Early Metoprolol Administration Before Coronary Reperfusion Results in Increased Myocardial Salvage
Analysis of Ischemic Myocardium at Risk Using Cardiac Magnetic Resonance

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Background—β-Blockers improve clinical outcome when administered early after acute myocardial infarction. However, whether β-blockers actually reduce the myocardial infarction size is still in dispute. Cardiac magnetic resonance imaging can accurately depict the left ventricular (LV) ischemic myocardium at risk (T2-weighted hyperintense region) early after myocardial infarction, as well as the extent of necrosis (delayed gadolinium enhancement). The aim of this study was to determine whether early administration of metoprolol could increase myocardial salvage, measured as the difference between the extent of myocardium at risk and myocardial necrosis.

Methods and Results—Twelve Yorkshire pigs underwent a 90-minute left anterior descending coronary occlusion, followed by reperfusion. They were randomized to metoprolol (7.5 mg during myocardial infarction) or placebo. Global and regional LV function, extent of myocardium at risk, and myocardial necrosis were quantified by cardiac magnetic resonance imaging studies performed 4 and 22 days after reperfusion in 10 survivors. Despite similar extent of myocardium at risk in metoprolol- and placebo-treated pigs (30.9% of LV versus 30.6%; \( P =\)NS), metoprolol resulted in 5-fold-larger salvaged myocardium (32.4% versus 6.2% of myocardium at risk; \( P =0.015\)). The LV ejection fraction significantly improved in metoprolol-treated pigs between days 4 and 22 (37.2% versus 43.0%; \( P =0.037\)), whereas it remained unchanged in pigs treated with placebo (35.1% versus 35.0%; \( P =\)NS). The extent of myocardial salvage was related directly to LV ejection fraction improvement (\( P =0.031\)) and regional LV wall motion recovery (\( P =0.039\)) at day 22.

Conclusions—Early metoprolol administration during acute coronary occlusion increases myocardial salvage. The extent of myocardial salvage, measured as the difference between myocardium at risk and myocardial necrosis, was associated with regional and global LV motion improvement. (Circulation. 2007;115:2909-2916.)

Key Words: imaging ■ magnetic resonance imaging ■ metoprolol ■ myocardial infarction

The major determinant of myocardial salvage during an acute myocardial infarction (MI) is the time to reperfusion.1,2 Beyond thrombolysis or immediate percutaneous coronary intervention, other therapies that may prevent myocyte death during MI have been sought. β-Blockers have indisputably been demonstrated to be clinically useful in the setting of acute MI,1 with a large body of evidence showing mortality reductions when administered early.4–7 β-Blockers also decrease the incidence of reinfarction, recurrent ischemia, or life-threatening arrhythmias and prevent left ventricular (LV) remodeling.8–10 Therefore, the use of oral β-blockade constitutes a class I indication in clinical practice guidelines.11 However, early intravenous administration of β-blockers during the acute phase of MI has not been universally adopted.12–14 Whether β-blockers actually reduce MI size is still an unanswered question. Some preclinical studies suggest that β-blockers decrease the extent of necrosis,15–17 whereas others have shown no effect.18–20 The results of human clinical studies, mostly performed in or before the thrombolytic era, also are controversial.5,21–24 In these investigations, MI size was usually quantified either by postmortem analysis15–20 or in vivo by indirect surrogates such as creatine kinase-MB fraction levels or ECG changes.5,21–23 With the advent of delayed-enhancement (DE) cardiac magnetic resonance imaging (CMR), it is now possible to accu-
rately quantify the extent of myocardial necrosis in vivo.25 It also has been shown that CMR can depict the area of myocardium at risk, which displays high signal intensity on T2-weighted images early after MI as a result of the presence of edema.26 Therefore, it is feasible to noninvasively evaluate with CMR the extent of myocardial salvage as the difference between myocardium at risk and myocardial necrosis. The aim of this study was to analyze the therapeutic benefit of early intravenous β-blocker administration on the ischemic myocardium at risk in a swine model of acute coronary occlusion.

