Myeloperoxidase-Generated Oxidants Modulate Left Ventricular Remodeling but Not Infarct Size After Myocardial Infarction

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Background—Inflammation after myocardial infarction (MI) heralds worse left ventricular (LV) function and clinical outcomes. However, whether inflammation affects LV function by extending myonecrosis and/or altering LV remodeling remains unknown. We hypothesized that cytotoxic aldehydes generated during oxidative stress may adversely affect remodeling and infarct size. One theoretical source of reactive aldehydes is oxidation of common α-amino acids by myeloperoxidase (MPO) released by leukocytes. However, a role for MPO in formation of aldehydes in vivo and the functional consequences of MPO-generated oxidants in ischemia/reperfusion models of MI have not been established.

Methods and Results—In studies with cell types found in vascular tissue, MPO-oxidation products of glycine (formaldehyde) and threonine (acrolein) were the most cytotoxic. Mass spectrometry studies of myocardial tissue from murine models of acute MI (both chronic left anterior descending coronary artery ligation and ischemia/reperfusion injury) confirmed that MPO serves as a major enzymatic source in the generation of these cytotoxic aldehydes. Interestingly, although MPO-null mice experienced 35.1% (P<0.001) less LV dilation and a 52.2% (P<0.0001) improvement in LV function compared with wild-type mice 24 days after ischemia/reperfusion injury, no difference in infarct size between wild-type and MPO-null mice was noted.

Conclusions—The present data separate inflammatory effects on infarct size and LV remodeling and demonstrate that MPO-generated oxidants do not significantly affect tissue necrosis after MI but rather have a profound adverse effect on LV remodeling and function. (Circulation. 2005;112:2812-2820.)

Key Words: amino acids • infarction • inflammation • remodeling

The inflammatory response to myocardial infarction (MI) has a significant role in determining the size of the infarct, as well as subsequent left ventricular (LV) remodeling.1,2 Activated leukocytes can promote myocardial injury through multiple mechanisms, including production of reactive oxidants and diffusible radical species, activation of protease cascades, and expression of proinflammatory cytokines.4–9 Myeloperoxidase (MPO), an enzyme released by activated neutrophils and monocytes, functions as a major enzymatic source of leukocyte-generated oxidants and is present in infarcted myocardium. MPO deposition has been shown in a murine model of acute myocardial infarction (AMI) to be increased near the sites of myocardial rupture.10 Using mice with a functional deficiency of MPO (ie, MPO knockout mice [MPO−/−]) and a chronic ischemia model of left anterior descending coronary artery (LAD) ligation, we recently identified a significant role for MPO in determining early ventricular rupture rates and LV size after AMI.8 A mechanism was proposed for these effects of MPO on ventricular remodeling after AMI: activation of the plasminogen/plasmin protease cascade via MPO-mediated oxidation of plasminogen activator inhibitor-1 (PAI-1).8 Whether alternative processes contribute to the effect of MPO on cell injury and necrosis in and around infarcted myocardium in this model, such as through generation of cytotoxic species, was not explored because an ischemia/reperfusion model was not used.

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MPO levels are commonly used as quantitative measures of the extent of inflammation in tissues. In addition to merely serving as a marker for leukocyte recruitment, this hemopro-
tein can participate in the injury process by virtue of generating reactive species. MPO forms cytotoxic oxidants such as hypochlorous acid (HOCl), molecular chlorine (Cl2), and monochloramines (RNHCl) that can damage cellular targets in vitro and in vivo.11-12 Several decades ago, Zgliczynski and colleagues13,14 suggested the formation of reactive carbonyl-containing products after interaction of amino acids with the MPO-H2O2-Cl- system. In subsequent in vitro studies, we structurally defined a family of aldehydes as the products formed, as well as their mechanism of generation via the oxidation of common α-amino acids by the MPO-H2O2-Cl- system of neutrophils.15,16 With the use of multinuclear NMR, high-resolution mass spectrometry, and isotopically labeled precursor amino acids, the mechanism was shown to involve interaction of HOCl with the α-amino moiety forming a labile Nα-monochloroamine intermediate, which rapidly decomposes into an aldehyde via a concerted deamination and decarboxylation reaction.16

