Contribution of Ischemic Mitral Regurgitation to Congestive Heart Failure After Myocardial Infarction

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OBJECTIVES

The purpose of this study was to define the contribution of ischemic mitral regurgitation (IMR) to the occurrence of congestive heart failure (CHF) after myocardial infarction (MI).

BACKGROUND

After MI, CHF is a frequent and serious complication, but its determinants and, particularly, the role of IMR are poorly defined.

METHODS

We analyzed 173 asymptomatic patients with previous Q-wave MI (>16 days) with echocardiographic quantitation of IMR (measuring effective regurgitant orifice [ERO] and regurgitant volume). The 102 patients with IMR were matched to 71 patients without IMR for age (71 ± 11 years vs. 68 ± 9 years; p = 0.11), gender (76% vs. 82% males; p = 0.41), and left ventricular ejection fraction (EF) (37 ± 14% vs. 36 ± 11%; p = 0.92).

RESULTS

Five-year rates of CHF and of CHF or cardiac death (CD) were 36 ± 5% and 52 ± 5%, respectively. Independent determinants of CHF were EF, sodium plasma level, and presence and degree of IMR (p < 0.0001). Five-year CHF rates were 18 ± 5% without mitral regurgitation (MR), 53 ± 7% with IMR, 46 ± 9% with ERO ≥19 mm² and 68 ± 12% with ERO ≥20 mm² (all p < 0.0001). The adjusted relative risk of CHF was 3.65 (95% confidence interval [CI] 1.86 to 7.75) for IMR presence and 4.42 (95% CI 1.9 to 10.5) for ERO ≥20 mm². The adjusted relative risk of CHF/CD was 2.97 (95% CI 1.77 to 5.16) for IMR presence and 4.4 (95% CI 2.4 to 8.2) for ERO ≥20 mm².

CONCLUSIONS

After MI, incidence of CHF and of CHF/CD are high even in patients with no or minimal symptoms at baseline and are higher in patients with IMR. Congestive heart failure is independently determined by larger ERO of IMR. These data suggest that detecting and quantifying IMR is essential for risk stratification after MI. Value of IMR treatment in improving post-MI outcome should be investigated. (J Am Coll Cardiol 2005;45:260–7) © 2005 by the American College of Cardiology Foundation

Survivors of acute myocardial infarction (MI) are at high risk for congestive heart failure (CHF) (1), which adversely affects subsequent outcome, particularly with poor survival (2,3). Therefore, identification of predictors of CHF in patients presenting with no or minimal symptoms after MI is essential in potentially altering post-MI management and minimizing CHF rate (4).

Ischemic mitral regurgitation (IMR) is a mitral incompetence due to coronary artery disease (CAD) in the absence of intrinsic valve lesions and is frequent after MI (5,6). Previous data from our institution (7) and others (5,6,8) were consistent in suggesting that IMR presence after MI affects survival. However, with regard to morbid cardiac complications such as occurrence of post-MI CHF, few data are available. The Survival And Ventricular Enlargement (SAVE) study provided seminal information that IMR may lead to higher CHF incidence (5). However, inclusion limited to the acute post-MI phase (<16 days), more advanced symptoms, and left ventricular (LV) alterations in patients with IMR and lack of multivariate confirmation left doubt on the intrinsic IMR influence on subsequent CHF. Moreover, the SAVE study was intriguing as it almost exclusively included patients with mild mitral regurgitation (MR). Therefore, the influence of IMR and, in particular, the influence of increasing degree of MR on subsequent occurrence of CHF in patients with MI presenting with no or minimal symptoms is uncertain.

To address this issue, we enrolled patients who were in New York Heart Association (NYHA) functional class I and II in the chronic post-MI phase (>16 days), simultaneously to extensive clinical and Doppler echocardiographic assessment. We hypothesized that IMR is a major determinant of the occurrence of subsequent CHF and that its quantitation provides important prognosis information. Verifying these hypotheses would emphasize the importance of the assessment of IMR for risk stratification after MI.

