Myocardial Redistribution of Technetium-99m-Methoxyisobutyl Isonitrile (SESTAMIBI)

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To determine whether technetium-99m-hexakis-2-methoxyisobutyl isonitrile (SESTAMIBI) remains fixed in the myocardium following its initial uptake or undergoes time-related redistribution, anesthetized dogs underwent occlusion of the anterior descending coronary artery for 6 min, followed by 3-hr reperfusion. Technetium-99m-SESTAMIBI and thallium-201 (^{201}Tl) were injected intravenously after 1 min occlusion and regional myocardial blood flow was measured with radioactive microspheres. Tomographic imaging of Tc-SESTAMIBI revealed a perfusion defect with slight but definite filling in over 2 hr. Quantitative analysis indicated a significant rise in the nadir and decrease in the width of the defect in circumferential profile curves. After 3-hr of reperfusion, Tc-SESTAMIBI activity in the previously ischemic area was always greater than the activity of microspheres injected during coronary occlusion (mean normalized values, 0.32 versus 0.11, $p < 0.0001$). Our results indicate that following transient ischemia and reperfusion, Tc-SESTAMIBI clearly undergoes myocardial redistribution, although more slowly and less completely than ^{201}Tl.

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Technetium-99-m-hexakis-2-methoxyisobutyl isonitrile (Tc-SESTAMIBI or Cardiolite) has been recently introduced as a potential substitute for thallium-201 (^{201}Tl) in the study of patients with suspected or proven coronary artery disease (*1–4*). Technetium-99m-SESTAMIBI has been shown to provide high quality images of the myocardium in animal models (*5*) and patients (*1–4*). Experimental studies have shown an excellent correlation between the myocardial distribution of blood flow and Tc-SESTAMIBI in animals with coronary artery stenoses (*5–10*). Because of its good correlation with perfusion and its apparent lack of myocardial redistribution, Tc-SESTAMIBI has been termed a "chemical microsphere." Okada et al. (*6*) found that clearance of Tc-SESTAMIBI was similar from normal and ischemic regions in anesthetized dogs, and that redistribution was not evident by either tissue counting or planar imaging. However, Okada's studies employed a model with fixed coronary stenosis and no reperfusion. Fixed stenoses without superimposed stress or coronary vasodilation may not represent the most appropriate way to model the clinical use of Tc-SESTAMIBI. Our own studies in the dog have employed transient coronary occlusion with simultaneous injection of Tc-SESTAMIBI and radioactive microspheres during ischemia (*5*). After 1 hr reperfusion, we have found a consistent excess of Tc-SESTAMIBI in the previously ischemic region relative to the level of ischemia that was present during coronary occlusion (reflected in the distribution of microspheres). If Tc-SESTAMIBI were indeed a "chemical microsphere," the tissue contents of Tc-SESTAMIBI and microspheres should have been identical.

This study was done to determine whether the excess Tc-SESTAMIBI content in regions of transient myocardial ischemia is caused by: (a) excess initial tracer uptake in areas of reduced blood flow or by (b) time-related accumulation of Tc-SESTAMIBI following arterial reperfusion. We also sought to determine the extent to which myocardial uptake during reperfusion is related to rapid uptake during early reperfusion, when the arterial blood concentration of Tc-SESTAMIBI is still relatively high.

MATERIALS AND METHODS

Sterile, pyrogen-free Tc-SESTAMIBI was prepared from a kit provided by E.I. duPont de Nemours and Company Biomedical Products, North Billerica, MA. Fifteen millicuries (for protocol A) or 2 mCi (for Protocol B and C) of [^{99m}Tc] pertechnetate in 0.1–3.0 ml was added to the kit, and the vial was placed in a boiling water bath for 15 min. After the vial had cooled, radiochemical purity was checked by chromatographic analysis (SEP-PAK). The radiochemical purity was >95% in all cases.

Mongrel dogs of either sex weighing between 40 and 60 pounds were anesthetized with sodium pentobarbital, intubated, and ventilated with a Harvard respirator. Cannulae were placed in the femoral artery for blood sampling, and in the femoral vein for injection of tracer. A left thoracotomy was performed in the fifth intercostal space. The proximal segment of the left anterior descending coronary artery (LAD)

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was isolated, and a pneumatic balloon occluder was placed around the exposed section of artery. A catheter was also placed in the left atrium for injection of radioactive microspheres. The chest was then closed and lead II of the electrocardiogram was monitored continuously during the experiment.

Protocol A was designed to determine whether Tc-SESTAMIBI redistribution could be detected by tomographic imaging in dogs with transient myocardial ischemia. In four dogs (Group 1), the LAD was occluded for a period of 6 min. One minute after occlusion, 15 mCi of Tc-SESTAMIBI and 2 mCi ^{201}Tl were injected intravenously. At the same time, 2 $\times$ 10^6 iodine-125 (^{125}I) microspheres (DuPont Co., N. Billerica, MA) with a mean diameter of 16 μm were injected into the left atrium. Arterial blood samples were withdrawn by a Harvard pump at a constant rate of 2.16 ml/min starting just before injection of the microspheres and continuing for 2 min afterward, for determination of regional myocardial blood flow.

