Myocardial Clearance Kinetics of Technetium-99m-SQ30217: A Marker of Regional Myocardial Blood Flow

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SQ30217 is a new, technetium-99m- (^{99m}Tc) labeled perfusion agent introduced for cardiac imaging. To evaluate the myocardial tracer kinetics, ^{99m}Tc-SQ30217, was injected intracoronarily in open-chested dogs under baseline conditions and after administration of intravenous (i.v.) dipyridamole. Myocardial first-pass retention fraction averaged 0.90 ± 0.04. Clearance of the tracer occurred in a biexponential manner. Sixty-seven percent of retained activity cleared with a half-time of 2.3 ± 0.6 min, while the residual activity demonstrated slow clearance. The clearance rate of the rapid phase correlated with myocardial blood flow ($r = 0.72$, $p < 0.001$). Myocardial SQ30217 clearance rate following i.v. injection as determined by dynamic imaging with tomography (SPRINT) averaged 21 ± 4 min and increased to 13 ± 4 min following dipyridamole. Thus, ^{99m}Tc-SQ30217 is a promising flow tracer with high initial myocardial retention and rapid tissue clearance, which allow repeated flow determinations within short time intervals using advanced SPECT technology.

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Myocardial perfusion scintigraphy with technetium-99m- (^{99m}Tc) labeled radiopharmaceuticals represents a promising advance in nuclear cardiology due to the physical properties of this radionuclide. The low energy of thallium-201 (^{201}Tl) results in a significant photon attenuation and the long half-life of ^{201}Tl limits the allowable dose. The photon energy of ^{99m}Tc is ideal for imaging with Anger camera based systems. In addition to a single 140 keV photopeak, a six-hour half-life allows the administration of larger activities and multiple studies in short time intervals.

Radiopharmaceuticals such as ^{99m}Tc-hexakis-2-methoxyisobutyl isonitrile (^{99m}Tc-MIBI, Dupont) and ^{99m}Tc-SQ30217 (Squibb Diagnostics, Princeton, N.J.) are among the newer agents introduced for clinical cardiac imaging (*1–5*). Technetium-99m-MIBI is a lipophilic cationic complex that accumulates in myocardium in proportion to blood flow (*1*). In isolated heart models, ^{99m}Tc-MIBI has been characterized as having a first-pass myocardial tissue extraction comparable to ^{201}Tl (*2*). However, in contrast to ^{201}Tl this tracer is avidly retained in the myocardium by intracellular protein binding and demonstrates a long tissue half-life (*2, 3*). The other technetium-labeled flow tracer ^{99m}Tc-SQ30217, a boronic acid adduct of technetium oxime (BATO), is a neutral lipophilic flow agent characterized by high myocardial extraction and rapid clearance kinetics (*4–6*). Because of these properties, ^{99m}Tc-SQ30217 has been proposed for use in diagnostic situations calling for the rapid completion of rest and exercise perfusion studies (*7*).

Since ^{99m}Tc-SQ30217 appears to represent, at least partially, a diffusible tracer, the clearance rate of this tracer from myocardium is expected to depend on blood flow. To test this hypothesis, myocardial retention and clearance of ^{99m}Tc-SQ30217 following intracoronary injection were assessed in the open chest dog model over a wide range of myocardial blood flow. In addition, images derived from high temporal resolution single-photon emission tomography (SPRINT) were used to assess the myocardial kinetics of ^{99m}Tc-SQ30217 following (i.v.) intravenous tracer injection in closed-chested dogs in order to more closely mimic clinical conditions.

METHODS

Open-Chested Heart Preparation

Ten mongrel dogs of both sexes weighing 12–25 kg were anesthetized with i.v. pentobarbital (30 mg/kg). Each dog was intubated and ventilated with oxygen-enriched room air. After electrocardiographic leads were placed, femoral artery catheters were inserted bilaterally for arterial blood sampling and pressure monitoring. A left thoracotomy was performed and the heart suspended in a pericardial cradle. A left atrial cath-

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eter was introduced for the injection of radiolabeled microspheres. After identification and isolation of the left anterior descending (LAD) coronary artery, a hollow stainless steel 23-gauge needle was inserted into the proximal portion of the artery for tracer injection (Fig. 1).

