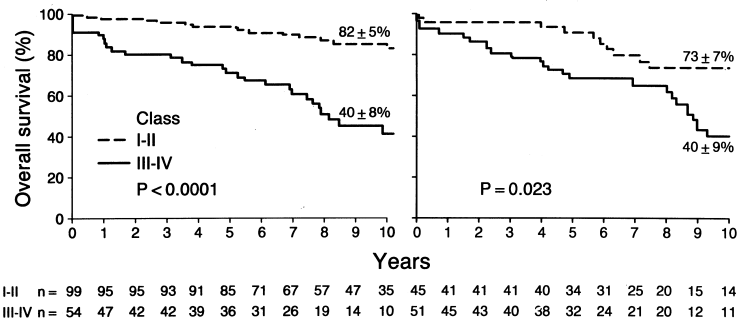


**Figure 5.** Long-term postoperative survival stratified according to preoperative symptoms in subgroups defined according to preoperative LVEF. Patients with functional class III or IV symptoms experienced significantly worse survival than those with class I or II symptoms whether the echocardiographic LVEF was ≥50% (**left**) or <50% (without CAD) (**right**).

several investigators have pointed to higher operative mortality rates (14,16,30) and worse postoperative survivals (6,14–16,30,34–36) in patients with class III/IV symptoms preoperatively, but this has not been uniformly confirmed (28,37–39). This lack of general agreement is related to series of small size, mostly old and of disputable applicability to current practice, and to the inclusion of few patients with mild symptoms. The absence of adjustment for baseline characteristics and for expected survival make these previous results of limited relevance to the assessment of the impact of severe symptoms on outcome after AVR and warrant a comprehensive analysis of this issue.

The present findings, based on a large cohort of patients undergoing surgical repair in the current era, suggest that patients with class III/IV symptoms before AVR for severe AR have a worse outcome than patients with class I/II symptoms with an excess operative mortality (odds ratio 5.5) and long-term mortality (hazards ratio 1.8). This marked impact of severe preoperative symptoms on postoperative outcome is confirmed by multivariate analysis, by taking into account the expected survival and also in all subsets of patients (23). This effect is not due only to patients in class IV preoperatively, because patients in class III and IV have identical survival. In contrast, in patients with no or mild preoperative symptoms, operative mortality was low and long-term survival was similar to that expected. This suggests that patients may have excellent long-term outcomes if operated on early in the symptomatic course of AR (26) and that symptoms of AR have important physiologic significance.

**Symptoms of AR: physiologic correlates.** The symptoms of AR usually occur after a long latent phase (29), even with severe regurgitation. Although previous reports linked symptoms to increased left atrial pressure and LV dysfunction (17), the EF of patients in the present series with class III/IV symptoms was significantly but only mildly reduced. Therefore, severe symptoms can occur in the absence of LV dysfunction at rest and still carry a poor prognosis. Similarly, associated CAD may cause symptoms (40) but is not more frequent with severe symptoms, which carry a poor prognosis even in the absence of CAD. Other physiologic abnormalities are probably associated with the occurrence of overt symptoms. Left ventricular systolic dysfunction with exercise (41) or diastolic dysfunction (42,43) may lead to the occurrence of symptoms but are difficult to analyze (44) because of the volume overload of patients with AR. Nevertheless, severe symptoms, even poorly explained, probably reveal profound physiologic changes that translate into an excess incidence of complications and death long after the correction of the AR and, thus, clinically should be avoided if possible.

**LV dysfunction.** Preoperative EF was not an independent predictor of postoperative outcome in the current study. This likely was due to the inclusion of a notable number of women, although AR principally affects men (45). Preoperative LV size and function were significant predictors of outcome in groups composed mainly of men (3–6,22), but not in a recent study of women with AR (23). When the present analysis was limited to men, the additional prognostic significance of preoperative LV function was confirmed in men. However, this does not affect the present study, because preoperative class III-IV symptoms were associated with an excess mortality in all subsets of patients.

**Clinical implications.** Because of the major benefit provided by surgical repair in patients in functional class III or IV, in comparison with medical treatment, patients with severe AR and advanced symptoms should continue to be offered an operation.

However, because of the excess postoperative mortality observed in classes III and IV, as compared with classes I and II, patients should preferentially be operated on before the severe symptoms develop. The very low operative mortality and excellent long-term survival, equivalent to expected survival, despite the presence of the aortic prosthesis, in patients in functional class I or II are further incentives to perform the operation at the less symptomatic stage. In view of the equivalent survival in classes I and II, the indications for surgical repair in patients with no or minimal symptoms can be summarized as follows: 1) class I and LV dysfunction (2,4,23)—preoperative LV dysfunction is associated with an excess late mortality in men (22) and a lower postoperative LVEF in both men and women (2,23) and therefore should be considered as an indication for surgical repair; 2) class I and extreme LV dilation (4,22)—because severe LV enlargement has been associated with sudden death (4), surgical repair in these patients appears to be a reasonable option, particularly in view of the good postoperative outcome observed (22); 3) class II symptoms—that is, even minimal dyspnea or angina. The essential conditions to perform an early operation in patients with no or minimal symptoms are, first, that the

degree of AR be defined as severe (at best, using quantitative methods) (46) and, second, that the risk of operation be low. In asymptomatic patients with preserved LV function and no severe ventricular dilation, no clear justification currently exists for surgical intervention, but additional natural history studies should further define the risk with medical treatment, particularly the risk of sudden death.

**Study limitations.** The present study did not investigate the natural history of patients with class I or II symptoms and thus cannot analyze the rate of progression to higher symptomatic classes. However, the predictability of symptomatic progression is usually poor (4,47,48); therefore, all patients in class II should be considered at risk for entering functional class III or IV, with the attached excess mortality noted in the present study. Future natural history studies should analyze the risk of direct progression from class I to class III and IV to make further recommendations in these patients. Also, because patients were older in the more symptomatic group, it may be argued that lead time bias accounted for part of the survival benefit in mildly symptomatic patients. However, there was a wide variation of age in all symptomatic classes, and after adjustment for age and for possible confounding variables in the analysis of survival, symptomatic status remained a major predictor of outcome. This was also confirmed by comparing survival with expected survival, which demonstrated an excess mortality in severely symptomatic patients, in contrast to survival that was equivalent to that expected in patients with no or minimal symptoms. Therefore, patients with severe symptoms display an excess postoperative mortality independent of age at operation, and this should be taken into account in clinical decision making.

**Conclusions.** In patients with severe chronic AR, the presence of preoperative functional class III/IV dyspnea or angina is an independent determinant of excess postoperative immediate and long-term mortality. The presence of minimal functional class II symptoms is associated with a very low operative mortality and excellent long-term survival and should be a strong incentive to consider immediate surgical correction of severe AR.

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