

Ischemic Mitral Regurgitation and Risk of Heart Failure After Myocardial Infarction

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Background: The development of ischemic mitral regurgitation (MR) after myocardial infarction may impose hemodynamic load during a period of active left ventricular remodeling and promote heart failure (HF). However, few data are available on the relationship between ischemic MR and the long-term risk for HF.

Methods: We prospectively studied 1190 patients admitted for acute myocardial infarction. Mitral regurgitation was assessed by echocardiography and was considered mild, moderate, and severe when the regurgitant jet area occupied less than 20%, 20% to 40%, and greater than 40% of the left atrial area, respectively. The median duration of follow-up was 24 months (range, 6-48 months).

Results: Mild and moderate or severe ischemic MR was present in 39.7% and 6.3% of patients, respectively. Af-

ter adjusting for ejection fraction and clinical variables (age, sex, Killip class, previous infarction, hypertension, diabetes mellitus, anterior infarction, ST-elevation infarction, and coronary revascularization), compared with patients without MR, the hazard ratios for HF were 2.8 (95% confidence interval [CI], 1.8-4.2; $P < .001$) and 3.6 (95% CI, 2.0-6.4; $P < .001$) in patients with mild and moderate or severe ischemic MR, respectively. The adjusted hazard ratios for death were 1.2 (95% CI, 0.8-1.8; $P = .43$) and 2.0 (95% CI, 1.2-3.4; $P = .02$) in patients with mild and moderate or severe MR, respectively.

Conclusions: There is a graded independent association between the severity of ischemic MR and the development of HF after myocardial infarction. Even mild ischemic MR is associated with an increase in the risk of HF.

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HEART FAILURE (HF) IS AN emerging worldwide epidemic that is affected by acute coronary syndromes.^{1,2} The development of late HF in patients after myocardial infarction (MI) is particularly ominous because these patients have a several-fold increase in the risk of death compared with other survivors of MI.³⁻⁵

A better understanding of the factors involved in the eventual development of HF in survivors of MI will better identify high-risk patients who are likely to benefit from implementation of preventive measures and to generate potential mechanistic information.² Several possible factors contribute to HF after acute MI, including the loss of functioning myocytes, development of myocardial fibrosis, and subsequent left ventricular remodeling. The resulting chamber dilatation and neurohormonal activation lead to progressive dysfunction of the remaining viable myocardium. Considerable attention has been given to mechanisms that affect loading conditions as

pathophysiological mechanisms for progression of HF.³⁻⁵ In this context, the development of ischemic mitral regurgitation (MR) may impose hemodynamic load during a period of active left ventricular remodeling.

Ischemic MR is recognized as a predictor of increased mortality following MI.⁶⁻⁹ However, few data are available regarding the relationship between ischemic MR and the risk for long-term development of HF.^{10,11} The objective of the present study was to prospectively determine the role of ischemic MR as a predictor of HF among survivors of acute MI.

METHODS

PATIENTS

The study cohort consisted of patients enrolled in a prospective observational study designed to determine predictors of postinfarction HF. All patients admitted to the intensive coronary care unit with acute MI were eligible for enrollment in the study if they had a

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diagnosis of MI using American College of Cardiology criteria,¹² and if they had survived the index event. Exclusion criteria included (1) patients with previous HF, (2) patients who underwent mitral valve surgery during the index hospitalization, and (3) patients with organic MR, defined as an intrinsic valve disease (including severe calcific mitral valve disease, mitral valve prolapse or flail leaflet, healed endocarditis, or chronic rheumatic disease). The investigational review committee on human research approved the study protocol.

STUDY END POINTS

The primary end points of the study were (1) all-cause mortality and (2) development of HF, defined as readmission to the hospital for the management of HF (the presence of new symptoms of dyspnea or edema with ≥ 1 concurrent signs, including ventricular gallop rhythm, bilateral posttussive rales in at least the lower third of the lung fields, elevated venous pressure, or pulmonary venous congestion seen on x-ray film with interstitial or alveolar edema). The diagnosis of HF was confirmed using hospital records and discharge summaries. Following hospital discharge, clinical end point information was acquired by reviewing the national death registry and by contacting each patient individually and independently reviewing the hospital course for major clinical events if the patient had been rehospitalized.

