

Sudden Death in Mitral Regurgitation Due to Flail Leaflet

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- OBJECTIVES** We sought to assess the incidence and determinants of sudden death (SUD) in mitral regurgitation due to flail leaflet (MR-FL).
- BACKGROUND** Sudden death is a catastrophic complication of MR-FL. Its incidence and predictability are undefined.
- METHODS** The occurrence of SUD was analyzed in 348 patients (age 67 ± 12 years) with MR-FL diagnosed echocardiographically from 1980 through 1994.
- RESULTS** During a mean follow-up of 48 ± 41 months, 99 deaths occurred under medical treatment. Sudden death occurred in 25 patients, three of whom were resuscitated. The sudden death rates at five and 10 years were $8.6 \pm 2\%$ and $18.8 \pm 4\%$, respectively, and the linearized rate was 1.8% per year. By multivariate analysis, the independent baseline predictors of SUD were New York Heart Association (NYHA) functional class ($p = 0.006$), ejection fraction ($p = 0.0001$) and atrial fibrillation ($p = 0.059$). The yearly linearized rate of sudden death was 1% in patients in functional class I, 3.1% in class II and 7.8% in classes III and IV. However, of 25 patients who had SUD, at baseline, 10 (40%) were in functional class I, 9 (36%) were in class II and only 6 (24%) in class III or IV. In five patients (20%), no evidence of risk factors developed until SUD. In patients with an ejection fraction $\geq 60\%$ and sinus rhythm, the linearized rate of SUD was not different in functional classes I and II (0.8% per year). Surgical correction of MR ($n = 186$) was independently associated with a reduced incidence of SUD (adjusted hazard ratio [95% confidence interval] 0.29 [0.11 to 0.72], $p = 0.007$).
- CONCLUSIONS** Sudden death is relatively common in patients with MR-FL who are conservatively managed. Patients with severe symptoms, atrial fibrillation and reduced systolic function are at higher risk, but notable rates of SUD have been observed without these risk factors. Correction of MR appears to be associated with a reduced incidence of SUD, warranting early consideration of surgical repair. (J Am Coll Cardiol 1999;34:2078-85) © 1999 by the American College of Cardiology
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Mitral regurgitation (MR) is a valvular heart disease that is increasingly observed because of the aging population and the high prevalence of degenerative lesions in the adult and elderly age strata (1). Patients with severe MR may remain asymptomatic (2), and the indications for surgical correction of MR are not widely agreed on (3). Patients progressing to severe symptoms (4) or congestive heart failure (2) can be operated on successfully (5,6), but sudden death (SUD) leaves no opportunity for review of therapeutic options. Sudden death is known to occur in patients with mitral valve disease managed conservatively. It is a rare complication in patients with isolated mitral valve prolapse (7,8), but it

appears more frequently in patients with mitral regurgitation due to flail leaflet (MR-FL) (9) or severe MR of any cause (10). However, the incidence of SUD may be underrecognized clinically if no systematic inquiry is made of patients lost to follow-up, and SUD has been the focus of few reports (8,11), despite its devastating consequences. A notable incidence of SUD in patients with

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severe MR, in particular, those cases not preceded by severe symptoms, would be an incentive for early suppression of the left ventricular (LV) volume overload due to MR by performing an early operation (12). Therefore, it is essential to analyze the incidence, correlates and predictability of SUD in patients with conservatively managed MR. For this purpose, the clinical course of patients with MR-FL, who

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Abbreviations and Acronyms

CAD	= coronary artery disease
CI	= confidence interval
EF	= ejection fraction
LA	= left atrium
LV	= left ventricle, ventricular
MR	= mitral regurgitation
MR-FL	= mitral regurgitation due to flail leaflet
NYHA	= New York Heart Association
SUD	= sudden death

invariably have a large degree of MR on the basis of their valvular lesion (13), allows characterization of the contemporary natural history of severe MR (2).

Accordingly, we studied a cohort of patients with MR-FL diagnosed by echocardiography to 1) determine the incidence of SUD; 2) define the clinical and echocardiographic features of those who died suddenly; and 3) identify predictors and effects of treatment on this catastrophic event.

