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Early Diagnosis of Myocardial Infarction in the Dog with ^{99m}Tc-Glucoheptonate

Jerome G. Jacobstein, Daniel R. Alonso, Arthur J. Roberts, Paul R. Cipriano, John R. Combes, and Martin R. Post

New York Hospital–Cornell Medical Center, New York, New York

Early gamma imaging of acute experimental myocardial infarcts was evaluated in mongrel dogs with ^{99m}Tc-glucoheptonate. From 15 to 20 mCi were injected between 1 and 27 hr after coronary artery occlusion. Nine dogs imaged 3 hr after injection (4 hr after occlusion) showed unequivocal uptake in the region of the infarct. Fifteen dogs imaged 5–7 hr after injection (6–8 hr after occlusion) showed sufficiently well-defined regions of abnormal uptake so that planimetry could be performed reliably. Five animals imaged serially showed improvement of the image only up to about 5–7 hr after injection. Infarct-to-normal myocardium and infarct-to-blood ratios were slightly higher in dogs injected 15–27 hr after infarction than in those injected 1 hr after infarction, implying that equally good results can be obtained with injection and imaging of ^{99m}Tc-glucoheptonate at any time within the first day. No other infarct-labeling radiopharmaceutical shares this capability for the early detection and delineation of acute infarcts.

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The recent development of radiopharmaceuticals that localize in acute myocardial infarcts has raised the possibility of substantially improving the diagnosis and management of this disease. Images obtained with such agents have the potential to help diagnose and locate infarcts and determine their size; to distinguish between old and recent infarcts, or between reversible ischemic events and infarcts; and to document infarct extension when clinical and laboratory signs are equivocal. Some of the radiopharmaceuticals investigated for these purposes include ^{99m}Tc-pyrophosphate (and related phosphate bone-scanning agents), ^{99m}Tc-tetracycline, and ^{67}Ga-citrate. None of these agents, however, is capable of yielding consistently good images within the first 24 hr after the onset of infarction, which is a serious disadvantage in the clinical situation. Some early work with ^{99m}Tc-glucoheptonate (*1,2*), together with some preliminary data of our own, suggested that this agent might be useful early in the course of infarction. Although this compound gives relatively poor image contrast in patients and has therefore been neglected recently, we felt that the potential advantages of such an early imaging agent justified further animal and patient studies to help clarify the possible areas of clinical application.

MATERIALS AND METHODS

Coronary artery occlusion was produced by two different methods in mongrel dogs weighing 15–27 kg. Most of the dogs underwent a left thoracotomy under anesthesia with 25 mg/kg of sodium pentobarbital. The left anterior descending coronary artery (LAD) was carefully dissected free from surrounding tissues and ligated with a double suture, except in one dog that underwent ligation of the left circumflex artery (LCx) instead. Toward the end

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For reprints contact: Jerome G. Jacobstein, Div. of Nuclear Medicine, Cornell University Medical College, 1300 York Ave., New York, NY 10021.

of the study, coronary artery occlusion was induced in five dogs, after similar anesthesia, by left coronary artery catheterization and embolization with a small metal bead delivered through the catheter. Occlusion of the LAD was produced in this manner in one dog, and occlusion of the LCx in the other four. Controls were provided by several dogs imaged before coronary artery occlusion, and several sham-operated dogs.

Between 1 and 27 hr after coronary artery occlusion, 15–20 mCi of ^{99m}Tc-glucoheptonate were injected intravenously. Imaging was performed* at varying times thereafter, and in five animals serial images were obtained between 3 and 24 hr after injection. Generally, four views were obtained: left lateral, left anterior oblique (LAO), anterior, and right anterior oblique (RAO). Each view was obtained with the animal on its side and the collimator angled appropriately, since this approach permitted positioning of the animal in a reproducible fashion in serial studies. One million counts were obtained in every case.

Images were obtained on Polaroid film and simultaneously the data were recorded on videotape for permanent storage. In each of the five dogs imaged serially, we selected the view that provided the best delineation of the infarct and clearest separation from uptake in the surgical incision (usually the RAO). The data for this view were then played from the videotape into a computer† at each imaging time, and areas of interest over the infarct and over a representative "background" region surrounding the infarct were chosen on digital printouts. Count rate normalized for area was calculated for these regions and infarct-to-background ratios computed. Thus, in each of these dogs, infarct-to-background ratios were obtained on the same view for every imaging time.