ECHOCARDIOGRAPHIC EXAMINATION

Analysis of left ventricular function and presence and degree of MR was carried out by one of us (D.A., J.L., D.M., S.R., or Y.A.) without knowledge of the patient outcome. Mitral regurgitation was sought from the parasternal long axis, apical 4- and 2-chamber, apical long axis, and subcostal views. Mitral regurgitation was graded by color Doppler flow mapping, jet eccentricity, and integrating jet expansion within the left atrium (jet area and atrial area).^{8,13} Mitral regurgitation was considered mild when the regurgitant jet area occupied less than 20% of the left atrial area in the absence of a wall jet, moderate in patients with a jet area between 20% and 40%, and severe in patients in whom the jet area was greater than 40% of the left atrial area.^{8,14} Mitral regurgitation was classified into 1 of the following 3 categories: no MR (including trace MR), mild ischemic MR, and moderate or severe ischemic MR. Interobserver agreement of MR severity was determined by use of the κ statistic among 50 randomly selected patients. Left ventricular ejection fraction (LVEF) was classified as normal ($\geq 55\%$), mildly reduced (45%-54%), moderately reduced (30%-44%), or severely reduced ($<30\%$).¹⁵

STATISTICAL ANALYSIS

Data are expressed as mean \pm SD. The baseline characteristics and echocardiographic variables of the study groups were compared using analysis of variance, with posttest for linear trend. The linear-by-linear χ^2 test was used to compare noncontinuous variables.

Survival curves were constructed using the Kaplan-Meier method, and comparisons were made using the log rank test. Multivariate Cox proportional hazards modeling was used to determine the relationship between ischemic MR severity and admission for the treatment of HF. The following known predictors of the development of HF in survivors of MI⁴ were forced into the model: age, baseline heart rate, Killip class at admission, previous MI, history of hypertension and diabetes mellitus (DM), and LVEF (stratified as normal, mildly reduced, moderately reduced, or severely reduced¹⁵). Other potential predictors

were considered (sex, anterior infarction, ST-elevation infarction, coronary revascularization, and use of reperfusion therapy) if they demonstrated an association with HF on univariate analysis ($P < .1$). Because recurrent MI increases the risk for HF,⁴ worsens previously existing MR, and leads to the development of new ischemic MR, Cox proportional hazards regression analyses were performed censoring the data to the time of recurrent infarction. Additional analyses were performed in which recurrent infarction was included as a time-dependent covariate in the Cox proportional hazards model.

Cox proportional hazards modeling was also performed to determine the relationship between ischemic MR and mortality. Left ventricular ejection fraction and clinical variables believed to have clinical importance¹⁶ (age, sex, smoking status, Killip class at admission, previous infarction, anterior infarction, baseline serum creatinine level, use of reperfusion therapy, coronary revascularization, and history of DM and hypertension) were included in a stepwise multivariate model.

Our analysis also focused on the possible interaction between LVEF and the severity of ischemic MR. The existence of an interaction was assessed using a Cox proportional hazards regression model incorporating terms for the main effect of ischemic MR, the main effect of LVEF, and the interaction between LVEF and ischemic MR.

The c statistic was used to evaluate the incremental additive information associated with the MR variable for the HF end point.¹⁷ Multivariate Cox proportional hazards regression models were constructed for clinical, clinical plus LVEF, and clinical plus LVEF plus MR variables. The discriminant accuracy of each model was quantified in terms of the c statistic, and the difference between the various models (representing the increment in prognostic power) was calculated using the method described by DeLong et al.¹⁸ Differences were considered statistically significant at the 2-sided $P < .05$ level. Statistical analyses were performed using SPSS software version 12.0 (SPSS Inc, Chicago, Ill) and MedCalc version 7.3 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Between July 1, 2001, and June 30, 2005, 1592 patients who were willing to participate were identified for further evaluation. Four hundred two patients were excluded because of inadequate quality of the echocardiogram ($n = 132$), early in-hospital death ($n = 130$), previous HF ($n = 100$), organic MR ($n = 35$), and mitral valve surgery during the index hospitalization ($n = 5$). The study population consisted of the 1190 remaining patients.