Aldehydes identical in structure to those that can be generated by MPO-mediated oxidation of plasma amino acids in model systems have been detected in vivo. However, direct demonstration of a role for MPO in formation of reactive aldehyde species in vivo is still lacking. For example, acrolein, a product of MPO-mediated oxidation of threonine,15,16-17 has been detected in vivo. However, the relative contribution of MPO-catalyzed threonine oxidation to acrolein formation in vivo and the subsequent effects of MPO-generated acrolein on myocardial necrosis after MI are unknown. A role for MPO in the generation of aldehydes in vivo has been suggested by detection of p-hydroxyphenylacetaldehyde (pHA), an aldehyde formed by exposure of free tyrosine to the MPO-H2O2-Cl- system, in tissues.18 However, the specificity of pHA as a marker of MPO-catalyzed amino acid oxidation in vivo has not yet been established. Moreover, the physiological consequences of aldehyde formation during MPO-catalyzed oxidation of amino acids have not yet been explored. The generation of cytotoxic aldehydes by MPO could have multiple potential implications on the pathophysiology of cardiovascular disease, including plaque rupture, aneurysm formation, and tissue necrosis after AMI.19,20

In this study we examined the cytotoxic properties of reactive aldehydes derived from MPO- and neutrophil-mediated oxidation of α-amino acids using cell types representative of those found in cardiovascular tissues. Furthermore, the potential role of MPO in the formation of specific cytotoxic aldehydes in ventricular tissues after AMI was examined with the use of MPO−/− mice. The results of the present studies demonstrate that MPO is capable of promoting oxidation of amino acids to form aldehydes that are extremely cytotoxic to cells of vascular origin. However, detailed studies using a model of ischemia/reperfusion suggest that these MPO-derived cytotoxic aldehydes do not significantly contribute to myocardial necrosis because infarct size in MPO-null mice was identical to that measured in wild-type mice. Rather, our data demonstrate markedly improved LV function and decreased LV dilation in the MPO-null mice at 24 days after MI. In aggregate, our data demonstrate that leukocyte-derived oxidants do not play a critical role in myonecrosis but rather have a significant impact on LV remodeling and ventricular function.

Methods

General Procedures

All glassware was soaked in NaOCl, extensively rinsed with H2O, and then baked at 300°C overnight before use. H2O was double glass distilled and stored in glassware with Teflon-lined caps to avoid low levels of contaminating short-chain aldehydes shed from plastic and degrading from water purification systems. Buffers and reagents were prepared and stored in pyrolyzed glassware capped with Teflon-lined caps. Buffers were demonstrated to be chlorine-demand free before use, as previously described.15 MPO (A280/A250 ratio >0.8) free of contaminating eosinophil peroxidase was isolated and stored as previously described.21 H2O2, NaOCl, and 4-hydroxy-2-nonalen (4-HNE) concentrations were determined spectrophotometrically (A292=39.4 mol/L·cm; A235=350 mol/L·cm; A230=13 750 mol/L·cm, respectively).22,23

Aldehydes derived from amino acid oxidation were synthesized by direct addition of HOCl/ClO− to amino acid solutions (1:1, mol:mol; oxidant:amino acid) at 37°C, as previously described.15 Aldehyde synthesis was confirmed through structural and chromatographic characterization by gas chromatography/mass spectrometry (GC/MS) as their oxime derivatives after reaction with pentaluro-benzyl hydroxylamine (PFBHA), as previously described.15 In the case of pH synthesis from tyrosine, purity was assessed by reverse-phase high-performance liquid chromatography as described.28 Throughout sample processing, care was taken to avoid losses of volatile aldehydes and derivatives through use of gas-tight syringes, septa-covered reaction vials, and refrigeration or freezing of samples during analyses. Total glutathione (GSH) content (GSH plus glutathione disulfide) was determined with the use of a spectrophotometric assay based on the reaction of GSH with Ellman’s reagent and the subsequent recycling of glutathione disulfide with glutathione reductase as described.28