METHODS

Population. Patients were consecutively enrolled at the Mayo Clinic, Rochester, Minnesota, between 1990 and 1997 if they: 1) were in NYHA functional class I or II at diagnosis and had no history of CHF; 2) had a Q-wave MI on electrocardiogram and a history of MI older than 16 days; 3) had transthoracic echocardiography during the same evaluation in routine clinical practice, showing either IMR, which was prospectively quantitatively assessed, or no MR. Exclusion criteria were: NYHA functional class ≥III, recent MI (≤16 days), previous cardiac surgery, papillary
muscle rupture, primary leaflet or chordal pathology, associated aortic valve, or congenital heart disease. No exclusions were made on the basis of treatment received or degree of MR. A computerized matching process was conducted between patients with and without IMR who satisfied inclusion criteria. To avoid baseline differences among these patients, patients without IMR were matched to those with IMR for age, gender, and LV ejection fraction (EF). The matching process was computerized on the basis of multivariate matched sampling incorporating the propensity score (9) and was performed in a blinded manner before any outcome information was obtained. Congestive heart failure during follow-up was diagnosed using validated criteria (10). Cardiac deaths (CDs) were ascertained by reviewing death certificates, coroners’ reports, or autopsy records. Medications were recorded if prescribed for three months or more.

**Echocardiographic methods.** Dimensions of the left ventricle (LV) and left atrium (LA) were obtained using two-dimensional–guided M-mode echocardiography. The EF was visually estimated in all and combined with calculated values in 119 patients (69%) (7,11). Data were used unaltered from the original echocardiographic report by means of electronic transfer. Presence of MR was detected by color flow imaging. When present, the degree of IMR was assessed with at least one of the following two quantitative methods. Results were eventually averaged.

Quantitative Doppler measured mitral and aortic stroke volumes, and the regurgitant volume (RVol) was calculated as the difference between these two stroke volumes (12,13). The effective regurgitant orifice (ERO) area was calculated as the ratio of RVol to regurgitant time–velocity integral (14).

The proximal isovelocity surface area method (15) analyzed the proximal flow convergence region, and ERO was the ratio of regurgitant flow to regurgitant velocity (16,17). The RVol was calculated as the product of ERO by regurgitant time–velocity integral.

**Statistical analysis.** Continuous variables are expressed as mean ± SD values. Group comparisons were performed with the standard t test or chi-square test, as appropriate. Event rates were estimated by the Kaplan–Meier method, censoring at the time of surgery if surgery was eventually performed. Comparisons between groups were evaluated using the two-way log-rank test. End points were CHF and the combined end point of CD or CHF. Impact of IMR on outcome was analyzed in two ways: 1) with presence of IMR at baseline used as the categorical determinant of adverse cardiac events, or 2) with quantitative degree of IMR (RVol and ERO). Among variables of MR (ERO and RVol), the strongest predictor (highest chi-square) of cardiac events was selected for the final model. Identification of other baseline predictors of events was accomplished by performing univariate Cox proportional hazards analysis on candidate clinical, laboratory, and echocardiographic variables. Risk ratio (RR) and 95% confidence interval (CI) associated with previously determined thresholds were defined (18).

To confirm independent predictive value, variables with p < 0.10 were tested in multivariate models, with IMR expressed as both a categorical and a quantitative variable. Final models were repeated with variables significantly different at baseline between patients with and without IMR. To assess the effects of events occurring after diagnosis (follow-up atrial fibrillation, MI, or percutaneous coronary intervention) on outcome, Cox proportional hazards analyses using time-dependent variables were used. Furthermore, because the role of NYHA functional class II versus I on outcome is unknown, analysis was repeated with NYHA functional class in the model. To address the concern of possible overestimation of EF with MR, we repeated the analysis using EF values decreased by 4% and 8% in patients with IMR. A value of p < 0.05 was considered significant.