Tomographic imaging (TOMO-1) was begun 30 min after injection of the Tc-SESTAMIBI (25 min after release of the occlusion) and took ~30 min to complete. A second set of tomographic images (TOMO-2) was obtained 150 min after injection of the Tc-SESTAMIBI. The dogs were immobilized throughout the two tomographic acquisitions.

Tomographic imaging was performed with a Technicare Omega 500 rotating large field of view camera (Solon, OH), which acquired 60 images (30 sec/image) through 180° from the right lateral to the left lateral position. A high-resolution parallel-hole collimator was used, with a 20% energy window centered on the 140-keV gamma ray peak. Raw images were obtained in 128 $\times$ 128 byte mode with 1.4$\times$ magnification and a 22-cm radius of rotation. Transverse slices were reconstructed by filtered backprojection, using a Hanning 0.65 filter. The data were then reoriented to display six to seven serial 1.0-cm thick short-axis slices from apex to base of the left ventricle.

Four short-axis slices, representing the middle of the left ventricle, were displayed in 64 $\times$ 64 byte mode and subjected to a semi-automated analysis of deficit severity. The radial distribution of imaged Tc-SESTAMIBI activity was quantitated using our modification of the "CIRMAX" circumferential profile program provided by Technicare. As in the standard program, the operator generates a region of interest by positioning a circle just outside of the outer perimeter of the myocardial slice. For each angular interval, the program finds the pixels which lie along the radial line at the desired angle, and determines the maximum count. The CIRMAX curve starts from three o'clock and proceeds counterclockwise. Unlike the standard program, however, we normalized the curve by the value located exactly 180° opposite the nadir of the curve, rather than by the highest value on the curve.

Gadolinium-153- (^{153}Gd) microspheres (2 $\times$ 10^6, 16 μm diameter) were injected into the left atrium at the end of the imaging. The heart was then removed, the right ventricle excised, and the left ventricle was sectioned transversely from apex to base into six to seven slices (thickness 1.0 cm), corresponding to the number of short-axis tomographic images. Each slice was then divided radially into 9–18 samples that were weighed and counted in a well-type scintillation counter (Packard Auto Gamma Scintillation Spectrometer Model 5986, Downers Grove, IL). Pulse-height analysis was used to differentiate activity from the four radionuclides (^{125}I, 10–34 keV; ^{153}Gd, 36–53 keV; ^{201}Tl, 58–96 keV; ^{99m}Tc, 124–170 keV). The [^{99m}Tc]SESTAMIBI was counted immediately, while ^{201}Tl and microsphere activities were measured two days later.

Regional myocardial blood flow (RMBF) was calculated using the formula:

$$\text{RMBF} = \text{R (Cm/Cr) (ml/min/g)},$$

where R = reference blood flow pump withdrawal rate, Cm = counts per gram in the myocardial samples, and Cr = counts in the reference blood sample. For each left ventricular slice, the RMBF of each sample was normalized by the RMBF of the sample located 180° away from the center of the ischemic zone, and expressed as a ratio.

In three dogs (Group 2), the protocol was the same except that postocclusion hyperemia was prevented by placing a stenosis on the LAD. Before coronary occlusion, a plastic screw occluder and electromagnetic flow probe were placed around the LAD and the occluder was adjusted to abolish reactive hyperemia following a 10-sec temporary flow occlusion. The LAD was then occluded for a period of 20 min and reperfused through the stenosis. Gadolinium-153-microspheres were injected into the left atrium immediately after reflow and scandium-46 (^{46}Sc) microsphere (duPont Co., N. Billerica, MA) were injected into the left atrium at the end of the second tomogram.

Protocol B was designed to determine whether Tc-SESTAMIBI redistribution could be detected in serial myocardial biopsies. Six dogs underwent the same preparative surgery and 6-min LAD occlusion as in Protocol A. One minute after occlusion, Tc-SESTAMIBI, 2 mCi, and ^{201}Tl-chloride, 0.5 mCi, were injected intravenously. At the same time, ^{46}Sc-microspheres were injected into the left atrium. Five minutes after occlusion, paired transmural myocardial specimens were obtained with a biopsy drill (24.0 $\times$ 2.0 mm) from the center of the regions of myocardium perfused by the LAD and the left circumflex coronary arteries. Bleeding from the biopsy site was stopped by purse-string sutures (00 silk). The arterial blood pressure remained stable during the biopsy procedure. The balloon occluder was released 6 min after occlusion, and 1 min later, microspheres (ruthenium-103, ^{103}Ru) were injected to document successful reperfusion. The second and third paired biopsies were obtained after 30 and 180 min of reperfusion. In four additional dogs, after bolus i.v. injection of 0.5–0.8 mCi Tc-SESTAMIBI and 0.1–0.3 mCi ^{201}Tl, serial 0.5–1.5-ml blood specimens were withdrawn from the aorta every 10 sec for the first 2 min, every 30 sec for 3 min, every 2 min for 25 min, and every 30 min until 2 hr postinjection. The injected dose was measured by counting the syringe before and after injection with appropriate corrections for geometry, counting efficiency, and decay. Results were expressed as the percent of injected dose per gram of blood (%i.d./g) at each time point.

