Evolution of Left Ventricular Ejection Fraction and its Relationship to Infarct Size After Acute Myocardial Infarction

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Objectives
The aim of this study was to investigate the evolution of left ventricular (LV) function and infarct size in patients with acute myocardial infarction (MI) treated with primary coronary stenting.

Background
Little evidence exists on the relationship between LV function and evolution of infarct size after MI.

Methods
This study included 626 patients with first acute MI who underwent 2 angiographic and 3 scintigraphic examinations within 6 months after the acute event. Angiographic left ventricular ejection fraction (LVEF) at baseline and at 6-month angiography, and perfusion defects before intervention and at 7- to 14-day and 6-month scintigraphy after intervention were measured. An analysis of 3-year follow-up was performed.

Results
Scintigraphic perfusion defect (median [25th, 75th percentiles]) was 24.6% [14.0%, 41.0%] of LV before intervention; it was reduced to 11.0% [5.0%, 24.0%] of LV at 7 to 14 days and further to 8.0% [2.0%, 19.0%] of LV at 6 months (p < 0.001). The LVEF was 51.6 ± 12.0% before intervention and increased to 57.4 ± 12.8% at 6 months (p > 0.001). Independent predictors of LVEF change were baseline LVEF (p < 0.001), initial perfusion defect (p < 0.001), early reduction in perfusion defect (p < 0.001), late reduction in perfusion defect (p < 0.001), peak creatine kinase-MB (p < 0.001), and smoking (p = 0.05). Three-year mortality was 1.2% in patients with improved LF function versus 5.6% in patients with worsened LV function (relative risk 0.29, 95% confidence interval 0.09 to 0.90; p = 0.03).

Conclusion
Patients with acute MI show an improvement in LV function and a reduction in infarct size within 6 months after coronary reperfusion. This improvement is associated with better long-term survival. (J Am Coll Cardiol 2007; 50:149–56) © 2007 by the American College of Cardiology Foundation

In recent years, numerous studies have evaluated the feasibility and efficacy of cell-based cardiac repair therapy after acute myocardial infarction (MI). Although it is unanimously accepted that mortality is the strongest index of clinical outcome, demonstration of efficacy of a novel therapy using mortality as an end point requires large numbers of patients and causes concerns related to exposure of such a large number of patients to a therapy with still unproven efficacy and unknown safety (1). Indeed, the majority of clinical studies of cell-based cardiac repair have used the change in global left ventricular ejection fraction (LVEF) as a primary end point, with an increase in the LVEF considered to indicate the efficacy of such therapy. Concomitant therapy with beta-blocking agents and angiotensin-converting enzyme inhibitors as well as the natural tendency of left ventricular (LV) function to improve within the first months after acute MI in a high proportion of patients cause concerns regarding the reliability of LVEF as an index of efficacy of such therapy. For these reasons, other parameters, among them infarct size, have been suggested to be more appropriate end points (2) and have been used (3) to assess the efficacy of cell transfer or mobilization in patients after acute MI (2). Information on the infarct size evolution after acute MI is rather limited (4,5).

The present study had a dual objective: 1) to investigate the magnitude and the direction of change (improvement or worsening) of LV function by assessing angiographic LVEF before and 6 months after reperfusion therapy in patients after acute MI; and 2) to investigate the evolution of infarct size...
using triple sestamibi scintigraphic examinations (before and 7 to 14 days and 6 months after reperfusion therapy) as well its relationship to LV function in a large series of patients after acute MI.