**RESULTS**

**Baseline characteristics.** We enrolled 173 patients with no or minimal symptoms (NYHA functional class I or II) in the chronic phase after MI in the study. The mean time after MI was 7.6 ± 7.4 years. The 102 patients with IMR (ERO 0.19 ± 0.11 cm² and RVol 36 ± 25 ml) were compared with 71 patients without IMR. Overall, age was 70 ± 10 years, 136 patients (79%) were male, and EF was 36 ± 13%. The diagnosis of previous MI was confirmed by electrocardiogram (in all patients) and by echocardiography as presence of regional wall motion abnormalities in 172 patients. A nuclear perfusion study available for 72 patients detected a previous MI in 67 (93%). Coronary angiography was ultimately performed in 102 patients, showing obstructive coronary disease in all.

Baseline characteristics of patients with and without MR are summarized in Table 1. Importantly, age, gender, comorbidity, most risk factors, prevalence of multivessel disease, and EF were similar in both groups. As expected,
The overall incidence of CHF at 3 and 5 years was 23 patients incurred CHF under conservative management. The differences between IMR and non-IMR patients did not affect the time to CHF are listed in Table 1.

In univariate analysis, presence of MR was strongly associated with occurrence of CHF (RR of MR, respectively, 4.90, 2.65, 3.29, 3.65 [95% CI 1.86 to 7.75]; p < 0.0001). The other univariate baseline predictors of time to CHF were EF (a measure of ventricular diastolic function), which was univariately associated with occurrence of CHF, and did not affect the independent predictive value of IMR for CHF (RR of IMR after adjustment for baseline atrial fibrillation, 3.7 [95% CI 1.9 to 7.8]; p < 0.0001; for hypertension, 3.7 [95% CI 1.9 to 8.0]; p < 0.0001; for MI location, 3.5 [95% CI 1.7 to 7.6]; p = 0.0003). The results were not altered after adjustment for NYHA (functional class I or II) distribution, which was not an independent predictor of CHF (p = 0.90) and did not affect the adjusted RR attached to presence of IMR (3.7 [95% CI 1.8 to 8.0]; p = 0.002). Accounting for events and procedures occurring after diagnosis, the independent predictive value of IMR for CHF was not affected (RR of IMR, adjusting for post-diagnosis atrial fibrillation, 2.8 [95% CI 1.3 to 5.9]; p < 0.01; or MI, 3.1 [95% CI 1.5 to 6.4]; p < 0.01). A higher degree of IMR was associated with a higher incidence of CHF. Patients with RVol ≥30 ml incurred higher CHF incidence (at 5 years, 54 ± 9%) than those with no MR (p < 0.0001), but only marginally higher than those with RVol 1 to 29 ml (49 ± 10%). However, patients classified according to ERO showed marked difference in CHF rates (at 5 years, 18 ± 5% without IMR, 46 ± 9% with ERO 1 to 19 mm², and 68 ± 12% with ERO ≥20 mm²; p < 0.0001) (Fig. 2).

In multivariate analysis, presence of IMR was a strong and independent determinant of occurrence of CHF (RR 3.65 [95% CI 1.86 to 7.75]; p < 0.0001) (Table 2). The other independent determinants of time to CHF were EF and baseline sodium level. Of note, atrial and ventricular diastolic and systolic dimensions and mitral deceleration time (a measure of ventricular diastolic function), which were univariately associated with occurrence of CHF, were not independently predictive of CHF and did not affect (when forced into the model) the significance and RR attached to IMR (at 5 years, 53 vs. 18%).

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Association to Time to CHF</th>
<th>Association to Time to CHF/Death</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>62 ± 9</td>
<td>0.11</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>82</td>
<td>0.41</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Comorbidity score ≥2 (%)</td>
<td>45</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>24</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>35</td>
<td>0.04</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>62</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>59</td>
<td>0.73</td>
</tr>
<tr>
<td>Anterior MI (%)</td>
<td>41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CAD, multivessel disease (%)</td>
<td>48</td>
<td>0.60</td>
</tr>
<tr>
<td>Sodium plasma level (mg/dl)</td>
<td>140</td>
<td>0.40</td>
</tr>
<tr>
<td>EF (%)</td>
<td>37 ± 14</td>
<td>0.92</td>
</tr>
<tr>
<td>LVSI (mm/m²)</td>
<td>27 ± 7</td>
<td>0.03</td>
</tr>
<tr>
<td>LVDi (mm/m²)</td>
<td>33 ± 5</td>
<td>0.02</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>48 ± 7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mitral deceleration time (ms)</td>
<td>224</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ERO (cm²)</td>
<td>0.19 ± 0.11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RVol (ml/beat)</td>
<td>36 ± 25</td>
<td>&lt; 0.001</td>
</tr>
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</table>

