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DETECTION AND LOCALIZATION OF EXPERIMENTAL MYOCARDIAL INFARCTION

WITH 99mTc-TETRACYCLINE

B. Leonard Holman, M. K. Dewanjee,
John Idoine, Christian P. Fliegel, Michael A. Davis, Salvador Treves, and Per Eldh

Harvard Medical School, Boston, Massachusetts

Images of myocardial infarcts were obtained with the Anger scintillation camera in five of six dogs 25 hr after coronary artery occlusion and 24 hr after the intravenous injection of 99mTc-tetracycline. The location and size of the infarct could be accurately estimated from the scintiphotos. In vitro counting of segments from the excised heart showed that the 99mTc-tetracycline was homogeneously distributed throughout the infarct (5.1–8.4 times greater than normal myocardium) in all six dogs, accurately delimiting the extent of infarction.

The possibility of detecting and sizing myocardial infarcts has intrigued investigators and clinicians for several decades. The detection of the infarcted region as a radioisotopic hot spot would be particularly desirable. The increased tetracycline fluorescence within myocardial infarcts in the dog (1) has led to the investigation of a number of hydroxymercuric derivatives as ischemia-detecting tracers (2–6). Extension of the technique to the clinical setting has been hampered by the poor physical characteristics of the isotopes used (7) and discouraging initial clinical trials (8).

In this study the concentration of 99mTc-tetracycline in acute canine myocardial infarcts was determined and the use of external monitoring techniques for infarct detection and localization was evaluated.

MATERIALS

Ten mongrel dogs (15–20 kg) anesthetized with pentobarbital (30 mg/kg) were studied. Technetium-99m-tetracycline was prepared using the stannous-chloride reduction method (9). Scintiphotos were obtained with a Pho/Gamma HP scintillation camera using the high-sensitivity low-energy collimator and a 25% window symmetrically peaked over the 140-keV 99mTc photopeak. Tissue samples

were counted in a gamma-well counter. Selective coronary arteriography was performed by femoral catheterization.

METHODS

Selective coronary arteriograms (5 ml of 76% Renografin) were obtained in the left lateral, anterior, and left anterior oblique positions in all dogs before embolization. Five control dogs were injected with 10–15 mCi of 99mTc-tetracycline and imaged 4 and 24 hr later. The myocardial concentration of 99mTc-tetracycline was determined in two of these dogs and three were used in the subsequent experiment.

A catheter-guidewire system with a 5-mm piece of occluded 6 French Kifa catheter placed on the tip of the guidewire was then substituted for the arteriographic catheter in eight dogs. After the system was positioned in the left anterior descending or circumflex artery, the guidewire was pulled back, releasing the 5-mm plug into the artery where it became lodged. Lidocaine (10 mg) was rapidly injected intravenously and followed for 20 min by a slow-drip infusion containing 50 mg lidocaine in 250 cc of saline. With the appearance of preventricular contractions, an additional 5–10 mg of lidocaine was injected. This regimen was instituted to prevent electrical death.

Repeat coronary arteriography was performed 30 min after the plug was released. One hour after infarction 10–15 mCi of 99mTc-tetracycline was injected intravenously. Scintiphotos in the left anterior oblique, anterior, and left lateral projections were obtained 4 hr later in five dogs and 24 hr later in six dogs.

Two dogs were killed after the 4-hr imaging and
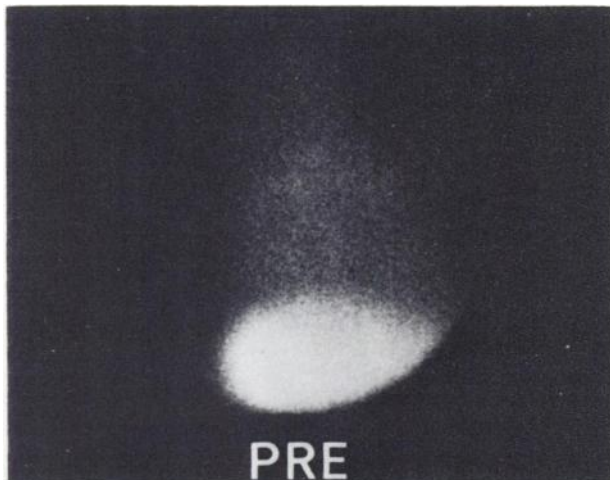
FIG. 1. Scintiphoto of thorax in anterior projection 24 hr after injection of ^{99m}Tc-tetracycline in control dog. Liver and gallbladder have concentrated tracer to great extent. Distribution throughout thorax is uniform, and activity is considerably lower than in abdominal organs.
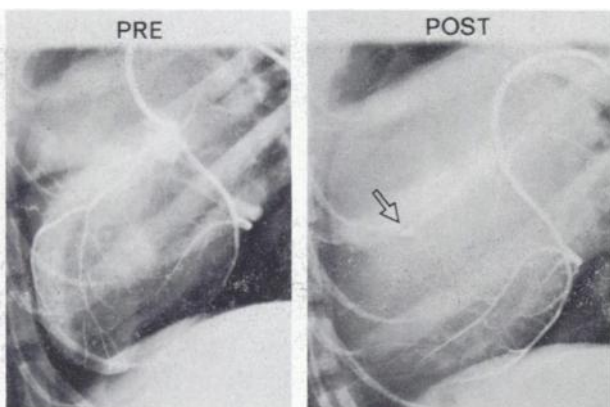
FIG. 2. Coronary arteriogram (left lateral projection) before and after embolization. Plug (arrow) has completely occluded left anterior descending artery.