After the final images were obtained, the dogs were killed. The heart was removed and imaged in an approximately anterior position, then sectioned transversely in a plane perpendicular to its long axis at 1-cm intervals. The slices were imaged and then incubated with Nitroblue tetrazolium, which stains normal myocardium blue (*3*). The infarct, which remains unstained, is thus clearly delineated. Multiple representative samples of the infarct and surrounding normal heart structures were removed, weighed and counted in a standard well counter. Blood activity was also assayed, and all tissue counts were expressed as counts per minute per gram. Myocardial tissue specimens immediately adjacent to the samples taken for radioassay were sectioned, fixed in 10% formalin, embedded in paraffin, stained with hematoxylin and eosin, and with PAS stain for glycogen, and examined microscopically. Infarct-to-normal myocardium and infarct-to-blood ratios were thus obtained and the actual state of the tissue was confirmed histologically.

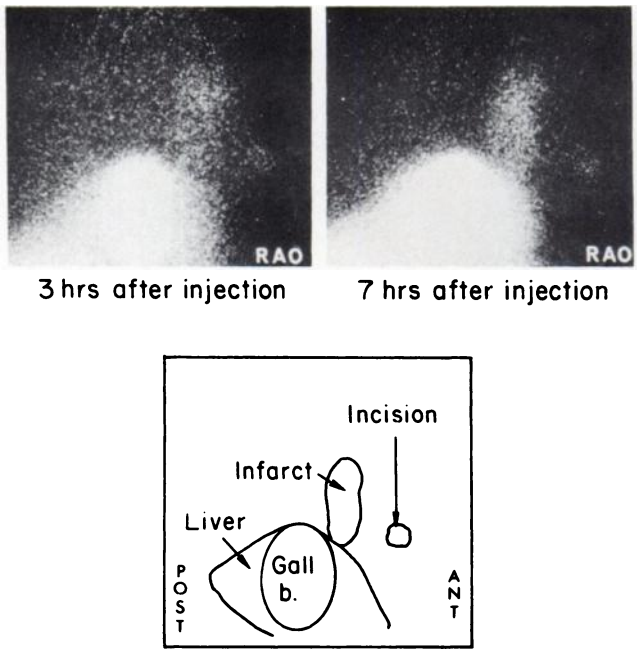


FIG. 1. Technetium-99m glucoheptonate was injected 1 hr after ligation of left anterior descending coronary artery (LAD). Clear evidence of uptake in anterior wall myocardial infarct at 3 hr after injection on right anterior oblique (RAO) view, but better infarct definition at 7 hr. Uptake also seen in surgical incision.

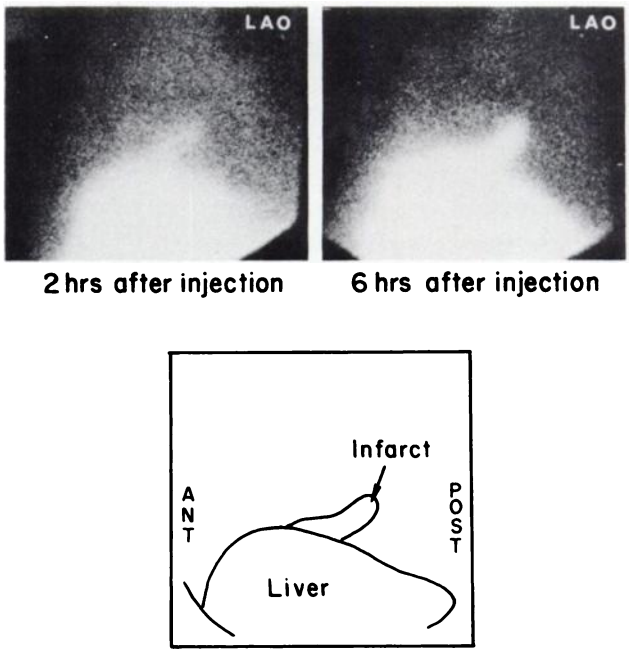


FIG. 2. Injection of ^{99m}Tc-glucoheptonate was at 1 hr after occlusion of left circumflex coronary artery. Uptake in inferior wall infarct is seen on LAO view at 2 hr after injection, although definition is better at 6 hr. No incision is visible because infarct was produced by embolization through a coronary artery catheter.