METHODS

Patients first diagnosed to have flail mitral leaflets on two-dimensional echocardiography between January 1, 1980 and December 31, 1994 at the Mayo Clinic were potential candidates for inclusion in the study. Patients were included in the present study if they did not undergo surgical correction within one month after diagnosis of MR-FL. Exclusion criteria were 1) papillary muscle rupture; 2) previous valve surgery; 3) associated moderate or severe mitral stenosis or aortic valve disease; and 4) coexistent congenital heart disease. Patients who subsequently were identified to have coronary artery disease (CAD) or underwent coronary artery bypass grafting with valvular surgery were not excluded.

Baseline clinical data were obtained from medical records, and follow-up was obtained through clinical records, postal survey and telephone calls to patients and their relatives and physicians. The mode of terminal events was corroborated by telephone calls to the patients' relatives and physicians and by examination of death certificates and autopsy records. Death was classified according to the criteria of Hinkle and Thaler (14), and SUD was inferred if it occurred within 1 h in a patient who was well or medically stable. Medications used during follow-up were recorded if prescribed for at least three months. Concomitant medical illnesses that could potentially affect survival were assigned weights and summated as a modified comorbidity index (15).

A comprehensive two-dimensional echocardiographic study was performed. The diagnosis of flail leaflets was based on failure of leaflet coaptation, with systolic eversion of the flail segment into the left atrium (LA) (16). The severity of MR was assessed semiquantitatively in patients

who had Doppler echocardiography (17). Left ventricular and LA dimensions were obtained by using M-mode echocardiography guided with two-dimensional imaging. Ejection fraction (EF) was visually estimated in all patients (18) and combined with calculated values (19) in 76% of patients, as previously reported (20,21), and was used unaltered from the original echocardiographic report by means of electronic transfer.

Statistical analysis. Continuous variables are expressed as the mean value \pm SD or median values and categorical data as percentages. Group comparisons were performed with the standard Student *t* test or chi-square test, as appropriate. After echocardiographic diagnosis, the rates of all-cause, cardiac and noncardiac mortality and SUD were estimated by the Kaplan-Meier method. Analysis was performed, with censor at the time of mitral valve surgery if this was eventually performed. Identification of baseline predictors of SUD was accomplished initially by performing univariate Cox proportional hazards analysis on candidate clinical, laboratory and echocardiographic variables. To confirm independent predictive value, variables with $p < 0.10$ were then tested in a multivariate model. To determine the impact of events occurring during follow-up (congestive heart failure or surgery) on SUD, time-dependent proportional hazards analyses were performed within multivariate models, including baseline variables predictive of SUD. To analyze the effect of surgery on SUD, the events and follow-up after the operation were accounted for. A value $p < 0.05$ was considered significant.

RESULTS

Baseline characteristics. From a cohort of 468 patients with MR-FL diagnosed by echocardiography from 1980 through 1994, 348 patients (age 67 ± 12 years, 74% male) met eligibility criteria. The cause of flail leaflet was idiopathic in 286 patients, endocarditis in 55, traumatic in 5 and miscellaneous in 2. The posterior leaflet was involved in 297 patients, the anterior leaflet in 45 and both in 6. At presentation, 214 patients (61%) were in New York Heart Association (NYHA) functional class I, 85 (24%) were in class II, 38 (11%) were in class III and 10 (3%) were in class IV. The functional class could not be determined in one patient. Among the 48 patients initially in functional class III or IV, 19 ultimately underwent the operation, 7 were not candidates for surgery, 7 refused and the others improved with medical treatment. The LV systolic and diastolic diameters and EF were 19 ± 4 and 33 ± 6 mm/m² and $63 \pm 10\%$, respectively. The LA diameter was 28 ± 6 mm/m². Among the 317 patients in whom the degree of MR was graded by Doppler echocardiography, 259 (82%) had grade 3+ or 4+/4+ regurgitation.