All myocardial biopsy specimens were blotted dry on filter paper, weighed to the nearest 20 mg, and counted in the multichannel gamma counter. Blood specimens were counted as in protocol A, except that additional energy windows were required for ^{46}Sc (850–1200 keV) and ^{103}Ru (448–500 keV).

Two additional dogs underwent the same biopsy protocol

except that the LAD was not reperfused and remained occluded for the entire 180 min.

Protocol C was designed to assess the myocardial uptake of Tc-SESTAMIBI in the first few minutes, before the onset of reperfusion. In three dogs, 1 min after coronary occlusion, ^{125}I-microspheres were injected into the left atrium and simultaneously, 2 mCi Tc-SESTAMIBI (n = 1), 0.5 mCi ^{201}Tl (n = 1), or both (n = 1) were injected intravenously. The animals were killed 5 min later without reflow. The activities of ^{99m}Tc, ^{201}Tl, and microspheres were determined in multiple left ventricular samples (0.5–1.0 g) and expressed as a fraction of the nonischemic activity.

Results are expressed as the mean ± s.d. The statistical significance of differences between mean Tc-SESTAMIBI, ^{201}Tl, and microsphere activities in myocardial samples was determined by paired t-test. Regression analysis was used to determine the relation between Tc-SESTAMIBI and microsphere activities in the center of the ischemic zone in all animals combined, as well as in multiple tissue samples from the three dogs that had direct counting of tissue Tc-SESTAMIBI and microsphere activities before reperfusion.

RESULTS

During reperfusion, there was evidence of partial redistribution of Tc-SESTAMIBI into the previously ischemic area in both the serial imaging and serial biopsy protocols. Tomographic imaging revealed slight but definite filling of the initial perfusion defect over 2 h (Fig. 1). Quantitative analysis of the short-axis images demonstrated a consistent rise in the nadir of activity and a reduction in the width of the perfusion defect between the initial and delayed images. The mean nadir of the activity curve rose from 0.25 ± 0.22 to 0.36 ± 0.24 ($p < 0.0001$) between the first and second set of images, while the mean defect width decreased from 159 ± 82 to 132 ± 79 degrees ($p < 0.004$) (Table 1). Tissue counting after the second imaging study showed that Tc-SESTAMIBI activity in the center of the previously ischemic area averaged 0.32 ± 0.11, similar to the value obtained from the images. In contrast, however, the corresponding microsphere content, reflecting the level of ischemia present before reperfusion, averaged only 0.11 ± 0.12. The greater tissue content of Tc-SESTAMIBI compared to microspheres is consistent with Tc-SESTAMIBI redistribution. This redistribution was considerably less than ^{201}Tl, however, since ^{201}Tl tissue content after the second imaging study averaged 0.79 ± 0.10.

The serial biopsy protocol was done to determine whether the increase in Tc-SESTAMIBI activity ratio during reperfusion was due to an absolute increase in