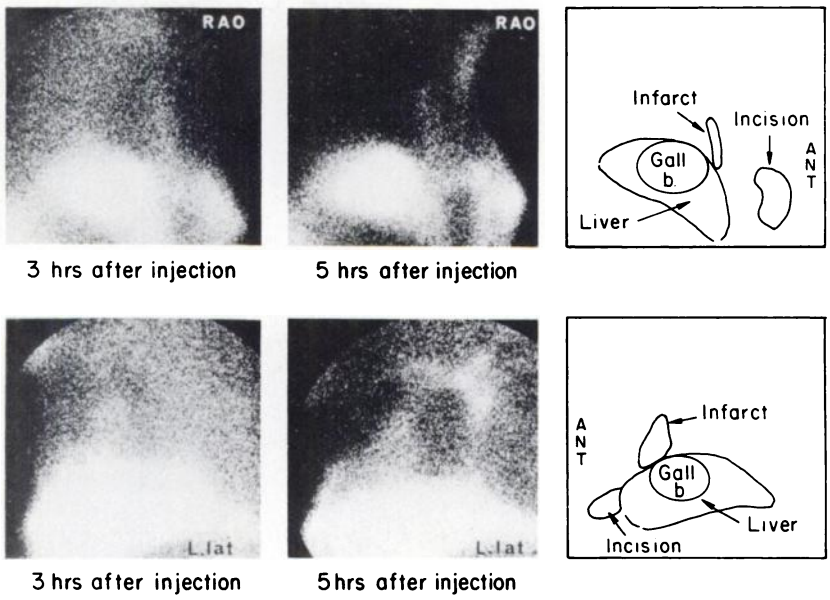


FIG. 3. Poorest infarct delineation in series. Anterior wall infarct is seen 3 hr after injection in RAO and left lateral projections. Definition improves with time. Injection was 1 hr after ligation of LAD, and uptake is seen in incision as well as in lung injured during thoracotomy.

RESULTS

Nine dogs injected at 1 hr after infarction were imaged as early as 3 hr after injection, and all showed unequivocal evidence of abnormal uptake in the region of the myocardium (Figs. 1–3). Control animals showed no uptake in this region (Fig. 4). Sham-operated animals showed a variable degree of uptake in the surgical incision; this might have been intense enough to mask a small infarct, but in no case was the distribution of uptake in the wound likely to have been mistaken for an infarct. Furthermore, our ability to distinguish infarct from surgical incision was confirmed on later views in which the infarct was more sharply defined (Figs. 1 and 3) and by histologic correlation.

A total of 17 dogs injected 1 hr after infarction was imaged 5 to 7 hr later. Two of these animals provided images of poor quality as a result of large hemothoraces induced by surgery and were excluded from the study. The remaining 15 dogs all had well-defined uptake in the region of the left ventricular myocardium that corresponded to the autopsy findings. Border definition was satisfactory in every case on one or more views (Fig. 5) such that planimetry of the area of uptake could be adequately performed.

The five dogs imaged serially were also injected 1 hr after infarction. Imaging and computer processing were performed at the times shown in Table 1. In vivo infarct-to-background ratios showed a gradual increase over the periods studied, with the exception of Dog 1 which for unexplained reasons showed a leveling off (or even a slight fall) between 5 and 7 hr after injection (Table 1). Examination of the serial images, however, revealed minimal subjective improvement in infarct definition after 5–7 hr and none after 12 hr (Fig. 6).