SUD rates. Follow-up was complete for 345 patients (99%) up to 1998 or until death. During a mean medical follow-up of 48 ± 41 months, 99 deaths occurred. Sudden

Table 1. Baseline Characteristics According to Outcome*

	Group I—SD (n = 25)	Group II—NSCD (n = 49)	Group III—NCD (n = 27)	Group IV—SURV (n = 247)	p Value†
Age (years)	71 ± 9	80 ± 8‡	77 ± 10‡	64 ± 11‡	0.0001
Male gender	21 (84%)	26 (53%)‡	20 (74%)	189 (77%)	0.004
NYHA functional class III-IV	6 (24%)	17 (35%)	5 (19%)	20 (8%)‡	0.001
Atrial fibrillation	9 (36%)	19 (39%)	4 (15%)	34 (14%)‡	0.001
Hypertension	7 (28%)	16 (33%)	9 (33%)	66 (27%)	0.80
Comorbidity index	0.92 ± 0.9	0.92 ± 0.8	1.30 ± 0.9	0.66 ± 0.8	0.009
Smoking	14 (56%)	16 (33%)	9 (33%)	105 (43%)	0.23
Serum creatinine (mg/dl)	1.5 ± 0.8	1.7 ± 2	1.7 ± 1.8	1.1 ± 0.6	0.002
Total cholesterol (mg/dl)	194 ± 45	188 ± 60	196 ± 51	209 ± 45‡	0.022
LDL cholesterol (mg/dl)	126 ± 50	128 ± 46	130 ± 61	137 ± 39	0.27
Ejection fraction (%)	57 ± 14	60 ± 14	63 ± 8	65 ± 8‡	0.0001
LVS diameter (mm/m ²)	22 ± 5	20 ± 4	20 ± 5	19 ± 4‡	0.01
LVD diameter (mm/m ²)	34 ± 5	33 ± 5	33 ± 6	32 ± 6	0.15
LA diameter (mm/m ²)	30 ± 5	32 ± 8	28 ± 6	27 ± 7‡	0.0001

*Continuous variables are expressed as the mean value ± SD and categorical variables as the number of patients (percentage). †Applies to analysis of variance comparison of four groups. ‡p < 0.05 vs. group I.

LA = left atrial; LDL = low density lipoprotein; LVD and LVS = left ventricular end-diastolic and end-systolic; NCD = noncardiac death; NYHA = New York Heart Association; NSCD = nonsudden cardiac death; SD = sudden death; SURV = survivors.

death occurred in 25 patients under conservative management, three of whom collapsed and were successfully resuscitated. Among those resuscitated, two died after the operation and one refused the operation and died six months later. In 10 patients, the cardiac rhythm during the episode of circulatory collapse could be ascertained—ventricular fibrillation in seven and ventricular tachycardia in three. Among the 25 patients with SUD, seven had a history of possible CAD. Among the other 18 patients, autopsy in one and angiography in three demonstrated an absence of coronary occlusive disease, exercise testing was negative in five and none of the others had signs suggestive of CAD. Ventricular tachycardia or frequent ventricular extrasystole on Holter monitoring was noted in six of the eight patients in whom it was performed. Only one of the 25 patients was treated using class I antiarrhythmic drugs. The other baseline descriptors of the patients with SUD are listed in Table 1. Of the other 323 patients, nonsudden cardiovascular deaths occurred in 49 and noncardiovascular deaths in 27. At 5 and 10 years, total mortality rates were 29 ± 3% and 53 ± 5%, respectively; cardiac death rates were 21 ± 3% and 43 ± 5%; and SUD rates were 8.6 ± 2% and 18.8 ± 4% (Fig. 1). The yearly linearized rate of SUD was 1.8% (95% confidence interval [CI] 1.2 to 2.6). The mean time to SUD was 44 ± 31 months.

Determinants of SUD. For descriptive purposes, the baseline characteristics of the patients with SUD (group I) during follow-up are presented in Table 1, along with those of patients who had nonsudden cardiovascular deaths (group II) or noncardiovascular deaths (group III) and those of patients who survived with conservative management (group IV). Multiple differences were noted between the groups. Using univariate Cox proportional hazards analysis,

the baseline predictors of SUD were functional class (p = 0.0001), atrial fibrillation (p = 0.001), history of CAD (p = 0.001), smoking history (p = 0.03) and creatinine plasma levels (p = 0.02). Echocardiographic univariate predictors were EF (p = 0.0001), LV end-systolic diameter (p = 0.002) and LA dimension (p = 0.002).

By multivariate analysis, baseline independent predictors of SUD were functional class (p = 0.006), EF (p = 0.0001) and atrial fibrillation (p = 0.059). The adjusted hazard ratios associated with these predictors of SUD are indicated in Table 2. Congestive heart failure developing in the course of medical surveillance, used as a time-dependent variable, was associated with SUD in univariate (p = 0.0001) and multivariate (p = 0.0001) analyses.

