Imaging Experimental Myocardial Infarction with Indium-111-labeled Autologous Leukocytes: Effects of Infarct Age and Residual Regional Myocardial Blood Flow

Mathew L. Thakur, Ph.D., Alexander Gottschalk, M.D., and Barry L. Zaret, M.D.

SUMMARY The external imaging patterns and the kinetics of infiltration of indium-111 labeled polymorphonuclear leukocytes (PMNs) occurring in the course of the inflammatory response associated with myocardial infarction were studied in dogs subjected to closed-chest anterior wall infarction. The effects of infarct age and regional residual myocardial blood flow upon PMN infiltration were investigated and quantified, and the capacity of indium-111 PMNs to image the experimental infarction was evaluated qualitatively. The epicardial accumulation of indium-111 PMNs occurred primarily in infarct zones with residual blood flow of 0.6 times normal and was maximal (14.8 ± 3.8 times normal) in the lowest blood flow zone (< 0.1 times normal). PMN accumulation in the endocardial infarct zones occurred in the regions with blood flow < 0.6 times normal and was maximal (26.8 ± 4.9 times normal) in the lowest blood flow zone. However, contrary to the maximal epicardial infiltration period, which occurred within the first 24 hours after infarction, the maximal endocardial infiltration occurred at 72 hours after infarction. In both endocardium and epicardium, PMN uptake was minimal at 120 hours after infarction. In vivo cardiac images were abnormal and revealed discrete, anatomically distinct areas of increased myocardial radioactivity uptake in the anterior wall of all dogs studied within 24–96 hours after infarction. All images obtained 120 hours after infarction were negative.

Thus, indium-111 PMNs provide a noninvasive means of in vivo imaging of the inflammatory response to myocardial infarction and allow quantification of this response at a tissue level.

THE INFILTRATION of polymorphonuclear leukocytes (PMNs) into regions of acute myocardial infarction is an event that has been well characterized histopathologically. The classic necropsy study of Mallory et al. in 1939 showed that in human infarction, PMN infiltration is detected initially within the first 24 hours and appears maximal at 4 days.1 Thereafter, there is an increasing degree of degenerative cellular change, with almost complete disappearance of PMNs at 14 days. Definition of the kinetics of PMN infiltration into acute infarct zones has become increasingly important because of recent observations suggesting that modification of the acute inflammatory response may limit the degree of ischemic necrosis resulting from acute myocardial infarction.2,3

The development of a technique for labeling autologous PMNs using the gamma-emitting radionuclide, indium-111 (111In), chelated to 8-hydroxyquinoline (oxine), provides a direct means of assessing the inflammatory response to acute infarction in vivo.4 111In-labeled PMNs retain the label intracellularly,5 maintain chemotactic function,6 and have already been used in the study of experimental and clinical abscess localization.7,8 A preliminary report by Weiss et al. showed that 111In PMN myocardial uptake could be imaged in experimental myocardial infarction.9 The present study was undertaken to evaluate further the potential of 111In PMNs as a means of in vivo imaging of the inflammatory response to acute myocardial infarction, and to study the effect of infarct age and residual regional blood flow upon myocardial PMN infiltration.

Methods

In vivo imaging and postmortem tissue distribution studies involving autologous 111In-labeled PMNs were performed in 24 dogs subjected to acute anterior wall myocardial infarction.

Preparation of 111In PMNs

Autologous leukocytes in each dog were isolated and labeled with 111In, according to previously described techniques.8 Briefly, 30 ml of venous blood were withdrawn in a disposable plastic syringe containing 150–200 IU preservative-free heparin (Abbott Labs). To the blood was added 3% volume/volume methyl cellulose (2% weight/volume, in 0.9% NaCl, 1500 cp, Fisher Scientific), mixed gently and allowed to stand for about 1 hour at room temperature. The leukocyte-rich plasma was separated carefully into equal volumes in two 15-ml (Falcon) polyethylene test tubes and centrifuged at 450 g for 5 minutes in a calibrated horizontal swing rotor table top centrifuge (IEC) at room temperature. The plasma was transferred and stored. The cell button was suspended...
in 5 ml normal saline (Viaflex-Travenol, pH 6.5) centrifuged at 450 g for 5 minutes and the step was repeated. The cells were finally suspended in 5 ml saline. On all occasions the cell suspension was readily obtained with no visible clumps present. The red cell contamination in these preparations was 10–25%. However, since these red cells accumulate less than 5% of the radioactivity label, they were not eliminated by hypotonic lysis, because this technique may damage the PMNs.