**Methods**

**Study Design**

Acute MI was experimentally induced in Yorkshire Albino pigs (n=12; weight, 33 ± 3 kg) by closed-chest, 90-minute left anterior descending coronary artery occlusion. Animals were randomized 1:1 to intravenous metoprol or placebo (sodium chloride). CMR studies were performed 4 and 22 days after MI to quantify LV global and regional functional parameters, area of edema, and MI size. Animals were euthanized within 1 hour after the last CMR study for histopathological validation. The study protocol was approved by an institutional animal research committee.

**Experimental Procedures**

Twelve hours before the experimental MI, a loading dose of clodopredol (150 mg) was administered. Subsequently, clodopredol (75 mg/d) was maintained for 5 days. Anesthesia for the intervention was induced by intramuscular injection of ketamine (30 mg/kg), xylazine (2.2 mg/kg), and atropine (0.05 mg/kg). Animals underwent endotracheal intubation, and anesthesia was maintained by isoflurane inhalation. Continuous infusions of amiodarone (300 mg, 75 mg/h) and lidocaine (150 mg, 37.5 mg/h) were initiated before the procedure in all pigs as prophylaxis for malignant ventricular arrhythmias. Cardiac rhythm and arterial oximetry were monitored continuously during the procedure. MI was induced by catheter-based 90-minute balloon occlusion of the left anterior descending coronary artery immediately after the origin of the first diagonal branch. Approximately 15 minutes after balloon inflation, intravenous metoprol (three 2.5-mg injections every 3 to 5 minutes for a total of 7.5 mg) was infused into the pigs assigned to the β-blocker arm. After balloon deflation, patency of the left anterior descending coronary artery was angiographically confirmed by contrast injection. Buprenorphine (0.03 mg/kg) and cefazolin (25 mg/kg) were administered every 12 hours for 5 days in all animals. For the CMR studies, pigs were anesthetized by intramuscular injection of ketamine, xylazine, and atropine. Anesthesia was maintained by continuous intravenous propofol infusion. Animals were kept under mechanical ventilation. After the last CMR, animals were heparinized (100 IU/kg) and euthanized with pentobarbital (Sleepaway 75 mg/kg, Fort Dodge, Wyeth, Overland Park, Kan), and the heart was excised for histopathological analysis. All animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals.

**Noninvasive CMR Protocol**

CMR studies were performed with a 1.5-T magnet (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany) using a phased-array cardiac coil by investigators blinded to the treatment arm. All images were acquired with ECG gating and during suspended respiration. First, contiguous short-axis cine images covering the LV from base to apex were acquired using a standard steady-state free-precession sequence (repetition time, 3.5 ms; echo time, 1.5 ms, flip angle, 60° to 90°; field of view, 200×150 mm; phase oversampling, 80%; generalized autocalibrating partially parallel acquisitions (GRAPPA) factor, 2; matrix, 192×115; slice thickness, 6 mm; no gap; bandwidth, 930 Hz per pixel; lines per segment, 11). Subsequently, edema imaging was performed with a T2-weighted, triple inversion-recovery fast spin-echo sequence27 (repetition time, 2 to 3 heartbeats; echo time, 65 ms; time interval, 100 ms; field of view, 300×225 mm; matrix, 256×125; slice thickness, 6 mm; bandwidth, 349 Hz per pixel; echo-train length, 17). Finally, DE imaging was performed 15 minutes after the administration of 0.2 mmol/kg gadopentetate dimeglumine using an inversion-recovery fast gradient-echo sequence28 (repetition time, 8 ms; echo time, 4 ms; time interval optimized to null normal myocardium; gating factor, 2 to 3; field of view, 300×225 mm; matrix, 256×144; slice thickness, 6 mm; bandwidth, 160 Hz per pixel; lines per segment, 23). The slice positions for both T2-weighted and DE acquisitions matched those of the cine images.