Echocardiography was performed during the hospital stay at a median of 2 days (interquartile range, 1-3 days) after admission. The agreement in MR grading between echocardiogram readers was high (Cohen κ , 0.83; 95% confidence interval [CI], 0.70-0.95). Mild ischemic MR was present in 473 patients (39.7%) and moderate or severe ischemic MR in 75 patients (6.3%) (67 patients with moderate ischemic MR and 8 patients with severe ischemic MR). The clinical characteristics of patients according to the severity of MR are given in **Table 1**. Patients with higher degrees of MR were more likely to be older and female, had higher baseline serum creatinine levels, and were more likely to have had a previous MI and to have a history of smoking, DM, and hypertension; they were admitted with higher heart rates, higher Killip class, and lower LVEF. There was less use

Table 1. Baseline Patient Characteristics According to Mitral Regurgitation (MR) Severity*

Characteristic	No or Trivial MR (n = 642)	Mild MR (n = 473)	Moderate or Severe MR (n = 75)	P for Trend
Age, mean ± SD, y	58 ± 12	64 ± 12	69 ± 13	<.001
Female sex	107 (16.7)	123 (26.0)	30 (40.0)	<.001
Serum creatinine level, mean ± SD, mg/dL	1.0 ± 0.6	1.1 ± 0.4	1.3 ± 0.5	<.001
Prior myocardial infarction	94 (14.6)	127 (26.8)	27 (36.0)	<.001
Diabetes mellitus	163 (25.4)	148 (31.3)	28 (37.3)	.005
Current smoker	85 (13.2)	104 (22.0)	19 (25.3)	<.001
Hypertension	287 (44.7)	266 (56.2)	56 (74.7)	<.001
Anterior infarction	307 (47.8)	196 (41.4)	25 (33.3)	.004
Killip class on admission, mean ± SD	1.2 ± 0.6	1.4 ± 0.8	1.8 ± 0.9	<.001
Ejection fraction, mean ± SD	47 ± 12	43 ± 12	39 ± 11	<.001
Percutaneous revascularization†	228 (35.6)	166 (35.1)	16 (21.3)	.09
Medications at discharge				
Antiplatelet agents	633 (98.6)	463 (97.9)	72 (96.0)	.12
ACE inhibitors or ARBs	540 (84.1)	395 (83.5)	63 (84.0)	.85
β-Blockers	557 (86.8)	394 (83.2)	57 (76.0)	.01
Statins	44 (6.9)	293 (61.9)	45 (60.0)	.009

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers.

SI conversion factor: To convert serum creatinine levels to micromoles per liter, multiply by 88.4.

*Data are given as number (percentage) unless otherwise indicated.

†During hospital course.

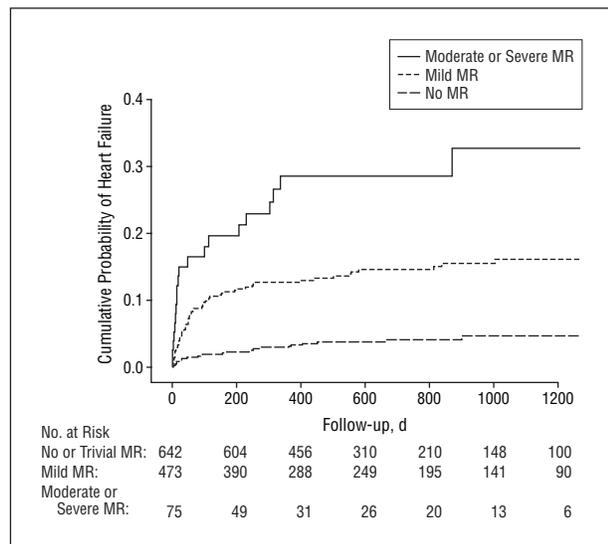


Figure 1. Kaplan-Meier plot showing the crude cumulative incidence of admission for the treatment of heart failure according to the degree of ischemic mitral regurgitation (MR). $P < .001$ by log rank test for the overall comparison among the groups.

of statins and β-blockers among patients with higher degrees of MR.

