Activatable Magnetic Resonance Imaging Agent Reports Myeloperoxidase Activity in Healing Infarcts and Noninvasively Detects the Antiinflammatory Effects of Atorvastatin on Ischemia-Reperfusion Injury

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Background—Ischemic injury of the myocardium causes timed recruitment of neutrophils and monocytes/macrophages, which produce substantial amounts of local myeloperoxidase (MPO). MPO forms reactive chlorinating species capable of inflicting oxidative stress and altering protein function by covalent modification. We have used a small-molecule, gadolinium-based activatable sensor for magnetic resonance imaging of MPO activity (MPO-Gd). MPO-Gd is first radicalized by MPO and then either spontaneously oligomerizes or binds to matrix proteins, all leading to enhanced spin-lattice relaxivity and delayed washout kinetics. We hypothesized that MPO imaging could be used to measure inflammatory responses after myocardial ischemia locally and noninvasively in a murine model.

Methods and Results—We injected 0.3 mmol/kg MPO-Gd (or Gd-DTPA as control) and performed magnetic resonance imaging up to 120 minutes later in mice 2 days after myocardial infarction. The contrast-to-noise ratio (infarct versus septum) after Gd-DTPA injection peaked at 10 minutes and returned to preinjection values at 60 minutes. After injection of MPO-Gd, the contrast-to-noise ratio peaked later and was higher than Gd-DTPA (40.8±10.4 versus 10.5±0.2; P<0.05). MPO imaging was validated by magnetic resonance imaging of MPO−/− mice and correlated well with immunoreactive staining (r²=0.92, P<0.05), tissue activity by guaiacol assay (r²=0.65, P<0.001), and immunoblotting. In time course imaging, activity peaked 2 days after coronary ligation. Flow cytometry of digested infarcts detected MPO in neutrophils and monocytes/macrophages. Furthermore, serial MPO imaging accurately tracked the antiinflammatory effects of atorvastatin therapy after ischemia-reperfusion injury.

Conclusions—MPO-Gd enables in vivo assessment of MPO activity in injured myocardium. This approach allows noninvasive evaluation of the inflammatory response to ischemia and has the potential to guide the development of novel cardioprotective therapies. (Circulation. 2008;117:1153-1160.)

Key Words: inflammation • magnetic resonance imaging • myocardial infarction • myeloperoxidase • reperfusion

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Gadolinium (Gd) chelates (eg, Gd-DTPA), currently the only clinically approved imaging agent in cardiovascular magnetic resonance imaging (MRI), distribute passively to the extracellular space and do not reflect the degree of active inflammation because acute infarction and chronic infarction enhance alike.11 We have recently developed an activatable and specific MPO sensor (5-hydroxytryptamide [MPO-Gd])12 and use it in the present study to image MPO activity in the heart. We hypothesize that during the inflammatory phase of myocardial ischemic injury, MPO activates the small-molecule substrate, which then polymerizes and exhibits increased T1 relaxivity, protein binding, and “trapping” in areas of high MPO activity, all leading to increased enhancement on T1-weighted MRI. We correlate noninvasive imaging data with ex vivo MPO tissue activity and study MPO activity in wild-type and MPO−/− mice with MI and ischemia-reperfusion injury. We further aimed to use this agent to characterize the time course of postinfarction MPO activity and to demonstrate that the agent possessed adequate dynamic range to image the antiinflammatory actions of statin therapy in vivo.