six dogs after the 24-hr imaging. The hearts were divided into 2–4-gm sections that were mapped according to chamber position and relationship to the coronary vessels and plug (*11*). In four of the experimental animals the gross boundaries of infarction could be determined and were mapped. Counts per gram of tissue were calculated for the heart sections as well as for sections from the liver, diaphragm, lung, and blood.

RESULTS

External imaging at 4 and 24 hr in the control dogs showed high concentrations of ^{99m}Tc-tetracycline in the liver, gallbladder, and kidneys. The uptake in the thorax was homogeneous and considerably less than in the abdominal organs (Fig. 1).

In the experimental animals, the coronary arteriograms performed 30 min after embolization showed

complete occlusion of the vessels in all but one of the dogs (Fig. 2). Five hours after coronary artery occlusion and 4 hr after injection of ^{99m}Tc-tetracycline, one of three dogs imaged showed high concentration of activity in the region distal to the occluded left anterior descending artery (Fig. 3). The intensity in this area was not as great as that in the liver, but the infarct could be easily delimited from surrounding normal heart and lungs.

External imaging at 24 hr showed increased activity relative to surrounding myocardial and lung tissue in the area distal to the coronary artery occlusion in five of the dogs. The infarct was clearly visualized on the 24-hr scans in the two dogs with no visible uptake at 4 hr. Uptake was further enhanced at 24 hr in the dog with uptake at 4 hr (Fig. 3 and Table 1). In this dog, the intensity approached that of the liver. In the one dog in which the area distal to the coronary occlusion could not be imaged at 24 hr, the plug was lodged in the distal portion of the circumflex artery and the area of infarction involved the diaphragmatic portion of the myocardium. The concentration of tracer in the infarct relative to normal myocardium was high (5.9:1) in this dog. Because the area of infarct was small and because of the high concentration of ^{99m}Tc-tetracycline in the adjacent liver, the infarct was not seen in the lateral, anterior, and left anterior oblique projections.

Concentration of ^{99m}Tc-tetracycline in tissue distal
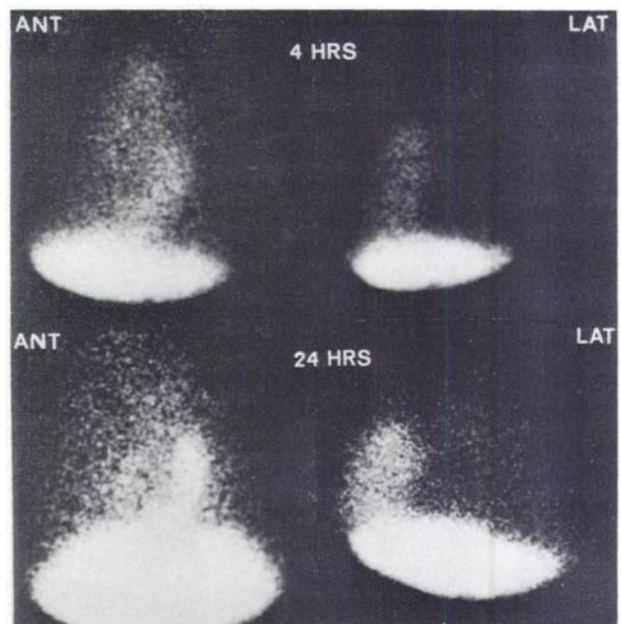
FIG. 3. Scintiscans 4 and 24 hr after injection of ^{99m}Tc-tetracycline. Area of infarction is barely visible at 4 hr but clearly defined by 24 hr. Uptake corresponds to tissue distal to occluded vessel on arteriogram.

