Ischemic Mitral Regurgitation: Long-Term Outcome and Prognostic Implications With Quantitative Doppler Assessment

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Ischemic Mitral Regurgitation

Long-Term Outcome and Prognostic Implications With Quantitative Doppler Assessment

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Background—Myocardial infarction (MI) can directly cause ischemic mitral regurgitation (IMR), which has been touted as an indicator of poor prognosis in acute and early phases after MI. However, in the chronic post-MI phase, prognostic implications of IMR presence and degree are poorly defined.

Methods and Results—We analyzed 303 patients with previous (>16 days) Q-wave MI by ECG who underwent transthoracic echocardiography: 194 with IMR quantitatively assessed in routine practice and 109 without IMR matched for baseline age (71±11 versus 70±9 years, $P=0.20$), sex, and ejection fraction (EF, 33±14% versus 34±11%, $P=0.14$). In IMR patients, regurgitant volume (RVol) and effective regurgitant orifice (ERO) area were 36±24 mL/beat and 21±12 mm^2, respectively. After 5 years, total mortality and cardiac mortality for patients with IMR (62±5% and 50±6%, respectively) were higher than for those without IMR (39±6% and 30±5%, respectively) (both $P<0.001$). In multivariate analysis, independently of all baseline characteristics, particularly age and EF, the adjusted relative risks of total and cardiac mortality associated with the presence of IMR (1.88, $P=0.003$ and 1.83, $P=0.014$, respectively) and quantified degree of IMR defined by RVol ≥30 mL (2.05, $P=0.002$ and 2.01, $P=0.009$) and by ERO ≥20 mm^2 (2.23, $P=0.003$ and 2.38, $P=0.004$) were high.

Conclusions—In the chronic phase after MI, IMR presence is associated with excess mortality independently of baseline characteristics and degree of ventricular dysfunction. The mortality risk is related directly to the degree of IMR as defined by ERO and RVol. Therefore, IMR detection and quantification provide major information for risk stratification and clinical decision making in the chronic post-MI phase. **(*Circulation*. 2001;103:1759-1764.)**

Key Words: infarction ■ mitral valve ■ prognosis ■ regurgitation

Ischemic mitral regurgitation (IMR) is mitral regurgitation (MR) due to complications of coronary artery disease, in particular, myocardial infarction (MI), and not the fortuitous association of coronary artery disease with intrinsic valve disease such as rheumatic disease. In the acute phase of MI, IMR is frequent[1] and appears to carry an adverse prognosis.[1–3] However, the prognostic implications of IMR in the chronic post-MI phase are uncertain. In pioneering series that underscored the potential importance of IMR, patients were often included early after MI,[4] and decreased survival of patients with IMR may have been due to inclusion of acute MI.[2,3] Furthermore, MR angiographic grade was not independently predictive of survival, and only a score combining MR grade with clinical data was a weak independent predictor of outcome.[4] Therefore, the SAVE (Survival And Ventricular Enlargement) study data proved of major interest by suggesting that mild IMR was associated with high mortality.[5] However, because the study design excluded MR grade 3 or 4 and limited inclusion to 16 days after MI, the prognostic implications of IMR remain uncertain, particularly regarding specific implications of the full range of chronic IMR. Nevertheless, these pioneering series had the undisputed merit of raising the hypothesis that IMR, which affects 19% of patients after MI,[4,5] may be a marker of poor outcome, suggesting that if observed in pure, chronic, definite IMR of all degrees, such an observation may have major prognostic and therapeutic implications.

For diagnosing IMR, murmur is of limited value,[6] and objective methods are required. Angiography has been widely used[4,5] but may imply referral based on severity of presentation; in addition, it has technical limitations and cannot define valvular anatomy and cause of MR. Echocardiography is highly accurate for anatomy, but standard color flow imaging is fraught with errors in IMR.[7] However, quantitative Doppler methods have been developed[8–11] that allow quantitative grading of MR in routine clinical practice.[12]

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Hence, our aim was to analyze, in the post-MI chronic phase, the independent prognostic implications of IMR presence and degree, quantitatively assessed by Doppler echocardiography in routine practice.