Methods

Mouse MI

This study used 56 C57BL6 mice (The Jackson Laboratory, Bar Harbor, Me; validation experiments, n=19; time course imaging, n=15; flow cytometry, n=10; ischemia-reperfusion experiments; n=12). In addition, we used 4 heterozygous and 3 homozygous MPO-deficient mice for validation purposes (The Jackson Laboratory). MI was induced by left coronary artery ligation as described previously.13 For sham surgery, a thoracotomy was performed and a suture was passed underneath the coronary artery that was not ligated. In animals subjected to ischemia-reperfusion injury, the coronary artery was ligated for 30 minutes, followed by removal of the ligature. In reperfusion-injury experiments, mice were treated per gavage with control treatment (n=10) or with 100 mg/kg atorvastatin (n=6) 24 hours and 1 hour before surgery. Mice were anesthetized for all surgical and imaging procedures by inhalation anesthesia (isoflurane 1.5% to 3% vol/vol plus 2 L O2). The institutional Subcommittee on Research Animal Care at Massachusetts General Hospital approved all animal studies.

Synthesis of MPO-Gd

The MPO-sensitive imaging agent bis-5-hydroxytryptamide-diethylenetriamine-pentaacetate [bis-SHT-DTPA(Gd)], MPO-Gd; molecular weight, 866 g/mol] was synthesized as described previously.12 Briefly, DTPA-bisahydridize was reacted with serotonin in dimethylformamide in the presence of an excess of triethylamine.12 The product bis-SHT-DTPA was isolated by recrystallization from methanol and acetone.

MRI Studies

We performed in vivo MRI after intravenous injection of MPO-Gd or gadopentetate dimeglumine (Gd-DTPA; Berlex Laboratories, Montville, NJ) at a dosage of 0.3 mmol/kg body weight. A T7 horizontal-bore scanner (Pharmscan, Bruker, Billerica, Mass) and a dedicated mouse heart birdcage coil (Rapid Biomedical, Wuerzburg, Germany) were used to obtain delayed hyperenhancement images of the left ventricle in its short axis. We used ECG and respiratory gating with a T1-weighted gradient-echo fast low-angle shot (FLASH) sequence13 with the following parameters: echo time, 2.7 ms; frames per heart cycle, 16 (repetition time, 7.0 to 12.0 ms, depending on heart rate); flip angle, 60°; in-plane resolution, 200×200 μm; slice thickness, 1 mm; and number of excitations, 8. The images were then analyzed with an OsiriX DICOM reader (free ware, Geneva, Switzerland; www.osiriX-viewer.com). Signal intensity was measured in the infarcted, akinetic lateral left ventricular (LV) wall, the noninfarcted interventricular septum, and a region outside the animal to calculate the contrast-to-noise ratio (CNR): CNR=[target signal–spectral signal]/(SD of the noise). The area enhanced after injection of MPO-Gd was quantified as a fraction of the entire LV myocardial area at the midventricular level for comparison with immunoreactive MPO presence in histological sections. In addition, we quantified the akinetic myocardial area as a percentage of total LV area in the midventricular imaging slice.

MPO Activity Assay

Apical infarcted portions of hearts from various time points after MI were homogenized (Omni International, Marietta, Ga) for 30 seconds on ice in potassium phosphate buffer, pH 7.0, with cetyltrimethylammonium bromide. Samples were sonicated, freeze-thawed 3 times, and centrifuged to remove debris, and 50-fold dilutions of heart samples were dissolved in potassium phosphate buffer containing 120 μmol/L guaiacol and 900 μmol/L H2O2. Change of absorption at 470 nm was measured with a Cary 50 spectrophotometer (Varian, Palo Alto, Calif). Purified MPO was used to obtain a standard curve. Units of MPO activity were defined as the molar change–oxidized guaiacol absorbance (E0.01 cm=26.6 mmol/L−1 cm−1) with time.14 Guaiacol oxidation progress curves were analyzed by least-squares fitting of a line equation to the data using Scientist software (MicroMath, St Louis, Mo). Bicinchoninic acid protein assays (Pierce, Rockford, Ill) were performed to determine the total protein concentration of heart samples and to normalize data.