**Methods**

**Patients.** This study included 626 patients with first acute MI who underwent 3 scintigraphic examinations (before mechanical reperfusion [stenting or angioplasty], and 7 to 14 days [median 10 days] and 6 months after reperfusion). The diagnosis of acute MI was established by the presence of chest pain lasting more than 20 min associated with electrocardiographic changes (ST segment elevation of ≥1 mm in at least 2 extremity electrocardiographic leads or ≥2 mm in at least 2 contiguous precordial leads or left bundle branch block of new onset). The exclusion criteria included recent history of stroke (within 3 months), cardiogenic shock (systolic blood pressure <80 mm Hg unresponsive to fluids or necessitating catecholamines), electrical instability, severe congestive heart failure and/or pulmonary edema, active bleeding or bleeding diathesis, recent history of trauma or major surgery (within 1 month), suspected aortic dissection, noncompressible vascular punctures, ongoing oral anticoagulant therapy with coumarin derivatives, severe uncontrolled arterial hypertension (defined as a systolic blood pressure of more than 180 mm Hg that was unresponsive to therapy), and pregnancy. Patients with prior MI or prior coronary artery bypass surgery, patients treated by thrombolysis, and those who required revascularization or biventricular pacing devices or had recurrent MI within the first 6 months after the index MI were excluded (Fig. 1). For purposes of the study, 6-month follow-up angiography was required, so that only patients who survived up to this point were included.

Patients were participants in various reperfusion trials in ST-segment elevation acute MI (6–10). Written informed consent was obtained from all patients. The protocols of the studies were approved by the institutional ethics committee.

In 523 patients (83.5%), coronary stenting was used. The remaining 103 patients (16.5%) were treated by plain balloon angioplasty. Stent implantation and periprocedural care were performed according to standard criteria. Bare metal stents were used. Antiplatelet therapy consisted of ticlopidine or clopidogrel for at least 4 weeks and aspirin indefinitely.

**Scintigraphic study.** Before stenting, patients received an intravenous injection of 27 mCi (1,000 MBq) for 99mTc-sestamibi single-photon emission computerized tomography (SPECT). The SPECT was performed within 6 to 8 h after the injection of radioactive agent. A follow-up myocardial scintigraphy was scheduled 7 to 14 days and 6 months after acute MI. A multihead camera system, equipped with low-energy high-resolution collimators was used for myocardial imaging. Images were acquired in a 64 × 64 matrix with an acquisition time of 40 s per image. With dedicated software (Icon version 6.0.2, Siemens Medical Systems, Inc., Hoffman Estates, Illinois) transaxial slices were reconstructed. A volumetric sampling tool was applied to create polar maps of relative distribution throughout the entire left ventricle. Each polar map was normalized to its individual maximum. The defect size was defined as the <50% uptake area. Evolution of perfusion defect was assessed by 3 measurements: initial perfusion.

<table>
<thead>
<tr>
<th>1115 patients with acute STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients not eligible:</td>
</tr>
<tr>
<td>Patient at risk for inclusion:</td>
</tr>
<tr>
<td>106 with prior MI</td>
</tr>
<tr>
<td>44 with prior CABG</td>
</tr>
<tr>
<td>20 treated with thrombolysis</td>
</tr>
<tr>
<td>16 recurrent acute MI</td>
</tr>
<tr>
<td>prior to 6-month follow-up</td>
</tr>
<tr>
<td>929 eligible patients</td>
</tr>
<tr>
<td>Patients excluded:</td>
</tr>
<tr>
<td>34 died without completing imaging studies</td>
</tr>
<tr>
<td>36 missing baseline EF</td>
</tr>
<tr>
<td>33 missing 7-14 day SPECT</td>
</tr>
<tr>
<td>183 missing 6-month SPECT</td>
</tr>
<tr>
<td>17 missing 6-month EF</td>
</tr>
<tr>
<td>626 patients analyzed</td>
</tr>
</tbody>
</table>

**Figure 1 Flowchart of Patients**

CABG = coronary artery bypass graft surgery; EF = ejection fraction; MI = myocardial infarction; SPECT = single-photon emission computerized tomography; STEMI = ST-segment elevation acute myocardial infarction.
defect before intervention and perfusion defect at 7- to 14-day and 6-month scintigraphy after index MI. Early reduction in the perfusion defect was calculated as initial perfusion defect minus perfusion defect at 7- to 14-day scintigraphy. Late reduction in the perfusion defect was calculated as perfusion defect in the 7- to 14-day scintigraphy minus perfusion defect in the 6-month scintigraphy. All measurements were performed in the scintigraphic core laboratory by investigators unaware of clinical or angiographic data.