**CMR Data Analysis**

All CMR images were analyzed by researchers blinded to the study arm or histopathology data. LV function analysis was performed with dedicated software (Argus, Siemens Corporate Research, Princeton, NJ).29 After manual tracing of epicardial and endocardial contours, a large region of interest was drawn within a remote normal myocardial segment. Abnormal areas for each sequence, defined as those with a signal intensity 3 SD above the mean signal intensity of normal myocardium,30 were automatically highlighted and quantified (Figure 1). Myocardial necrosis was defined by the extent of abnormal DE; myocardium at risk was defined by the extent of edema (high signal intensity on T2-weighted images) in the day 4 CMR study;31 and salvaged myocardium was defined as the difference between myocardium at risk and myocardial necrosis. All measurements were expressed as percentage of the total LV myocardial volume; the absolute MI size also was quantified in grams (calculated as volume multiplied by myocardial density [1.05 g/cm³]). The transmural extent index of MI within each segment was calculated as a percentage of the total segment area as previously described.31 Global transmural extent index of MI was calculated as the mean of all segmental transmural extent indexes of MI in the DE-positive segments. In addition, 3 consecutive short-axis slices containing both edema and DE were selected in each animal for the segmental (regional) analyses of edema and DE distribution.

In the T2-weighted and DE images, the signal-to-noise ratios of both normal and abnormal myocardium were quantified as the average of the mean signal intensity within a region of interest divided by the mean value of noise (obtained from a region of interest in the air). Contrast-to-noise ratios of abnormal versus normal myocardium were defined as the difference of their signal-to-noise ratios.26

**Histological Infarct Size Analysis**

After the animals were sacrificed, the hearts were perfused with cold PBS and stiffened by overnight immersion in isotonic agar solution at 4°C. After stiffening, hearts were washed with cold PBS, and the LV was sliced (short-axis, 6-mm-thick slices without gap) with a commercial meat slicer. Slices were incubated for 5 to 7 minutes in warm 1% trimethyl tetrazolium chloride (TTC) solution at 37°C.32 After TTC incubation, the slices were immersed in 4% paraformaldehyde for 12 hours. After paraformaldehyde fixation, high-resolution digital images from all slices were acquired, and areas of infarction (negative for TTC staining) and normal myocardium (positive TTC staining) were quantified with Image J software (National Institutes of Health, Bethesda, Md) (Figure 2, top). The MI volume was expressed as a percentage of the total LV myocardium.
Statistical Analysis
Continuous variables are expressed as mean±SEM. Statistical comparisons of means were made by Student’s paired and unpaired t tests. To calculate the correlation of variables, Pearson’s coefficients were used. The limits of agreement between infarct size in DE CMR and histology were analyzed by the Bland-Altman plot. Two multivariate linear regression models were performed to predict the change of global LVEF and segmental systolic thickening, respectively. Baseline (day 4 CMR) variables that either had a clinically plausible relation to improvement of function or appeared to be associated with an increase in LVEF or regional systolic thickening, indicated by a value of P<0.20 in univariate analysis, were used as independent variables. For the global and regional functional improvement, the independent variables were LVEF, volume of noninfarcted myocardium, global transmural extent index of MI, and extent of salvaged myocardium (global) and percentage of systolic thickening within each segment, segmental volume of noninfarcted myocardium, transmural extent index of MI, and the extent of segmental salvaged myocardium (regional). A value of P<0.05 (2 tailed) was considered statistically significant. All statistical analyses were performed with the statistical software package SPSS 11.0 (SPSS Inc, Chicago, Ill).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Successful left anterior descending coronary artery occlusion was achieved in all 12 cases. Two animals died of refractory ventricular fibrillation during the procedure. Therefore, a total of 10 pigs (6 in the metoprolol arm, 4 in the placebo group) made up the final study. Both groups showed a similar mean heart rate during the procedure (66±2 and 65±3 bpm for the metoprolol and placebo groups, respectively; P=NS). The metoprolol group showed a significantly lower incidence of ventricular fibrillation than the placebo group (33% versus 66%, respectively; P=0.047) and a similar rate of ventricular tachycardia (33% versus 33%; P=NS) during the procedure.