Cell Culture

Human aortic vascular smooth muscle cells, bovine pulmonary artery endothelial cells, and the human monocytic cell line designated 28SC were obtained from ATCC, Rockville, Md (cell lines CRL-1999, CRL-1733, and CRL-9855, respectively). Cells were maintained according to the vendor’s specifications in the following cell culture media: for human vascular smooth muscle cells: Ham’s F12K medium with 2 mmol/L L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate supplemented with 10 mmol/L HEPES, 10 mmol/L TES, 0.05 mg/mL ascorbic acid, 0.01 mg/mL insulin, 0.01 mg/mL transferrin, 10 ng/mL sodium selenite, 0.03 mg/mL ECGS; for bovine pulmonary artery endothelial cells: Ham’s F12K medium with 2 mmol/L L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate); and for the human peripheral blood-derived monocytic cell line 28SC: Iscove’s modified Dulbecco’s medium with 4 mmol/L L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate); and for the human peripheral blood-derived monocytic cell line 28SC: Iscove’s modified Dulbecco’s medium with 4 mmol/L L-glutamine adjusted to contain 1.5 g/L, 0.02 mmol/L thymidine, 0.1 mmol/L hypoxanthine, 0.05 mmol/L mercaptoethanol, 0.11 mmol/L sodium lactate, 10 mg/mL antioxidants. All media were supplemented with 10% fetal bovine serum, and all cultures were maintained at 37°C in 5% CO2 and air in humidified incubators (NuAire). HA1 Chinese hamster ovary fibroblasts were maintained in Eagle’s MEM as previously described.29 Wild-type and MPO knockout mice (MPO−/−) were obtained and maintained as previously described.26

MPO- and Neutrophil-Mediated Oxidation Reactions

Amino acid stock solutions (2 mmol/L, except for His and Trp, which were 1 mmol/L) were prepared in Dulbecco PBS with MgCl2 and CaCl2 (Gibco-BRL). Amino acids (100 μmol/L, unless otherwise indicated) were incubated with H2O2 (100 μmol/L) and MPO (25 mmol/L) in sealed reaction vials at 37°C for 1 hour. Catalase was then added (30 μg/mL) to scavenge any residual H2O2, and the resulting solutions were incubated with cultured cells for survival
experiments for 1 hour, unless otherwise indicated. Formation of the anticipated aldehydes in reactions was confirmed before use for all studies by GC/MS analysis of oxime derivatives after reaction of aliquots with PFBHA by methods previously described, as well as described below.

All protocols for blood donation for neutrophils were approved by the Cleveland Clinic Foundation institutional review board, and patients gave written informed consent. Human neutrophils were isolated by buoyant density centrifugation from plasma anticoagulated with EDTA (5 mmol/L) as described. Experiments were performed in Dulbecco PBS (pH 7.2) with MgCl₂ and CaCl₂ (Gibco-BRL) supplemented with 100 μmol/L diethylenetriaminepentaacetic acid (DTPA). Amino acid oxidation experiments with human neutrophils were performed in gas-tight vials to prevent loss of volatile aldehydes generated during the prolonged neutrophil incubations. After incubation, formation of reaction products was confirmed as their PFBHA oxime derivatives by GC/MS.

Assays of Cellular Injury
Cytotoxicity was monitored by assessing reproductive integrity with the use of the clonogenic cell survival assay; metabolic viability was monitored by trypan blue dye exclusion; and maintenance of cell membrane integrity was determined by monitoring lactate dehydrogenase (LDH) release, as previously described. Briefly, for survival analysis, cells were treated with reaction mixtures containing aldehydes for 1 hour at 37°C and rinsed, and then cells recovered by exposure to trypsin (0.1%) and EDTA (500 μmol/L). Cells in suspension were then diluted in complete media and plated at different densities generated by serial dilutions for clonogenic survival for each exposure, and control/sham conditions were used to calculate the data shown. Thus, each data point arises from multiple dishes. Metabolically viable cells were counted by mixing cells with trypan blue (1:1, vol/vol with 0.4% trypan blue in saline), and >100 cells counted under a phase-contrast microscope with blue cells were identified with the use of a surgical microscope (Leica M500) after retraction of the left atrium and ligated with 7-0 Prolene. Blanching was confirmed as their PFBHA oxime derivatives by GC/MS. We have previously extensively described the mass spectrometric analyses of oxime derivatives of aldehydes in biological matrices, where fragmentation analyses revealed conserved fragmentation pathways, and the utility of monitoring structurally informative ions (eg, the molecular anion \([M]^-\), molecular ion \([M-HF]^-\), \([M-HF-HCN]^-,\) or \([M-181]^+\)) and common ions shared by all oxime derivatives of aldehydes (mass-to-charge ratio 178 or 181). Aldehyde identification was therefore confirmed by demonstrating comigration of at least 2 structurally informative ions and 1 common ion, with an identical retention time to that observed with authentic derivatized material (commercial or generated with HOCI/NaOCl) in the selected ion-monitoring mode, as described.

