

Long-term follow-up of asymptomatic or mildly symptomatic patients with severe degenerative mitral regurgitation and preserved left ventricular function

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Objectives: The timing for mitral valve surgery in asymptomatic patients with severe mitral regurgitation and preserved left ventricular function remains controversial. We analyzed the immediate and long-term outcomes of these patients after surgery.

Methods: From January 1992 to December 2012, 382 consecutive patients with severe chronic degenerative mitral regurgitation, with no or mild symptoms, and preserved left ventricular function (ejection fraction $\geq 60\%$) were submitted to surgery and followed for up to 22 years (3209 patient-years). Patients with associated surgeries, other than tricuspid valve repair, were excluded. Cox proportional-hazard survival analysis was performed to determine predictors of late mortality and mitral reoperation. Subgroup analysis involved patients with atrial fibrillation or pulmonary hypertension.

Results: Mitral valvuloplasty was performed in 98.2% of cases. Thirty-day mortality was 0.8%. Overall survival at 5, 10, and 20 years was $96.3\% \pm 1.0\%$, $89.7\% \pm 2.0\%$, and $72.4\% \pm 5.8\%$, respectively, and similar to the expected age- and gender-adjusted general population. Patients with atrial fibrillation/pulmonary hypertension had a 2-fold risk of late mortality compared with the remaining patients (hazard ratio, 2.54; 95% confidence interval, 1.17-4.80; $P = .018$). Benefit was age-dependent only in younger patients (<65 years; $P = .016$). Patients with atrial fibrillation/pulmonary hypertension (hazard ratio, 4.20, confidence interval, 1.10-11.20; $P = .037$) and patients with chordal shortening were at increased risk for reoperation, whereas patients with P2 prolapse (hazard ratio, 0.06; confidence interval, 0.008-0.51; $P = .037$) and patients with myxomatous valves (hazard ratio, 0.072; confidence interval, 0.008-0.624; $P = .017$) were at decreased risk.

Conclusions: Mitral valve repair can be achieved in the majority of patients with low mortality ($<1\%$) and excellent long-term survival. Patients with atrial fibrillation/pulmonary hypertension had compromised long-term survival, particularly younger patients (aged <65 years), and are at increased risk of mitral reoperation. (J Thorac Cardiovasc Surg 2014;148:2795-801)

Mitral valve (MV) surgery is recommended for symptomatic patients with severe primary mitral regurgitation (MR), and MV repair is the procedure of choice whenever it is feasible and expected to be durable.^{1,2} The management of patients with degenerative MR has changed dramatically during the past 2 decades, mainly because of the refinement and standardization of MV repair techniques that led to predictable and durable results. In centers of excellence, the reparability rate can reach approximately 100% and operative mortality is less than 1% in selected cases, such as isolated P2 prolapse,

and the need for reoperation because of repair failure in the long-term may be as low as 5%.³⁻⁵ Finally, the extensive knowledge of the natural history of MR and the dire consequences when it is left untreated propelled the rationale to intervene early, before complications supervene.

However, indications for mitral surgery, as expressed in the current guidelines, were based on levels of evidence B and C (consensus opinion of experts and retrospective studies), and not on randomized clinical trials (level A). This becomes even more critical in asymptomatic patients without signs of left ventricular (LV) deterioration. Two lines of thought have emerged on how to deal with this particular group of patients, one more conservative, also referred to as “watchful waiting,” mainly based on a report from Rosenhek and colleagues,⁶ who advocated delay of surgery until the end points expressed in the guidelines are reached. By contrast, others have proposed a more proactive attitude with the argument that early surgery saves the patient from the unnecessary risks associated with chronic MR.⁷ They suggest that these patients should be

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Abbreviations and Acronyms

AF	= atrial fibrillation
CI	= confidence interval
HR	= hazard ratio
LV	= left ventricular
MR	= mitral regurgitation
MV	= mitral valve
NYHA	= New York Heart Association
PHT	= pulmonary hypertension
SPAP	= systolic pulmonary artery pressure

referred to highly skilled centers for MV repair. Few studies have reported the long-term clinical behavior of asymptomatic patients with severe chronic MR and preserved LV function who underwent MV surgery, currently considered class IIB indications (surgery may be considered; usefulness/efficacy is less well established by evidence/opinion) in the European Guidelines¹ and class IIa (surgery should be considered; weight of evidence/opinion is in favor of usefulness/efficacy) in the American guidelines.² Therefore, we aimed at evaluating our perioperative and long-term (up to 22 years) outcomes in this population and identifying predictors of impaired survival that could lead to changes on the timing for mitral surgery.

METHODS**Patient Population and Data Collection**

From January 1992 to December 2012, 2126 patients with severe pure or predominant MR underwent MV surgery, 382 of whom were asymptomatic or mildly symptomatic, in New York Heart Association (NYHA) class I or II, and had severe degenerative MR ($\geq 3+$) and preserved LV function. These patients constitute the object of this study.