MR AND HF

The median duration of follow-up after hospital discharge was 24 months (range, 6-48 months). During follow-up, 137 patients (11.5%) were readmitted for the treatment of HF, with 113 HF events (9.5%) occurring without a preceding recurrent infarction. Admission for HF occurred after an episode of recurrent infarction in 24 patients. The incidences of recurrent infarction were 0.6%, 3.6%, and 4.0% among patients with no MR, mild MR, and moderate or severe MR, respectively ($P = .001$).

Kaplan-Meier analysis showed a graded increased probability for HF during follow-up with increasing degrees of ischemic MR (**Figure 1**).

Table 2 gives the results of the model examining the relationship between the level of ischemic MR and the risk of HF. There was a graded association between increasing severity of MR and risk of HF. Even mild MR was associated with increased risk for future HF after adjustments for LVEF and known clinical predictors of HF (Table 2, model 1). Other independent predictors of HF in the model included age (hazard ratio [HR], 1.3 [95% CI, 1.1-1.5] per 10 years; $P = .001$), presence of diabetes (HR, 1.5 [95% CI, 1.1-2.1]; $P = .04$), Killip class higher than I at admission (HR, 2.2 [95% CI, 1.5-3.2]; $P < .001$), moderately reduced LVEF (HR, 2.7 [95% CI, 1.8-4.2]; $P < .001$), and severely reduced LVEF (HR, 3.5 [95% CI, 2.0-6.1]; $P < .001$).

The *c* statistic of the model containing only clinical variables (0.769 ± 0.027) increased significantly when LVEF data were added to the model (0.796 ± 0.026 [$P = .01$] compared with the model containing clinical variables). The overall predictive performance of the model elaborated with MR data further increased the predictive performance of the model (0.826 ± 0.022 [$P = .02$] compared with the model containing LVEF and clinical variables).

Similar results were obtained after adjusting for recurrent infarction during follow-up as a time-dependent variable (Table 2, model 2). Finally, we calculated HRs for HF after excluding patients with evidence of HF (Killip class >I at admission) during the hospital course ($n = 260$). Using patients without MR as the reference group, the adjusted HRs for HF were 2.9 (95% CI, 1.5-5.7; $P = .001$) in patients with mild MR and 4.6 (95% CI, 2.0-10.6; $P < .001$) in patients with moderate or severe MR.

Table 2. Unadjusted and Adjusted Cox Proportional Hazards Model for Admission for Heart Failure According to Severity of Mitral Regurgitation (MR)*

MR Severity	No. of Patients	No. (%) of Events	Unadjusted†	Adjusted for Clinical Variables‡	Adjusted for LVEF and Clinical Variables‡
Model 1					
None or trivial	642	20 (3.1)	1.0	1.0	1.0
Mild	473	67 (14.2)	3.7 (2.4-5.8)	2.9 (1.9-4.5)	2.8 (1.8-4.2)
Moderate or severe	75	26 (34.7)	8.4 (4.7-15.0)	4.4 (2.5-7.7)	3.6 (2.0-6.4)
Model 2					
None or trivial	642	23 (3.6)	1.0	1.0	1.0
Mild	473	84 (17.8)	4.0 (2.6-6.1)	2.8 (1.8-4.3)	2.7 (1.7-4.1)
Moderate or severe	75	30 (40.0)	8.4 (4.9-14.5)	4.4 (2.5-7.9)	3.8 (2.1-6.7)

Abbreviation: LVEF, left ventricular ejection fraction.

*Data are given as hazard ratio (95% confidence interval) unless otherwise indicated. The final models were adjusted for age, sex, LVEF, Killip class at admission, previous infarction, anterior infarction, ST-elevation infarction, coronary revascularization, and history of hypertension and diabetes mellitus. In model 1, patients (n = 24) were censored if recurrent infarction occurred before heart failure. Model 2 was also adjusted for recurrent infarction as a time-dependent variable.

†P < .001 for trend for all.

MR AND MORTALITY

During the follow-up period, 131 patients (11.0%) died. Among patients who died during follow-up, the frequency of readmission for HF before death increased with higher degrees of ischemic MR (16.6%, 40.9%, and 47.8% in patients without MR, patients with mild MR, and patients with moderate or severe MR, respectively; $P < .001$).