The radioactive label \(^{111}\text{In}\) oxine (1 mCi in 50 \(\mu\)g oxine in 50 \(\mu\)l ethanol, obtained from Diagnostic Isotopes) was obtained in a conical vial, to which was added 150 \(\mu\)l 0.9% NaCl by means of a 1-ml disposable syringe. The mixture and a 100-\(\mu\)l saline wash were transferred dropwise to the cell suspension and incubated for 15 minutes at room temperature. To determine labeling efficiency, at the end of this period a 10-\(\mu\)l cell suspension sample was transferred to a test tube containing 1 ml 0.9% NaCl, centrifuged at 1000 g for 5 minutes and the radioactivity associated with the cells and supernatant was counted in a well-type scintillation counter (Picker). Generally, 90–95% of the radioactivity was incorporated with the cells. In cases of less than 90% labeling efficiency, the cell suspension was centrifuged (450 g, 5 minutes), the supernatant retracted, and the leukocytes were resuspended in 5 ml of 0.9% NaCl. An equal volume of plasma then was added to the final cell suspension and the mixture was administered intravenously to the dogs.

Infarct Preparation

Acute anterior wall transmural myocardial infarction was induced by a previously described catheter plug embolization technique.\(^{11}\) Adult dogs of either sex weighing 20–30 kg were used for all studies. After anesthesia with intravenous sodium pentobarbital (30 mg/kg), a \#7 Sones catheter was introduced via carotid cutdown and positioned fluoroscopically in the orifice of the left anterior descending coronary artery. A plug made of catheter material and impaled at the distal tip of a guide wire within the Sones catheter was then dislodged. The plug usually lodged in the distal one-half to one-third of the left anterior descending coronary artery at the point of origin of the last large diagonal branch. After embolization, the catheter was removed. Electrocadiographic monitoring was carried out during the induction of infarct. All dogs were pretreated with lidocaine (50 mg) before infarction. Ventricular ectopy in the immediate postinfarction period was common, and was treated with additional 50-mg boluses of lidocaine. When the dogs had stabilized, the neck incision was closed, and they were allowed to recover. This method of closed-chest infarct induction is particularly well suited for imaging studies involving labeled PMNs, since there is no chest wall incision to provide a source of PMN infiltration that might either obscure the region of myocardial PMN uptake or make the interpretation of images difficult. Furthermore, none of the dogs in this study developed visible infections at the site of catheter introduction.

Protocol

The dogs were divided into five separate groups, each consisting of four to six dogs. The five groups were defined by the postinfarction temporal sequence in which the dogs received autologous \(^{111}\text{In}\) leukocytes and involved administration of PMNs to individual dogs at 2, 24, 48, 72 or 96 hours after infarction. In each group of four to six dogs, in vivo cardiac imaging was performed on one occasion 20–24 hours after PMN administration. In this manner the dogs receiving autologous \(^{111}\text{In}\) PMNs 2 hours after infarction were imaged at 24 hours, those receiving PMNs 24 hours after infarction were imaged at 48 hours, etc. The delay from the time of injection to imaging was necessary to allow clearance of PMNs from the blood pool. Images obtained earlier primarily reflect blood pool rather than myocardial activity. For the imaging procedure, the dogs were lightly anesthetized with sodium pentobarbital and positioned beneath a scintillation camera (Searle Pho Gamma HP) equipped with a pinhole collimator. Pinhole collimation eliminated most of the liver and spleen activity and was helpful in effective infarct imaging. Initially, multiple views were obtained in each dog. Left anterior oblique images with the dog lying on its right side were found to be most helpful. Fifty thousand count images were obtained using a 20% window about the 247 keV photo peak of \(^{111}\text{In}\).