Flow Cytometry

After the mice were killed, hearts were excised and the tissue was prepared as described previously.3 To visualize monocytes/macrophages and neutrophils, the suspension was incubated with a mixture of monoclonal antibodies. The following antibodies were used: anti–CD90–PE, 53.2-1; anti–B220–PE, RA3-6B2; anti–CD49b–PE, DX5; anti–NK1.1–PE, PK136; anti–Ly-6-G–PE, 1A8; anti–CD11b–APC-Cy7, M1/70 (all BD Biosciences, San Jose, Calif); and anti–MPO, 8F4 (Hycult Biotechnology, Canton, Mass). Monocytes/macrophages were identified as CD11b+CD100− (target signal/CNRseptal signal)/(SD of the noise)). Neutrophils were identified as CD11b+CD100−. Neutrophils were identified as CD11b+CD100−. For intracellular staining of MPO, cells were permeabilized and fixed with a Cytofix/Cytoperm Kit (BD Biosciences). Flow cytometry was performed on an LSRII (BD Biosciences).

MPO Genotyping

MPO-deficient mice were obtained from The Jackson Laboratory. Genomic DNA was isolated from overnight proteinase K (50 μg) digestion of tail clips at 55°C. Primers flanking the insertion site of the neomycin cassette were used to generate a 155-bp product band after digestion of tail clips at 55°C. Primers flanking the insertion site of the neomycin cassette were used to generate a 155-bp product band. To verify the MPO genotype, Western blotting for MPO was performed as described below for heart homogenates 2 days after MI.

Western Blot Analysis

Samples of heart homogenates were subjected to SDS gel (4% to 15%, BioRad, Hercules, Calif) electrophoresis. Blots were incubated with rabbit primary antibodies for MPO (Millipore, Billerica, Mass), intracellular adhesion molecule 1 (ICAM)-1, ICAM-2, and vascular cell adhesion molecule 1 (VCAM)-1 (Santa Cruz Technologies, Santa Cruz, Calif); washed with PBS/0.5% Tween 20; and visualized with Western Lightning (PerkinElmer, Waltham, Mass) oxidation by horseradish peroxidase–conjugated goat anti-rabbit secondary antibody (Jackson Immunoresearch, West Grove, Pa). To verify that similar amounts of protein were loaded, blots were stripped with...
MPO-Gd Accumulates in Acutely Infarcted Myocardium and Exhibits Delayed Washout Kinetics Compared With Gd-DTPA

To study the enhancement pattern and kinetics after injection of MPO-Gd, we imaged 4 mice per group 2 days after coronary ligation before and up to 2 hours after injection of equal doses of MPO-Gd and Gd-DTPA. Delayed enhancement was observed in the akinetic infarct at 10 and 30 minutes after injection of the conventional gadolinium chelate, with complete return of CNR to baseline at 60 minutes (Figure 1). Peak CNR after injection of Gd-DTPA was observed at 10 minutes (10.5 ± 0.2). After injection of MPO-Gd, the peak CNR was significantly higher (CNR at 60 minutes, 40.8 ± 10.4), and enhancement was observed even at 120 minutes after injection (Figure 1). Comparison of both curves using a 2-tailed Kolmogorov-Smirnov test showed significantly brighter enhancement for MPO-Gd (P=0.026).

MPO-Gd Specifically Targets MPO Activity

Experiments using transgenic mice evaluated the specificity of MPO-Gd for MPO activity. We compared the CNR 1 hour after injection in 4 wild-type mice, 4 heterozygous mice, and 3 homozygous mice deficient for MPO 2 days after coronary ligation. MPO−/− mice exhibited significantly diminished enhancement (ANOVA, P=0.02 for MPO−/− versus MPO+/+), and an intermediate CNR was observed in MPO+/− mice (Figure 2A through 2D). The akinetic LV wall area was not different between homozygous and heterozygous mice deficient for MPO and wild-type mice (MPO+/+, 50 ± 4%; MPO−/−, 49 ± 4%; MPO+/−, 49 ± 6%; P=0.9). Therefore, it is unlikely that differences in enhancement observed between genotypes are caused by varying infarct size. Genotypes of mice were confirmed by polymerase chain reaction, and the absence of MPO protein in homozygous mice deficient for the MPO gene was observed by immunoblotting (Figure 2E). These experiments established that enhancement after MPO-Gd injection correlates closely with MPO activity.