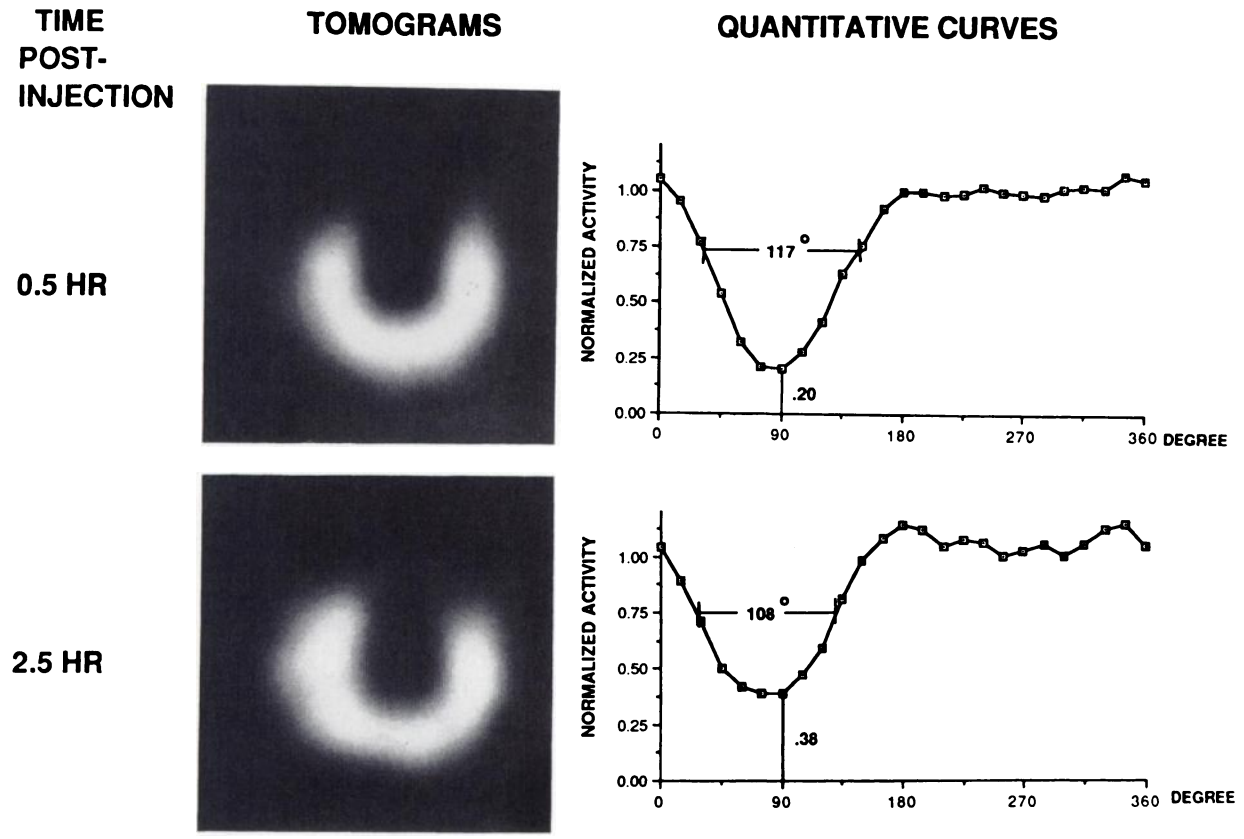

FIGURE 1
Some redistribution of Tc-SESTAMIBI is evident in this short axis tomographic slice following 2-hr reperfusion in a representative animal. Quantitative analysis of the circumferential profile curves shows an increase in the nadir and a decrease in the angular width of the perfusion defect.

TABLE 1
Comparison of Imaging and Tissue-Counting Data in Protocol A

	Tomographic Quantitative Curves				Tissue Counting Data				
	TOMO-1		TOMO-2		Tc-MIBI	^{201}Tl	Microspheres		
Group	Nadir	Width	Nadir	Width			OCCL	Reflow	End
1	0.25* ± 0.22	159 ± 82	0.36‡ ± 0.24	132‡ ± 79	0.32* ± 0.11	0.79 ± 0.10§	0.11 ± 0.12	3.95*¶ ± 0.29	0.82* ± 0.19
2	0.37* ± 0.28	120 ± 68	0.44‡ ± 0.26	105† ± 65	0.32* ± 0.11	0.67 ± 0.04§	0.15 ± 0.17	0.73* ± 0.28	0.38* ± 0.20

Group 1 = full reperfusion (5 min occl, 120 min reperfusion).
Group 2 = restricted and delayed reperfusion (20 min occl, 120 min reperfusion through a coronary stenosis).
Nadir = ratio of lowest activity in perfusion defect to activity in opposite wall.
Width = length in degrees of the circumferential profile curve falling below an activity level of 0.75 (see Fig. 1).
OCCL = coronary occlusion, Reflow = 1 min after release of occlusion, End = end of tomographic acquisition.
Statistical comparisons are within each group: * $p < 0.01$ vs. microspheres during OCCL; † $p < 0.05$, ‡ $p < 0.01$ vs. TOMO-1; § $p < 0.01$ vs. Tc-SESTAMIBI, and ¶ data from Protocol B.

Tc-SESTAMIBI activity in the previously ischemic area, a decrease in Tc-SESTAMIBI activity in the normal area, or both. After 3 hr of reperfusion, Tc-SESTAMIBI activity increased 57% in the previously ischemic area and decreased 19% in the normal area (Fig. 2). By comparison, over the same time period, ^{201}Tl activity increased 202% in the previously ischemic area and decreased 66% in the normal area. The Tc-SESTAMIBI activity ratio in the previously ischemic area increased from 0.18 ± 0.04 to 0.23 ± 0.06 after 30 min ($p = 0.125$) and increased further to 0.30 ± 0.05 after 180 min ($p = 0.03$ versus end ischemia) (Fig. 3). In contrast, the activity ratio for ^{201}Tl increased from 0.12 ± 0.03 to 0.94 ± 0.15 at 30 min ($p < 0.0005$) and to 0.96 ± 0.07 at 180 min. These data support the notion that true myocardial redistribution of Tc-SESTAMIBI occurs (i.e., an increase in activity in the previously ischemic area combined with a decrease in activity in the normal area), although not to the same extent as with ^{201}Tl.