Methods

Eligibility Criteria

Inclusion criteria were, first, presence of Q-wave MI on ECG, with history of MI older than 16 days before baseline assessment. The 16-day criterion was based on the SAVE study report of prognostic effect of IMR diagnosed within and not beyond 16 days after MI.[5] Second, these patients underwent transthoracic echocardiography during the same clinical evaluation in routine practice from 1990 through 1997, showing either IMR, which was quantitatively assessed, or no MR. Exclusion criteria were recent MI (≤16 days), previous cardiac surgery, papillary muscle rupture, MR due to primary organic valve disease, or associated aortic valve or congenital heart disease. Diagnosis of IMR was based on normal leaflets with enlarged annulus and was easily differentiated from organic MR, such as rheumatic disease or prolapse.

Matching Process

Patients were all post-MI and satisfied all eligibility criteria. Patients without MR were matched to those with MR for age, sex, and left ventricular (LV) ejection fraction (EF) to ensure baseline comparability of these major determinants of outcome. The matching process was computerized, blinded, and performed before any outcome information was obtained.

Follow-up was achieved for 294 patients (97%) up to 1999 or death. Medications used during follow-up were recorded if prescribed for ≥3 months. Comorbid diseases were summated as a comorbidity index.

Echocardiographic Methods

LV and left atrial (LA) dimensions were obtained by M-mode echocardiography, guided by 2D imaging. EF was visually estimated[13] in all patients and combined with calculated values[14] in 205 (68%) and used unaltered from original echocardiographic report via electronic transfer. This method has high prognostic value in our laboratory.[15] Color flow imaging was used to determine presence or absence of MR, but in all patients with MR, degree of MR was graded with quantitative measurements using at least 1 of the following 2 quantitative methods, and final results were averages of measured values:

1. Quantitative Doppler[8,9]—Mitral and aortic stroke volumes were calculated, and regurgitant volume (RVol) was the difference between these 2 stroke volumes. The effective regurgitant orifice (ERO) area was the ratio of RVol to regurgitant time velocity integral (RTVI).[16]
2. Proximal isovelocity surface area (PISA) analyzed the proximal flow convergence, and ERO was the ratio of regurgitant flow to regurgitant velocity.[10,11] RVol was the product of ERO by RTVI.

Statistical Analysis

Continuous variables are expressed as mean±SD. Group comparisons used *t* test or χ^2 test, as appropriate. Event rates after diagnosis were estimated by Kaplan-Meier method. Analysis was performed by censoring follow-up at time of cardiac surgery if eventually performed (n=45). End points were overall survival and cardiac mortality. IMR impact on outcome was analyzed in 2 ways, with presence of IMR at baseline used as the categorical determinant of survival or with quantified degree of IMR (RVol and ERO) used as continuous variables. Risk ratios (RRs) associated with previously determined thresholds[12] were defined. Other baseline predictors of survival were identified by Cox proportional hazards analysis. Variables with $P<0.10$ were tested in multivariate modeling, and presence and quantitative degree of IMR were added in final models.

We observed previously that EF decreases by 4% after surgical correction of IMR. To examine the hypothesis that EF is overestimated in patients with IMR, we analyzed the effect of IMR on mortality with EF of patients in whom IMR decreased by 4 points and that of patients with no change in IMR. This analysis was also repeated with EF of patients in whom IMR decreased by 8 and 10 points. $P<0.05$ was considered significant.