**Angiographic evaluation.** Coronary angiography was performed according to standard criteria. A repeat coronary angiography was scheduled 6 months after the stenting procedure. Offline analysis of digital angiograms was performed in the core laboratory using an automated edge detection system (CMS, Medis Medical Imaging Systems, Neuen, the Netherlands) by personnel blinded to the scintigraphic data. Identical projections were used for initial and follow-up angiographic examinations. The initial and postprocedural blood flow in the infarct-related artery was graded according to the Thrombolysis In Myocardial Infarction (TIMI) system (11). Collateral circulation was quantified according to Rentrop et al. (12). Global LVEF was determined by using the area-length method (13).

**Follow-up.** After discharge, the clinical follow-up was achieved by means of a phone interview at 1 month, a visit at 6 months, and telephone interviews at 1-year intervals thereafter. As a standard practice in our institution, all patients were scheduled to undergo coronary angiography 6 months after the procedure or whenever they showed symptoms or signs of myocardial ischemia. Furthermore, patients were advised to contact our outpatient clinic or their referring physicians in case of chest pain or other cardiac symptoms. Restenosis was defined as a diameter stenosis ≥50% at the target lesion at follow-up angiography.

**Statistical analysis.** Data are presented as median [25th, 75th percentiles], mean ± SD, counts, or percentages. The normality of distribution was assessed with the 1-sample Kolmogorov-Smirnov test. Continuous data were compared with the Kruskal-Wallis rank-sum test or *t* test. Categoric data were compared with the chi-square test. Analysis of survival was performed by applying the Kaplan-Meier method and log-rank test, which allowed the calculation of relative risk (95% confidence intervals) associated with increase or decrease in the LVEF. Multiple linear regression modeling was used to identify independent predictors of LVEF change (LVEF at 6 months minus baseline LVEF).

### Table 1 Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group With Worsened LV Function (n = 130)</th>
<th>Intermediate Group (n = 130)</th>
<th>Group With Improved LV Function (n = 366)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60.5 [52.7, 70.0]</td>
<td>59.8 [52.4, 69.1]</td>
<td>60.6 [52.7, 67.9]</td>
<td>0.92</td>
</tr>
<tr>
<td>Female gender</td>
<td>34 (26.2)</td>
<td>29 (22.3)</td>
<td>82 (22.4)</td>
<td>0.66</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (10.0)</td>
<td>30 (23.1)</td>
<td>63 (17.2)</td>
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<tr>
<td>Arterial hypertension</td>
<td>87 (66.9)</td>
<td>80 (61.5)</td>
<td>250 (68.3)</td>
<td>0.37</td>
</tr>
<tr>
<td>Current smoking</td>
<td>57 (43.8)</td>
<td>62 (47.7)</td>
<td>151 (41.3)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypercholesterolemia (≥240 mg/dl)</td>
<td>72 (55.4)</td>
<td>69 (53.1)</td>
<td>210 (57.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Infarct localization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>46 (35.4)</td>
<td>46 (35.4)</td>
<td>183 (50.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Inferior</td>
<td>49 (37.7)</td>
<td>59 (45.4)</td>
<td>117 (32.0)</td>
<td>0.23</td>
</tr>
<tr>
<td>Lateral</td>
<td>35 (26.9)</td>
<td>25 (19.2)</td>
<td>66 (18.0)</td>
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</tr>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
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<td>105 (80.8)</td>
<td>102 (78.5)</td>
<td>282 (77.0)</td>
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<tr>
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<td>20 (15.3)</td>
<td>25 (19.2)</td>
<td>67 (18.3)</td>
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<td>1 (0.8)</td>
<td>2 (1.5)</td>
<td>8 (2.2)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (3.1)</td>
<td>1 (0.8)</td>
<td>9 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>125.0 [115.0, 140.0]</td>
<td>125.5 [110.0, 143.5]</td>
<td>130.0 [120.0, 140.0]</td>
<td>0.12</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>70.0 [60.0, 75.0]</td>
<td>70.0 [60.0, 80.0]</td>
<td>75.0 [68.0, 80.0]</td>
<td>0.006</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75.0 [67.0, 83.0]</td>
<td>72.0 [65.0, 85.0]</td>
<td>77.0 [67.0, 86.0]</td>
<td>0.43</td>
</tr>
<tr>
<td>Peak creatine kinase-MB (U/l)</td>
<td>217.3 [101.2, 419.2]</td>
<td>233.4 [127.1, 403.1]</td>
<td>169.1 [78.2, 317.4]</td>
<td>0.003</td>
</tr>
<tr>
<td>Time-to-admission interval (min)</td>
<td>525.0 [165.0, 1,200.0]</td>
<td>420.0 [150.0, 975.0]</td>
<td>510.0 [180.0, 942.3]</td>
<td>0.53</td>
</tr>
<tr>
<td>Time-to-treatment interval (min)</td>
<td>658.2 [279.2, 1,338.8]</td>
<td>558.5 [264.8, 1,034.8]</td>
<td>649.0 [292.5, 1,080.0]</td>
<td>0.44</td>
</tr>
<tr>
<td>Therapy at discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ACE inhibitors</td>
<td>125 (96.2)</td>
<td>125 (96.2)</td>
<td>352 (96.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>Statins</td>
<td>124 (95.4)</td>
<td>126 (96.9)</td>
<td>350 (95.6)</td>
<td>0.78</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>127 (97.7)</td>
<td>126 (96.9)</td>
<td>361 (98.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>3 (2.3)</td>
<td>1 (0.8)</td>
<td>3 (0.8)</td>
<td>0.35</td>
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<tr>
<td>Nitrates</td>
<td>2 (1.5)</td>
<td>5 (38.3)</td>
<td>6 (1.6)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Data are median [25th, 75th percentiles] or n (%).