CMR Analysis
The average signal-to-noise ratio for the T2-weighted images was 9.94±0.5 in the edematous myocardium and 3.77±1.7 in the remote normal myocardium (P<0.001). The corresponding values on the DE images were 6.68±0.3 for infarcted myocardium and 1.57±0.1 for normal myocardium, respectively (P<0.001). The contrast-to-noise ratio between abnormal and normal myocardium was similar for both sequences (6.17±0.5 for T2-weighted images, 5.11±0.3 for DE images: P=NS).

The results of CMR-derived parameters at days 4 and 22 after MI are presented in the Table. At day 4, no significant differences were observed in LVEF between study groups. From day 4 to 22, the LVEF significantly improved in the metoprolol arm (P=0.037), whereas it remained unchanged in the placebo arm. Change in the LVEF from day 4 to 22 was higher in metoprolol animals (5.8 versus −0.1; P=0.079). Metoprolol treatment resulted in a significantly smaller extent of MI in terms of both absolute infarct mass and percentage of the LV myocardium, noticeable at day 4. The extent of myocardium at risk (volume of edema at day 4 CMR) did not differ between the 2 groups. As a result, the percentage of salvaged myocardium (the primary comparison of the study)
was significantly larger in metoprolol animals (32.4±6.0%) than in the placebo group (6.2±6.8%; P=0.015; the Table and Figure 3).

In all cases, the transmural extent index of MI was 100% in ≥4 segments. Regional analysis of DE-positive segments showed a nonsignificant difference in the transmural extent index of MI (73±3% in metoprolol versus 68±3% in the placebo group; P=NS; Figure 4).

Overall, at day 4, edema-positive segments showed a statistically significant lower percentage of systolic thickening than nonedematous segments (20±2% versus 38±3%; P<0.001). In addition, we found a statistically significant inverse correlation (R=−0.42, P<0.001) between the presence of edema and percentage systolic thickening at day 4.

To examine which CMR parameters at day 4 predict global or segmental functional improvement over time, multivariate regression models were used. The basal LVEF (β=0.979, P=0.004) and the extent of salvaged myocardium at day 4 (β=0.897, P=0.039) were strongly associated with improvement of LVEF over time. The global transmural extent index also showed a nonstatistically significant (β=0.854, P=0.065) association with LVEF improvement.

At a segmental level, the regional size of salvaged myocardium at day 4 was the only variable associated with the improvement in percentage of wall thickening between days 4 and 22 (β=0.333, P=0.036).

Histopathology–CMR Correlation
Excellent correlation (R=0.844, P=0.008) and agreement (mean bias, −2%; limits of agreement, 4.1% and −8%) were observed between infarct volume in histology (TTC staining) and the volume of DE in the last CMR (Figure 2). No correlation was observed between infarct volume on histology and volume of edema in the last CMR study.

Discussion
In this study, we describe the benefits associated with early administration of metoprolol on LV function and myocardial salvage in an experimental model of acute coronary occlusion. The porcine model of acute MI was selected because of the anatomophysiological similarities with humans. The functional and structural LV performance was evaluated in a reproducible swine model of anterior wall MI over a 3-week period. The reproducibility of the experimental model is highlighted by the small dispersion values of the volume of myocardium at risk (30.7±1.6% of LV). We exploited the versatility and the noninvasive characteristics of high-resolution CMR, validating the results with the most conventional histopathological analysis. The main findings of the present study are that (1) intravenous metoprolol during coronary occlusion and before mechanical reperfusion is a highly effective cardioprotective agent, resulting in a 27% smaller MI than placebo, despite an initially equivalent amount of myocardium at risk, a cardioprotective effect that was independent of its negative chronotropic effects, and (2) the extent of myocardial salvage was an independent predictor of LV functional recovery, both global and regional wall motion.