Cellular MPO Studies

We next investigated the individual cellular contributions to MPO activity in the healing infarct by flow cytometry. Flow cytometry of single-cell suspension obtained from digested infarcts revealed that neutrophils, the most numerous cell

**Figure 1.** In vivo imaging of MPO activity 2 days after MI. A, Strong and persistent hyper-enhancement is seen in the infarct zone in mice injected with MPO-Gd. Two hours after injection, the infarcted LV free wall is brightly enhanced at a time when conventional Gd-DTPA has been washed out completely (B). C, The CNR shows higher values and delayed washout after injection of MPO-Gd vs conventional Gd-DTPA.
type in a 2-day-old mouse myocardial infarct, contributed predominantly to local MPO activity, followed by monocytes/macrophages. All other cell types such as lymphocytes contributed negligibly to the MPO signal (Figure 3).

MRI Enhancement of MPO-Gd Corresponds to Immunoreactive MPO Protein

To further investigate the specificity of MPO-Gd, we performed immunoreactive staining of hearts after MRI. The enhanced fraction of the LV myocardium visualized by MRI was not significantly different from and correlated well with the MPO-positive fraction quantified by immunostaining for the enzyme (MRI, 45 ± 10%; histology, 44 ± 12%; P = 0.9; r² = 0.92, P < 0.05). Adjacent sections were stained for the presence of neutrophils and macrophages, and both cell types colocalized with MPO (Figure 4).

Time Course of MPO Activity During Infarct Healing

We next followed the time course of MPO activity in healing myocardial infarcts. Three to 4 mice per day were imaged on days 1 to 8 after coronary ligation and killed after MRI to correlate ex vivo tissue activities to in vivo MRI data. The peak enhancement occurred on day 2 after coronary ligation. This observation was corroborated by tissue activity measurements and immunoblotting, which also showed that MPO activity peaked on day 2 after infarction (Figure 5A through 5C). Very little enhancement remained by day 8, consistent with decreasing cellularity and inflammatory activity in the infarcted myocardium at this later time point. Comparison of MRI-derived CNR with ex vivo tissue activity and immunoblotting corroborated the time course (Figure 5D and 5E) and yielded a significant correlation (r² = 0.65, P < 0.001; Figure 5F). The peak MRI-derived CNR on day 2 was 6.1 times higher than on day 8, comparable to the 10-fold difference detected in vitro. The moderate value of the correlation coefficient most likely results from CNR being measured in the midventricular slice, whereas the whole apical portion of the LV was used for the guaiacol assay, possibly also reflecting differences in individual infarct sizes.

In Vivo Imaging of the Action of an Antiinflammatory Intervention

Detection of moderately expressed targets, serial imaging, and monitoring of therapy effects are benchmarks for any new molecular imaging technology. We therefore used MPO-Gd to follow the development of ischemia-reperfusion staining was conducted to detect MPO levels and is represented as mean fluorescent intensities (MFI). Mean and SEM are shown; n = 3. On day 2 after MI, neutrophils are the main contributors to MPO activity in the infarct, followed by monocyte/macrophages.