These in vivo infarct-to-background ratios suggest that infarct-to-normal myocardium (I/Nl) and infarct-to-blood (I/Bl) ratios increase with time after injection. Table 2 compares I/Nl and I/Bl ratios determined by tissue counting after death in two groups of animals, one of which was killed 6–9 hr after injection (five animals) and the other 25 hr

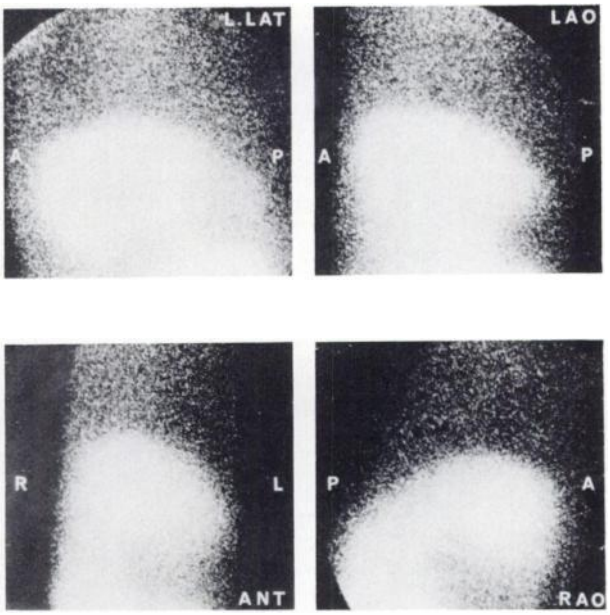
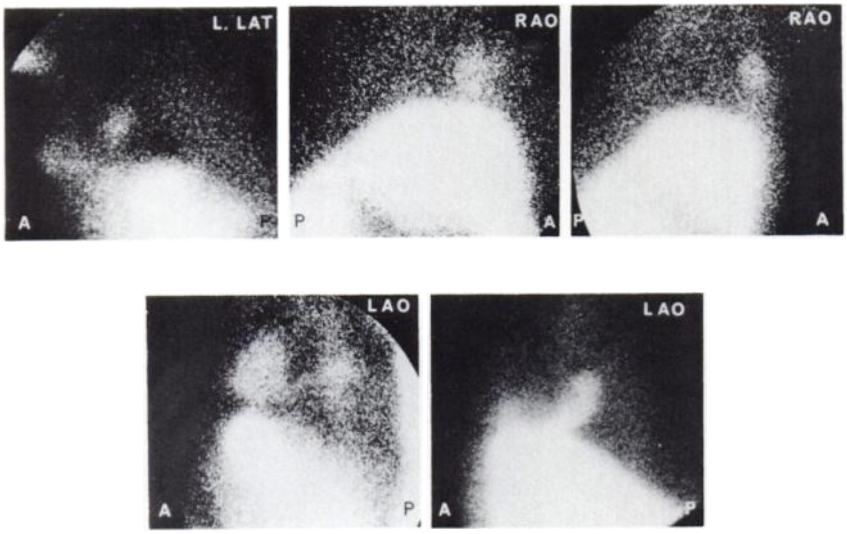


FIG. 4. No uptake is seen in myocardial region in control animal 7 hr after injection of ^{99m}Tc-glucoheptonate.



Five different dogs imaged at 5-7 hours after injection

FIG. 5. Five dogs show well-defined areas of uptake in region of myocardium between 5 and 7 hr after injection of ^{99m}Tc-glucoheptonate. All had LAD occlusion except lower right, in which inferoseptal infarct resulted from occlusion of left circumflex artery. Injection performed 1 hr after coronary artery occlusion in all animals.

after injection (two animals). In both groups ^{99m}Tc-glucoheptonate was injected at 1 hr after coronary artery ligation. In spite of the small number of animals involved, the substantially higher I/Nl and I/Bl ratios at the later time are significant ($p < 0.01$).

Most of our data on imaging infarcts (including unpublished data) are based on injection and imaging in the early hours after coronary artery occlusion, since that is when ^{99m}Tc-glucoheptonate excels over other agents. Nonetheless, the clinical situation requires that satisfactory imaging be obtainable with an injection at least throughout the first 24 hr after infarction, since numerous factors often delay a patient's appearance at the hospital. Table 3 compares I/Nl and I/Bl ratios obtained by tissue counting after death at 6–9 hr after injection in two groups of dogs, five of them receiving ^{99m}Tc-glucoheptonate at 1 hr after coronary artery occlusion, and four others between 15 and 27 hr after occlusion. Both ratios appear higher in those dogs injected at later times, although the difference for I/Nl is not significant ($p < 0.1$).