To the best of our knowledge, this is the first in vivo, noninvasive evaluation of the effect of β-blockade on MI size with high-resolution CMR. In addition, we could perform detailed in vivo characterization of the entire ischemic region, not only of the MI size but also of the salvaged myocardium (noninfarcted myocardium at risk). A controlled model of experimental MI enabled us to evaluate the independent effects of intravenous metoprolol administration on MI size. This may be more difficult to achieve in a clinical environment, where many other factors such as duration and degree of coronary occlusion, completeness of reperfusion, and prior medication use play a role in final MI size.
The efficacy of β-blockers as cardioprotective agents has been widely studied. Preclinical animal studies have shown contradictory results: Experimental models of reperfused \(^15,19\) and nonreperfused \(^16,18,20\) MI showed either a reduction in \(^15,16\) or no effect on the final MI size. \(^18–20\) Most of the animal studies analyzed the MI size ex vivo (postmortem) early after the MI induction without follow-up.

In clinical practice, β-blockers have unquestionably demonstrated to be beneficial in the setting of acute MI, resulting in reduced mortality when administered early. \(^4–6\) As a result, current practice guidelines recommend early β-blockade in subjects after an acute MI, \(^11\) although no general consensus exists on the optimal timing of administration. In this clinical scenario, the effect of β-blockade on MI size is controversial.

In the prethrombolytic era, several clinical trials investigated the impact of β-blockade on MI size. In the Multicenter Investigation of the Limitation of Infarct Size trial, intravenous propranolol followed by oral treatment failed to reduce MI size. \(^24\) Comparable results were found with similar regimens of propranolol administration by other investigators. \(^33\) Contrarily, other studies have demonstrated a significant reduction in MI size in patients receiving β-blockers compared with control subjects. \(^4,21,23\) In the thrombolytic era for MI reperfusion, the results were also inconclusive. Van de Werf et al \(^34\) showed that the intravenous administration of atenolol followed by oral therapy to MI patients receiving...

<table>
<thead>
<tr>
<th>CMR-Derived Parameters</th>
<th>Metoprolol</th>
<th>Placebo</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 4 CMR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>96±6</td>
<td>123±12</td>
<td>0.06</td>
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<tr>
<td>LVESV, mL</td>
<td>59±3</td>
<td>82±15</td>
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<tr>
<td>LVEF, %</td>
<td>37.2±3.3</td>
<td>35.1±5.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Myocardium at risk,* % of LV with edema</td>
<td>30.9±1.9</td>
<td>30.6±1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Infarct volume, % of LV</td>
<td>20.9±1.6</td>
<td>28.7±2.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Infarct mass, g</td>
<td>12.7±0.7</td>
<td>21.9±2.3</td>
<td>0.002</td>
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<tr>
<td>Salvaged myocardium,† % of LV</td>
<td>10.0±2.3</td>
<td>1.9±1.2</td>
<td>0.028</td>
</tr>
<tr>
<td>Percent salvaged myocardium‡</td>
<td>32.4±6.0</td>
<td>6.2±6.8</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Day 22 CMR</strong></td>
<td></td>
<td></td>
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<tr>
<td>LVEDV, mL</td>
<td>109±8</td>
<td>132±9</td>
<td>0.1</td>
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<tr>
<td>LVESV, mL</td>
<td>62±5</td>
<td>86±10</td>
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<tr>
<td>LVEF, %</td>
<td>43.0±2.8§</td>
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<td>0.1</td>
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<tr>
<td>LV with edema, %</td>
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<td>20.0±2.5§</td>
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<tr>
<td>Infarct volume, % of LV</td>
<td>16.6±1.3</td>
<td>20.6±1.7§</td>
<td>0.1</td>
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<tr>
<td>Infarct mass, g</td>
<td>11.5±1.2</td>
<td>16.4±1.4§</td>
<td>0.04</td>
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</table>

Values are mean±SEM where appropriate. LVEDV indicates LV end-diastolic volume; LVESV, LV end-systolic volume.

