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Valvular Heart Disease

Outcome of Watchful Waiting in Asymptomatic Severe Mitral Regurgitation

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Background—The management of asymptomatic severe mitral regurgitation remains controversial. The aim of this study was to evaluate the outcome of a watchful waiting strategy in which patients are referred to surgery when symptoms occur or when asymptomatic patients develop left ventricular (LV) enlargement, LV dysfunction, pulmonary hypertension, or recurrent atrial fibrillation.

Methods and Results—A total of 132 consecutive asymptomatic patients (age 55 ± 15 years, 49 female) with severe degenerative mitral regurgitation (flail leaflet or valve prolapse) were prospectively followed up for 62 ± 26 months. Patients underwent serial clinical and echocardiographic examinations and were referred for surgery when the criteria mentioned above were fulfilled. Overall survival was not statistically different from expected survival either in the total group or in the subgroup of patients with flail leaflet. Eight deaths were observed. Thirty-eight patients developed criteria for surgery (symptoms, 24; LV criteria, 9; pulmonary hypertension or atrial fibrillation, 5). Survival free of any indication for surgery was $92\pm2\%$ at 2 years, $78\pm4\%$ at 4 years, $65\pm5\%$ at 6 years, and $55\pm6\%$ at 8 years. Patients with flail leaflet tended to develop criteria for surgery slightly but not significantly earlier. There was no operative mortality. Postoperative outcome was good with regard to survival, symptomatic status, and postoperative LV function.

Conclusions—Asymptomatic patients with severe degenerative mitral regurgitation can be safely followed up until either symptoms occur or currently recommended cutoff values for LV size, LV function, or pulmonary hypertension are reached. This management strategy is associated with good perioperative and postoperative outcome but requires careful follow-up. (***Circulation***. 2006;113:2238-2244.)

Key Words: valves ■ mitral valve ■ regurgitation

Degenerative mitral regurgitation (MR) is the second most common valvular heart disease after calcific aortic stenosis in developed countries[1] and is frequently diagnosed in still-asymptomatic patients.[2] Surgery has been shown to be the only efficient treatment, but its optimal timing remains a matter of controversy.[3] The ultimate goal of patient care is obviously no longer the relief of limiting symptoms but the achievement of an optimal long-term outcome with regard to mortality and morbidity. Preoperative development of severe symptoms,[4] left ventricular (LV) dysfunction,[5–7] LV enlargement,[8,9] chronic atrial fibrillation,[10] or progressive pulmonary hypertension[11] were found to be associated with an unfavorable outcome, whereas reported long-term mortality and morbidity were lowest in patients who underwent surgery before such findings occurred.[6,8,9,12] In addition, reports of low mortality and improved success rates of valve repair favor early elective surgery.[13] Current guidelines recommend surgery even if symptoms are still mild or when asymptomatic patients develop early signs of LV dysfunction, pulmonary hypertension, or atrial fibrillation.[3,14] Some groups have

suggested an even more liberal approach.[15] A recent study[16] reported a 5-year cardiac mortality rate of almost 40% and a cardiac event rate of >60% for asymptomatic severe MR and concluded that all of these patients should be promptly considered for surgery. However, according to national database reports, operative mortality is certainly not negligible.[17] Furthermore, the majority of patients who undergo mitral valve surgery ultimately require valve replacement,[18] which is associated with a markedly higher operative mortality rate[19] and prosthetic valve–related long-term mortality and morbidity.

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Thus, risk and benefit must be weighed carefully. Unfortunately, no data have been available on the outcome of patients treated according to current practice guidelines. The purpose of the present study was, therefore, to prospectively evaluate the outcome of such a treatment strategy with regard to long-term mortality and morbidity.

Materials

Study Population

All patients seen in our outpatient clinic for valvular heart disease between 1995 and 2002 were prospectively included when they fulfilled the following criteria: severe MR of degenerative origin documented by echocardiography (prolapse or flail leaflet; other terms used to describe these pathologies include myxomatous MR and fibroelastic deficiency), lack of symptoms, normal LV function (fractional shortening $\geq$0.32, ejection fraction $\geq$0.60, end-systolic diameter <45 mm, or end-systolic diameter index <26 mm/m^2, considering body surface area), Doppler sonographically estimated systolic pulmonary artery pressure $\leq$50 mm Hg, and sinus rhythm. Patients were excluded if they had additional hemodynamically significant valve lesions (more than mild), congenital heart disease, ischemic heart disease, or cardiomyopathy. The study protocol was approved by the ethics committee of the Medical University of Vienna.