Kaplan-Meier estimates indicated an increased probability of death during follow-up with greater severity of ischemic MR (**Figure 2**). In a multivariate Cox proportional hazards regression model, moderate or severe MR was independently associated with an increased adjusted risk for mortality (**Table 3**).

MR AND COMBINED ADVERSE EVENTS

Event rates for the combined end point of HF and death according to LVEF and degree of MR are shown in **Figure 3A**. In patients without ischemic MR or with mild MR, there was a graded increase in HF or death with decreasing LVEF. However, in patients with moderate or severe MR, event rates were high regardless of LVEF.

In a Cox proportional hazards regression analysis, there was a significant interaction between LVEF and moderate or severe ischemic MR in an unadjusted model containing only the main effects of LVEF and ischemic MR severity ($P = .01$) and in the adjusted model ($P = .03$), such that the relative risk for the combined end point of HF and death was higher in patients with preserved LVEF. Therefore, subsequent analyses were performed after dividing the study population into 6 groups based on the severity of ischemic MR and the presence of preserved ($\geq 45\%$) or reduced LVEF. Figure 3B shows that at each level of ischemic MR severity the event rate was higher among patients with reduced LVEF. However, within the group of patients with reduced LVEF, the HR for the combined end point of HF and death in patients with

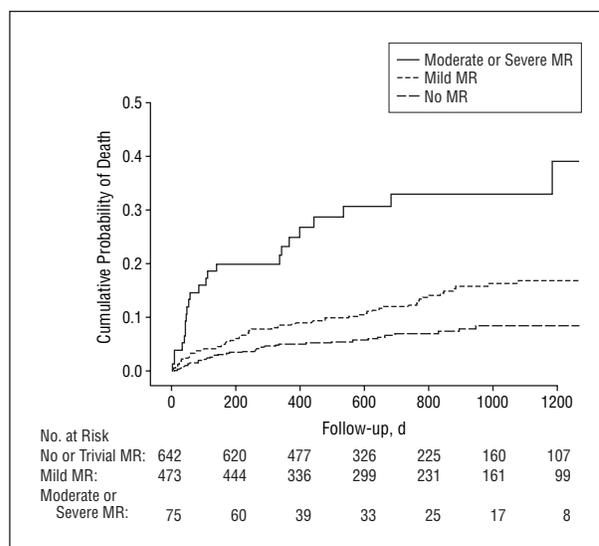


Figure 2. Kaplan-Meier plot showing the crude cumulative incidence of death according to the degree of ischemic mitral regurgitation (MR). $P < .001$ by log rank test for the overall comparison among the groups.

moderate or severe ischemic MR compared with patients without ischemic MR was 2.2 (95% CI, 1.3-3.6; $P = .004$), whereas in patients with preserved LVEF, the HR for HF or death associated with the presence of moderate or severe MR was 4.1 (95% CI, 1.8-9.4; $P = .001$).

COMMENT

In the present study, we sought to prospectively determine whether the severity of ischemic MR in survivors of acute MI provided prognostic information with regard to HF and death following hospital discharge. We demonstrate a positive graded association between the severity of MR and the long-term development of HF and all-cause mortality. Even mild MR was associated with an increase in the risk of HF. Mitral regurgitation severity added independent and incremental

Table 3. Unadjusted and Adjusted Cox Proportional Hazards Model for All-Cause Mortality According to Severity of Mitral Regurgitation (MR)*

MR Severity	No. of Patients	No. (%) of Events	Unadjusted		Adjusted for Clinical Variables		Adjusted for LVEF and Clinical Variables	
			HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
None or trivial	642	42 (6.5)	1.0	<.001†	1.0	.003†	1.0	.03†
Mild	473	66 (14.0)	2.0 (1.4-3.0)	<.001	1.3 (0.9-2.0)	.20	1.2 (0.8-1.8)	.43
Moderate or severe	75	23 (30.7)	5.5 (2.3-9.1)	<.001	2.5 (1.3-3.9)	.001	2.0 (1.2-3.4)	.02

Abbreviations: CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.

*The final model was adjusted for age, sex, LVEF, Killip class at admission, previous infarction, anterior infarction, ST-elevation infarction, coronary revascularization, and history of hypertension and diabetes mellitus.