ACE = angiotensin-converting enzyme; LV = left ventricular.
Comparison between correlation coefficients was performed with the Fisher z transformation test. All analyses were performed using the S-Plus statistical package (Insightful Corp., Seattle, Washington). A p value of < 0.05 was considered to indicate statistical significance.

**Results**

Of 1,115 patients with ST-segment elevation acute MI, 929 patients were eligible for the study. Of them 303 patients (83 women, 27%; mean age 66.4 ± 14.1 years) were excluded (Fig. 1). Their initial perfusion defect (median [25th, 75th percentiles]) and LVEF (mean ± SD) were 22.0% [12.0%, 41.0%] of LV and 48.0 ± 11.4%, respectively. Thirty-four patients died within 6 months after acute MI. The remaining 626 patients were analyzed in this study (Fig. 1).

Clinical and angiographic data. In the entire group of patients, baseline (before intervention) LVEF was 51.6 ± 12.0%, and it increased to 57.4 ± 12.8% in the 6-month angiography with an absolute increase (ΔEF) of 5.7 ± 11.3% (p < 0.001). The greatest increase in the LVEF was observed in patients with more reduced baseline LVEF values (Fig. 2). Based on the change between 6-month and baseline LVEF (ΔEF) and considering a margin of error of 3% in the measurement of LVEF by angiography, patients were divided into 3 groups: group with worsened LV function (ΔEF ≤ −3%; n = 130), intermediate group (ΔEF > −3% and < 3%; n = 130), and group with improved LV function (ΔEF ≥3%; n = 366). Baseline characteristics of the patients are shown in Table 1. With the exception of proportions of patients with diabetes and anterior infarction and the values of diastolic blood pressure and peak creatine kinase-MB, which showed significant differences among patients of various groups, the remaining characteristics appeared to differ little among the groups. Angiographic data are shown in Table 2. The only parameter that differed significantly between groups was baseline LVEF, which was significantly lower among patients with improved LV function than among those with worsened LV function.

The LVEF in the 6-month angiography was 48.9 ± 13.6% in patients with worsened LV function, 54.2 ± 12.4% in patients in the intermediate group, and 61.5 ± 10.8% in patients with improved LV function (p < 0.001). Angiographic restenosis was found in 39 patients (24.6%) in the group with worsened LV function, 34 patients (26.2%) in the intermediate group, and 110 patients (30.1%) in the group with improved LV function (p = 0.42). In up to 3 years of follow-up after 6-month angiography, the Kaplan-Meier estimates of target vessel revascularization in patients with were worsened, intermediate, or improved LVEF were 10.0%, 16.9%, and 15.8%, respectively (p = 0.15).