Clinical Data

At study entry, the following clinical data were collected: age, gender, history of hypercholesterolemia (cholesterol >200 mg/dL or patient undergoing lipid-lowering therapy at study entry), diabetes mellitus, arterial hypertension (blood pressure >140/90 mm Hg on the basis of the average of repeated measurements), and coronary artery disease (documented previous myocardial infarction or angiographically documented coronary artery stenosis). Information on concomitant statin, β-blocker, and angiotensin-converting enzyme inhibitor treatment was recorded.

Echocardiography

Echocardiographic data were obtained with commercially available ultrasound systems. All patients underwent a comprehensive examination, including M-mode echocardiography, 2-dimensional echocardiography, and conventional and color Doppler ultrasonography conducted by experienced echocardiographers.

Mitral valve prolapse was defined as displacement of 1 or both leaflets into the left atrium below the mitral annulus level during systole. Flail leaflet was diagnosed when the leaflet tip turned outward, becoming concave toward the left atrium.

MR was quantified by an integrated approach that included valve morphology, LV volume load, proximal regurgitant jet width, proximal flow convergence, and pulmonary venous flow pattern. Specifically, the following criteria were used for severe MR: A flail leaflet with clearly visible coaptation defect was considered a definite sign of severe MR. In patients with prolapse without flail, a proximal jet width >6 mm and a flow convergence radius >7 mm at a Nyquist limit of 55 to 65 cm/s were considered specific signs of severe MR. LV enlargement with normal LV function in the absence of any causes of LV dilatation other than MR was considered supportive of severe MR. In case of uncertainty, pulmonary venous flow was studied, and holosystolic flow reversal was then considered a specific sign of severe MR. When different parameters yielded discrepant results, investigators looked carefully for technical and physiological explanations for these discrepancies and relied on the components that had the best-quality primary data and that were the most accurate given the specific clinical condition. The approach to quantification used in the present study is in agreement with current guidelines published by the American Society of Echocardiography and the European Association of Echocardiography.[20] LV diameters, fractional shortening, and ejection fraction, as well as systolic pulmonary artery pressure (using tricuspid regurgitant velocity), were measured as recommended.[21]

Patient Evaluation and Management

Patient assessment included history, physical examination, and echocardiography at baseline. Stable patients with previous examinations were reevaluated every 12 months, including echocardiography. Intervals were shortened to 6 or 3 months if patients had had no previous examinations that demonstrated stable findings, if there were changes compared with previous measurements, or if measurements were close to the predefined cutoff values (see below).

Patients were referred to surgery at the onset of symptoms even if they were mild or if asymptomatic patients developed 1 or more of the following: LV end-systolic diameter $\geq$45 mm or end-systolic diameter index $\geq$26 mm/m^2 (considering body surface area), fractional shortening <0.32 or ejection fraction <0.60, systolic pulmonary artery pressure >50 mm Hg, or recurrent atrial fibrillation. Patients were reevaluated 3 to 6 months and 12 months after surgery and yearly thereafter. For the assessment of outcome, the primary end point was death. Because the purpose of the study was to evaluate the outcome of a predefined treatment strategy with regard to timing of surgery, perioperative deaths and late deaths were included in this analysis. Deaths were classified as cardiac or noncardiac on the basis of discussion with the primary care physician, review of medical records, or review of medical records that included autopsy records. Deaths due to cardiac causes were further classified as being directly related to MR (sudden death or death due to congestive heart failure) or as related to other cardiac conditions (ie, ischemic heart disease or inflammatory heart disease).

Events were defined as development of any criteria that indicated surgery or death. For the assessment of outcome with regard to morbidity, postoperative symptoms, LV function, and presence of atrial fibrillation at last follow-up were assessed.

Statistical Analysis

Continuous variables are described by their mean$\pm$SD. Overall and event-free survival functions were calculated by means of the Kaplan-Meier method, with the follow-up quantified by means of the reverse Kaplan-Meier method.[22]

For each patient included in the study, the corresponding average age- and gender-specific annual mortality rates of the Austrian general population were obtained. These data were taken from the Austrian life tables of 2002, which are provided by the Austrian Statistical Office. On the basis of these mortality data, the probability of cumulative expected survival was determined for the beginning of each year, which resulted in an expected survival curve. Overall survival (taking into account perioperative deaths and postoperative follow-up for those patients who required surgery) was also quantified and related to the expected survival. A possible departure of the mortalities of the study population from those of the general population was assessed by means of a log-rank test. For this test, expected numbers of deaths of the study cohort under the null hypothesis were determined from the Austrian life tables of 2002, taking into account age and gender of the study patients. A separate analysis of the patients with MR due to flail leaflets was performed, because this defines an unambiguous subgroup of patients with uniformly severe disease[23] that can be reliably diagnosed with echocardiography[24] and compared with previously published series.[2]