Additional experiments were done to determine whether postischemic uptake of Tc-SESTAMIBI could be explained by rapid accumulation during early reperfusion, related to both myocardial hyperemia and persistently elevated arterial blood concentration of Tc-SESTAMIBI. During the first 2 min after i.v. bolus injection, the arterial blood concentration of Tc-SESTAMIBI fell rapidly, although the decline was not as great as with ^{201}Tl between 0.75 and 2 min. However, after 2 min, the arterial blood concentrations of Tc-SESTAMIBI and ^{201}Tl reversed. After 5 min, the arterial blood concentration of Tc-SESTAMIBI was only 0.098% ± 0.029% of injected dose per gram. By 20 min, the concentration had fallen to only 0.039 ± 0.010% of the injected dose per gram. By contrast, the residual blood activity of ^{201}Tl was considerably higher, averaging 0.26% ± 0.05% of the injected dose per gram at 5 min and 0.090% ± 0.020% at 20 min (Fig. 4).

Myocardial uptake during early redistribution was limited in a subset of dogs by delaying reperfusion for 20 min after Tc-SESTAMIBI injection to allow time for greater clearance of tracer from the blood. In addition, a coronary artery stenosis was left in place to prevent reactive hyperemia (Table 1, Group 2). Despite these maneuvers, serial tomographic imaging again demonstrated a rise in the mean nadir of the Tc-SESTAMIBI activity curve from 0.37 ± 0.28 to 0.44 ± 0.26 ($p < 0.0006$) between the first and second set of images and a decrease in the width of the perfusion defect from 120 ± 68 to 105 ± 65 degrees ($p < 0.02$). When full reperfusion was permitted 5 min after Tc-SESTAMIBI, the nadir of the Tc-SESTAMIBI activity curve increased 44%; however, when reperfusion was delayed for 20 min and restricted by a coronary stenosis, the increase in the nadir was only 19% (Table 1).

Finally, experiments were performed to evaluate why the initial tomographic study appeared to underestimate the severity of the perfusion defect (i.e., why the TOMO-1 nadir exceeded the activity ratio of microspheres injected during coronary occlusion [Table 1]). This was done by comparing the tissue contents of Tc-SESTAMIBI and microspheres in ischemic myocardium before reperfusion in order to determine whether there was a true excess of Tc-SESTAMIBI relative to blood flow. During coronary occlusion, the myocardial distributions of Tc-SESTAMIBI and microspheres (MS) were highly correlated Tc-SESTAMIBI = 0.07 + 0.86 MS, $r = 0.99$, Fig. 5). Agreement between the two tracers was excellent over a wide range of normalized flows from 0.2 to 1.0 (mean MS = 0.73 ± 0.29, mean [^{99m}Tc]SESTAMIBI = 0.74 ± 0.28). However, an excess of Tc-SESTAMIBI was observed for low flow values. For normalized flows <0.2, mean Tc-SESTAMIBI content was 0.09 ± 0.05, compared to 0.04 ± 0.04 for MS ($p < 0.0001$). At high flow values (>1.0), there was a relative deficiency of Tc-SESTAMIBI (MS = 1.21 ±