### Table 2 Angiographic Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group With Worsened LV Function (n = 130)</th>
<th>Intermediate Group (n = 130)</th>
<th>Group With Improved LV Function (n = 366)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF at baseline (%)</td>
<td>58.2 ± 12.2</td>
<td>54.1 ± 12.4</td>
<td>48.2 ± 10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of affected vessels</td>
<td></td>
<td></td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>1</td>
<td>48 (36.9)</td>
<td>52 (40.0)</td>
<td>146 (39.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>2</td>
<td>49 (37.7)</td>
<td>40 (30.8)</td>
<td>131 (35.8)</td>
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<tr>
<td>3</td>
<td>33 (25.4)</td>
<td>38 (29.2)</td>
<td>89 (24.3)</td>
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<tr>
<td>Multivessel disease</td>
<td>82 (63.1)</td>
<td>78 (60.0)</td>
<td>220 (60.1)</td>
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<tr>
<td>Vessel treated</td>
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<td></td>
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<tr>
<td>Left main coronary artery</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>48 (36.9)</td>
<td>48 (36.9)</td>
<td>188 (51.4)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex coronary artery</td>
<td>37 (28.5)</td>
<td>29 (22.3)</td>
<td>71 (19.4)</td>
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<tr>
<td>Right coronary artery</td>
<td>45 (34.6)</td>
<td>53 (40.8)</td>
<td>106 (28.9)</td>
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<td>TIMI flow grade before intervention</td>
<td>0.25</td>
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<tr>
<td>0</td>
<td>85 (65.4)</td>
<td>76 (58.4)</td>
<td>200 (54.6)</td>
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<tr>
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<td>11 (8.5)</td>
<td>42 (11.5)</td>
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<td>19 (14.6)</td>
<td>21 (16.2)</td>
<td>64 (17.5)</td>
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<td>11 (8.8)</td>
<td>22 (16.9)</td>
<td>60 (16.4)</td>
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<td>Collateral Rentrop class</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>98 (75.4)</td>
<td>96 (73.8)</td>
<td>256 (69.9)</td>
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<tr>
<td>1</td>
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<td>50 (13.7)</td>
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<td>8 (6.2)</td>
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</tr>
<tr>
<td>3</td>
<td>12 (9.2)</td>
<td>11 (8.5)</td>
<td>33 (9.0)</td>
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</tr>
<tr>
<td>TIMI flow grade after intervention</td>
<td>0.17</td>
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<td></td>
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</tr>
<tr>
<td>0</td>
<td>3 (2.3)</td>
<td>1 (0.8)</td>
<td>2 (0.6)</td>
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</tr>
<tr>
<td>1</td>
<td>3 (2.3)</td>
<td>3 (2.3)</td>
<td>2 (0.6)</td>
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</tr>
<tr>
<td>2</td>
<td>13 (10.0)</td>
<td>7 (5.4)</td>
<td>29 (7.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>111 (85.4)</td>
<td>119 (91.5)</td>
<td>333 (90.9)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD, median [25th, 75th percentiles], or n (%).
LV = left ventricular; LVEF = left ventricular ejection fraction; TIMI = Thrombolysis In Myocardial Infarction.
Scintigraphic data. In the entire group of patients, initial perfusion defect was 24.6% [14.0, 41.0] of LV. It was reduced to 11.0% [5.0, 24.0] of LV in the 7- to 14-day scintigraphy and to 8.0% [2.0, 19.0] of LV in the 6-month scintigraphy (p < 0.001). Reduction in the perfusion defect was greatest in the 7- to 14-day scintigraphy (10.0% [5.0, 20.0] of LV), potentially related to salvaging capacity of mechanical reperfusion. A further late reduction in perfusion defect (1.0% [0.0, 6.0] of LV) was observed in the 6-month scintigraphy (Fig. 3). There was a total reduction of perfusion defect of 12.7% [6.0, 23.2] of LV within 6 months after acute MI.