†For trend.

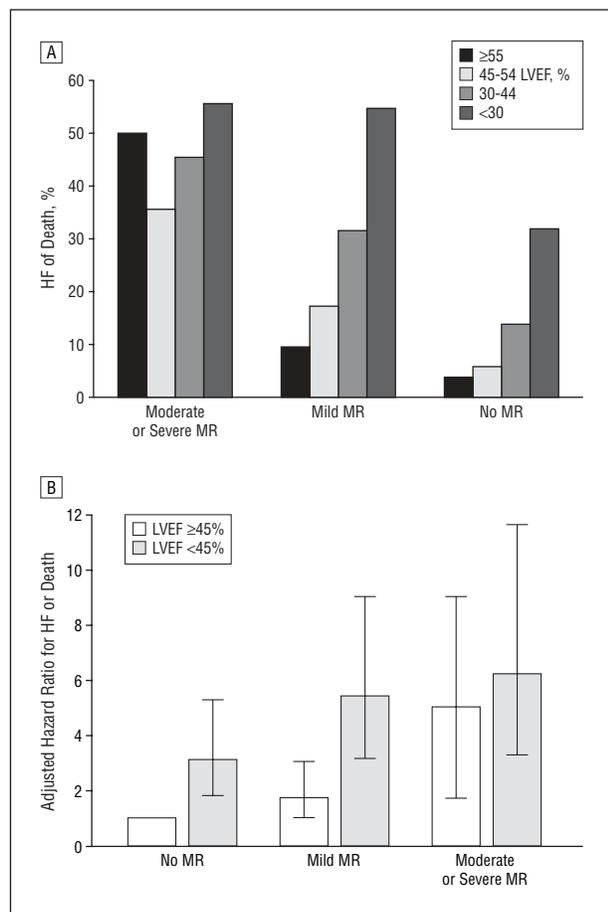


Figure 3. Interaction between the degree of ischemic mitral regurgitation and left ventricular ejection fraction. A, Event rates for the combined end point of heart failure (HF) and death according to left ventricular ejection fraction (LVEF) and the degree of ischemic mitral regurgitation (MR). B, Adjusted hazard ratios for mortality or admission for HF after hospital discharge according to LVEF ($\geq 45\%$ vs $< 45\%$) and the degree of ischemic MR. The reference group is patients without ischemic MR and with LVEF of at least 45%.

prognostic information to that provided by LVEF and clinical variables (age, sex, Killip class at admission, previous infarction, anterior infarction, ST-elevation infarction, coronary revascularization, and history of DM and hypertension). The effect of moderate or severe MR was particularly striking among low-risk patients with preserved LVEF.

MR AND HF

The development of HF in patients after MI portends several-fold higher risk of death compared with survivors of MI without HF.³⁻⁵ Several clinical predictors for the development of HF after MI have been identified, with advanced age, DM, and reduced LVEF being the most consistent.^{3,4} Our results indicate that echocardiographic data regarding the presence and severity of ischemic MR are useful in identifying patients at high risk for HF after MI. Even patients with mild ischemic MR and patients with ischemic MR and preserved LVEF are at a considerable risk. Therefore, ischemic MR is an important determinant in the transition to HF in patients after MI. Furthermore, our data suggest that HF represents a common intermediate step that heralds death in many of these patients.

Two previous studies reported an association between ischemic MR and HF. Grigioni et al¹¹ demonstrated an increase in the risk of HF with greater degrees of ischemic MR, with relative risks of 3.5 and 4.4 in patients with effective regurgitant orifices of 1 to 19 mm² and at least 20 mm², respectively. In a population-based cohort study, Bursi et al¹⁰ showed that moderate or severe MR was associated with HF in patients discharged with diagnoses compatible with MI, according to target codes from the *International Classification of Diseases, Ninth Revision*.

To our knowledge, our study is the first to prospectively assess the effect of ischemic MR on HF in patients after MI. Although the use of quantitative measurements of MR severity has been emphasized for risk stratification of patients with ischemic MR,^{11,19} the results of the present study indicate that a semiquantitative assessment of MR severity, as part of a routine echocardiographic evaluation, provides incremental prognostic information with regard to the risk of HF. We also show for the first time (to our knowledge) the importance of ischemic MR in patients with preserved LVEF.