Statistical Analyses
All data are expressed as mean±SD. Statistical analysis was performed with use of SPSS software (version 10.0 for Windows, SPSS Inc). Continuous variables were compared with the use of nonparametric 1- and 2-factor Wilcoxon rank sum tests. A value of \(P<0.05\) was considered statistically significant.

Results
Identification of MPO-Generated Aldehydes Produced During Oxidation of Amino Acids That Are Cytotoxic
To identify cytotoxic products of MPO-mediated oxidation of amino acids, we exposed cells to culture media conditioned by prior incubation of the MPO-H₂O₂-CI⁻ system alone (control) or in the presence of each of the 20
common α-amino acids. The cytotoxic properties of the MPO-generated oxidation products were then initially assessed by performing clonogenic cell survival assays after 1-hour exposures to cultured HA1 fibroblasts (Figure 1). Although no significant toxicity was noted in cells exposed to low levels of the MPO-H₂O₂-Cl⁻ system alone, enhanced clonogenic killing was noted if specific amino acids were included in the MPO-H₂O₂-Cl⁻ reaction mixtures, consistent with formation of more stable cytotoxic by-products of amino acid oxidation. The greatest extents of cytotoxicity were seen after exposure to media containing lysine and tryptophan (Figure 1). Glycoaldehyde, derived from serine oxidation and a precursor of advanced glycation end products,15,17 demonstrated minimal cytotoxicity. Similarly, exposure to media containing tyrosine plus the MPO-H₂O₂-Cl⁻ system, which produces pHA in high yield,18 demonstrated nominal toxicity.

The Product(s) Formed During MPO-Catalyzed Oxidation of Threonine Is a Potent Cytotoxin to Cells Found in Cardiovascular Tissues

MPO-H₂O₂-Cl⁻ treatment of l-threonine produced a cytotoxic species that was significantly more toxic than 4-HNE on a molar basis and comparable in toxicity to authentic acrolein, as monitored by clonogenic cell survival assays in HA1 fibroblasts (Figure 2A) and pulmonary artery endothelial cells (Figure 2B). The MPO-H₂O₂-Cl⁻ oxidation products of neither tyrosine nor serine (pHA and glycolaldehyde, respectively) elicited significant toxicity on exposure to cells, even at levels as high as 1 mmol/L (Figure 2A). To determine the cytotoxic potencies of l-threonine oxidation products of the MPO-H₂O₂-Cl⁻ system, we compared the relative toxicity of products formed from the MPO-H₂O₂-Cl⁻ system alone versus the MPO-H₂O₂-Cl⁻ system plus l-threonine, as well as authentic 4-HNE and glycolaldehyde, using alternative cell types present in cardiovascular tissues, including vascular smooth muscle cells and a monocytic cell line. Each of the cell types examined demonstrated significantly enhanced toxicity on exposure to the MPO-H₂O₂-Cl⁻ system in the presence versus absence of l-threonine. The toxicity of the product formed by the MPO-H₂O₂-Cl⁻-threonine system was more toxic on a molar basis than 4-HNE.

Neutrophil Activation in Media Containing the Amino Acid l-Threonine Forms a Cytotoxic Aldehyde via the MPO-H₂O₂-Cl⁻ System: Cytoprotective Effects of Intracellular Glutathione