*P < 0.001.
Four hours after the onset of reperfusion, control mice exhibited a patchy enhancement pattern in the hypokinetic LV free wall, and the signal consolidated further at 24 hours (Figure 6), at which time the peak CNR was comparable to permanent ligation (24.3 ± 4.5 versus 26.0 ± 6.4; *P = 0.65). In mice treated with atorvastatin, similarly increased CNR values were observed at 4 hours; however, the signal was significantly attenuated at the 24-hour time point (Figure 6). Importantly, the preinjection scan at the second time point did not show enhancement in either group. Therefore, complete washout of MPO-Gd was achieved within 24 hours. Flow cytometry of cells harvested from infarcts revealed that the absolute number of neutrophils and monocyte/macrophages per 1 mg infarct tissue diminished in mice treated with atorvastatin, providing an explanation for lower MPO activity in this group (Figure 7). Immunoblotting of VCAM-1, ICAM-1, and ICAM-2 showed decreased levels in atorvastatin-treated mice, thus likely leading to the decreased cell recruitment and lower MPO activity observed by in vivo MRI (Figure 6) and in Western blotting (Figure 7).

**Discussion**

Although a wealth of preclinical data have implicated oxidative stress in the pathogenesis of reperfusion injury, clinical trials of free radical scavengers have yielded conflicting results. We show here that an MPO-activatable gadolinium chelate can be used to directly image MPO activity in the injured myocardium, providing a new tool for monitoring the efficacy of therapeutic interventions targeting oxidative stress.
heart noninvasively by MRI. This agent might improve the understanding of the pathophysiology of oxidative injury in acute myocardial ischemia and may help to implement successful clinical strategies. The described imaging technology has high inherent sensitivity because it not only reported massive oxidative stress related to inflammatory cell recruitment on day 2 after MI but also detected subtle increases in MPO activity as early as 4 hours after the onset of reperfusion injury, even with agent concentrations in the clinically plausible range. Studies in MPO−/− mice and correlation of MPO imaging with biochemical and morphological assays provide strong evidence supporting the specificity of the imaging signal as a reporter for MPO activity.

MPO-Gd is a small molecule, with a size comparable to that of clinically used gadolinium chelates. This property facilitates delivery of the molecule to the target area in the injured myocardium. MPO activates the probe through the oxidation of the hydroxytryptamide moieties on the chelate. The ligands then react with each other, leading to polymerization of the agent into dimers, tetramers, and occasionally even pentamers. This polymerization decreases the tumbling rate of gadolinium, activates the probe, and enhances the T1-shortening effect of the imaging agent. Furthermore, the increased size of the polymer and cross-linking to surrounding matrix proteins promote the retention of the probe in areas of high MPO activity, which results in substantially decelerated washout kinetics. Therefore, we found very bright enhancement at 1 hour after injection, at a time when conventional Gd-DTPA and nonactivated MPO-Gd have been washed out of the myocardium completely. Nevertheless, as demonstrated in serial imaging of reperfusion injury, the washout also is rapid enough to facilitate frequent serial imaging. Of note, this study shows that MPO-Gd–derived signal exhibits an adequate dynamic range to detect changes in MPO activity. MPO expression was modulated in several ways. Wild-type, heterozygous, and homozygous MPO-deficient mice were imaged, and a strong linear relationship was seen between the MR signal intensity and the genotype of the mouse imaged. In addition, imaging with MPO-Gd visualized antiinflammatory effects of atorvastatin after myocardial reperfusion injury in mice in vivo. In our study, we used MPO-Gd in a murine model and at high field strength. Because the longitudinal relaxivity of gadolinium chelates increases at lower field strength, lower doses of MPO-Gd will likely be detectable at 1.5 T. It is quite possible that the dose of 0.3 mmol/kg used in our study at 7 T could be reduced to the clinically approved dose of 0.1 mmol/kg at 1.5 T. This prediction, however, will need to be confirmed by imaging larger animals at clinical field strengths.

Recent studies have used magnetofluorescent nanoparticles to image inflammation after ischemic injury of the myocardium. The biological target of this strategy is different, however. Although nanoparticles are ingested by phagocytes and therefore report their presence, MPO-Gd is a functional reporter that probes activity of a pro-oxidant enzyme. Combined strategies using both magnetic nanoparticles and the MPO-Gd chelate could provide novel and complementary information, a conjecture that requires further study.