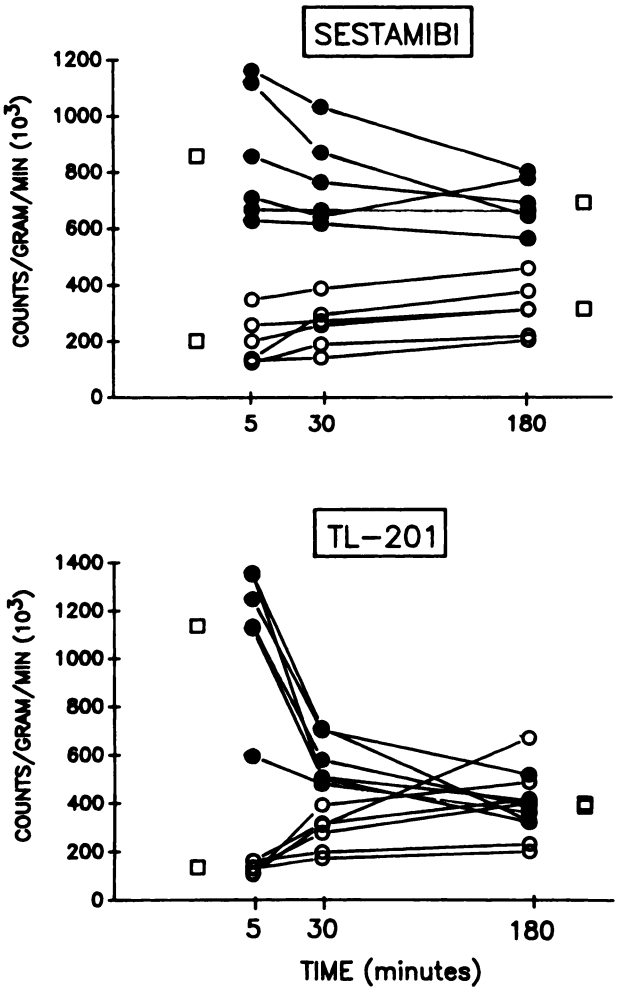

FIGURE 2
Tc-SESTAMIBI and ^{201}Tl activities in myocardial biopsies from the normal (closed circles) and ischemic zones (open circles) in six dogs 5 min, 30 min, and 180 min after injection of the tracers. The dogs were reperfused just after the 5-min biopsies. The squares represent mean activity values in each zone. For both Tc-SESTAMIBI and ^{201}Tl, note the consistent fall in normal zone activity and rise in ischemic zone activity consistent with redistribution. However by 180 min, redistribution is complete for ^{201}Tl but not Tc-SESTAMIBI.

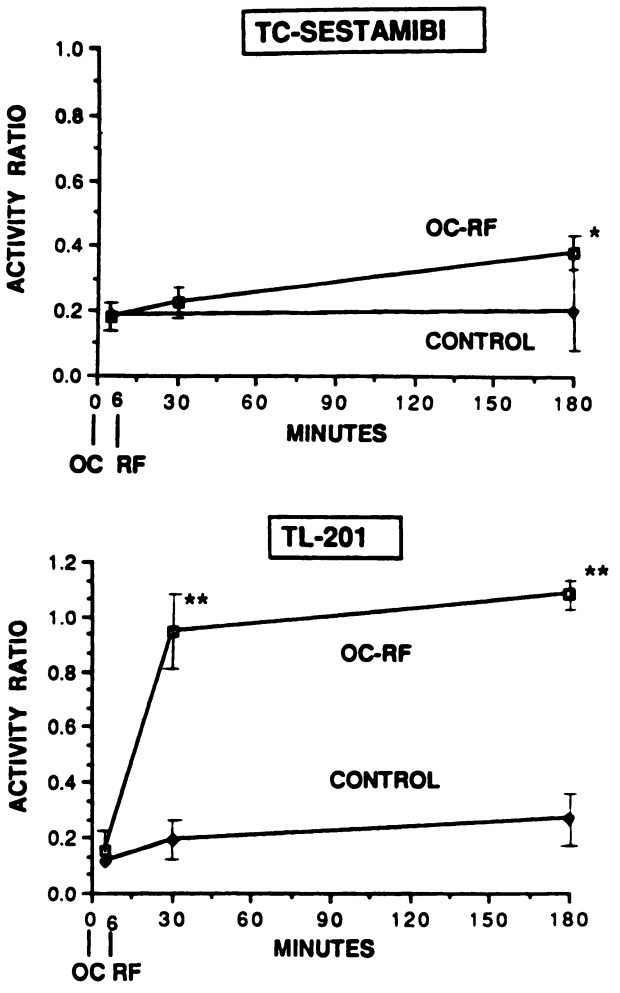

FIGURE 3
Mean activity ratios (activity in ischemic zone/activity in normal zone) of Tc-SESTAMIBI and ^{201}Tl in myocardial biopsies taken at 5, 30, and 180 min after injection from two dogs with permanent coronary occlusion (CONTROL) and six dogs with reflow (OC-RF). Note progressive increase in activity of Tc-SESTAMIBI over the 180-min observation period, whereas the increase in ^{201}Tl activity occurs within the first 30 min. Values are mean ± s.e.m. *$p < 0.05$, **$p < 0.001$ vs. initial value.

0.14; Tc-SESTAMIBI = 1.08 ± 0.13, $p < 0.0001$). As shown in Table 2, similar flow-related differences in relative myocardial uptake were found for ^{201}Tl.

DISCUSSION

Our results indicate that following injection of Tc-SESTAMIBI during transient myocardial ischemia, there is redistribution of tracer during reperfusion, resulting in a progressive underestimation of the severity of ischemia that was originally present. The existence of redistribution of Tc-SESTAMIBI in this model is supported both by visual and quantitative analysis of serial tomographic images and by serial myocardial biopsies. The biopsy data document an increase in absolute Tc-SESTAMIBI activity in the previously ischemic myocardium combined with a reduction of activity in the normal myocardium, findings characteristic of redistribution with other tracers such as ^{201}Tl (*11*).