Technetium-99m-SQ30217 Preparation

Kits containing vials of ^{99m}Tc-SQ30217 in a lyophilized form were supplied by Squibb Diagnostics, Princeton, NJ. Technetium-sodium pertechnetate was obtained from ^{99}Mo/^{99m}Tc generators that had been eluated within 24 hr of radiopharmaceutical preparation. All eluates were used within 6 hr, and radionuclide purity, radiochemical purity, aluminum ion content, and pH were determined prior to use. Each vial was reconstituted with 1 ml of [^{99m}Tc]sodium pertechnetate, containing ~2–4 mCi of radioactivity. Following reconstruction, each vial was heated for 15 min at 100°C in a boiling water bath. The prepared radiopharmaceutical was cooled to room temperature, and the radiochemical purity of the prepared product was determined utilizing 1.3 × 11 cm Whatman 31 ET chromatography strips and two individual mobile-phase solvent systems. The developed chromatograms were air-dried and counted. The percentage of free ^{99m}Tc, ^{99m}Tc-SQ30217, and the ratio of reduced/hydrolyzed ^{99m}Tc-SQ30217 was determined. Chromatographic results indicated that the sum of the free ^{99m}Tc and reduced/hydrolyzed ^{99m}Tc-SQ30217 was routinely <10% while the mean radiochemical purity was 94.7% ± 1.2%.

Experimental Protocol

The study protocol is depicted in Figure 2. The animals were allowed to recover for 30 min following surgical instrumentation. Technetium-99m-SQ30217 (150–300 μCi) was injected as a small bolus (<0.3 ml) into the proximal LAD artery. Myocardial activity was recorded for 30 min after bolus injection by a 1× 1-in. NaI (Tl) probe fitted with a single-hole lead collimator placed over the left ventricle. The probe was connected to a single-channel analyzer (Ortec, Oak Ridge, TN) and data were acquired using a personal computer. Tracer injections were performed in each animal under baseline conditions and following pharmacologic vasodilatation by dipyridamole (0.20–0.56 mg/kg i.v.) in order to determine tracer kinetics over a wide flow range. Myocardial blood flow was determined prior to each tracer injection with radiolabeled microspheres (tin-111, cesium-141, ruthenium-106, 15 ± 3 μm, Dupont-NEN) injected into the left atrium over 10 sec. A maximum of three tracer injections together with blood flow determinations were performed in one animal preparation.