To demonstrate that activated neutrophils (polymorphonuclear leukocytes [PMNs]) could mediate the formation of cytotoxic products of l-threonine oxidation, clonogenic survival was monitored in HA1 cells after a 1-hour exposure to the l-threonine oxidation products generated by PMNs (Figure 3A). We have previously shown that acrolein is formed by this system.11,17 Similar to the requirements for acrolein formation, production of a cytotoxic product required leukocyte activation with phorbol ester and the presence of l-threonine (Figure 3A). Furthermore, production of a toxic product by leukocytes was inhibited by the addition of active catalase or the heme protein inhibitor aminotriazole, demonstrating a critical role for cell-generated H₂O₂ and peroxidase activity, respectively. The aldehydic nature of the cytotoxic product was revealed by the effectiveness of catalytically active aldehyde dehydrogenase (ADH) in partially detoxifying the l-threonine oxidation product (Figure 3A). Confirmation of a role for the MPO-H₂O₂-Cl⁻ system in neutrophils for the generation of cytotoxic products from l-threonine was achieved by demonstrating that the cell-free system (MPO-H₂O₂-Cl⁻) similarly generated oxidation products of l-threonine that were cytotoxic (Figure 3B). Furthermore, the aldehydic nature of the cytotoxic product was again con-
firmed by showing that catalytically active ADH partially detoxified the L-threonine oxidation product (Figure 3B).

These results are consistent with acrolein, an aldehyde produced during exposure of L-threonine to the MPO-H2O2-Cl− system, as a major cytotoxic species formed during neutrophil activation in the presence of L-threonine. Acrolein is a known cytotoxin, which induces cell death via pathways sensitive to intracellular GSH levels.29,30 We therefore sought to examine the influence of cellular GSH levels on the cytotoxicity of the product formed by exposure of L-threonine to the MPO-H2O2-Cl− system.

MPO Serves as a Primary Source for Generating Cytotoxic Aldehydes in Ventricular Tissues After AMI

To determine whether amino acid–derived aldehydes are formed in a MPO-dependent fashion in vivo, we harvested normal and ischemic ventricular tissues from wild-type and MPO−/− mice that were sham operated versus those after MI. AMI was induced in mice by direct LAD ligation. The LAD was either chronically ligated (hearts collected 72 hours after AMI) or ligated for 30 minutes followed by reperfusion (hearts collected 24 hours after AMI). Mass spectrometry analyses of these hearts revealed that low levels of amino acid–derived aldehydes were observed in normal myocardial tissue (ie, sham operated) from wild-type and MPO−/− ani-
mals (P>0.50 for all comparisons between wild-type and MPO−/− mice). In both AMI models, significant increases in the level of all aldehydes monitored were noted in wild-type compared with MPO−/− mice (Figure 4). Interestingly, a significant amount of aldehyde generation in wild-type mice (72% formaldehyde and 42% acrolein relative to 72-hour chronic ligation model) occurred within the first 24 hours after AMI, during early neutrophil recruitment.

MPO-Generated Oxidants Do Not Significantly Affect Ventricular Infarct Size After Ischemia/Reperfusion Injury but Dramatically and Adversely Affect LV Remodeling and Function After MI

To determine whether MPO-generated cytotoxic aldehydes have a role in myonecrosis after AMI, we compared infarct size using an ischemia/reperfusion model. After 30-minute ischemia and 72-hour reperfusion, we found no significant difference in infarct size whether expressed directly or as a percentage of the area at risk (Figure 5A). Although these results suggest that MPO may not directly participate in myonecrosis after AMI, we further examined whether MPO might participate in long-term LV remodeling and cardiac function in a model of ischemia/reperfusion using wild-type and MPO−/− mice. Echocardiographic studies 24 days after 30 minutes of LAD ischemia in wild-type (n=9) and MPO-null (n=8) mice as measured by 2-dimensional M-mode echocardiography are shown. At 24 days, the anterior wall was thicker (P<0.05), the ventricle was less dilated (P<0.001), and shortening fraction was significantly greater (P<0.001) in the MPO-null mice. Data represent mean±SD.

Discussion

Inflammation and the subsequent oxidant generation after AMI are correlated with a worse clinical outcome.2,31,32 The white blood cell count at presentation in patients with acute coronary syndrome has been shown to predict mortality at 6 months.31 Similarly, the peak monocyte count after MI was shown to predict LV size2 and ultimately the development of congestive heart failure.32 Although there is compelling evidence that inflammation and oxidant generation are linked with worse outcomes in patients with MI, the mechanism(s)
of this effect is still unclear. Whether inflammation after MI is linked to infarct expansion, altered LV remodeling, or both is unknown.