After imaging, the dog was placed on a Harvard respirator and a left lateral thoracotomy performed. The left atrial appendage was isolated and cannulated and two to four million 15 ± 5 \(\mu\) strontium-85 (\(^{85}\text{Sr}\)-labeled) carbonized microspheres (3M Corporation) were administered via the atrial cannula. The uptake of microspheres in myocardial tissue samples provided an index of relative regional myocardial blood flow. Five minutes after microsphere injection the hearts were isolated, removed and washed free of blood. Several extirpated hearts also were imaged to provide further anatomic correlation with in vivo images. Multiple myocardial samples were dissected free and obtained for tissue radioactivity assay. Approximately 20 samples of 0.5–1.0 g were obtained from the grossly evident infarct zone and six samples were obtained from the normal myocardium supplied by the circumflex coronary artery. Each sample was divided into approximately equal endocardial and epicardial halves. Two additional tissue samples from normal and abnormal myocardium were taken from each dog and submitted for routine histopathologic evaluation. Radioactivity assays of \(^{111}\text{In}\) and \(^{85}\text{Sr}\) activities in each sample were obtained using a high-resolution 15 cm\(^2\) Ge (Li) detector (Princeton Gamma Tech) coupled to a multichannel pulse-height analyzer (Technical Management Corporation) and a printer (Technical Instrument, Inc.). The radioactivity of \(^{111}\text{In}\) was determined by summing counts from its characteristic
photo peaks at 173 and 247 keV, while that for $^{85}$Sr was determined from counts in its characteristic 514-keV photo peak. After appropriate background subtraction, the activity for each radionuclide was calculated as counts per minute per gram of tissue. Tissue accumulation of $^{111}$In (reflecting PMN infiltration) and $^{85}$Sr (reflecting relative regional myocardial blood flow) were then expressed as radioactivity uptake ratios obtained by comparing activity in the infarct sample to the mean activity from the six samples obtained from normal myocardium. Similar ratios were established for endocardial and epicardial samples in each dog. In this manner, relationships could be established between PMN accumulation and residual regional myocardial blood flow with infarcts of various ages. Data were expressed for each group as mean ± SD. Comparison of the differences in $^{111}$In uptake ratios in myocardial samples of different blood flow at different times after infarction was made by group $t$ tests.

In two additional dogs with 72-hour-old infarcts, microspheres were not administered. Rather, the hearts were sectioned into 1-cm-thick transverse slices for in vitro imaging studies. Each slice was imaged with the gamma camera and the imaging correlated with gross pathologic evaluation.

Two types of control dogs were also used. In one group of two dogs, a sham infarct procedure was performed with carotid cutdown and left anterior descending catheterization, but without infarct production. Forty-eight hours later, the dogs received autologous $^{111}$In PMNs followed 24 hours later by imaging and tissue distribution studies. In an additional two dogs, the regular infarct production procedure was
Table 1. Infarct/Normal Myocardium $^{111}$In Radioactivity Ratios as a Function of Relative Blood Flow

<table>
<thead>
<tr>
<th>Hours after infarction†</th>
<th>No. of dogs</th>
<th>0.0–0.1†</th>
<th>0.1–0.2</th>
<th>0.2–0.4</th>
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<td></td>
<td>END</td>
<td>EPI</td>
<td>END</td>
<td>EPI</td>
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<tr>
<td>2/24 hr</td>
<td>5</td>
<td>8.8 ± 2.9*</td>
<td>14.8 ± 3.8*</td>
<td>8.9 ± 2.9*</td>
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<td>n = 21</td>
<td>n = 13</td>
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<tr>
<td>24/48 hr</td>
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<td>10.4 ± 3.2*</td>
<td>6.5 ± 2.5*</td>
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<tr>
<td></td>
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<td>n = 19</td>
<td>n = 14</td>
</tr>
<tr>
<td>48/72 hr</td>
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<td>26.8 ± 4.9*</td>
<td>8.4 ± 2.5*</td>
<td>9.0 ± 1.8*</td>
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<td></td>
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<td>n = 17</td>
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<tr>
<td>72/96 hr</td>
<td>4</td>
<td>14.6 ± 3.8*</td>
<td>—</td>
<td>4.8 ± 3.2</td>
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<td>n = 20</td>
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<tr>
<td>96/120 hr</td>
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<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Sham Infarct</td>
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<td>—</td>
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<td>$^{111}$In leukocytes</td>
<td></td>
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<td>—</td>
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<td>1.9 ± 0.4</td>
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<tr>
<td>In-oxine$^{111}$</td>
<td></td>
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Values are expressed as mean ± SEM.

*p < 0.05 compared with normal control samples (either endocardial or epicardial) obtained during the same time period.

†Refers to time of $^{111}$In leukocyte injection/time of imaging and sacrifice.

‡Relative regional myocardial blood flow as assessed by $^{85}$Sr microspheres with 1.0 = 100% control activity.

Abbreviations: END = endocardium; EPI = epicardium.

carried out, and at 48 hours, the dogs received 1 mCi of oxine not labeled to PMNs. Twenty-four hours later, some of the dogs underwent the standard imaging and tissue distribution protocol described above.