Predictability of SUD. The yearly rates of SUD according to baseline functional class are 1.0% in class I, 3.1% in class

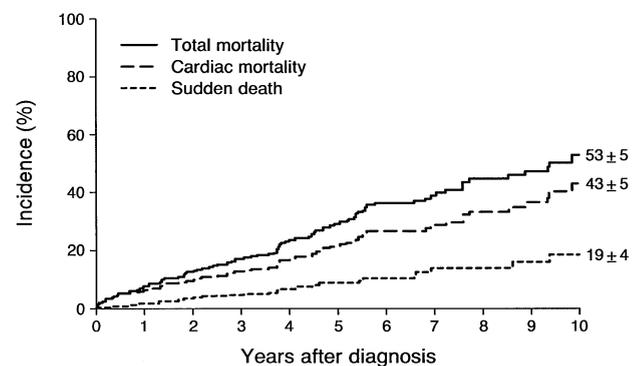


Figure 1. Incidence of total mortality, cardiac mortality and sudden death in patients with MR-FL. The event rates ± SEE at 10 years are indicated.

Table 2. Multivariate Predictor of Sudden Death*

	Unit	Risk Ratio	95% CI	p Value
EF (%)	Per percent	0.94	0.91–0.97	0.0001
NYHA functional class	Per class	1.91	1.20–3.04	0.006
AF	Per AF present	2.40	0.97–5.95	0.059

*There were 347 patients in the model.

AF = atrial fibrillation; CI = confidence interval; EF = ejection fraction; NYHA = New York Heart Association.

II and 7.8% in class III or IV ($p < 0.0001$) (Fig. 2). However, of the 25 patients with SUD, 10 were in functional class I at diagnosis, 9 were in class II, 5 were in class III and only 1 was in class IV. Among the 19 patients in class I or II at baseline, 10 (five in each class) had worsening of symptoms before SUD. These patients did not undergo surgery because the symptoms improved rapidly with treatment and were not considered disabling. The rate of SUD was higher in functional class II than in class I ($p < 0.01$). However, this difference was confined to patients with either atrial fibrillation or $EF < 60\%$ ($p = 0.002$). When only patients in sinus rhythm and $EF \geq 60\%$ were considered, yearly rates of SUD in patients in functional class II and I were not different (0.5% and 0.9%, respectively; $p = 0.60$; average 0.8%). The linearized rate of SUD in patients in functional class I or II, in sinus rhythm, with $EF \geq 60\%$ and with no history of CAD was also 0.8% per year.

The yearly linearized rates of SUD in patients with a baseline $EF < 50\%$ were 12.7%, 0.9% for an EF 50% to 59% and 1.5% for an $EF \geq 60\%$ ($p < 0.0001$) (Fig. 3). Among the 25 patients with SUD, EF at diagnosis was $\geq 60\%$ in 17 (68%), 50% to 59% in 2 (8%) and $< 50\%$ in 6 (24%). Echocardiography, repeated in five patients within six months of SUD, showed a decrease of EF under 60% in only one patient, whereas EF was confirmed $> 60\%$ in three and $< 50\%$ in one patient. Of the 19 patients in functional class I or II who had SUD, 15 had an $EF \geq 60\%$ (eight in class I and seven in class II).

The yearly linearized rates of SUD in patients in sinus rhythm was 1.3%, whereas it was 4.9% in patients with atrial

fibrillation at diagnosis ($p = 0.0004$) (Fig. 4). Among the 25 patients with SUD, 16 (64%) were in sinus rhythm at baseline and 13 remained so until SUD.

Overall, five patients who experienced SUD (20%) presented no evidence at any time during their follow-up of atrial fibrillation, LV dysfunction or severe symptoms, until SUD.

Associated treatment—SUD. No significant differences were detected comparing the medical treatment during follow-up of group I versus group II or III with respect to angiotensin-converting enzyme inhibitors, calcium channel blockers, beta-blockers, digoxin, hydralazine, class I antiarrhythmic agents, diuretics or nitrates (all $p > 0.10$). However, when compared with survivors, group I patients were more often taking digoxin (68% vs. 43%; $p = 0.008$), diuretics (80% vs. 28%; $p = 0.001$), calcium channel blockers (28% vs. 11%; $p = 0.001$) and nitrates (16% vs. 5%; $p = 0.03$) and were less often taking beta-blockers (4% vs. 17%; $p = 0.09$).