The statistical significance between survival curves of patient subgroups was determined by a log-rank test. A probability value <0.05 was considered to indicate statistical significance.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Three patients were lost to follow-up; thus, follow-up information was complete for 129 patients (98%). The Table shows the baseline characteristics of the total 132 patients enrolled in the study and the subgroup of 58 patients with flail leaflet. This group did not differ from the entire population with regard to baseline clinical and echocardiographic characteristics.

Survival

During an estimated median follow-up of 69.2 months (interquartile range 41.8 to 81.3 months), 8 deaths were

Patient Characteristics at Study Entry

	All Patients (n=132)	Patients With Flail Leaflet (n=58)
Clinical characteristics		
Gender, % female	37	23
Age, y	55±15	57±12
Cholesterol, mg/dL	229±41	235±37
Creatinine, mg/dL	1.11±0.39	1.09±0.19
Coronary artery disease, %	8	9
Hypertension, %	58	60
Diabetes mellitus, %	4	4
History of hypercholesterolemia, %	50	43
Atrial fibrillation, %	20	11
Echocardiographic characteristics		
LV end-systolic diameter, mm	34±5	32±5
Indexed LV end-systolic diameter, mm/m^2	19±3	18±3
LV end-diastolic diameter, mm	56±6	56±6
Indexed LV end-diastolic diameter, mm/m^2	31±4	30±4
LV ejection fraction, %	66±5	67±6
LV fractional shortening, %	40±5	42±6
Left atrial size, mm	60±10	62±10
Systolic pulmonary artery pressure, mm Hg	38±11	40±12
Mitral valve morphology		
Anterior leaflet involvement, %	14.4	10.3
Posterior leaflet involvement, %	56.8	89.7
Bileaflet involvement, %	28.8	...
Medications at study entry		
ACE inhibitor, %	28	19
β-Blocker, %	23	32
Statin, %	6	5

observed. Three of the deaths occurred in patients with flail leaflet and 5 in patients with valve prolapse. There was 1 sudden cardiac death in an 82-year-old man who had refused surgery after development of symptoms in the presence of normal LV function and size. The exact reason of death remained unknown in 1 asymptomatic patient who had refused surgery indicated by an enlarged LV. In the absence of evidence to the contrary, these 2 deaths were considered to be related to MR. One patient died of myocarditis (according to autopsy) 3 days after running a marathon.

Three noncardiac deaths involved stroke (n=1) and cancer (n=2). There were 2 late postoperative deaths in patients after mechanical mitral valve replacement: 1 stroke 31 months after mitral valve replacement, and 1 acute myocardial infarction 3 weeks after mitral valve replacement. Overall survival including perioperative and late deaths after mitral valve surgery was 99±1% at 2 years, 96±2% at 4 years, and 91±3% at 8 years (Figure 1). Overall survival for patients with flail leaflets was 100% at 2 years, 95±3% at 4 years, and 92±4% at 8 years (Figure 1). Survival of patients with severe asymptomatic MR did neither differ substantially nor significantly from the expected cumulative survival, (P=0.34) (Figure 1). The same was true for the subgroup with flail leaflet (P=0.22).

Need for Surgery and Nonfatal Events

During follow-up, 38 patients developed 1 or more criteria that indicated a need for surgery. Twenty-four patients developed symptoms. Of these, 5 patients had developed additional criteria for surgery: atrial fibrillation, 3; pulmonary hypertension, 1; and LV dysfunction, 1. Of the 14 patients who underwent surgery while asymptomatic, 5 had developed LV dysfunction (additional pulmonary hypertension, 1; atrial fibrillation, 1) and 4 reached the cutoff for LV size (additional pulmonary hypertension, 1). Finally, 5 patients had only new onset of atrial fibrillation or pulmonary hypertension.

Figure 2 shows survival free of symptoms, survival free of asymptomatic LV dysfunction, and survival free of asymptomatic pulmonary hypertension or recurrent atrial fibrillation. Survival free of any indication for surgery was 92±2% at 2 years, 78±4% at 4 years, 65±5% at 6 years, and 55±6% at 8 years (Figure 2). Thirty-four of these 38 patients eventually underwent mitral valve surgery, whereas 4 patients refused. One patient who had not developed a criterion that indicated surgery underwent surgery at his own request.