Although redistribution of Tc-SESTAMIBI was directionally similar to ^{201}Tl the extent of redistribution was quantitatively much less. Comparative percent redistribution can be calculated for Tc-SESTAMIBI and ^{201}Tl from Protocol A assuming initial tracer distribution during coronary occlusion equal to that of simultaneously injected microspheres, and "complete redistribution" to represent homogeneous activity throughout the left ventricle. After 3 hr of reperfusion in Protocol A, redistribution was 24% complete for Tc-SESTAMIBI compared to 76% for ^{201}Tl (Table 1). From directly measured initial and 3-hr delayed tracer

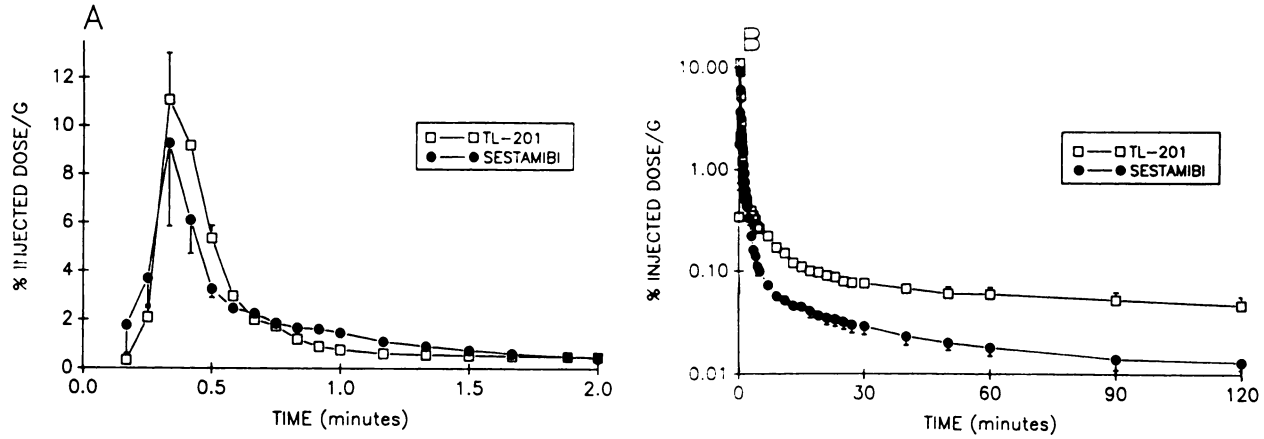

FIGURE 4
Blood activity following i.v. bolus injection of Tc-SESTAMIBI and ^{201}Tl, expressed as %ID/g of blood at each time point. Values represent mean ± s.e.m. of four dogs. Points without error bars have s.e.m. less than the size of the point. (A) First 2 min after injection. Note linear vertical axis. (B) Blood activity for 120 min after injection. Note logarithmic scale on vertical axis.

distributions in the biopsy protocol (Protocol B), there was a 15% redistribution of Tc-SESTAMIBI versus 96% redistribution of ^{201}Tl.

A number of investigators have reported that Tc-SESTAMIBI redistributes "minimally" or not at all in animal models or patients (*6, 7, 12, 13*). However, these findings may be related to the use of models with persistent coronary occlusion stenoses (*6, 13*). Where reperfusion has been employed, Tc-SESTAMIBI has redistributed 17%–28% over 2 hr compared to 58%–76% with ^{201}Tl (*8, 14–16*). Technetium-SESTAMIBI redistribution is therefore about one-third as great as ^{201}Tl under these experimental conditions.