TABLE 1. IN VIVO INFARCT-TO-BACKGROUND RATIOS

	Time after injection* (hr)				
Dog	3	5	7	12	24
1	2.32	2.76	2.62		
2	1.41	1.46	1.70		
3	1.31	1.38	1.45		
4	2.25		2.45	2.98	4.07
5	1.47	1.67	1.83	2.17	2.69

* Injection of ^{99m}Tc-glucoheptonate 1 hr after infarction.

DISCUSSION

In 1974, Bonte's group showed that ^{99m}Tc-labeled pyrophosphate localized in acute myocardial infarcts with sufficient activity to permit external imaging (*5*). Shortly thereafter, Holman et al. showed that ^{99m}Tc-tetracycline could also be used to image infarcts (*6*), and more recently ^{99m}Tc-glucoheptonate (*1,2,7*) and ^{67}Ga citrate (*8*) have been reported to have similar properties. Of these agents, pyrophosphate and similar bone-scanning agents have the disadvantage of localizing in overlying ribs, although this does not appear to be an insurmountable obstacle. Of greater concern is the waiting time of at least 24 hr after infarction before consistently good imaging can be obtained (*9,10*). Tetracycline, first shown to localize in infarcts by Malek in 1963 (*11*), produced good images when labeled with ^{99m}Tc but has the major disadvantage of requiring a delay of 24 hr after injection before imaging can be performed, with the result that early diagnosis and size estimation are not possible (*12*). Aside from the undesirable delay, this necessarily means low counting rates and relatively long imaging times due to the 6-hr half-life of ^{99m}Tc.

Gallium-67 citrate has a relatively poor energy spectrum and contributes a fairly high radiation dose to the patient. Its major disadvantage, however, is that it requires a 24–48-hr interval between injection and scanning to allow for soft-tissue clearance and adequate infarct delineation (*8*). Therefore, results cannot be obtained early in the course of infarction.

Our data suggest that ^{99m}Tc-glucoheptonate may overcome many of these disadvantages. With injections in dogs as early as 1 hr after coronary artery occlusion, we have consistently seen uptake in infarcts that were clearly recognizable although not always well-delineated by 3 hr after injection, and

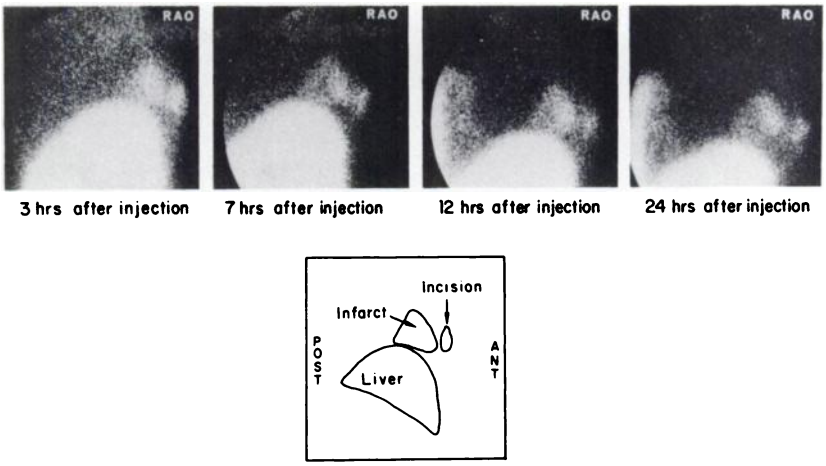


FIG. 6. Serial images obtained at 3, 7, 12 and 24 hr after injection, which was performed 1 hr after ligation of LAD. Minimal improvement in infarct definition occurs beyond 7 hr after injection and none beyond 12 hr.

this in spite of the artifacts induced by the surgery that were present in the seven animals studied at this time (Figs. 1 and 3). Such artifacts generally would not be present in patients.