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TABLE 1. CONCENTRATION OF 99mTc-TETRACYCLINE IN NORMAL AND INFARCTED MYOCARDIUM

Dog	Location of plug	Gross appearance of infarct	Infarct imaged at 24 hr	Contrast beyond occlusion†	Time after 99mTc-tetra-cycline (hr)	99mTc-tetracycline concentration		
						Infarct tissue*	Normal tissue*	Infarct normal
Experimental animals								
1	Proximal LAD	Hemorrhagic	Yes	None	24	4.44	.53	8.38
2	Proximal LAD	Pale	Yes	None	24	5.17	.76	6.76
3	Mid-CFX	No evidence	Yes	Slight	24	4.21	.58	7.19
4	Proximal LAD	Pale	Yes	None	24	3.01	.42	7.12
5	Distal-CFX	Pale	No	None	24	2.73	.46	5.93
6	Mid-LAD	Pale	Yes	None	24	1.85	.36	5.11
7	Proximal LAD	No evidence	—	None	4	1.01	.36	2.76
8	Distal-LAD	No evidence	—	None	4	1.18	.60	1.96

* Concentration of 99mTc-tetracycline $\left(\dfrac{\text{counting rate tissue sample}}{\text{gm}} \Big/ \dfrac{\text{counting rate blood}}{\text{gm}} \right)$ normalized to concentration in blood at the time animal was killed.

† Evaluation on coronary arteriogram 30 min after embolization.

to the coronary artery occlusion was 5.1–8.4 times greater than normal myocardium at 24 hr (Table 1). At 4 hr the ratio was 2.8 and 2.0 to 1. In the two control dogs studied at 24 hr after injection of 99mTc-tetracycline, the relative concentrations in tissue taken from various parts of the heart varied by 35%. The concentration of 99mTc-tetracycline relative to blood was high in the liver at 4–24 hr (Table 2) and varied considerably at 24 hr (range: 5.3–23.0). The relative concentration in the lung varied to a lesser extent (range: 0.7–2.1). Blood levels fell from 28.7% (range: 18.3–36.7%) of the injected dose at 4 hr to 9.3% (range: 5.2–11.3%) at 24 hr. Concentration in the infarct was less than that in the liver but considerably greater than the concentration in the lung and blood.

The gross appearance of the tissue distal to the occlusion after 24 hr was hemorrhagic in one dog and pale in four dogs; the ischemic zone was indistinguishable in appearance from normal myocardium in one dog. In all cases the concentration in infarcted myocardium was 5.1–8.4 times greater than normal myocardium, indicating increased uptake of 99mTc-tetracycline in not only hemorrhagic

but also pale infarcts with poor perfusion through collateral vessels. However, the greatest concentration of 99mTc-tetracycline was in the hemorrhagic infarct.

In those animals in which the infarct could be localized grossly, the high uptake of 99mTc-tetracycline corresponded to the area of infarction and was homogeneously distributed throughout this tissue (Fig. 4). The dropoff in concentration at the borders of the infarct was dramatic, producing an accurate measure of infarct size.

DISCUSSION

The concentration of 99mTc-tetracycline in areas of myocardial infarction mirrors the pathological changes occurring within the tissue (11). The very early change is primarly redistribution of electrolytes. Neutrophil infiltration occurs at 3–4 hr in response to lysosomal release; edema and the beginning of cell breakdown become significant only after 6–8 hr. The concentration of 99mTc-tetracycline within the infarct was only 2.0–2.8 times the con-

TABLE 2. CONCENTRATION OF 99mTc-TETRACYCLINE RELATIVE TO BLOOD $\left(\dfrac{\text{COUNTING RATE TISSUE}}{\text{GM}} \Big/ \dfrac{\text{COUNTING RATE BLOOD}}{\text{GM}} \right)$