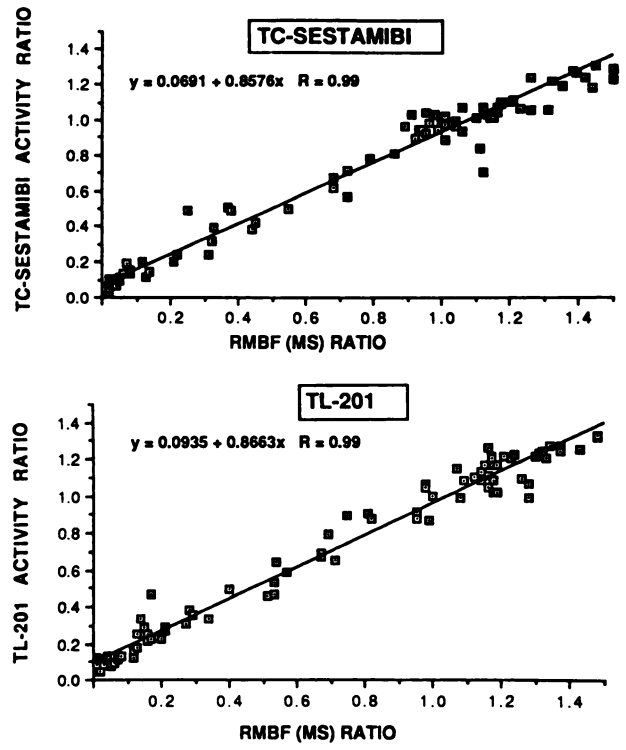

FIGURE 5
Relation during coronary occlusion between microsphere (MS) determined regional myocardial blood flow (RMBF) and Tc-SESTAMIBI or ^{201}Tl activity in multiple myocardial samples from two dogs (Protocol C). Values for RMBF, Tc-SESTAMIBI, and ^{201}Tl are normalized to their respective activities in non-ischemic myocardium. Lines represent the calculated linear regressions. Despite excellent correlations, Tc-SESTAMIBI and ^{201}Tl both tend to overestimate RMBF at low flows and underestimate it a high flows.

In this study, we determined whether the major portion of Tc-SESTAMIBI redistribution occurred during early reperfusion, as a consequence of myocardial hyperemia and persistently elevated Tc-SESTAMIBI arterial blood concentration. As shown in Figure 2, some redistribution was seen by 30 min reperfusion, but the redistribution process continued throughout the 3-hr observation period. Furthermore, when reactive hyperemia was prevented by placement of a coronary stenosis, and reperfusion was delayed until 20 min after Tc-SESTAMIBI injection to allow the blood level to fall to <0.5% of peak level (Fig. 4), significant redistribution of Tc-SESTAMIBI was still observed. Compared to experiments in which full reperfusion was permitted 5 min after trace injection, the extent of Tc-SESTAMIBI redistribution was reduced only modestly (Table 1). Thus, the bulk of Tc-SESTAMIBI redistribution was actually delayed and presumably occurred gradually over the period of reperfusion.

The accumulation or loss of Tc-SESTAMIBI from the myocardium over time represents a net balance between myocardial uptake and clearance. Technetium-SESTAMIBI is a lipophilic cationic molecule which appears to be retained in the myocardium by virtue of intracellular binding to a 10,000 dalton protein (*17*). Uptake is not affected by ouabain (*18–20*) but may be reduced by hypoxia (*20*) or by marked metabolic inhibition (*21*). Studies in isolated blood perfused rabbit hearts have demonstrated a first-pass extraction of 21%–52%, with an inverse relation to blood flow

TABLE 2
Relation Between Myocardial Blood Flow (MBF) by Microspheres and Tc-SESTAMIBI or ^{201}Tl Content in Myocardium

	Tc-SESTAMIBI			^{201}Tl		
MBF level	n	MBF	SESTAMIBI	n	MBF	^{201}Tl
Low (<0.2)	27	0.04 ± 0.04	0.09* ± 0.05	30	0.08 ± 0.06	0.15* ± 0.09
Middle (0.2-1.0)	35	0.73 ± 0.29	0.74 ± 0.28	35	0.69 ± 0.30	0.71 ± 0.28
High (>1.0)	36	1.21 ± 0.14	1.08* ± 0.13	36	1.25 ± 0.13	1.17* ± 0.09

Values are myocardial activity/g, normalized to activity in nonischemic myocardium (±s.d.).
n = number of tissue samples in each category.
* $p < 0.0001$ vs. corresponding MBF value.

(*22*). The factors responsible for myocardial clearance have not been well defined, but clearance is not a simple function of flow rate. Clearance may actually be increased at ischemic flows and Tc-SESTAMIBI may be lost from necrotic regions of myocardium, although not to the same extent as ^{201}Tl (*23*).

Do our findings have relevance for the clinical use of Tc-SESTAMIBI? Although we found partial filling of perfusion defects on serial tomographic images, the degree of filling was visually not great and there was certainly no difficulty in identifying the defects after 2 hr. Other investigators have commented on the stability of Tc-SESTAMIBI images in the clinical setting (*1–4*). Two factors tended to maximize redistribution in our study. First, reperfusion was accompanied by reactive hyperemia, whereas in the clinical setting it would probably be limited by a coronary stenosis (as in the second part of Protocol A). Second, we performed serial imaging over 2 hr, while clinical use generally calls for imaging only 1 hr after injection, although recent studies evaluating thrombolytic agents in acute myocardial infarction have utilized Tc-SESTAMIBI imaging 3–8 hr after injection (*24–25*). On the other hand, our study employed more intense ischemia than is usually encountered during clinical exercise testing. A less marked initial perfusion defect might be more likely to be masked by redistribution. In addition, although we found faster clearance of Tc-SESTAMIBI than ^{201}Tl from the blood in the dog model, clinical studies have reported slower clearance of Tc-SESTAMIBI than ^{201}Tl (*2, 26, 27*), which could contribute to greater Tc-SESTAMIBI redistribution. The study of Liu et al. (*28*) demonstrated that Tc-SESTAMIBI redistribution was augmented by higher blood Tc-SESTAMIBI concentration.

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