Figure 3 shows the event-free survival of patients with flail leaflet (n=58) versus valve prolapse (n=74). After 2.5 years, the curves started to separate; however, the difference did not
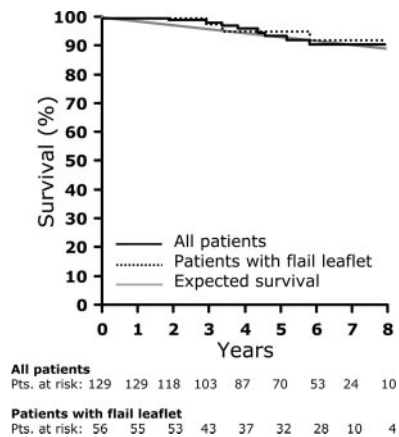
Figure 1. Kaplan-Meier overall survival of patients with asymptomatic severe degenerative MR managed according to a watchful waiting strategy (solid black line indicates total patient population; dotted line, patients with flail leaflet). Survival functions did not differ significantly from expected cumulative survival (solid gray line). This analysis includes perioperative and postoperative deaths for those patients who required valve replacement during follow-up. Pts indicates patients.

Figure 3. Kaplan-Meier event-free survival for patients with mitral valve prolapse (gray line; n=74) vs flail leaflet (black line; n=58). *P*=0.23. Pts indicates patients.

reach statistical significance (*P*=0.23). Survival free of indications for surgery was 91±4% at 2 years, 69±7% at 4 years, 60±8% at 6 years, and 52±9% at 8 years for patients with flail leaflets and 93±3% at 2 years, 84±5% at 4 years, 69±7% at 6 years, and 59±9% at 8 years for patients with prolapse.

Outcome of Surgery

Of the 35 patients who underwent mitral valve surgery, mitral valve repair was performed in 29 patients (82.9%), whereas a mechanical valve was implanted in 6 (17.1%). Eight patients (22.9%) underwent concomitant aortocoronary bypass grafting at the time of surgery. Additional tricuspid valve repair was performed in 5 patients (14.3%). There were no perioperative deaths. Reoperation was necessary in 2 patients: Mitral valve replacement was performed in 1 patient 8
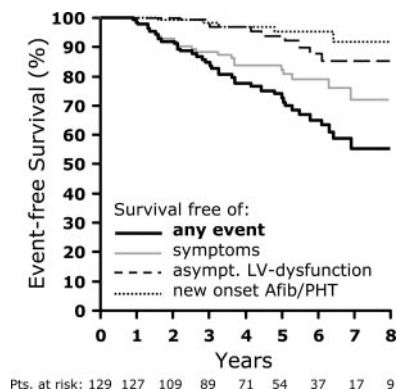
months postoperatively after unsuccessful repair and in another patient 5 months postoperatively because of mitral valve endocarditis.

All patients had good functional status after surgery: Twenty-three patients were asymptomatic, and 12 had only mild symptoms (4 in New York Heart Association [NYHA] class I–II and 8 in NYHA class II). Four of the 35 patients had impaired LV function after surgery. Two of them had undergone mitral valve replacement (both had normal preoperative ventricular function). The other 2 patients underwent mitral valve repair with concomitant coronary bypass surgery and had mildly reduced preoperative LV function.

Discussion

Within the background of ongoing controversy about the management of asymptomatic patients with severe degenerative MR, this is the first study to provide prospective outcome data on a specific treatment strategy. Excellent outcome was achieved when patients were followed up carefully until either symptoms developed or until asymptomatic patients reached currently proposed criteria for surgery with regard to LV size, LV function, and pulmonary hypertension or until they developed recurrent atrial fibrillation. Twenty-four of the 38 patients who required surgery had developed symptoms, whereas asymptomatic LV dilatation or dysfunction only accounted for 24% of surgical indications. Thus, development of symptoms appears to be the most frequent indication for surgery and precedes LV impairment in the majority of patients. Overall survival was 91±3% at 8 years, which was not statistically different from expected survival. Even the survival of the subgroup of patients with flail leaflet did not differ from the expected survival. After 2.5 years, these patients tended to develop indications for surgery slightly earlier than patients with prolapse. Nevertheless, even in the group with flail leaflet, 52% of patients did not reach the defined criteria for surgery at 8 years. Even more importantly, those patients who eventually underwent valve surgery had a good postoperative outcome with regard to functional class and LV function. These data, therefore, strongly support adherence to current practice guidelines