All patients underwent isolated mitral surgery, with or without concomitant tricuspid valve annuloplasty for functional regurgitation. Patients with other associated procedures were excluded from this analysis. Also excluded were patients in NYHA class III or IV, with LV ejection fraction less than 60% and LV end-systolic internal diameter 45 mm or greater, and patients with coronary artery disease, aortic valve disease, hypertrophic cardiomyopathy, ascending aortic aneurysms, and previous mitral surgery.

Data were retrieved from a dedicated database and included relevant preoperative demographic, clinical, and echocardiographic variables; surgical information; and postoperative records. A thorough investigation of all operation reports was undertaken to separate accurately the various forms of degenerative MV disease—myxomatous (including Barlow's disease), fibroelastic disease, and isolated annular dilatation—and the valve segments involved.

Myxomatous involvement was seen as those valves with thickened and opaque leaflets, moderate enlargement of the annulus, and sometimes thickened and elongated/ruptured chordae. Barlow's valves were defined as those with severe myxoid infiltration, severe annular dilatation, multiple segments of prolapse and billowing, and thin or thickened elongated chordae. Fibroelastic disease was defined as those valves with thin leaflets, fairly normal sizes, and translucence, with the exception of the prolapsed segment, and the chordae were often thin and ruptured.

Follow-up information was collected through a mailed questionnaire or by telephone interview with surviving patients, family members, or

the patient's personal physician, and included vital status and need for MV reoperation. The cumulative follow-up for the entire cohort was 3732 patient-years (mean, 8.6 ± 7.5 years; range, 0.6-21.9 years) and was complete for 98% of the patients.

Echocardiographic Evaluation

All patients had a detailed echocardiographic examination preoperatively, and Doppler examinations and the severity of MR were analyzed. In the earlier years, it was assessed qualitatively (valve morphology: flail leaflet, large coaptation defect; reversal of pulmonary vein flow) and semiquantitatively (size of the regurgitant jet in the left atrium, regurgitant jet area). In recent years, other methods, such as the vena contracta, regurgitant volume, and effective regurgitant orifice area, have been used more frequently. Left chamber dimensions, LV function (fractional shortening, ejection fraction), and systolic pulmonary artery pressure (SPAP) were measured as recommended.⁸ Intraoperative transesophageal echocardiography, both pre- and post-repair, was routinely used from the beginning of the study, and no patient left the operating room with greater than mild MR.

Operative Findings and Procedure

The operation was standardized for all patients, including cardiopulmonary bypass with moderate hypothermia (28°C-30°C) and intermittent antegrade cold crystalloid cardioplegia through the aortic root. MV exposure was through a left atriotomy, posterior to the Waterston's groove in the majority of cases. In a few cases, the valve was reached through the right atrium and interatrial septum.

A comprehensive valve analysis of all the MV components was performed routinely. Myxomatous pathology involved 272 patients (71.2%), of whom 65 (17.0%) had severe myxomatous involvement (Barlow's disease). Isolated posterior prolapse was present in 211 patients (55.2%), isolated anterior prolapse was present in 50 patients (13.1%), and bileaflet prolapse was present in 102 patients (26.7%). Segment P2 was the most frequently involved (268 patients, 70.2%), followed by A2 (106 patients, 27.7%). Repair was oriented to correct all lesions causing mitral dysfunction, following the classic Carpentier principles.

Statistical Analysis

Continuous variables are reported as mean \pm standard deviation and compared by a Student *t* test or Mann-Whitney *U* test. Categorical variables are reported as percentages and were compared using chi-square tests. Actuarial survival and survival free of mitral reoperation were plotted using the Kaplan-Meier method, and group comparison, when available, was made using log-rank analysis. Multivariate analysis to identify independent risk factors for time-dependent events was performed using a stepwise Cox proportional hazards multivariable model and included clinical, echocardiographic, and operative variables. Criteria for entry and retention in the multivariable models were set at the 0.1 and 0.05 confidence level, respectively.

For each patient included in the study, the corresponding average age- and gender-specific annual mortality of the Portuguese general population was obtained (National Institute of Statistics, census 2012). On the basis of these mortality data, the probability of cumulative expected survival was ascertained and an expected survival curve was built. Comparison was made using a 1-sample log rank test.

A subgroup analysis was undertaken for patients with atrial fibrillation (AF) or pulmonary hypertension (PHT), defined as an SPAP at rest greater than 50 mm Hg. Patients with AF/PHT were treated as a composite covariate to be accommodated in class of IIa recommendation for mitral surgery of the American Heart Association/American College of Cardiology and European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines. These patients were compared with the remaining patients, but because the groups were different in age

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