CAD = coronary artery disease; CHF = congestive heart failure; EF = left ventricular ejection fraction; ERO = effective regurgitant orifice; IMR = ischemic mitral regurgitation; LA = left atrial diameter; LVDi = left ventricular end-diastolic diameter indexed to body surface area; LVSI = left ventricular end-systolic diameter indexed to body surface area; MI = myocardial infarction; MR = mitral regurgitation; RVol = regurgitant volume.

Limited clinical differences were noted regarding history of hypertension and location of the causal MI. Other differences between patients with and without IMR were linked to the IMR, with larger atrial dimension, higher prevalence of atrial fibrillation, and larger ventricular size. No differences were noted for treatment by beta-blockers (p = 0.98), statins (p = 0.98), and vasodilators (p = 0.06), but IMR patients were more often treated with diuretics and digoxin (both p < 0.003).

**IMR and CHF.** During follow-up of 3.8 ± 2.4 years, 49 patients incurred CHF under conservative management. The overall incidence of CHF at 3 and 5 years was 23 ± 4% and 36 ± 5%, respectively. Patients with IMR experienced significantly higher incidence of CHF than those without IMR (at 5 years: 53 ± 7% vs. 18 ± 5%, respectively; p < 0.0001) (Fig. 1).

In univariate analysis, presence of MR was strongly associated with occurrence of CHF (RR 4.3 [95% CI 2.2 to 8.9]; p = 0.0001). The other univariate baseline predictors of time to CHF are listed in Table 1.

In multivariate analysis, presence of IMR was a strong and independent determinant of occurrence of CHF (RR 3.65 [95% CI 1.86 to 7.75]; p < 0.0001) (Table 2). The other independent determinants of time to CHF were EF and baseline sodium level. Of note, atrial and ventricular diastolic and systolic dimensions and mitral deceleration time (a measure of ventricular diastolic function), which were univariately associated with occurrence of CHF, were not independently predictive of CHF and did not affect (when forced into the model) the significance and RR attached to IMR (RR of IMR, respectively, 4.90, 2.65, 3.29, 3.41; all p < 0.01). Furthermore, adjustment for differences between IMR and non-IMR patients did not affect the independent predictive value of IMR for CHF (RR of IMR after adjustment for baseline atrial fibrillation, 3.7 [95% CI 1.9 to 7.8]; p < 0.0001; for hypertension, 3.7 [95% CI 1.9 to 8.0]; p < 0.0001; for MI location, 3.5 [95% CI 1.7 to 7.6]; p = 0.0003). The results were not altered after adjustment for NYHA (functional class I or II) distribution, which was not an independent predictor of CHF (p = 0.90) and did not affect the adjusted RR attached to presence of IMR (3.7 [95% CI 1.8 to 8.0]; p = 0.002). Accounting for events and procedures occurring after diagnosis, the independent predictive value of IMR for CHF was not affected (RR of IMR, adjusting for post-diagnosis atrial fibrillation, 2.8 [95% CI 1.3 to 5.9]; p < 0.01; or MI, 3.1 [95% CI 1.5 to 6.4]; p < 0.01). A higher degree of IMR was associated with a higher incidence of CHF. Patients with RVol ≥30 ml incurred higher CHF incidence (at 5 years, 54 ± 9%) than those with no MR (p < 0.0001), but only marginally higher than those with RVol 1 to 29 ml (49 ± 10%). However, patients classified according to ERO showed marked difference in CHF rates (at 5 years, 18 ± 5% without IMR, 46 ± 9% with ERO 1 to 19 mm², and 68 ± 12% with ERO ≥20 mm²; p < 0.0001) (Fig. 2). Univariately, in comparison to patients with no MR, ERO 1 to 19 mm² was associated with a high risk of CHF (RR 3.55 [95% CI 1.67 to 7.87]; p < 0.001) and ERO ≥20 mm² with an even higher risk of CHF (RR 6.4 [95% CI 2.9 to 14.3]; p < 0.0001).