Results

Cardiac Imaging

In vivo cardiac imaging revealed regions of increased anterior wall myocardial $^{111}$In accumulation in all dogs in the groups imaged at 24, 48, 72 and 96 hours after infarction (figs. 1 and 2). In contrast, all dogs in the final group receiving $^{111}$In leukocytes at 96 hours and imaged at 120 hours had negative images with no $^{111}$In myocardial uptake. The abnormal myocardial uptake was identified anatomically by its relationship to activity in the liver. There was no activity present in overlying skeletal structures. Faint activity was seen frequently in the region of the sternum, but not in overlying ribs. Optimal image quality was

![In vivo](image1)

![In vitro](image2)

Figure 2. In vivo and in vitro imaging studies obtained in a dog receiving $^{111}$In leukocytes at 48 hours and imaged at 72 hours. The in vivo image is shown on the left; the image of the extirpated heart (in vitro) is shown on the right. For the in vivo image, a linear external radioactivity marker has been placed across the sternum. There is an area of increased myocardial uptake to the right of the external source and above the hepatic activity. This correlates well with the appearance of the image of the extirpated heart.
TABLE 1.  (Continued)

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<td>1.8 ± 0.7</td>
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<td>2.6 ± 0.4</td>
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<td>—</td>
<td>0.4 ± 0.1</td>
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<td>1.5 ± 0.2</td>
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obtained in dogs injected with $^{111}$In leukocytes at 48 hours and imaged 72 hours after infarction. In vivo imaging correlated well with the anatomic patterns demonstrable after imaging of the extirpated heart in seven dogs so studied (fig. 2). In addition, there was a good anatomic correlation between the sites of increased $^{111}$In PMN accumulation after imaging of transverse cardiac slices from the extirpated heart, and the gross anatomic sites of infarction (fig. 3).

**Tissue Distribution Studies**

Comparison of tissue uptake of $^{111}$In and $^{85}$Sr microspheres in multiple myocardial samples allowed

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**Figure 3.** Relationship between images of transverse slices of the left ventricle and pathologic zones of infarction in a dog receiving $^{111}$In leukocytes at 48 hours and imaged 72 hours after infarction. The zones of infarction are indicated diagramatically by the stippled areas, which were obtained from tracings of ventricular slices stained by the dehydrogenase technique. The zones of abnormal $^{111}$In leukocyte accumulation are evident in the images of the tissue slices. Each tissue slice is approximately 1 cm thick.
us to determine the effects of regional myocardial blood flow and infarct age upon regional PMN deposition (table 1, figs. 4–6). At 24 hours, the epicardial accumulation of $^{111}$In PMNs was significantly different from control ($p < 0.05$) in infarct zones with residual blood flow $< 0.6$ times normal (fig. 4). These same trends continued up to 96 hours postinfarction. PMN accumulation was maximal ($14.8 \pm 3.8$ times normal) in the lowest flow zones ($< 0.1$ times normal) and occurred within the first 24 hours after infarction. Epicardial uptake in this lowest flow zone was significantly different ($p < 0.05$) from that noted at later periods in regions with the same flow decrement. Likewise, significant endocardial accumulation of PMNs ($p < 0.05$ compared with control) occurred predominantly in regions with residual myocardial blood flow $< 0.6$ times normal (fig. 5). Maximal endocardial deposition ($p < 0.05$ compared with uptake in other flow zones in the same time period) occurred in lowest flow regions ($< 0.1$ times normal). However, in contrast to the temporal sequence of epicardial deposition, endocardial PMN accumulation was maximal (26.8 $\pm$ 4.9 times normal, $p < 0.05$ compared with uptake at other times in regions of comparable decrement in flow) 72 hours after infarction. In both endocardium and epicardium, PMN accumulation was trivial at 120 hours postinfarction. A comparison of the kinetics of PMN infiltration as a function of infarct age in endocardial and epicardial low-flow zones of maximal uptake is summarized in fig. 6.

Histopathologic assessment showed PMN in all the infarct specimens that were evaluated (fig. 7). Although all samples were associated with significant myocardial necrosis, the magnitude of the inflammatory response was decreased qualitatively in samples from 120-hour-old infarcts in each dog.