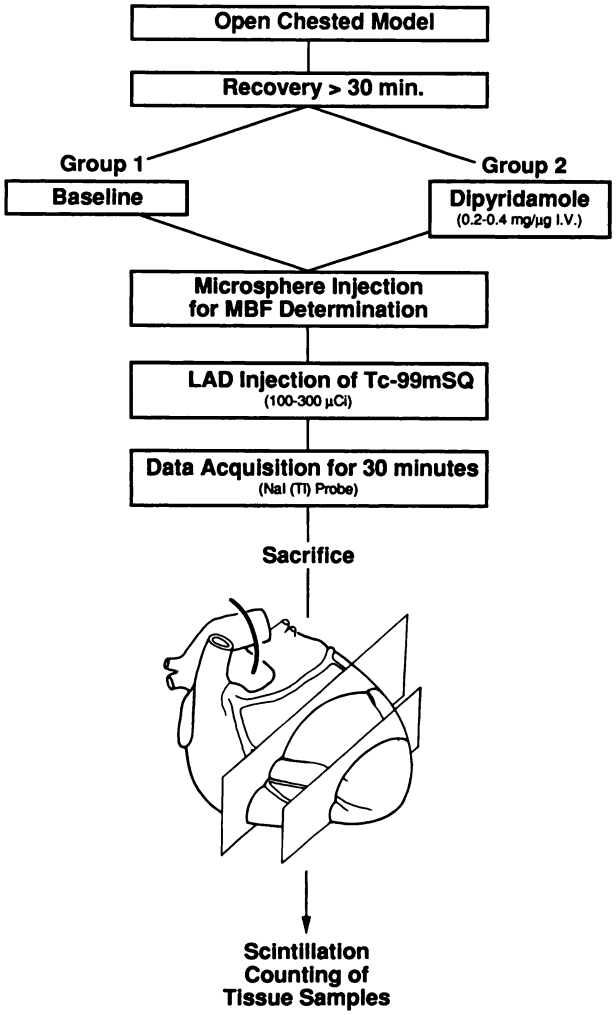

FIGURE 2
Experimental protocol for the open-chested dogs. Baseline and dipyridamole injection was performed in each animal.

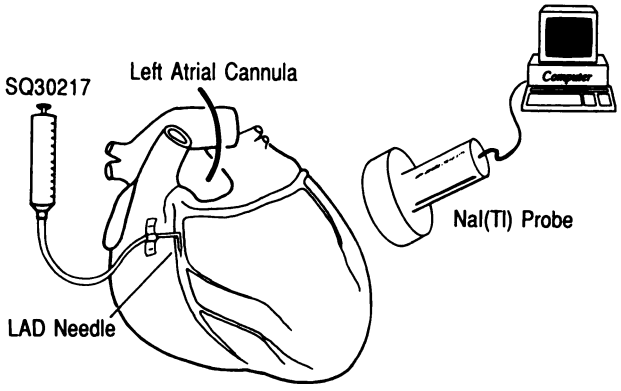

FIGURE 1
Instrumented canine heart. Microspheres were injected into the left atrium. A needle was inserted into left anterior descending artery for intracoronary tracer injection. The NaI(TL) probe was placed 2–4 cm over the left ventricle and connected to a microcomputer.

At the completion of all experimental runs, cardiac arrest was induced by i.v. administration of a saturated solution of potassium chloride. At the time of cardiac arrest, the tissue distribution of the LAD coronary artery was determined by injection of 3 ml of monostral blue dye into the coronary artery. Stained myocardium was sectioned, weighed, and counted in an automated gamma scintillation counter. Microsphere activities were determined by multi-energy window counting. Activity spillover between energy windows was corrected based on prior counting of activity standards. Regional myocardial blood flow was determined as described previously (*8*), and expressed as ml/min/g of tissue for each experimental run (Fig. 2).

Imaging Protocol

In order to compare the tracer kinetics following intracoronary injection, with those following i.v. tracer administration, a subset of dogs were studied using single-photon emission tomography (SPECT). Dynamic image acquisition was accomplished by SPECT instrumentation developed at the University of Michigan (SPRINT) (*9*). The SPRINT camera system consists of 72 discrete NaI detectors arranged in a fixed ring 70 cm in diameter, and allows for the acquisition of single slice dynamic studies by simultaneous sampling from multiple angles. A complete set of fan-beam projections for the 20-cm field of view is acquired by means of a rotating lead aperture ring containing eight slits. In-plane resolution is 11 mm full width at half maximum (FWHM), and slice resolution is 10.0 mm FWHM. The ring is stepped 45° in 78 increments, with a total dead-time of 5 sec. A detailed description of this camera system can be found elsewhere (*10*).

Four mongrel dogs weighing 8–10 kg, were injected with 8–11 mCi of ^{99m}Tc-SQ30217 in a small i.v. bolus. Data acquisition began within 30 sec after ^{99m}Tc-SQ30217 injection. Dynamic imaging with high temporal resolution was then performed as follows: 10 frames (30 sec duration), 5 frames (60 sec duration), 2 frames (2 min duration) 1 frame (5 min duration). As in the open-chested model, studies were carried out under baseline conditions (n = 4) and after infusion of 0.56 mg/kg of dipyridamole (n = 2). Images were reconstructed using least squares fitting of the projection data, followed by filtered backprojection with a ramp filter.