Moreover, ERO remained an independent predictor of CHF once adjusted for the other independent predictors of CHF with adjusted RR 3.45 (95% CI 1.58 to 7.9), p < 0.002 for ERO 1 to 19 mm² and 4.42 (95% CI 1.9 to 10.5), p < 0.001 for ERO ≥20 mm².
IMR and combined adverse events. During follow-up 62 patients died, 46 from cardiac cause (14 sudden, 15 progressive CHF, and 16 miscellaneous causes such as new MI or CAD complications, thromboembolic complications, and bleeding due to anticoagulation). Thus, a total of 80 patients incurred either CHF or CD during follow-up under conservative management. The incidence of this combined end point at 3 and 5 years was, overall, 33 ± 4% and 52 ± 5%, respectively. Patients with IMR experienced higher incidence of events compared to those without MR (at 5 years, 69 ± 6% vs. 30 ± 6%; p < 0.0001) (Fig. 3). In univariate analysis, presence of MR was strongly associated with higher event rates (RR 3.3 [95% CI 2.0 to 5.6]; p < 0.0001). The other univariate predictors of time to CHF/CD are listed in Table 1 (right column).

In multivariate analysis, IMR was a strong independent predictor of the combined end point (adjusted RR 2.97 [95% CI 1.77 to 5.16]; p < 0.0001). The other independent determinants of the combined end point were age, sodium level, and EF with a borderline significance (Table 3). Of note, ventricular diastolic and atrial dimension, hyperlipidemia, and presence of multivessel disease did not affect (when forced into the model) the significance magnitude of effect of IMR (RR attached to IMR, respectively, 2.2, 2.86, 2.94, 2.79; all p < 0.01). Furthermore, adjustment for differences between IMR and non-MR patients did not affect the independent predictive value of IMR for the combined end point (RR of IMR after adjustment for baseline atrial fibrillation, 3.0 [95% CI 1.8 to 5.2], p < 0.0001; for hypertension, 2.9 [95% CI 1.7 to 5.0], p < 0.0001; for MI location, 2.8 [95% CI 1.6 to 5.0], p < 0.0001). The results were not altered after adjustment for NYHA (functional class I or II) distribution, which was not an independent predictor of the combined end point (p = 0.86) and did not affect the adjusted RR attached to presence of IMR (2.9 [95% CI 1.7 to 5.2]; p < 0.0001).

Accounting for events and procedures occurring after diagnosis, the independent predictive value of IMR for the combined end point was not affected (RR of IMR adjusting for post-diagnosis atrial fibrillation, 2.5 [95% CI 1.4 to 4.4], p < 0.01; or MI, 2.5 [95% CI 1.5 to 4.5], p < 0.01; or PCI, 2.8 [95% CI 1.6 to 4.9], p < 0.01).

A higher degree of IMR was associated with a higher incidence of the combined end point of CHF or CD. In comparison to patients with no MR (at 5 years, 31 ± 6%), patients with RVol 1 to 29 ml and ≥30 ml incurred higher risk (at 5 years, 62 ± 9% and 71 ± 7%, respectively; p < 0.0001). Patients with ERO 1 to 19 mm² and ≥20 mm² also were at high risk (68 ± 9% and 78 ± 9%, respectively; p < 0.0001) (Fig. 4). Univariately, in comparison to patients with no MR, ERO 1 to 19 mm² was associated with a high risk of CHF (RR 2.8 [95% CI 1.6 to 5.1]; p < 0.001) and ERO ≥20 mm² with an even higher risk of CHF (RR 4.4 [95% CI 2.4 to 8.2]; p < 0.0001). The ERO area remained independently predictive of the combined end point after adjustment for the other independent predictors of CHF with adjusted RR 2.8 (95% CI 1.5 to 5.2), p < 0.001 for ERO 1 to 19 mm² and 3.42 [95% CI 1.7 to 6.7], p = 0.0006 for ERO ≥20 mm².