In the control dogs no demonstrable excess $^{111}$In myocardial uptake was noted in tissue samples from either dogs with 72-hour-old infarcts receiving free oxine or sham infarct dogs receiving $^{111}$In PMNs. (table 1) Likewise, cardiac images were negative in both types of controls.
Discussion

This study shows that, within a given time after coronary occlusion, $^{111}$In-labeled autologous leukocytes may be used to image the inflammatory response to experimental canine infarction. In this way, our data are similar to those reported by Weiss et al. However, administration of PMNs and imaging within the first 96 hours of infarction invariably resulted in abnormal $^{111}$In PMN cardiac images, while administration of labeled leukocytes and imaging thereafter (i.e., 120 hours postinfarction) did not. Furthermore, tissue distribution studies indicated that within the above temporal sequence, PMN accumulation occurs primarily in myocardial regions where regional blood flow was reduced to $<0.6$ times normal. Indeed, maximal accumulation occurred in the lowest flow zones.

A different time sequence was associated with the greatest endocardial or epicardial PMN accumulation. Epicardial uptake was maximum at 24 hours, while endocardial accumulation was maximum at 72 hours. This is concordant with previous histopathologic studies that have shown that PMN infiltration starts peripherally and then spreads centrally. However, it should be emphasized that in contrast to histopathologic assessment, in vivo imaging and tissue distribution studies provide direct dynamic data concerning PMN infiltration within any given time after infarction. While a histologic section will provide anatomic data concerning the degree of myocardial necrosis and the extent of total PMN accumulation occurring over several days, the $^{111}$In PMN technique provides information concerning only the kinetics of PMN infiltration during the 20–24 hours between $^{111}$In PMN injection and subsequent imaging or tissue studies. Thus, the radionuclide-labeled PMN technique offers pathophysiologic insights that would not be obtainable by more conventional means.

The data concerning the different temporal sequences of maximal transmural PMN accumulation seem to indicate that perhaps different chemotactic stimuli or different degrees of the same stimulus are present in the endocardial and epicardial zones of infarction at different times after coronary occlusion. Alternatively, the phenomenon of delayed maximal endocardial PMN uptake may be a manifestation of gradual development of additional collateral flow into the lowest flow infarct zones over the first several days of infarction, thereby conferring an augmented means of delivery of PMNs to regions that may have been virtually without flow during the first 48 hours of infarction.

The issue of studying the inflammatory response to infarction has been given further impetus by the demonstration that modulation of inflammation may affect the extent of resultant myocardial necrosis.
Various pharmacologic agents, each with presumably different effects upon the inflammatory response, have been used in experimental models. These include corticosteroids, cobra venom factor, protease inhibitors and ibuprofen. Whereas cobra venom factor is believed to affect inflammation by reducing specific complement activity (C₃ and C₅) and thereby reducing generation of chemotactic factor, other agents, such as ibuprofen, may exert an effect by inhibiting prostaglandin-mediated components of the inflammation. Whatever the exact mechanism of action, administration of these agents has resulted in apparent salvage of ischemic myocardium, associated with decreased chemotactic activity emanating from the
coronary sinus of the infarcted canine heart. The use of the 111In PMN technique appears ideal for further detailed experimental studies involving anti-inflammatory drugs and potential infarct size modification, and should provide firm data about the mechanisms of drug action.

The use of 111In PMNs as a biologic marker for studying inflammation appears justified. It has been shown that 111In PMNs retained chemotactic ability when tested in vitro systems. Furthermore, the labeled PMNs respond appropriately by localizing in experimentally induced abscesses, as well as in abscesses in man. The physical characteristics of 111In are well suited for cell labeling studies, for its half-life of 67 hours ensures that sufficient activity will remain at the time of imaging, 20-24 hours after injection. This delay is necessitated by the need to clear PMNs from the circulating blood pool before imaging. The gamma photons of 111In are emitted at 147 and 273 keV, energies suitable for external detection by currently available scintillation cameras.

Although clearly not meant to be a replacement for the currently available clinical infarct imaging agents, technetium-99m pyrophosphate and thallium-201, there are certain situations where 111In PMN imaging would be clinically valuable. A positive 111In PMN image would indicate acute necrosis, and therefore could provide insight into situations of combined old and new infarction where thallium-201 imaging might be nondiagnostic. 111In PMN imaging might be of additional aid in persistently positive pyrophosphate images due to either myocytolysis or metastatic calcification. The results of the present study in dogs indicate that further trials of 111In leukocyte imaging in human infarction are justified at this time. Furthermore, 111In leukocyte imaging might also prove useful in the study of cardiac conditions other than infarction, such as myocarditis, in which the inflammatory response plays a major role.

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