The arterial input function was defined by serial arterial blood sampling which began simultaneously with ^{99m}Tc-SQ30217 injection, In order to calibrate blood sample activities to the acquired images, the samples were counted in a well-counter together with an aliquot sample from a cylinder phantom containing ^{99m}Tc activity (2 mCi), which had been imaged at the end of each animal study. All blood sample counts were then converted to imaging counts based on the derived calibration factor.

Data and Image Analysis

Count data from the NaI (TL) probe were acquired into a personal computer and transferred to a VAX 8300 computer system (Digital Equipment Corp., Maynard, MA). Each ^{99m}Tc time-activity curve was analyzed by biexponential least square curve fitting using a routine based on the Marquardt algorithm (*11*). An example of a typical tissue ^{99m}Tc time-activity curve is shown in Figure 3. The slope of each curve component was defined by the corresponding clearance half-times ($T_{1/2}$). The relative size of each component (RP_1, RP_2) was determined by extrapolation of the monoexponential slope of each component to the time of peak activity (A), followed by dividing the counts at the intercepts of each slope by the maximal activity derived from the extrapolated tissue time-activity curve. The first-pass retention fraction (RF) was derived from a high temporal resolution time-activity curve acquired during the initial 100 sec after injection (see insert Fig. 3). RF was calculated as the intercept (B) divided by peak activity (A) times 100 and expressed as a percentage (*12*).

Myocardial ^{99m}Tc-SQ30217 clearance following i.v. tracer administration was evaluated from dynamic SPRINT images. Regions of interest (ROIs) were placed over the entire left ventricle and the imaging phantom. Data from each image frame were expressed as mean cts/pixel/min. Technetium-99m-SQ30217 clearance half-times were derived from dynamic SPRINT image time-activity curves using the least squares method of linear regression.

Statistical Analysis

Data are expressed as mean and standard deviation (s.d.). Comparison of unpaired samples was subject to t-tests. A probability value of <0.05 was considered significant. Linear regression was calculated by the least squares method.

RESULTS

Myocardial Retention and Clearance of Technetium-99m SQ30217

Seventeen experimental runs were completed. Under baseline conditions (Group 1; n = 5) regional myocardial blood flow averaged 0.93 ± 0.69 ml/min/g as determined by radiolabeled microspheres. Following dipyridamole infusion (Group 2; n = 12), regional

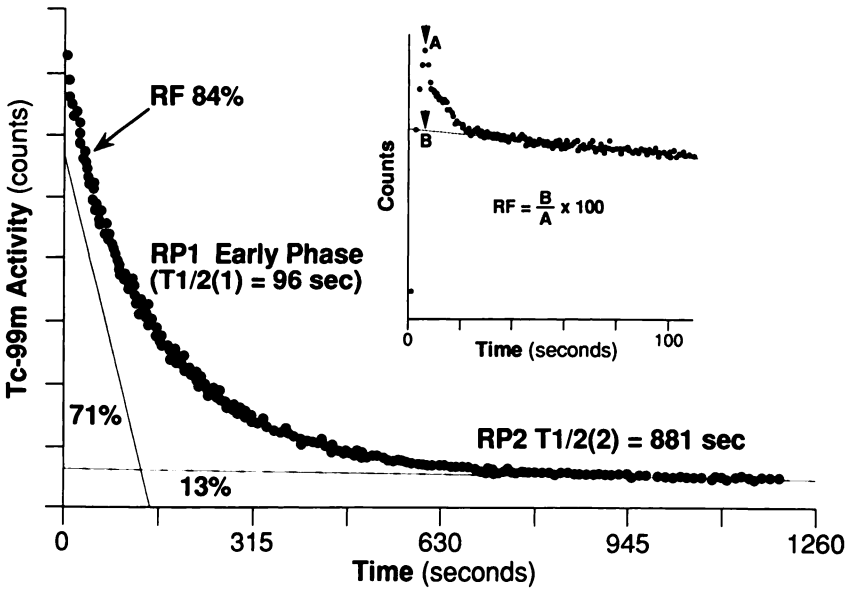

FIGURE 3
Analysis of ^{99m}Tc time-activity curves. The tissue data are displayed over a time period of 1,260 sec in this example. Retention fraction (RF) was derived from the high temporal resolution curves obtained for the first 100 sec (see insert in figure). Peak activity (A) is proportional to total activity injected. As shown by the slow temporal resolution curve, the tissue clearance of ^{99m}Tc is biexponential, with an early "rapid phase" (RP_1) and a late "slow phase" (RP_2). Each curve component can be defined by half-time and relative size (see text for details).

myocardial blood flow increased to 4.20 ± 2.20 ml/min/g ($p = 0.004$) (see Table 1).