Results

Baseline Characteristics

Eligibility criteria were fulfilled by 303 patients evaluated in the chronic post-MI stage: 109 without MR and 194 with IMR quantitatively assessed in routine practice. The degree of MR was determined by quantitative Doppler in 30 patients, by the PISA method in 146, and by both techniques in 18. Diagnosis of previous MI was confirmed by electrocardiography in all 303 patients (100%). Echocardiography detected regional wall motion abnormalities in 301 patients (99%) (single territory in 173 [57%], multiple territories in 128 [42%] with scar in 49 [16%] patients). Nuclear perfusion studies were available for 125 patients (41%) and indicated previous MI in 117 (94%). Of 185 patients who ultimately underwent coronary angiography, all had stenoses ≥70%, and only 83 (45%) had single-vessel disease, with no significantly different distribution between patients with and without IMR ($P=0.08$). Baseline characteristics of patients with and without IMR are compared in Table 1. Most risk factors were similar for the 2 groups. Despite identical age and EF, patients with IMR had more symptoms, more atrial fibrillation, more LV and LA enlargement, lower blood pressure, and shorter deceleration time. Mean time between MI and index echocardiogram was 86±90 months, similar for patients with and without IMR ($P=0.17$), and MI was less often anterior with IMR.

Impact of MR on Overall Survival

During total conservative follow-up of 817 patient-years, 118 deaths occurred.

IMR Presence

Patients with IMR experienced higher long-term mortality rates than those without MR (62±5% versus 39±6% at 5 years, $P\leq0.001$; univariate RR [95% CI], 2.32 [1.56 to 3.52]) (Figure 1).

In multivariate analysis, independent baseline predictors of overall survival were age ($P<0.001$), EF ($P=0.008$), New York Heart Association (NYHA) class III or IV ($P=0.003$), diabetes ($P=0.044$), atrial fibrillation ($P=0.023$), and 1/creatinine ($P=0.006$). When IMR presence was added into the model, it negatively and independently influenced outcome, with adjusted RR of 1.88 (Table 2).

Notably, IMR remained independently predictive of survival, adjusting for diastolic dysfunction (mitral deceleration time) ($P=0.027$), comorbidity index ($P=0.0026$), extent of coronary disease on coronary angiography ($P=0.016$), and for all variables showing baseline differences between patients with and without IMR (all $P<0.003$). The assumption that patients with IMR had a "true" EF decreased by 4%, 8%,

TABLE 1. Comparison of Baseline Characteristics of Patients With IMR and Those Without IMR

	Patients With IMR (n=194)	Patients Without IMR (n=109)	*P*
Age, y	71±11	70±9	0.20
Men	135 (70%)	86 (79%)	0.08
NYHA class III–IV	92 (47%)	38 (35%)	0.034
Atrial fibrillation	30 (15%)	5 (5%)	0.004
Chest pain	61 (31%)	33 (30%)	0.81
Systolic blood pressure, mm Hg	132±26	141±26	0.004
Diabetes mellitus	51 (26%)	29 (27%)	0.95
Hypertension history	103 (53%)	47 (43%)	0.10
Smoking	106 (55%)	72 (66%)	0.066
Hypercholesterolemia	92 (47%)	52 (48%)	0.96
Anterior MI	40 (21%)	44 (40%)	0.001
EF, %	33±14	34±11	0.14
LVS, mm/m^2	28±6	26±6	0.003
LVD, mm/m^2	33±5	31±5	<0.001
LA, mm/m^2	27±7	22±4	<0.001
Mitral deceleration time, ms	169±58	225±63	<0.001

Values are mean±SD or n (%). LVD and LVS indicate end-diastolic and end-systolic left ventricular diameters, respectively; LA, left atrial diameter.

or even 10% did not eliminate the IMR effect on overall mortality. Adjusted RRs associated with IMR presence under these assumptions were, respectively, 1.79, 1.66, and 1.60, with probability values of 0.008, 0.039, and 0.049.