*Edematous myocardium.
†The volume of LV showing edema but not DE in the day 4 CMR.
‡Obtained as follows: 100×extent of salvaged myocardium/extent of edematous myocardium in the day 4 CMR.
§Significant differences between day 4 and 22 CMR.

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**Figure 3.** Percent salvaged myocardium (salvaged myocardium normalized to myocardium at risk). The y axis corresponds to “100×extent of salvaged myocardium/extent of myocardium at risk.” A, Mean and SE of the mean of both treatment arms; B, the individual data.

**Figure 4.** Distribution of the transmural extent index of MI in DE-positive segments. Center line represents the 50th percentile; box plots illustrate the 25th and 75th percentiles.
alteplase did not reduce MI size. In the Thrombolysis Early in Heart Attack Trial,35 patients from the recombinant tissue plasminogen activator plus metoprolol arm had smaller MIs than those in the recombinant tissue plasminogen activator alone arm. In the age of percutaneous interventions for coronary revascularization, the effect of β-blockade has been analyzed in a limited and nonrandomized fashion. Although several observations have confirmed the beneficial clinical effect of early β-blockade after MI with this invasive reperfusion modality,36–38 the effect of β-blocker administration in MI size remains unclear. The administration of β-blockers before elective percutaneous coronary interventions also has been associated with significant discrepancies; although intracoronary propranolol resulted in less myocardial damage,39 the oral administration of metoprolol failed to demonstrate any evidence of less myocardial injury.40 Finally, prior chronic treatment with β-blockers was associated with smaller MIs after primary percutaneous intervention.41 One limitation in the interpretation of the clinical results is that the MI size measurement was done mostly by indirect methods such as ECG changes or creatine kinase-MB fraction release.

Our study represents a model of mechanical MI reperfusion closely mimicking the human scenario. The findings reported here suggest that initiation of this therapy while the artery is still occluded results in significant cardioprotection, a finding that might have significant clinical implications. We started the metoprolol infusions 75 minutes before reperfusion to mimic a hypothetical human scenario in which the intravenous β-blocker agent could be initiated at MI diagnosis (in patients without contraindications). In addition, metoprolol injection was associated not only with smaller MI size at day 4 but also with significant LVEF recovery at day 22. These observations are in agreement with the results from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial in which early intravenous β-blockade was associated with greater improvements in LVEF over time.37

The exact mechanism(s) of action by which β-blockers could result in reductions in MI size remain to be fully elucidated. It has been widely suggested that β-blockers lessen the magnitude of the MI by decreasing oxygen consumption secondary to slow heart rate during or early after MI.11 However, in our study, the reduction in MI size was independent of the heart rate achieved during the MI induction.

Early after a coronary occlusion, the ischemic area at risk of necrosis is characterized by substantial interstitial and intracellular edema, which may be further increased by reperfusion.42,43 In addition, reperfusion may further increase the production of edema.44 Postischemic edematous area can be visualized with the use of T2-weighted “black-blood” CMR, and the use of this approach to depict the ischemic myocardium at risk has been validated by different groups using different experimental models.26,42 In addition, the extent of myocardial necrosis can be depicted accurately with the use of DE CMR as validated with histopathology in our and other studies,25 enabling noninvasive visualization of both the infarcted tissue and the myocardium at risk.