	Experimental								Control	
Dog no.	1	2	3	4	5	6	7	8	9	10
Time after 99mTc-tetracycline (hr)	24	24	24	24	24	24	4	4	24	24
Liver	6.2	23.0	10.4	5.3	5.7	10.2	5.2	4.9	31.5	17.3
Diaphragm	—	—	0.6	0.4	0.5	0.5	0.6	—	—	0.6
Lung	1.4	2.1	0.9	0.7	0.9	2.6	1.1	0.8	2.4	1.4
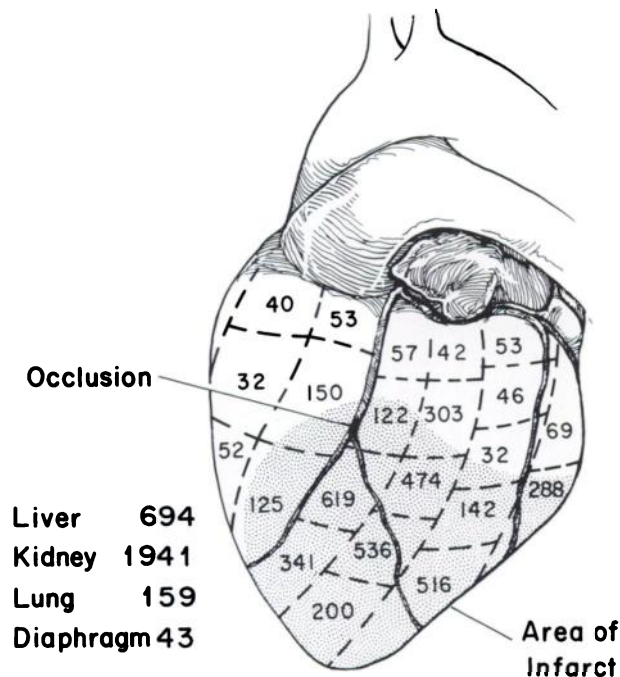
FIG. 4. Counting rates (X 100 cpm) per gm obtained from sectioned myocardium after killing dog imaged in Fig. 3. Gross infarct conforms to stippled area. Counting rates are uniformly high throughout area and accurately define boundaries of infarct.

centration in normal myocardium at 4 hr when cell breakdown was beginning; it reached a ratio of 7:1 at 24 hr when cell breakdown was maximal. The improvement in infarct imaging at 24 hr compared with imaging at 4 hr reflects both the increase in activity in the infarct and the clearance of ^{99m}Tc-tetracycline from the blood with time.

The uniform distribution of ^{99m}Tc-tetracycline throughout the infarct is somewhat surprising. After ligation of the left anterior descending artery, Malek, et al (1) observed that tetracycline concentrated primarily in the peri-infarct tissue. The uptake was not only in the lateral margins of the infarct but in the endocardial and epicardial margins as well, enclosing the infarct completely by a wall of tetracycline. In these experiments, the concentration of ^{99m}Tc-tetracycline in the infarct area implies some perfusion into this tissue either through collaterals opened up by the coronary artery occlusion or by trickling around the plug obstructing the vessel. Coronary arteriography 30 min after embolization showed no contrast past the obstruction in all but one animal where a small amount of contrast escaped beyond the plug with very slow subsequent runoff. It is possible that collaterals could have developed from adjacent vessels during the intervening time between coronary arteriography and the 24-hr scan, perfusing the infarct with labeled tetracycline.

The concentration of ^{99m}Tc-tetracycline relative to blood varied considerably in the liver and to a lesser extent in other tissues. However, concentration in blood varied by more than two-fold at 24 hr in the six dogs and accounted for the variability in the relative concentrations in lungs and diaghragm, but not in the liver. Variable tissue uptake in the liver probably reflected different rates of bile excretion of the labeled tetracycline before death and perhaps variable amounts of colloid formation during the preparation of the radiopharmaceutical.

This method for infarct labeling appears promising for the detection, localization, and sizing of myocardial infarcts in man. Clearly, the coronary circulation is quite different in normal man and in dogs, the latter having considerably greater collateral circulation. Unless the dying or dead cells are perfused to some extent, no ^{99m}Tc-tetracycline will reach these cells. Nevertheless, there are several reasons to expect this technique to detect infarction in patients with coronary artery disease. Most patients have developed a substantial collateral circulation due to progressive arteriosclerotic disease by the time they have true infarction (12). Even if the infarcted tissue itself receives no blood at all, the ischemic areas surrounding the infarct, comprised of hypoxic cells undergoing cell breakdown, are being perfused to some extent. Here one would expect ^{99m}Tc-tetracycline to concentrate, outlining the perimeters of the infarct. As a result, patients with previous coronary artery disease might be expected to have positive scans. However, the acutely infarcted dog heart is probably not analogous to the human heart with infarction, the result of naturally developing arteriosclerosis, and utility in the clinical setting will have to await human trials.

Although the usefulness of this technique needs to be evaluated in man, its suitability for sizing and locating the infarct in the dog is now apparent. Consequently the relative effectiveness of various pharmaceutical and physiological interventions for altering infarct size in the dog can be tested either by external imaging or by in vitro counting.

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