Examples of time-activity curves at two different myocardial blood flows (1.52 ml/min/g and 5.13 ml/min/g, respectively) are shown in Figure 4. First-pass retention fraction was comparable under both conditions. The ^{99m}Tc clearance half-time of the rapid early phase decreased from 97 sec at low flow to 69 sec at high flow.

The kinetic data from all 17 experimental runs are summarized in Table 1. The first-pass RF of ^{99m}Tc-SQ30217 averaged 90% ± 4% for all experimental runs. Mean RF for Group 1 (baseline) was 88% ± 5%, and 91% ± 3% for Group 2 (Table 1). There was no significant relationship between RF and myocardial blood flow over a wide range of flows (0.30 ml/min/g to 7.70 ml/min/g, $r = 0.4$, p = n.s) (Fig. 5).

The "rapid clearance" component of the biexponential tissue time-activity curves (RP_1) represented 67% ± 11% of retained activity. There was no significant difference of the relative size of the rapid component at baseline (63% ± 19%) and following dipyridamole (69% ± 8%). The size of this component was not related to changes of blood flow (Fig. 6). Under baseline conditions (Group 1), the clearance half-time of the initial rapid phase averaged 2.3 ± 0.6 min and decreased to a mean of 1.5 ± 0.3 min after dipyridamole infusion in Group 2 ($p < 0.01$). The clearance half-time correlated significantly with regional myocardial blood flow ($r = 0.72$, $p = 0.001$, s.e.e. = .41) (Fig. 6).

The size of the "slow clearance" component (RP_2) averaged 18% ± 8% and did not correlate significantly with tissue blood flow (Fig. 6). Clearance half-time for the slow component (RP_2) averaged 20.0 ± 9 min for Group 1 and 34.0 ± 9 min for Group 2 (NS). The clearance half-time did not correlate significantly with flow as shown in Figure 6.

Dynamic Tomography

The myocardial clearance of ^{99m}Tc-SQ30217 following intravenous injection in closed-chested dogs was investigated using single-photon ring tomography (SPRINT). Figure 7 shows dynamic SPRINT images of one myocardial cross-section obtained following i.v. injection of 10 mCi of SQ30217 at baseline and following dipyridamole infusion. Total counts collected in the initial image frames were ~75,000, yielding excellent image quality. Images following dipyridamole indicate markedly faster tracer clearance as compared to baseline. Regional time-activity curves derived from these

TABLE 1
Myocardial Retention and Clearance of ^{99m}Tc-SQ30217

Group	n	MBF (ml/min/g)	RF (%)	$T_{1/2}(1)$ (min)	$T_{1/2}(2)$ (min)	RP_1 (%)	RP_2 (%)
I	5	0.93 ± 0.69	88 ± 5	2.3 ± 0.6*	20 ± 9†	63 ± 19	19 ± 12
II	12	4.2 ± 2.0	91 ± 3	1.5 ± 0.3*	34 ± 9†	69 ± 8	16 ± 5