Peak MPO activity occurred in the infarct on day 2, during the initial proinflammatory phase after infarction. This time point coincides with the dominant presence of neutrophils and Ly6C+ monocytes, the inflammatory monocyte subtype that accumulates in the first phase of leukocyte recruitment after MI. Both of these cell types are first-line responders that express high levels of MPO. Systemic neutrophilia and monocytosis after acute MI are associated with graver prognosis in patients. In addition, MPO deficiency alleviated the evolution of heart failure in mice after coronary ligation. The ability to image MPO activity in vivo could provide novel insights into the functional status of inflammatory cells and thus facilitate the development of novel therapies to optimize infarct healing.

Using serial noninvasive MPO imaging, we followed leukocyte recruitment and monitored a significant attenuation of MPO activity by atorvastatin therapy. This may reflect the ability of statins to reduce infarct size. In patients with coronary artery disease, atorvastatin reduced MPO-derived oxidants independently of changes in lipid parameters, and statins attenuated myocardial ischemic injury in patients with acute coronary syndromes. We used immunoblotting and flow cytometry to investigate the underlying mechanism of the treatment effect observed by MPO imaging in the present study. Atorvastatin decreased the expression of VCAM-1, ICAM-1, and ICAM-2, the endothelial binding sites for the integrins VLA-4 on monocytes and LFA-1 on neutrophils. As a part of the leukocyte adhesion cascade, these adhesion proteins regulate inflammatory cell recruitment. Therefore, atorvastatin treatment likely reduced leukocyte recruitment via reduced expression of adhesion molecules, analogous to the situation in atherosclerosis. In addition, statin therapy also may decrease MPO expression in macrophages. Our findings are consistent with reports of reduced infarct size in mice after HMG-CoA reductase inhibition and indicate how MPO imaging might facilitate the discovery process for novel therapy targeting ischemia-reperfusion injury.

The present study shows that a novel activatable MRI probe can image MPO activity in the myocardium in vivo. We further demonstrate that MPO-Gd accurately reported MPO activity in vivo and possessed adequate sensitivity and dynamic range to detect treatment effects. Inflammation after ischemia may vary in the clinical setting, impressively shown in clinical trials demonstrating severe adverse effects of steroids on infarct healing. MPO-Gd gauges activity of MPO in vivo, which can serve as a surrogate for the intensity of leukocyte influx. Preclinical data support that inflammation affects the extent of post-MI remodeling and therefore prognosis. Molecular MRI of MPO activity in animals, and ultimately in humans, could facilitate noninvasive imaging of the natural history of inflammation and its impact on myocardial healing/remodeling. This would allow the role of inflammation in animal models and humans to be compared directly and the efficacy of various immune modulators to be better understood. MPO imaging could ultimately be used as part of a “personalized” regimen in those patients at highest risk of remodeling (large anterior infarction) to guide novel therapeutic strategies. Furthermore, leukocyte recruitment is a general component of inflammation. This molecular imag-
ing sensor thus could play an important translational role in not only ischemic heart disease but also other inflammatory cardiovascular conditions such as atherosclerosis, myocarditis, and transplant rejection.

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Disclosures

None.

References


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**CLINICAL PERSPECTIVE**

Myeloperoxidase is a signature enzyme of inflammatory cells (neutrophils, monocytes, and macrophages) and can serve as a surrogate marker for the extent of tissue inflammation in myocardial infarction. Here, we present a novel approach to noninvasive imaging of myeloperoxidase activity locally in the myocardium. Using an “activatable” paramagnetic myeloperoxidase substrate with magnetic resonance imaging, the approach could be used to identify patients at risk for adverse remodeling after myocardial infarction and may guide novel therapeutic strategies to prevent heart failure. Because neutrophils and/or monocytes/macrophages play key roles in inflammation and tissue repair, the imaging agent also could be used to assess atherosclerosis, myocarditis, or transplant rejection.
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