In patients who underwent the operation, SUD occurred postoperatively in seven, leading to a total number of 32 SUDs in the cohort. In a multivariate proportional hazards analysis that included the significant predictors of SUD, surgery performed at any time (time-dependent variable) independently and favorably influenced the incidence of unexpected death (adjusted hazard ratio 0.29 [95% CI 0.11 to 0.72], $p = 0.007$). This effect persisted when the entire cohort ($n = 468$) was analyzed ($p = 0.0001$) and when the

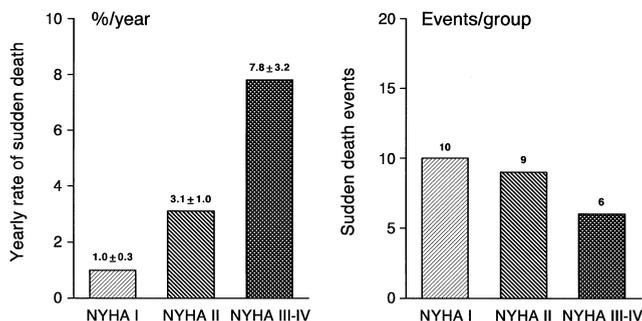


Figure 2. Relation between New York Heart Association (NYHA) functional class at baseline and sudden death. **Left,** Yearly rates of sudden death (\pm SEE) according to functional classes I, II and III or IV. **Right,** Number of sudden death events according to functional classes I, II and III or IV.

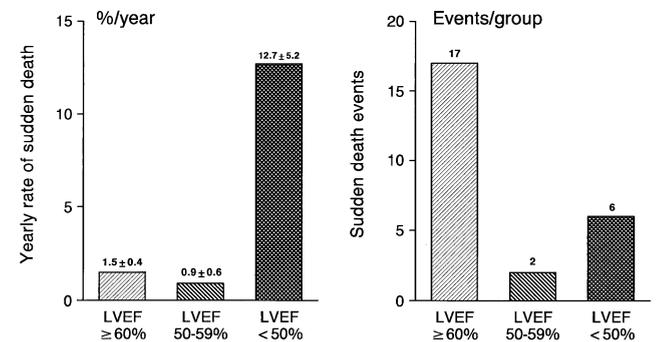


Figure 3. Relation between left ventricular ejection fraction (LVEF) at baseline and sudden death. **Left,** Yearly rates of sudden death (\pm SEE) according to LVEF classified as $\geq 60\%$, 50% to 59% and $< 50\%$. **Right,** Number of sudden death events according to LVEF classified as $\geq 60\%$, 50% to 59% and $< 50\%$.

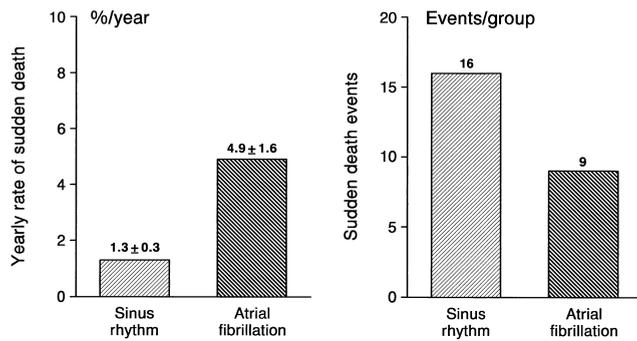


Figure 4. Relation between cardiac rhythm (sinus rhythm or atrial fibrillation) at baseline and sudden death. **Left,** Yearly rates of sudden death (\pm SEE) in patients in sinus rhythm and atrial fibrillation. **Right,** Number of sudden death events observed in patients in sinus rhythm and atrial fibrillation.

occurrence of heart failure during follow-up was included in the model ($p = 0.01$).