DISCUSSION

The present study showed that in patients with no or minimal symptoms in the chronic phase after MI, the incidence of CHF and that of CHF or CD are high but are unequally distributed. Compared with patients without IMR of similar age, gender, and EF, patients with IMR incur markedly higher event rates, unadjusted or adjusted for all possible differences between groups. The risk of event is approximately tripled with IMR even after adjustment for all other baseline predictors of CHF and for all differences in baseline characteristics in multivariate analysis. A higher degree of MR, particularly quantified by the ERO, is independently associated with higher risk of CHF and of the combined end point of CHF or CD. Therefore, identifying the presence and quantifying the degree of IMR in the chronic phase after MI is essential for post-MI risk stratification, even in patients presenting with no or minimal symptoms.

IMR: challenges and opportunities. During the past decade, the large-scale trials have significantly contributed to improve prognosis of patients with acute MI (19). However, the reduced fatality rate from acute MI has resulted in

Table 2. Baseline Independent Predictors of Subsequent Congestive Heart Failure After MI

<table>
<thead>
<tr>
<th>Variables</th>
<th>RR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.98–1.05</td>
<td>0.41</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.98</td>
<td>0.50–2.11</td>
<td>0.98</td>
</tr>
<tr>
<td>Comorbidity index &gt;2</td>
<td>1.37</td>
<td>0.96–2.02</td>
<td>0.08</td>
</tr>
<tr>
<td>EF (per 1%)</td>
<td>0.97</td>
<td>0.94–0.99</td>
<td>0.013</td>
</tr>
<tr>
<td>Sodium plasma level (per mEq)</td>
<td>0.88</td>
<td>0.80–0.97</td>
<td>0.014</td>
</tr>
<tr>
<td>IMR</td>
<td>3.65</td>
<td>1.86–7.75</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CI = confidence interval; RR = risk ratio; other abbreviations as in Table 1.
The current study showed that presence of IMR in patients with no or minimal symptoms seen in the chronic phase after MI was independently associated with a higher long-term incidence of CHF. This high risk is not related to differences in baseline characteristics, as matching and adjustment in multivariate analysis showed that IMR remained an independent predictor of CHF after diagnosis. The outcome implications of IMR are additive to those of EF or hyponatremia, a marker of neurohormonal activation (26), and to adjustment for mitral deceleration time, a major marker of LV diastolic function (27), showing that IMR in and by itself is associated with subsequent high risk of CHF. The pioneering data from the SAVE study suggested that IMR in acute MI was associated with increased risk of CHF episodes, but could not confirm it independently (5). Therefore, to our knowledge the current study, using the strength of matching patients with and without IMR for age, gender, and EF (9), for the first time independently links IMR with occurrence of CHF in the chronic phase after MI. These findings extend and emphasize the importance of IMR as a determinant of poor outcome in ischemic heart disease, in the acute (5), the chronic (7), or both phases (6), or after percutaneous intervention (8) and for mortality or for morbid events. An important point is that the higher rate of CHF in asymptomatic patients with IMR is not due to longer time at risk because of lower cardiac mortality, as the combined end point of CD and CHF also occurred more frequently in patients with IMR.

**Degree of IMR and subsequent CHF.** Another important finding is the direct degree-effect relationship between quantified IMR severity and CHF risk. Indeed, patients with ERO ≥20 mm² (0.20 cm²) displayed CHF risk more than six times higher than patients without IMR in univariate analysis and more than four times higher after adjustment for all predictors of CHF. The analysis of the combined end point of CD and CHF again confirmed that this gradient of CHF occurrence paralleling the degree of IMR is not due to lower mortality.