IMR Degree

The RVol and ERO in IMR patients were 36±24 mL/beat and 21±12 mm^2, respectively. Patients with RVol ≥30 mL demonstrated higher mortality than those with RVol <30 mL (65±7% versus 56±9% at 5 years, $P<0.001$, RR=1.13 per 10-mL RVol increase) (Figure 2). Patients with ERO ≥20 mm^2 displayed higher 5-year mortality than those with ERO <20 mm^2 (71±9% versus 53±8%, $P<0.001$, RR=1.40 per 10-mm^2 ERO increase) (Figure 3). Adjusted for independent predictors of mortality, RVol and ERO independently and unfavorably influenced mortality (Tables 3 and 4).

In analysis limited to patients with MR, ERO remained independently predictive of survival, with similar RR (1.33 per 10-mm^2 increase, $P<0.001$). Adjusted for extent of coronary disease by coronary angiography, ERO remained independently predictive of survival, with similar RR (1.37 per 10-mm^2 increase, $P<0.001$). In models including classic clinical or echocardiographic signs of MR, ERO and RVol remained significantly predictive of excess mortality (all $P<0.05$), and no additional significant predictor of survival was noted. When EF in IMR was decreased by 4%, 8%, or 10%, the adjusted RRs associated with ERO ≥20 mm^2 were, respectively, 2.01, 1.81, and 1.72 ($P=0.014$, 0.046, and 0.077). In multivariate models with both ERO and RVol, ERO remained independently determinant of excess mortality ($P=0.017$), but RVol tended to be less significant ($P=0.13$).

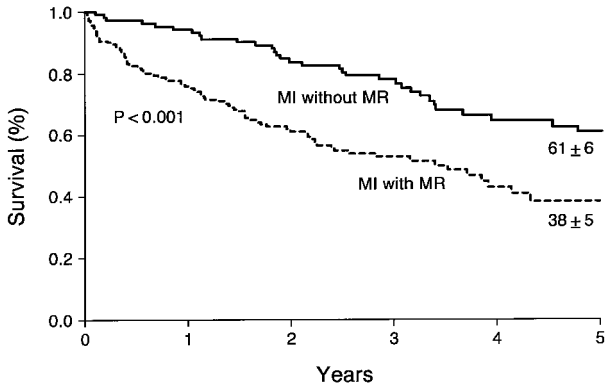

Figure 1. Survival (±SE) after diagnosis according to presence of IMR.

Subgroup Analysis

Excess mortality with IMR presence remained significant when analysis was restricted to males ($P<0.001$) or females ($P=0.071$), to patients younger ($P=0.010$) or older ($P=0.005$) than 75 years, and to patients in sinus rhythm ($P=0.002$), with diabetes ($P=0.041$) or without

TABLE 2. Multivariate Predictors of Overall Survival With IMR Used as a Categorical Variable

	RR*	95% CI	*P*
Age	1.03	1.02–1.05	<0.001
EF	0.98	0.96–0.99	0.020
NYHA class III–IV	1.87	1.26–2.77	0.002
Diabetes mellitus	1.50	1.01–2.23	0.046
Atrial fibrillation	1.61	1.00–2.61	0.052
1/Creatinine	0.44	0.20–0.93	0.033
MR	1.88	1.23–2.86	0.003

*RRs are expressed per unit of each determinant.

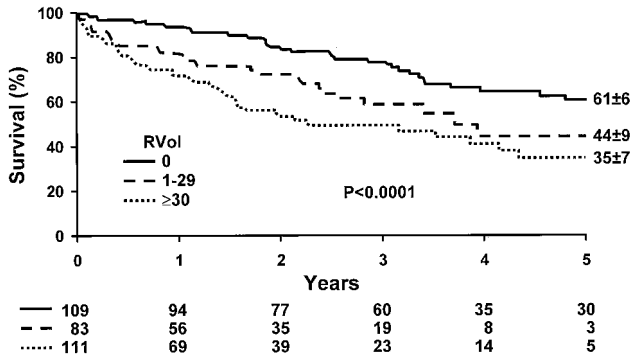

Figure 2. Survival (±SE) after diagnosis according to degree of MR as graded by RVol ≥30 mL/beat or <30 mL/beat. Numbers at bottom indicate patients at risk for each interval.