PROGNOSTIC SIGNIFICANCE OF MILD MR

Hemodynamically significant ischemic MR, caused by altered ventricular geometry and function after infarction, can promote further adverse remodeling,⁹ although this is not a consistent finding.²⁰ The intriguing

ing observation that even mild MR was associated with an increase in the risk for HF is not easily explained. It has been postulated that mild ischemic MR is a marker of geometric abnormalities that lead to progressive remodeling and increased load on the noninfarcted myocardium.⁷ Some of the patients with mild ischemic MR may experience progressive left ventricular remodeling and dilatation after infarction,⁹ with development of HF.

Stress-induced geometric ventricular changes may increase the regurgitant orifice area,^{19,21,22} and the degree of MR at rest is unrelated to exercise-induced changes.²³ In patients with chronic ischemic left ventricular dysfunction, large exercise-induced increases in the effective regurgitant orifice are associated with greater risk of HF and mortality.^{19,22} Therefore, the association between HF mild resting ischemic MR may be related to a subgroup of patients with large dynamic increases in MR severity.

Regardless of the mechanism underlying the association between HF and mild ischemic MR, patients with mild MR are also at higher risk for HF. Echocardiographic follow-up may be warranted in these patients because ventricular dilatation and distortion may progress beyond the index event, despite appropriate medical therapy,²⁴ leading to worsening of ischemic MR.

PATIENTS WITH ISCHEMIC MR AND PRESERVED LVEF

The development of ischemic MR requires conformational changes of left ventricular shape, and the severity of MR is mainly related to the extent of left ventricular geometric changes rather than to the severity of left ventricular dysfunction.^{9,25} Although ischemic MR is frequently observed in patients with small MIs,^{26,27} no data are available on the outcome of patients with ischemic MR and preserved LVEF, to our knowledge. In the present study, patients with moderate or severe ischemic MR and preserved LVEF incurred a striking excess mortality and morbidity. Because ischemic MR dramatically modifies the generally good prognosis of patients with preserved LVEF, these patients would probably derive the greatest absolute risk reduction from medical and surgical interventions.

STUDY LIMITATIONS

Ischemic MR is a dynamic lesion, and its severity may vary over time because of ongoing ventricular remodeling. In contrast to previous investigations,¹¹ the severity of MR in the present study was assessed in the early postinfarction period. Because echocardiograms were not obtained after hospital discharge, it is unknown whether progressive ventricular remodeling resulted in increasing severity of MR over time in some patients. In addition, measures of the degree of left ventricular remodeling such as end-systolic volume index were not available.

The use of color Doppler for determining MR severity is inaccurate because of technical and hemodynamic limitations¹³ but is part of the routine echocardiographic examination.

Therefore, it is possible that misclassification of MR severity occurred in some patients.

CONCLUSIONS

In patients with a recent acute MI, ischemic MR is a predictor of long-term HF and death and provides incremental prognostic information when added to LVEF and clinical risk predictors. The risk for HF and death increases with higher degrees of MR and is particularly striking among apparently low-risk patients with preserved LVEF.

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Author Contributions: Dr Aronson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Aronson, Goldsher, Mutlak, and Agmon. *Acquisition of data:* Aronson, Goldsher, Zukermann, Kapeliovich, Lessick, Mutlak, Dabbah, Markiewicz, Beyar, Hammerman, Reisner, and Agmon. *Analysis and interpretation of data:* Aronson, Goldsher, Zukermann, Kapeliovich, Lessick, Dabbah, Markiewicz, Beyar, Hammerman, Reisner, and Agmon. *Drafting of the manuscript:* Aronson, Goldsher, and Agmon. *Critical revision of the manuscript for important intellectual content:* Aronson, Goldsher, Kapeliovich, Lessick, Mutlak, Dabbah, Markiewicz, Beyar, Hammerman, Reisner, and Agmon. *Statistical analysis:* Aronson. *Administrative, technical, and material support:* Goldsher, Zukermann, Kapeliovich, Lessick, Mutlak, Dabbah, Markiewicz, Beyar, Hammerman, Reisner, and Agmon.

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