Scintigraphic data in groups with improved or worsened LV function are shown in Table 3. Initial perfusion defect and perfusion defect in the 7- to 14-day scintigraphy did not differ significantly among patients of both groups. Perfusion defect in the 6-month scintigraphy was significantly larger among patients with worsened LV function than in patients with improved LV function. There was a greater early reduction in the perfusion defect in the group with improved LV function than in the group with worsened LV function.

Correlation between perfusion defect and LVEF. Initial perfusion defect correlated moderately but significantly with baseline LVEF (R = −0.52; p < 0.001). The correlation between perfusion defect and LVEF at 6 months (R = −0.62; p < 0.001) was stronger than correlation between these parameters in baseline measurements (p = 0.004). There was an inverse correlation between initial perfusion defect and the ΔEF (R = −0.4; p < 0.001).

Results of multivariable analysis. The multiple linear regression model was used to identify the independent predictors of 6-month LVEF change (ΔEF). The following variables were entered into the model: age, gender, diabetes, arterial hypertension, hypercholesterolemia, smoking, infarct localization, multivessel disease, therapy at discharge (statins, angiotensin-converting enzyme inhibitors, and beta-blockers), peak creatine kinase-MB, time-to-treatment interval, vessel affected, baseline TIMI flow grade, postintervention TIMI flow grade, collateral class, initial perfusion defect, early reduction in perfusion defect, late reduction in perfusion defect, baseline LVEF, and restenosis. The ΔEF was entered as a continuous variable. The model identified baseline LVEF, initial perfusion defect, early reduction in perfusion defect, late reduction in perfusion defect, previous coronary artery bypass surgery, and smoking as independent predictors of the 6-month ΔEF. The level of significance and the direction of association are shown in Table 4.

3-year survival. In up to 3 years of follow-up after the 6-month examinations, 15 patients died: 5 patients in the group with improved LV function, 4 in the intermediate group, and 6 in the group with worsened LV function (Kaplan–Meier estimates of mortality: 1.2%, 4.4%, and 5.6%, respectively; relative risk 0.29, 95% confidence inter-

Table 3 Scintigraphic Data According to Change in the LVEF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group With Worsened LV Function (n = 130)</th>
<th>Intermediate Group (n = 130)</th>
<th>Group With Improved LV Function (n = 366)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion defect</td>
<td>20.7 [13.0, 33.5]</td>
<td>21.8 [12.6, 35.4]</td>
<td>25.0 [14.0, 41.9]</td>
<td>0.16</td>
</tr>
<tr>
<td>Perfusion defect at 7 to 14 days (% of LV)</td>
<td>12.0 [4.5, 23.2]</td>
<td>10.0 [3.3, 25.8]</td>
<td>9.8 [3.0, 22.0]</td>
<td>0.39</td>
</tr>
<tr>
<td>Perfusion defect at 6 months (% of LV)</td>
<td>10.5 [3.0, 21.8]</td>
<td>8.0 [2.7, 20.0]</td>
<td>7.0 [2.0, 17.0]</td>
<td>0.012</td>
</tr>
<tr>
<td>Reduction in perfusion defect</td>
<td>9.0 [4.0, 13.9]</td>
<td>7.0 [3.1, 15.6]</td>
<td>12.0 [6.0, 23.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early reduction in perfusion defect (% of LV)</td>
<td>1.0 [0.0, 5.0]</td>
<td>1.0 [−0.7, 6.6]</td>
<td>1.2 [0.0, 6.1]</td>
<td>0.36</td>
</tr>
<tr>
<td>Late reduction in perfusion defect (% of LV)</td>
<td>10.0 [6.0, 16.0]</td>
<td>10.5 [6.0, 18.7]</td>
<td>14.4 [7.0, 29.0]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ΔEF = left ventricular ejection fraction (LVEF) at 6 months minus baseline LVEF.
val 0.09 to 0.90; \( p = 0.03 \) for comparing improved LV function with worsened LV function) (Fig. 4).

**Discussion**

**Main findings.** In a large series of patients who survived the first 6 months and received a contemporary reperfusion and chronic therapy, we assessed the LV function and evolution of infarct size after acute MI using reliable tools.