DISCUSSION

To our knowledge, the present study reports the largest series of MR-FL and analyzes the outcome during conservative and postsurgical outcome. It showed that 1) SUD is a common terminal event in MR, occurring at a linearized rate of 1.8% per year and accounts for one-fourth of all deaths under conservative management; 2) risk factors for SUD can be defined—namely, more severe symptoms, LV dysfunction and atrial fibrillation; 3) in the absence of risk factors, a notable yearly rate of SUD of 0.8% is nevertheless observed; and 4) surgical correction of MR is associated with a reduced incidence of SUD in patients with MR-FL.

SUD in MR. Sudden death is a major issue in the management of patients with MR. The frequency and dismal outcome of LV dysfunction resulting from the overload due to MR (20,22) have been the basis for advocating early operation (12). There is no wide agreement on the indications for surgery in asymptomatic patients without signs of LV dysfunction (3,23). When a conservative approach is selected, it is possible to proceed with surgery when severe symptoms occur, unless SUD prevents therapeutic intervention (10). Therefore, analyzing the incidence and predictability of SUD in patients with MR is a central argument in the rationale for early operation.

An association between SUD and mitral valve disease has been recognized in pathologic studies (9,24,25) and has been variably assessed in clinical studies (7,10,11,26-28). Attention has focused principally on mitral valve prolapse rather than on MR per se, because of the limitations of the methods of assessment of the degree of MR. However, the reported incidence of SUD in mitral valve prolapse has been highly variable (7,29). One major source of confusion concerns the definition of mitral valve prolapse, which has been inconsistent (30-32). Thus, mitral valve prolapse in these previous studies encompassed very different condi-

tions, from morphologically normal but superiorly displaced leaflets to thick myxomatous valves or flail leaflets with severe MR (7,27). As echocardiographic criteria for identifying mitral prolapse have evolved (33,34), the definition of the populations at risk in older studies is questionable and represents a limitation in the estimation of the risk of SUD. More recent data suggest that a higher degree of regurgitation in mitral valve prolapse is an important determinant of the incidence of SUD (27,35,36) and that LV volume overload is associated with a high recurrence rate of ventricular tachyarrhythmias (37).

Sudden death has been observed in the course of conservative management of severe MR (10,26). However, most clinical series reporting outcome of patients with MR observed small numbers of SUDs (10,26,27,35,36). In the largest series yet reported, 11 cases of SUD accounted for 60% of all cardiovascular deaths (10). However, this series included patients with ischemic MR. Therefore, the rate of SUD in severe organic MR has not been established. In the present study, in the context of uniformly pure organic MR of large degree (13), the rate of SUD of 1.8% per year was noteworthy in patients who were mostly asymptomatic and had little comorbidity. This rate results in approximately one-fourth of the total mortality with conservative management. Remarkably, the hazard of sudden death per year is approximately equivalent to the operative risk of valve repair (5,38). Therefore, it is essential to examine the predictability of this catastrophic complication.

Factors predisposing to SUD. In all patients in whom cardiac rhythm has been documented during an episode of SUD, the underlying substrate for SUD was ventricular tachyarrhythmia. Several reports have documented the prevalence of high grade ventricular arrhythmia in mitral valve prolapse and have inferred a causal role in SUD (27,39-43). It has been speculated that abnormal traction on papillary muscles results in arrhythmia that may culminate in SUD (7,8,44). Complex ventricular arrhythmias have also been documented in patients with isolated MR (26,45). The importance and predictive value of ventricular ectopy leading to SUD have been disputed (46-48) and may be a surrogate for reduced LV function (11,26). In our cohort, ventricular arrhythmias were documented in 6 (75%) of 8 patients who underwent Holter monitoring before SUD, but these arrhythmias were frequent in matched control subjects (49), in population-based studies (50) and in patients with valvular heart disease (51). In the absence of systematic recordings of these arrhythmias with a control group for objective comparison, causality must be considered tentative. The role of heart rate variability in the prediction of SUD deserves analysis in future studies (52).