diabetes ($P<0.001$), and with mitral valve deceleration time shorter ($P=0.064$) or longer ($P=0.064$) than 170 ms. IMR was associated with excess mortality with EF ≥40% (RR=4.40, $P<0.001$) or <40% (RR=1.84, $P=0.0065$) even after adjustment for age, sex, EF, and NYHA class ($P=0.0036$ and 0.018, respectively). Similarly, IMR was associated with excess mortality with NYHA class I to II (RR=2.19, $P=0.007$) or III to IV (RR=2.15, $P=0.005$) even after adjustment for age, sex, and EF (both $P<0.04$).

Impact of IMR on Cardiac Mortality

Of 118 deaths, 91 (77%) were cardiovascular. Patients with IMR experienced higher cardiac mortality than those without MR (50±6% versus 30±5% at 5 years, $P\leq0.001$; RR [95% CI], 2.30 [1.47 to 3.72]).

In multivariate analysis, independent predictors of cardiac death were age ($P<0.001$), EF ($P=0.004$), NYHA class III to IV ($P=0.021$), diabetes ($P=0.048$), chest pain at presentation ($P=0.050$), atrial fibrillation ($P=0.019$), and 1/creatinine ($P=0.085$). IMR independently influenced cardiac mortality (adjusted RR [95% CI], 1.83 [1.13 to 2.96], $P=0.014$). When EF was decreased in IMR by 4%, 8%, or 10%, the adjusted RRs associated with IMR presence were, respectively, 1.76, 1.60, and 1.53.

Cardiac death at 5 years was 52±7% with RVol ≥30 mL and 46±9% with RVol <30 mL ($P<0.001$). Adjusted RRs (95% CIs) of cardiac death compared with patients without

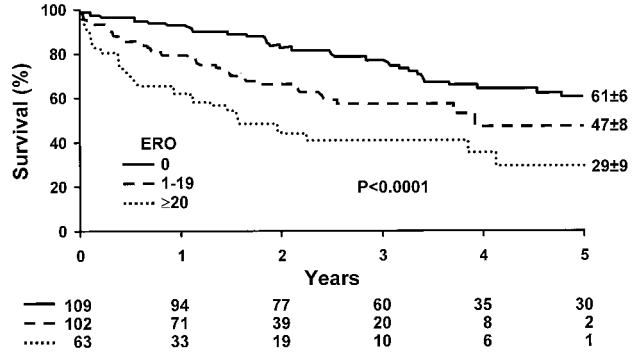

Figure 3. Survival (±SE) after diagnosis according to degree of MR as graded by ERO ≥20 mm² or <20 mm². Numbers at bottom indicate patients at risk for each interval.

TABLE 3. Multivariate Predictor of Overall Survival Factoring in the Impact of MR Severity Expressed as RVol

	RR	95% CI	*P*
Age	1.03	1.01–1.05	<0.001
EF	0.98	0.97–1.00	0.030
NYHA class III–IV	1.88	1.27–2.79	0.002
Diabetes mellitus	1.48	0.99–2.20	0.054
Atrial fibrillation	1.62	1.00–2.62	0.049
1/Creatinine	0.44	0.21–0.94	0.034
RVol <30 mL	1.64	0.98–2.75	0.059
RVol ≥30 mL	2.05	1.30–3.23	0.002

MR remained similar to those calculated for total mortality: 1.58 (0.89 to 2.86), $P=0.13$ for RVol <30 mL and 2.01 (1.19 to 3.38), $P=0.009$ for RVol ≥30 mL, respectively. At 5 years, cardiac death with ERO <20 mm² and ≥20 mm² was 43±9% and 63±10%, respectively ($P<0.001$). The adjusted RR (95% CI) of cardiac death compared with patients without MR was 1.56 (0.88 to 2.76) for ERO <20 mm² ($P=0.13$) and 2.38 (1.31 to 4.31) for ERO ≥20 mm² ($P=0.004$).