The main findings of this study are as follows: 1) in the majority of patients with acute MI undergoing mechanical reperfusion, there is a reduction in the infarct size and an improvement in the LV function size up to 6 months after an acute event; 2) the greatest improvement in the LV function occurred in patients with more depressed baseline LVEF; 3) the early and late reduction in the perfusion defect are independent predictors of LVEF improvements at 6 months; and 4) LV function improvement is associated with beneficial effects in the long-term survival.

**Evolution of infarct size and LVEF.** The present study showed an improvement in the 6-month global LV function in a majority of patients with acute MI undergoing current mechanical reperfusion therapy. These findings are supported by earlier (4,5) and recent (14) studies using sestamibi imaging (4,5) or magnetic resonance imaging (14) that have reported recovery of LV function after acute MI. Initial perfusion defect, baseline LVEF, and markers of myocardial salvage (particularly early reduction in perfusion defect) were the strongest independent predictors of the change in the LVEF, demonstrating that patients with more depressed LV function and those with greater myocardial salvage showed the greatest improvement in the LV function. Although the mechanism of the inverse relationship between the baseline LVEF and the magnitude of the improvement of 6-month LV function is not entirely clear, functional recuperation of hibernating or ischemic myocardium seems a reasonable explanation. Furthermore, functional recuperation of stunned myocardium after restoration of blood flow by mechanical reperfusion may be another factor that contributes to improvement in the LV function. Because the uptake and retention of \(^{99m}\)Tc-sestamibi do not appear to be affected by stunning (15,16), reperfused but stunned myocardium areas may explain perfusion-contraction mismatch observed in patients with acute MI. As previously reported by Christian et al. (17), 25% of patients with acute MI had a “mismatch stunned” pattern, meaning that these patients had an LVEF lower than expected by their infarct size at hospital discharge owing to myocardial stunning, and these patients showed a late increase in the LVEF. The apparent paradox with respect to univariate analysis is caused by the concomitant presence of myocardial salvage in the multivariable analysis. With regard to relationship between initial perfusion defect and the change in LVEF, the results of multivariable analysis should be interpreted as indicating that both a small initial perfusion defect and a large amount of salvage are independently associated with improvement in LV function. The actual relationship observed in univariate analysis, where a larger perfusion defect was observed among patients with greater improvement in LV function, may be merely the consequence of interrelationship between large initial perfusion defects and large amount of salvage.
The information on the evolution of the infarct size after acute MI is very limited. Galli et al. (4) reported a significant late reduction in the resting perfusion defect in paired sestamibi studies performed at 5 weeks and 7 months in 47 of 68 patients with acute anterior MI. Owing to the timing of the paired sestamibi examinations, that study does not offer information on the early reduction in the perfusion defect or the impact of reperfusion therapy on myocardial salvage. A more recent study, which included 24 patients with acute MI, reported a progressive decrease in the perfusion defect up to 3 months after primary angioplasty (5). The progressive decrease in the perfusion defect was associated with significant improvement in the LVEF (from 40% at baseline to 50% at 3 months). The present study showed that perfusion defect reduced up to 6 months after acute MI. The greatest reduction occurred earlier after MI and was quantified in the 7- to 14-day sestamibi imaging and reflects the salvaging capacity of reperfusion therapy. A late reduction in the perfusion defect was observed between 7 to 14 days and 6 months after acute MI. Hypothetically, several factors may explain the late reduction in the perfusion defect. First, there is evidence that sestamibi imaging underestimates myocardial viability in the presence of hibernating myocardium (18). Because sestamibi uptake is a function of blood flow and myocardial viability in the presence of flow-limiting coronary stenoses, hibernating (viable but underperfused) myocardium may be poorly differentiated from true fibrotic tissue. Restoration of the blood flow through previously hibernating regions may increase the sestamibi uptake and the capacity of imaging to better differentiate viable from fibrotic tissue, resulting in diminution of the perfusion defect. Importantly, the presence and functional recovery of hibernating myocardium may be another factor that explains improvement in the LV function, particularly in patients with reduced LV function, owing to the reperfusion-contraction mismatch that characterizes hibernating myocardium. Second, it has been reported that vascular stunning in the region of infarction may persist for weeks to months after restoration of blood flow by balloon angioplasty (19). Gradual recuperation of the microvascular function improves tissue reperfusion and sestamibi uptake and may result in further reduction in the reperfusion defect. Prolonged time course of the recuperation in the microvascular function after acute MI allows us to assume that at least a part of this recuperation may occur in the weeks after second sestamibi imaging in the present patients. Third, there may be an inherent property of infarct size to shrink in the days to weeks after acute MI owing to edema reabsorption and phagocytation of dead myocardial cells (early shrinkage) and collagen production and contraction (late shrinkage) (20).