In the present study, the presence of symptoms was a significant predictor of SUD in multivariate analysis. In the presence of severe symptoms, the yearly rate of SUD was considerable at 7.8%. However, most patients who subsequently died suddenly had no or minimal symptoms at

presentation (10,26). Another important issue is that although patients in functional class II experienced overall a higher rate of SUD than did those in class I, a similar yearly rate of SUD between these classes was noted in the absence of other risk factors. Therefore, the risk of SUD does not justify, in and by itself, making a stringent distinction between functional class II and I. In 10 of the 19 patients who presented with no or minimal symptoms, an episode of heart failure occurred before SUD. However, these patients did not have an operation because of rapid clinical improvement with medical therapy. Therefore, symptomatic progression may not always be a sufficient warning sign. Another predictor of SUD is reduced LV systolic function, mostly if it is markedly reduced with an EF <50% (26). Notwithstanding, most patients who died suddenly also had a baseline EF \geq 60% (10). Therefore, in patients with MR-FL or possibly MR due to other causes (10), SUD can occur in those who have no or few symptoms and no sign of LV dysfunction. Similarly, the predictive value of atrial fibrillation, although significant, is low. Therefore, the occurrence of this catastrophic event at a yearly rate of 0.8% in patients who are apparently doing well is important to take into account in the management strategy of patients with MR.

Clinical implications. The major question raised by the relatively high incidence of SUD in patients with MR-FL conservatively managed is whether this should lead to the recommendation of early operation even in those without severe symptoms or signs of LV dysfunction (3,23). In the absence of a randomized study, it is uncertain that early mitral valve surgery will reduce or nullify the risk of sudden cardiac death.

However, there are several arguments in favor of a role for surgery. Surgery, in the present study, was independently associated with a reduced risk of SUD ($p = 0.007$). Patients with mild MR tended to display low rates of SUD (7,29,53), whereas those with mostly severe regurgitation incurred excess mortality and SUD (2,10). These data suggest that the degree of LV volume overload that can be corrected surgically (20) is a determinant of overall and sudden mortality. Furthermore, the abnormalities of autonomic tone resulting from LV volume overload may be a predisposing factor to lethal arrhythmia (52,54), and suppressing the LV volume overload surgically results in a marked decrease in the frequency of complex ventricular arrhythmia (51). Moreover, early operation in patients with MR-FL is associated with a marked decrease in overall, and particularly cardiac, mortality (12). Finally, by minimizing the occurrence of atrial fibrillation (55), operating may also tend to prevent SUD.

Another important issue is that despite a large study group, which allowed the present study to have sufficient power to assess predictors of SUD, from a clinical point of view, a large proportion of patients who died suddenly were minimally symptomatic, were in sinus rhythm and had an

EF >60%. Therefore, individual, clinically meaningful prediction of SUD is limited. A symptomatic progression is an essential warning sign and should lead to prompt consideration of surgery (2), but because of rapid improvement with modern treatments, it is not always taken seriously.

Therefore, in our opinion, the risk of SUD with conservative management, roughly equivalent over one year to the operative risk, is one of the incentives for early operation and should be an important part of the discussion with patients when therapeutic options are considered. In future studies, the potential protective effect of surgery should be evaluated in appropriately sized prospective studies.

Study limitations. The causal link between valvular heart disease and SUD is difficult to establish. The contribution of occult CAD to the rate of SUD (14) cannot be dismissed; however, in most patients who died suddenly, no ischemic cardiac symptoms and no evidence of CAD were noted on invasive or stress tests. Autopsy studies have confirmed that SUD may occur in patients with MR without CAD (25,56). Importantly, the rate of SUD in our cohort is at least twice that observed in a similar age strata in population-based studies (0.37% per year) (57), suggesting that indeed MR-FL is linked to the observed mortality.

Antiarrhythmic medications have a proarrhythmic effect (58), which may contribute to SUD. However, only one SUD occurred in a patient treated long term with quinidine. Patients who died suddenly received less therapy with beta-blockers than did the survivors. These medications appear to have important protective effects (59), but the determination of the potential benefit of treatment will require appropriately sized clinical trials.

Conclusions. The present study of a large cohort of patients with MR-FL followed conservatively shows that SUD is relatively frequent, at 1.8% per year, and represents approximately one-fourth of the causes of death. In patients with no or minimal symptoms, sinus rhythm and normal LV function, a linearized rate of 0.8% per year is observed. Surgery is associated with a reduced incidence of SUD. Therefore, the risk of operating should be balanced against the likelihood of other complications of severe MR, in particular the risk of SUD. It is an additional concern that this complication of devastating consequence may occur in patients in sinus rhythm without symptoms or signs of LV dysfunction, and in our opinion, supports the concept of early operation.

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