Discussion

The present study showed that compared with patients of similar age, sex, history of MI, and EF, patients with ischemic MR, that is, MR due to a previous MI (>16 days), have a marked excess mortality due to excess cardiac mortality. This excess mortality was observed independently of all baseline characteristics and in all subgroups. A higher degree of quantitatively defined IMR, in particular, a larger ERO of IMR (≥20 mm²), is directly and independently associated with a higher mortality risk. These data underscore the importance of IMR presence and of quantitatively defined higher IMR degree as markers of poor outcome in the post-MI chronic phase. These data also underscore the importance of Doppler echocardiography in defining IMR presence and in quantifying its degree for risk stratification of post-MI patients.

MI and MR

IMR is defined as MR due to coronary disease (and not fortuitously associated with it). IMR is caused by ischemic myocardial alterations despite normal mitral leaflets and chordae. The hyperacute papillary muscle rupture in acute MI

TABLE 4. Multivariate Predictor of Overall Survival Factoring in Impact of MR Severity Expressed as ERO

	RR	95% CI	*P*
Age	1.03	1.01–1.05	0.002
EF	0.97	0.96–0.99	0.006
NYHA class III–IV	1.78	1.17–2.71	0.007
Diabetes mellitus	1.57	1.04–2.37	0.033
Atrial fibrillation	1.37	0.80–2.36	0.25
1/Creatinine	0.50	0.22–1.13	0.096
ERO <20 mm²	1.65	1.00–2.71	0.049
ERO ≥20 mm²	2.23	1.31–3.79	0.003

is well defined, requiring urgent surgery.[17] Conversely, prognosis and management of IMR not due to papillary muscle rupture are poorly defined. The mechanisms leading to development of IMR are debated,[18] but recent reports suggest that LV remodeling and papillary muscle displacement may play an important role.[19,20] Irrespective of mechanistic issues, the presence of IMR in acute[1–3] or recent (≤16 days)[5] phases of MI is associated with adverse prognosis.

Conversely, prognosis of MR in the post-MI chronic phase (>16 days)[5] has not been specifically analyzed. Pioneering series from the SAVE[5] and Duke databases[4] suggested that IMR may be associated with poor outcome. However, these series included patients in acute or recent post-MI phases.[4,5] Furthermore, uncertainties concerning the effect of IMR on survival stemmed from exclusion of severe MR[5] or from the combination of MR and clinical severity scoring.[4] Therefore, we analyzed the specific prognostic impact of MR in the chronic post-MI phase (>16 days) using routine practice Doppler for defining IMR to avoid selection bias[4,5] and to characterize valvular anatomy. To avoid disputable adjustment,[4] we matched patients with and without IMR for age, sex, history of MI, and EF. To avoid overestimation by color flow imaging,[7] quantitative methods used extensively in our laboratory[9,10,16] measured IMR degree.

The present study demonstrated that in the chronic post-MI phase, IMR presence is associated with excess mortality of cardiac cause. Although patients without MR exhibited notable mortality because of their history of MI with LV dysfunction,[21] those with IMR and identical EF displayed marked excess mortality. Even when the potential artificial EF increase in IMR due to regurgitation was taken into account, IMR presence remained an independent marker of marked excess mortality. Importantly, IMR is associated with more severe symptoms and pulmonary hypertension.[22] However, IMR remains an independent predictor of excess mortality in patients with and without baseline symptoms and with adjustment for all baseline predictors of survival,[4] which is confirmed by the independent association of IMR with cardiac mortality. Importantly, IMR is not a mere marker, but rather its detrimental consequences increase with its degree.