One mechanism by which inflammatory infiltrate could lead to infarct expansion or adverse ventricular function is through the generation of cytotoxic aldehydes. Aldehydes derived from lipid peroxidation have long been implicated as mediators of cell injury and oxidant stress during inflammation and cardiovascular diseases. Several years ago, an alternative pathway for aldehyde formation involving MPO-dependent oxidation of common plasma α-amino acids was proposed. Enhanced cytotoxicity of MPO-generated aldehydes similarly promotes cytotoxicity, as well as contrib-

In the present study the cytotoxic potential for MPO-generated aldehydes during amino acid oxidation was examined with the use of a variety of toxicity assays including clonogenic cell survival, a sensitive measure of cellular reproductive integrity. Oxidation products of several amino acids markedly enhanced the cytotoxic potential of the MPO-H2O2-Cl– system in multiple cell types. The most potent species were produced during incubation of the MPO-H2O2-Cl– system with glycine and threonine, reactions known to produce formaldehyde and acrolein, respectively, in vitro. Furthermore, studies with isolated human leukocytes and cell-free MPO-H2O2-Cl– systems confirmed the aldehydic nature of the cytotoxic species formed, as evidenced by its detoxification in the presence of catalytically active aldehyde dehydrogenase. Although acrolein and its analogue, 4-HNE, both possess reactive α-β-unsaturated, γ-hydroxy aldehyde moieties that give rise to the chemical reactivity of these species, acrolein is ≈200-fold more potent as an electrophile. Enhanced cytotoxicity of MPO-generated acrolein, relative to less reactive aldehydes including 4-HNE, is thus consistent with the toxic potential of these species depending on their chemical reactivity with critical intracellular nucleophilic targets. Thus, GSH depletion, a common feature of oxidant stress attendant with inflammation, enhanced the cytotoxic potential of MPO-generated reactive aldehydes (Figure 3). Prior studies have demonstrated that 4-HNE induces cytotoxicity in target cells that is dependent on GSH conjugation of 4-HNE for cytoprotection. The present studies suggest that MPO-generated aldehydes similarly promote cytotoxicity, as well as contribute to the enhanced cytotoxicity seen at sites of GSH depletion, such as during inflammation.

To determine the in vivo relevance of aldehydes produced during amino acid oxidation and their dependence on MPO for generation, the levels of the cytotoxic species formalde-
catalyzed oxidative inactivation of PAI-1, ultimately resulting in enhanced plasmin activity, may thus serve as an additional potential mechanism by accelerating matrix degradation, a requisite process for ventricular wall thinning and chamber dilation.

In summary, the present studies serve to clarify the role of inflammation after MI and identify MPO as a rational target to optimize LV remodeling and attenuate development of heart failure after MI.

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Disclosure
Dr Heinecke has served on the speakers’ bureaus of and/or received honoraria from Merck and diaDexus and has served as a consultant to Oxis International.

References
Inflammation and oxidant generation after acute myocardial infarction (AMI) have correlated with a worse clinical outcome in multiple studies. The white blood cell count at presentation in patients with acute coronary syndrome has been shown to predict mortality at 6 months. Similarly, the peak monocyte count after AMI predicts left ventricular (LV) size and ultimately the development of congestive heart failure. Whether inflammation after myocardial infarction is linked to infarct expansion, altered left ventricular remodeling, or both is under active investigation. Myeloperoxidase (MPO), an enzyme released by activated neutrophils and monocytes, functions as a major enzymatic source of leukocyte-generated oxidants. MPO-generated oxidants have been shown to produce cytotoxic aldehydes and lipid oxidation products and to inhibit the activity of protease inhibitors. We hypothesized that in an ischemia/reperfusion model, MPO-null mice would have significantly smaller infarcts because of the decreased generation of cytotoxic aldehydes like acrolein and formaldehyde. Contrary to our hypothesis, we found no difference in infarct size between the 2 groups despite a dramatic decrease in cytotoxic aldehyde generation in the MPO-null group. Interestingly, we observed significantly less LV dilation and improved cardiac function in the MPO-null group. Our results indicate that worse outcome associated with an increased white blood cell count and/or inflammation at the time of AMI is due to adverse LV remodeling and not increased infarct size. These findings suggest that LV remodeling and functional parameters, but not infarct size, are the appropriate end points for clinical trials focused on modulating inflammation in patients with AMI.
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