By 5–7 hr after injection (6–8 hr after coronary artery occlusion), infarct definition was excellent in all 15 dogs and permitted accurate localization and planimetric measurement of infarct borders. Evaluation of serial images in five dogs revealed minimal improvement in actual image quality after 7 hr in spite of the fact that in vivo infarct-to-background ratios and postmortem infarct-to-normal myocardium and infarct-to-blood ratios continued to increase over the 24-hr period studied. It thus appears that for ^{99m}Tc-glucoheptonate, the optimal time for the sizing and localization of acute infarcts in dogs is approximately 5–7 hr after injection. Indeed, we have found that for both LAD and circumflex occlusion, the correlation was good between the true infarct weight determined at autopsy and the area of uptake measured by planimetry on the RAO and LAO views, respectively, at 5 hr after injection. Correlation coefficients of 0.85 for LAD occlusion and 0.88 for circumflex occlusion were obtained. These results will be described in a separate communication.

The counting of autopsy tissues showed that the animals can be injected any time within the first day after infarction with similar results. This is of clinical importance since the time of injection relative

TABLE 2. EFFECT OF TIME AFTER INJECTION ON INFARCT-TO-NOMAL MYOCARDIUM AND INFARCT-TO-BLOOD RATIOS

	I/NI		I/BI	
Time of death	Average	Range	Average	Range
6–9 hr after injection*† (5 dogs)	18.2†	11.2–24.0	8.0*	5.3– 9.5
25 hr after injection* (2 dogs)	42.1	34.5–49.7	30.3	29.2–31.4

(I) infarct; (NI) normal myocardium; (BI) blood.
* All injections 1 hr after infarction.
† The results at 6–9 hr are very similar to those reported by Rossman et al. (4).

TABLE 3. EFFECT OF INFARCT AGE ON INFARCT-TO-NORMAL MYOCARDIUM AND INFARCT-TO-BLOOD RATIOS

	I/NI		I/BI	
Time of injection	Average	Range	Average	Range
1 hr after infarction (5 dogs)	18.2	11.2–24.0	8.0	5.3– 9.5
15–27 hr after infarction (4 dogs)	24.1	16.2–30.2	11.2	9.7–14.4

(I) infarct; (NI) normal; (BI) blood.
* Death and tissue counting at 6–9 hr after injection in both groups.

to the onset of infarction is likely to vary greatly from patient to patient, and a delay of up to 24 hr, or occasionally more, will not be infrequent. Fink/Bennett et al. (*2*), using ^{99m}Tc-glucoheptonate, showed that there is a substantial decrease in infarct-to-normal myocardium ratios in the dog by 48 hr after ligation. Taken in conjunction with our data, this suggests that ^{99m}Tc-glucoheptonate will probably be most effective within the first 24 hr after infarction. This interval is, in fact, the most critical for purposes of infarct diagnosis, localization, and size estimation, so that appropriate therapeutic measures can be taken early in the course of the disease. Furthermore, early diagnosis and sizing have the potential advantage that the results of various interventions designed to decrease infarct size and protect ischemic but viable myocardium may be observed by repeat studies performed after the intervention. The other infarct-imaging agents cannot perform this function because little or no reversibly damaged myocardium remains by 24 hr after infarction (*13,14*), when these agents first become effective.

A recent clinical study with ^{99m}Tc-glucoheptonate in 27 patients showed that imaging with this agent is useful for the identification and size estimation of moderate to large infarcts but is inconsistent in the identification of small subendocardial infarcts (*15*). Our own early observations in over 60 patients tend to confirm these findings. Less satisfactory results described in another report (*16*) may be due to a somewhat different injection and imaging schedule.

In spite of the fact that imaging with ^{99m}Tc-glucoheptonate may be unable to identify some small subendocardial infarcts in patients and may, therefore, not be useful as a screening test, it has great potential nonetheless for both experimental and clinical application in measuring the effects of intervention on infarct size at a time when intervention is still likely to be effective according to present concepts, namely, within the first several hours after onset (*13,14*). In addition, ^{99m}Tc-glucoheptonate imaging may be a useful diagnostic adjunct in patients with moderate or large infarcts because of its ability to estimate infarct location and size early after infarction, at a time when such information can be most useful in the management of the patient.

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FOOTNOTES

* Picker 2C Dynacamera or a Series 120 Ohio-Nuclear mobile scintillation camera.

† IBM 1130, Rochester, N.Y.

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