Figure 2. Kaplan-Meier event-free survival. Solid black line shows survival free of any event to indicate surgery. Gray line shows survival free of symptoms. Dashed line shows survival free of asymptomatic (asympt) LV dysfunction. Dotted line shows survival free of asymptomatic development of atrial fibrillation (Afib) and/or pulmonary hypertension (PHT) to indicate surgery.
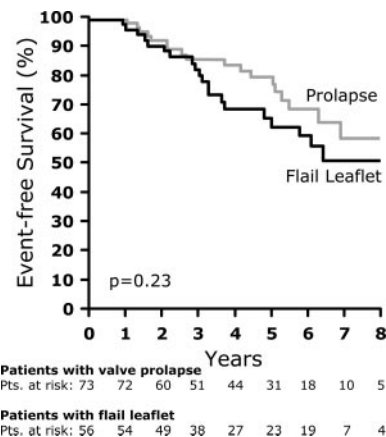
instead of consideration of surgery in any asymptomatic patient with severe MR, as has recently been proposed.[16]

Natural History of Chronic Severe Degenerative MR

The asymptomatic phase of chronic severe MR may last for many years.[25] In early studies on the natural history of MR, survival varied widely. Wilson and Lim[26] and Rappaport[27] reported high survival rates of 95% at 20 years and 70% at 10 years, respectively, whereas others[28,29] estimated survival rates of only 46% or 50% at 5 years. Finally, survival was as low as 27% at 5 years in the report by Horstkotte and Loogen.[30] These studies were limited in part by small study populations, multiple selection biases, poor definition of regurgitation severity, and variation in the causes of mitral valve disease. In a more recent study that included only patients with severe MR due to flail leaflet, Ling et al[2] reported a 6.3% yearly mortality rate. Independent determinants of mortality were older age, presence of symptoms, and a low ejection fraction. Yearly mortality reached 34% in patients who were transiently in NYHA functional class III or IV but was still 4.1% for those in class I or II. In addition, high morbidity was reported in that study. At 10 years, the mean rates of heart failure, atrial fibrillation, and death or surgery were $63\pm8\%$, $30\pm12\%$, and $90\pm3\%$, respectively, in the study by Ling et al.[2] Several years later, the same group[31] reported that sudden death is not uncommon in patients with flail leaflet, ranging from 1% per year in patients in NYHA class I to 7.8% in those in NYHA class III and IV. These studies were limited by their retrospective nature. Most recently, Enriquez-Sarano et al[16] published the first prospective data on this subject; in that report, asymptomatic patients with normal LV function and severe MR defined by an effective regurgitant orifice area ≥40 mm^2 had a cardiac mortality rate of $36\pm9\%$ at 5 years and a cardiac event rate, including cardiac death, congestive heart failure, and new-onset atrial fibrillation, of $62\pm8\%$, which suggests that the outcome of severe MR is much worse than previously assumed. The present study, however, questions such a poor outcome of asymptomatic patients with severe MR provided that they are carefully followed up and referred to surgery according to currently recommended criteria. Although Enriquez-Sarano et al[16] used an effective regurgitant orifice area ≥40 mm^2 to define severe MR, whereas the integrated approach was used in the present study, it is unlikely that the patient groups differed significantly with regard to MR severity. This should particularly be true for the group with flail leaflet.

Outcome of Surgery for Degenerative MR

Surgery can improve symptoms in patients with severe MR[29,32]; however, LV function frequently worsens, with surgery ultimately leading to the development of congestive heart failure.[32,33] Loss of ventricular function is greatest after mitral valve replacement with resection of the mitral apparatus and to a lesser extent when part of the valve apparatus is preserved.[34] The best results with regard to postoperative LV function in general have been reported for valve repair.[13,35] Both preservation of LV function and

the avoidance of anticoagulation and prosthesis-associated complications by this technique may also improve long-term results.[13,35] Nevertheless, outcome has been reported to be disappointing in particular circumstances.[4–7,36] Patients who undergo surgery when already markedly symptomatic and those with reduced preoperative LV function were found to have particularly poor outcomes.[4–7] It has been recognized that the prolonged burden of volume overload may have already resulted in irreversible myocardial damage and LV dysfunction when patients are still mildly symptomatic or even asymptomatic. Such observations suggest that surgery should be performed at an early stage. The best operative outcome has indeed been reported for patients who underwent surgery with no or only mild symptoms and an ejection fraction >0.60.[4,15]