Degree of IMR and Outcome

Higher RVol and ERO are independently predictive of greater mortality after diagnosis. With ERO ≥20 mm^2, risk is considerable (adjusted RR 2.23 versus patients without MR). The link between higher IMR degree and greater mortality is independent of EF and involves several mechanisms. IMR is a major determinant of filling pressures[22] and can directly cause heart failure, independently of but potentiated by the frequent association of restrictive LV filling[23] and its related worse hemodynamics[22] and outcome.[23] Also, volume overload of IMR stimulates LV remodeling,[24] leading to long-term mortality after MI.[25]

These mechanistic rationales support the present results with larger degrees of IMR associated with worse survival independently of background EF decrease. The seminal, provocative observation of SAVE[5] that even mild IMR is associated with poor outcome was limited by exclusion of severe MR. The present observation is the first to report that the quantification of IMR, in particular as ERO area, has major consequences for outcome. Of note, ERO is a stronger prognostic indicator than RVol. A large ERO can lead to large regurgitant kinetic energy (large RVol) but also to potential energy, with low RVol but high LA pressure and V wave. The latter hemodynamic situation may be deceiving without quantitative measurements, simulating a mild regurgitation but nevertheless having severe outcome consequences.[22]

Of note, ERO ≥20 mm^2 is associated with marked excess mortality in IMR, whereas in organic MR, ERO ≥40 mm^2 is considered severe,[12] probably owing to different LV and LA function and compliance. Nevertheless, ERO ≥20 mm^2 defines IMR with severe consequences consistently with previous observations,[22] allowing risk stratification of patients with previous MI.

Clinical Implications

The present data underscore the importance of detecting and quantifying (by Doppler echocardiography) IMR after MI. The independent link between RVol and ERO measured in routine practice and subsequent survival emphasizes the clinical relevance of these indices.

A high degree of IMR is associated with considerable excess mortality, suggesting that aggressive therapeutic interventions should be considered. The decrease in IMR caused by vasodilators[26] is an important part of their clinical effect.[5,27] The roles of isolated revascularization[28,29] or associated mitral repair[30] have not been well defined. Because of the considerable excess mortality observed with ERO ≥20 mm^2, an appropriately sized clinical trial is warranted to determine whether mitral repair may improve the long-term outcome of these patients.

Limitations of the Study

MR after MI cannot be randomized, and baseline differences are expected between patients with and without IMR,[4] but matching ensures comparability for major variables such as age, sex, and EF. Adjustment for other variables (eg, symptoms or atrial fibrillation) or analysis of subgroups defined with these variables confirmed that IMR was an independent determinant of excess mortality. Also, no difference in treatment with aspirin, β-blockers, or statins was noted (all $P>0.20$), and patients with IMR received ACE inhibitors more often than those without IMR (71% versus 59%, $P=0.035$). Therefore, the excess mortality of IMR cannot be attributed to medical therapy. Furthermore, mortality was related to IMR degree even when analysis was restricted to patients with IMR ($P<0.001$), and in patients without MR (39% at 5 years), the mortality rate was similar to previous studies,[1,2] in particular SAVE,[5] showing that the control group did not affect present study results.

The association of IMR with excess mortality may reflect more severe LV alterations than occur in those without MR. Such issues will be addressed when a clinical trial demonstrates that surgical correction of IMR improves survival. However, IMR was predictive of overall and cardiac mortality in all subgroups and independently of EF, even after EF was decreased by 4%, 8%, or even 10% in patients with IMR,

suggesting that assessment of survival improvement provided by treatment of IMR is necessary.

Conclusions

The present study demonstrated that in the post-MI chronic phase, independently of all baseline characteristics, the presence and degree of IMR, quantified by Doppler echocardiography, both have major prognostic implications. The excess mortality, which was considerable for ERO $\geq$20 mm^2, suggests that quantification of MR in the post-MI chronic phase is essential for risk stratification. Furthermore, the high risk associated with IMR suggests that such patients should be managed actively and that all therapeutic options of medical and surgical treatment should be considered promptly.

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