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**IMR and subsequent CHF.** The current study showed that presence of IMR in patients with no or minimal symptoms seen in the chronic phase after MI was independently associated with a higher long-term incidence of CHF. This high risk is not related to differences in baseline characteristics, as matching and adjustment in multivariate analysis showed that IMR remained an independent predictor of CHF after diagnosis. The outcome implications of IMR are additive to those of EF or hyponatremia, a marker of neurohormonal activation (26), and to adjustment for mitral deceleration time, a major marker of LV diastolic function (27), showing that IMR in and by itself is associated with subsequent high risk of CHF. The pioneering data from the SAVE study suggested that IMR in acute MI was associated with increased risk of CHF episodes, but could not confirm it independently (5). Therefore, to our knowledge the current study, using the strength of matching patients with and without IMR for age, gender, and EF (9), for the first time independently links IMR with occurrence of CHF in the chronic phase after MI. These findings extend and emphasize the importance of IMR as a determinant of poor outcome in ischemic heart disease, in the acute (5), the chronic (7), or both phases (6), or after percutaneous intervention (8) and for mortality or for morbid events. An important point is that the higher rate of CHF in asymptomatic patients with IMR is not due to longer time at risk because of lower cardiac mortality, as the combined end point of CD and CHF also occurred more frequently in patients with IMR.
The quantitative analysis also provides important insights into potential mechanistic aspects of the link between CHF and IMR. The ERO exhibited stronger predictive power for subsequent CHF than the RVol. This result is in agreement with previous results obtained by our group (7,28) and probably reflects the mechanisms of LV-to-LA energy transfer. Indeed, the regurgitant LV energy can be transferred as kinetic (flow) or potential (pressure) to the LA (29). The RVol reflects purely kinetic energy, whereas the regurgitant orifice is linked to both, with increase in LA pressure leading to subsequent development of CHF. In that regard, the observation of higher filling pressures independently related to the ERO area (28) fits well with the clinical consequences of IMR and the higher rate of CHF with larger ERO. Hence, the current study emphasizes the relevance of IMR severity assessment through ERO determination.

A threshold of 20 mm² appeared to identify patients at highest risk to develop adverse cardiac events. This cutoff is lower than the 40 mm² threshold used in patients with organic MR (18), as IMR volume is usually smaller (14). Such ERO threshold of 20 mm² is probably related to the profound LV alteration of post-MI patients (5,6), explaining the poor LV tolerance to IMR and the severe clinical consequences observed. This threshold fits well with previous observations of links between ERO and hemodynamic consequences (28,30), and between ERO and clinical outcome (7) in such patients. Therefore, IMR of a degree that may otherwise be qualified as moderate (31) imposes severe clinical implication in post-MI patients (5), even those presenting with no or minimal symptoms.

**Clinical implications.** The present data expand the growing body of evidence that IMR is a major complication of MI with severe outcome consequences (5–8,24). Therefore, in clinical practice it is essential to detect the presence of IMR. Clinically, detection of IMR on the basis of a murmur is unreliable (5,32), but detection can routinely be done by Doppler echocardiography (31). As routine evaluation of LV function after MI is recommended (33,34) even in asymptomatic patients, detection of IMR does not represent an additional cost burden in the risk stratification of such patients.

The risk of adverse cardiac events is directly related to the severity of regurgitation quantitatively assessed by Doppler echocardiography. The quantitative measurements are not always routinely done, but the recent recommendations of the American Society of Echocardiography (31) emphasize this approach in routine practice. Our data support this emphasis by demonstrating the link between quantitative measurements and outcome and support quantitative assessment of IMR progression in future studies.

The severe consequences of IMR suggest that it should be the focus of targeted and vigorous treatment. In our series, 23 patients underwent cardiac surgery (with 22 coronary bypass and 6 MR corrections), but the benefit of these procedures cannot be defined, and the notable risk of surgical therapy (35,36) of IMR should lead to prudent clinical implications. Medical (37,38), pacing (39), surgical therapy (35,36) of IMR should lead to prudent clinical implications. Medical (37,38), pacing (39), surgical therapy (35,36), and possibly future catheter-based procedures (40) may all be relevant options. The results of the present study suggest that clinical trials testing these approaches are warranted and that currently individualized therapeutic decisions for IMR are warranted to prevent the occurrence of CHF after MI.