An important finding of our study is that the extent of salvaged myocardium at day 4 was identified as an independent predictor of LV functional recovery. This is in agreement with the study by Aletras et al,26 who showed improvement in contractility in edematous areas early after experimental MI in a canine model. Coronary occlusion in dogs usually leads to subendocardial MI as a result of a well-developed net of collaterals.45 In such cases, it is difficult to ascertain whether the presence of edema provides incremental information over the transmural extent of MI for the prediction of contractile function recovery. In our study, we found that the extent of salvaged myocardium was a strong predictor of regional and global functional improvement independently of total volume of noninfarcted myocardium,46 transmural extent of MI,47,48 or global size of edematous area,26 providing valuable further comprehensive information.

This novel predictor of LVEF improvement highlights the value of visualizing both the final size of necrosis and the extent of salvaged myocardium. This may be important in evaluations of the efficacy of cardioprotective and regenerative therapies.49

Study Limitations

Given the small sample size, a relatively large number of statistical tests were performed. Despite this potential source of statistical bias, all the results in this work point the same direction; therefore, we believe that the totality of the evidence is strong enough to support the results reported here.

We administered metoprolol in a single time point. Thus, our investigation does not allow conclusions regarding the potential additive gains associated with maintained β-blockade in the post-MI period. Similarly, whether chronic use of β-blockers before the MI lessens the beneficial effect of intravenous therapy, as suggested by some studies,37,41 requires further investigation. In our protocol, we used continuous infusion of amiodarone during the entire procedure as prophylaxis for malignant arrhythmias. Amiodarone also exerts a small β-blocker activity, which probably explains the similar heart rate in both groups, and thus could have mitigated the differences between the metoprolol and placebo groups. Although the use of a different antiarrhythmic drug without β-blocker properties would have been desirable, in our experience, the mortality of MI induction without amiodarone infusion is very high in this animal model. Nevertheless, because both study arms received the same dose of medication, the potential benefits associated with the use of amiodarone should be identical in both groups. Thus, the significant differences seen in our study should be associated exclusively with the administration of metoprolol.

Conclusions

In a swine MI model closely mimicking human cardiac anatopathology, a single dose of metoprolol during ongoing MI results in 5-fold-larger salvaged myocardium (27% reduction in MI size). This increase is independent of decreases in heart rate with the administration of the drug. Our results suggest that, in the setting of acute MI, β-blockers should be administered as early as possible, while the
coronary artery is still occluded. The cardioprotective effect was demonstrated by the smaller infarct size and larger area of salvaged myocardium. In addition, this study shows the predictive value of the quantification of salvaged myocardium on regional and global LV function recovery at 3 weeks.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Beyond time to reperfusion (the major determinant for myocardial salvage in acute myocardial infarction), interventions to reduce myocardial death (cardioprotection) are strongly needed to move ahead in this field. β-Blockers have been shown to reduce mortality in the acute myocardial infarction setting, but early intravenous administration before mechanical reperfusion is not widely adopted. In fact, ST-segment–elevation myocardial infarction practice guidelines catalogue oral β-blocker administration as a class I indication; the intravenous route is a class IIA indication. In the era of mechanical reperfusion for ST-segment elevation myocardial infarction, the reperfusion injury is a frequently observed phenomenon. It has been suggested that some cardioprotective therapies may act by reducing this reperfusion-related incident. If this were the case, effective circulating levels of the eventually cardioprotective drug at reperfusion would be crucial. Whether the cardioprotection observed in this study is related to a reduction in reperfusion-related myocyte loss is not addressed, but it is plausible and therefore deserves to be fully elucidated. Cardiac magnetic resonance imaging allows direct visualization of cardioprotection early after acute myocardial infarction, as shown here. This provides an accurate tool to explore the effect of certain interventions in humans. In this work, the extent of salvaged myocardium, as directly assessed by cardiac magnetic resonance imaging 4 days after acute myocardial infarction, correlated with the local and global left ventricular motion recovery. This novel predictor of left ventricular recovery may be used in the clinical area as a surrogate end point for early assessment of cardioprotective-regenerative therapies.
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