Optimal Timing of Surgery in Severe Degenerative MR

The poor long-term outcome of severe MR together with the low mortality and good durability of valve repair led some experienced centers to consider surgery in any asymptomatic patient with severe MR and a potentially repairable valve.[16] However, operative risk cannot be considered negligible. According to the Society of Thoracic Surgeons' National Adult Cardiac Surgery Database 2005,[17] isolated mitral valve repair has a mortality rate in the range of 2%. More importantly, mitral valve repair is not always possible, and the majority of patients having mitral valve surgery still end up with a prosthetic valve.[18] Valve replacement is, however, associated with a significantly higher operative mortality, which increases continuously from 4% for patients younger than 50 years to 17% for those older than 80 years in the Society of Thoracic Surgeons' database.[19] Furthermore, prosthetic valve–related long-term mortality and morbidity must be considered. On the basis of currently available outcome data and the identified preoperative predictors of surgical outcome in MR, American and European practice guidelines[3,14] recommend surgery in asymptomatic patients (class I and IIa indications) when LV ejection fraction decreases below 0.60, LV end-systolic diameter exceeds 45 mm (end-systolic diameter index >26 mm/m^2), systolic pulmonary artery pressure exceeds 50 mm Hg, or recurrent atrial fibrillation occurs. However, no study to date has evaluated the safety and long-term outcome of such a treatment strategy. The results of the present study support adherence to current recommendations instead of consideration of elective surgery in all patients with severe MR, as recently suggested.[16]

Study Limitations

The present study included only patients with chronic severe degenerative MR. The results can therefore not be applied to other forms of MR. One might argue that results may change with longer postoperative follow-up; however, given presently available data, it is unlikely that patients who underwent surgery and have normal postoperative LV function and good functional status should deteriorate with extended follow-up.[15]

No quantitative measurements of regurgitant orifice area or regurgitant volume were used in the present study; however, the careful, integrated approach to semiquantitative assessment of MR is in full agreement with current guidelines.[20] In addition, it may indeed be safer to use the integrated approach and combine a number of different independent signs instead of adhering to a single value that is prone to various significant sources of error.[20] Furthermore, cutoff values for regurgitant orifice area and regurgitant volume were validated against the same criteria. Finally, the population followed up in the present study reflects the population of patients with severe MR that is presently being treated in most institutions.

Clinical Implications

Given the results of the present study, prophylactic surgery for all patients with asymptomatic severe degenerative MR can definitely not be recommended. The present data strongly suggest that these patients can be safely followed up either until symptoms occur or until currently recommended cutoff values for LV size, LV function, or pulmonary hypertension are reached in asymptomatic patients. This management strategy is associated with good perioperative and postoperative outcome; however, it must be emphasized that this approach requires careful clinical follow-up, including serial echocardiographic examinations, in experienced hands.

Disclosures

None.

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CLINICAL PERSPECTIVE

This is the first study to evaluate the safety and long-term outcome of a treatment strategy for asymptomatic severe degenerative mitral regurgitation according to current American and European practice guidelines. These guidelines recommend surgery in asymptomatic patients (class I and IIa indications) when left ventricular (LV) ejection fraction decreases below 0.60, LV end-systolic diameter exceeds 45 mm, systolic pulmonary artery pressure exceeds 50 mm Hg, or recurrent atrial fibrillation occurs. A total of 132 consecutive asymptomatic patients with severe degenerative mitral regurgitation (flail leaflet or valve prolapse) were prospectively followed up for 62 ± 26 months. Patients were referred for surgery when the criteria mentioned above were fulfilled. Overall survival was not statistically different from expected survival either in the total group or in the subgroup of patients with flail leaflet. Survival free of any indication for surgery was $92\pm2\%$ at 2 years, $78\pm4\%$ at 4 years, $65\pm5\%$ at 6 years, and $55\pm6\%$ at 8 years. Patients with flail leaflet tended to develop criteria for surgery slightly but not significantly earlier. There was no operative mortality. Postoperative outcome was good with regard to survival, symptomatic status, and postoperative LV function. Thus, prophylactic surgery for all patients with asymptomatic severe degenerative mitral regurgitation can definitely not be recommended. The present data strongly suggest that these patients can be safely followed up until either symptoms occur or currently recommended cutoff values for LV size, LV function, or pulmonary hypertension are reached in asymptomatic patients. This management strategy is associated with good perioperative and postoperative outcome but requires careful follow-up.