The present study demonstrated that early and late reduction in the perfusion defect contributed independently to the improvement in the LV function. This is an important and, to our knowledge a novel finding. The magnitude of the early reduction in the perfusion defect (10% of the LV mass) may reasonably explain the positive association between early reduction in the perfusion defect and the degree of the LV function improvement. In a previous study, we have reported that the amount of myocardium salvaged by reperfusion therapy (equivalent to early reduction in the present study) is an independent predictor of 6-month mortality after acute MI (21). Because early reduction in the perfusion defect is a marker of efficacy of reperfusion therapy, we offer further evidence that the amount of myocardium salvaged by reperfusion therapy is an important predictor of the improvement of the LV function as well. Although the positive relationship between late reduction in the perfusion defect and improvement in the LV function is not easily explainable, 2 putative mechanisms may be proposed: first, reduction in perfusion defect of the magnitude of 1% of the LV mass may be functionally important for LV function improvement; and second, late reduction in the perfusion defect may be a marker of positive LV remodeling in general.

**Clinical implications.** The present study has implications regarding the use of LVEF or infarct size as end points in trials of cell-based cardiac repair after acute MI. First, LV function improves and infarct size reduces within the first 6 months after acute MI. The magnitude and direction of the change of these parameters should be considered when evaluating the efficacy of cell-based cardiac repair therapy or estimating sample size of the study groups. Second, the fact that the greatest improvement in the LV function occurs in those with more reduced LV function deserves attention when assessing the efficacy of cell-based cardiac repair therapy, because LV function improvement may result from imbalances in the patients’ characteristics (inherent feature of LVEF to increase in patients with reduced LV function) rather than from the therapy itself. In fact, in the REPAIR-AMI (Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction) trial, which used autologous mononuclear progenitor cells, improvement in LV function was observed only in patients with LVEF <49% but not in those with LVEF >49% (22). Third, because the greatest myocardial salvage occurs early after acute MI owing to salvaging capacity of reperfusion therapy, the efficacy of cell-based cardiac repair therapy may be masked by the powerful effect of reperfusion therapy if both therapies are closely applied. The REPAIR-AMI trial demonstrated that intracoronary delivery of bone marrow cells in patients with acute MI improved LV function only for patients who received therapy >5 days after acute MI (22).
scintigraphy to quantify the perfusion defect after acute MI. Another alternative may be the use of magnetic resonance imaging as a quantifier of infarct size. However, contrast-enhanced magnetic resonance imaging is a less standardized test than sestamibi scintigraphy for quantification of infarct size (1), and there are reports that contrast-enhanced magnetic resonance imaging overestimates infarct size in rats (23) and humans (24). An eventual impact of regression to the mean phenomenon in the observed results has to be mentioned. The similar values of perfusion defect and LVEF in patients included and excluded does not show any important selection bias regarding these parameters. Furthermore, inclusion of patients with better rather than worse LV function and overall improvement in the LVEF at 6 months of follow-up do not seem to support any important role of regression to the mean phenomenon in the observed results.

Conclusions

The present study demonstrated that in patients with acute MI treated by mechanical reperfusion, LV function is improved and infarct size is reduced within the first 6 months after acute MI. The improvement in LV function is greatest in patients with reduced LV function. Early and late reductions in the perfusion defect are independent predictors of 6-month LV function improvement. Improvement in the LV function positively affects long-term survival.

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REFERENCES