**Study limitations.** We matched patients with and without IMR for age, gender, and LVEF. However, it may be argued that with MR, EF may be higher than expected. Such a conceptual effect is, at most, of low magnitude (41) because of low volume of IMR. Nevertheless, other, less load-dependent indices of LV function, such as wall-stress adjusted EF or end-systolic dimension, did not affect the link between IMR and outcome. Furthermore, even when EF of IMR patients was decreased by four and even eight points, IMR remained independently determinant of subsequent CHF, with, respectively, RR of 3.35 (p = 0.0005) and 3.0 (p = 0.003), demonstrating that uncertainties about EF do not alter the independent effect of IMR on outcome.

Ischemic MR may be considered as a surrogate for coronary disease and is the consequence of local LV alterations (42). Differences in coronary disease extent are unlikely in view of the observations in patients with coronary angiograms. Also, we adjusted for all baseline differences in LV size, and systolic pressure leading to subsequent development of CHF. In that regard, the observation of higher filling pressures independently related to the ERO area (28) fits well with the clinical consequences of IMR and the higher rate of CHF with larger ERO. Hence, the current study emphasizes the relevance of IMR severity assessment through ERO determination.

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Table 3. Multivariate Predictors of the Combined End Point of Congestive Heart Failure or Cardiac Death in Asymptomatic Post-MI Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>RR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.01–1.07</td>
<td>0.004</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.23</td>
<td>0.72–2.21</td>
<td>0.46</td>
</tr>
<tr>
<td>EF (per 1%)</td>
<td>0.98</td>
<td>0.97–1.001</td>
<td>0.07</td>
</tr>
<tr>
<td>Sodium plasma level (per mEq)</td>
<td>0.90</td>
<td>0.84–0.97</td>
<td>0.004</td>
</tr>
<tr>
<td>IMR</td>
<td>2.97</td>
<td>1.77–5.16</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1 and 2.

**Figure 4.** Survival free of congestive heart failure or cardiac death (event-free survival) in asymptomatic patients after myocardial infarction according to the degree of mitral regurgitation measured by effective regurgitant orifice (ERO) ≥20 mm² (continuous line), 1 to 19 mm² (dashed line), and absent mitral regurgitation (ERO = 0) (dotted line) at diagnosis. The event-free survival rates at five years are indicated ± the standard error.
and diastolic function, which did not reduce the independent effect of IMR on outcome. Furthermore, the physiologic link between IMR and filling pressures (28) and the outcome link between degree and clinical outcome of IMR support the fact that IMR is the direct determinant of the high CHF rate and justifies consideration of therapy directly aimed at reducing its degree.

We could not adjust for all neurohormonal activation markers, but IMR is linked to outcome independently of hyponatremia, which reflects in part this activation (26). In view of our results, future studies should evaluate the link between IMR, hormonal activation, and outcome.

Various therapies affect the outcome of post-MI patients, but their utilizations were similar in patients with and without IMR. However, to ensure that these therapies did not affect our results, we forced them into the model predictive of subsequent CHF. Statin, beta-blockade, aspirin, or angiotensin-converting enzyme inhibitor use did not reduce the impact of IMR on CHF occurrence (all RR >3.0; all p < 0.001). Therefore, the impact of IMR on outcome does not appear related to concomitant treatment.

CONCLUSIONS

Patients with previous MI and no or minimal symptoms are at high risk for subsequent CHF. Patients with IMR, assessed by Doppler echocardiography in routine practice, are at markedly increased risk of CHF, independent of all other clinical and LV characteristics. Moreover, the risk of CHF and CD is directly related to IMR severity as it is quantitatively defined. Particularly, patients with ERO ≥20 mm² incur a risk of CHF more than four times higher than patients without IMR, with an absolute rate close to 70% at five years. Therefore, detecting and quantifying IMR is essential after MI, and prospective randomized trials are needed to analyze the effect of treatment in preventing IMR complications.

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REFERENCES