*$p < 0.01$
†$p < 0.05$

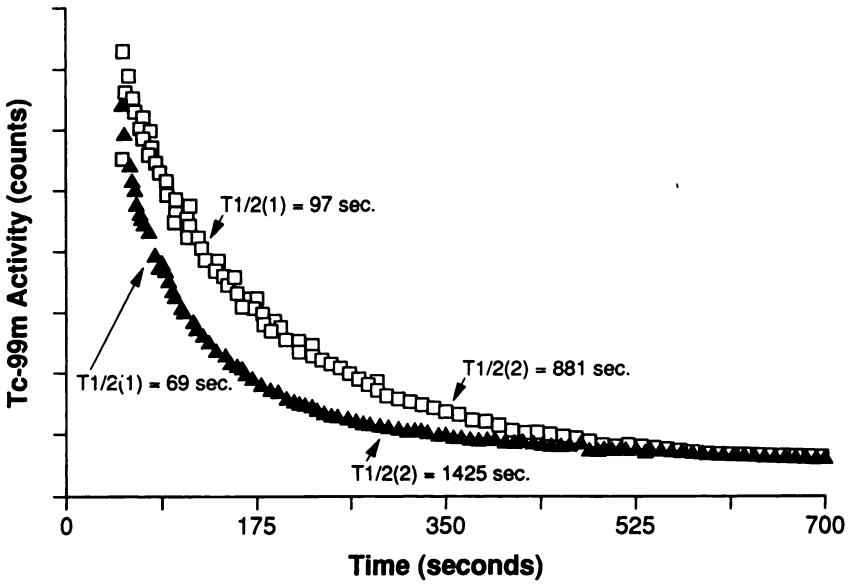

FIGURE 4
Examples of ^{99m}Tc time-activity curves at mean myocardial tissue blood flows of 1.52 ml/min/g (□) and 5.13 ml/min/g (▲).

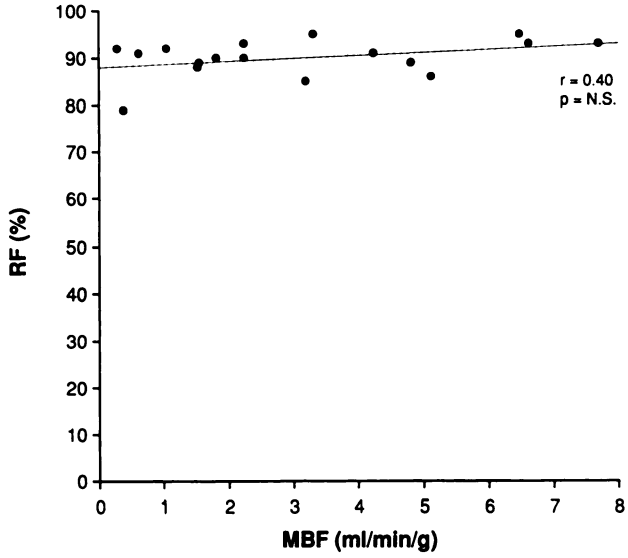

FIGURE 5
Retention fraction (RF,%) versus mean myocardial blood flow (MBF, ml/min/g). Range of mean tissue blood flows was 0.30–7.70 ml/min/g.

images are shown in Figure 8. Under baseline conditions, the clearance half-time was calculated at 20.0 min, and decreased to 15.2 min after dipyridamole. In contrast to the probe studies, myocardial activity cleared in a monoexponential pattern. In all four animals the myocardial clearance half-time of ^{99m}Tc-SQ30217 averaged 21 ± 4.0 min under baseline conditions and decreased to 12.7 ± 3.5 min (n = 2 studies) following the infusion of dipyridamole.

Blood activity cleared rapidly following i.v. injection of SQ30217. Two minutes after injection, blood-activity averaged 8% ± 3% of peak activity. At 5 min, only 4% ± 2% of peak-activity remained in the vascular space. The blood clearance pattern did not differ significantly between baseline and dipyridamole studies.

DISCUSSION

The data presented indicate that the new technetium-labeled blood flow tracer, ^{99m}Tc-SQ30217, has myocardial kinetics suitable for the evaluation of blood flow at rest and following i.v. administration of dipyridamole (*13*). This study, employing intracoronary injection of the tracer, demonstrated high first-pass retention of ^{99m}Tc-SQ30217, which was stable over a wide flow range. After initial retention, the activity cleared from myocardium in a biexponential fashion. About 70% of the clearance occurred within the first 5 min. The rapid phase was followed by a slow clearance component with a half-life of ~20 min. The presented imaging data

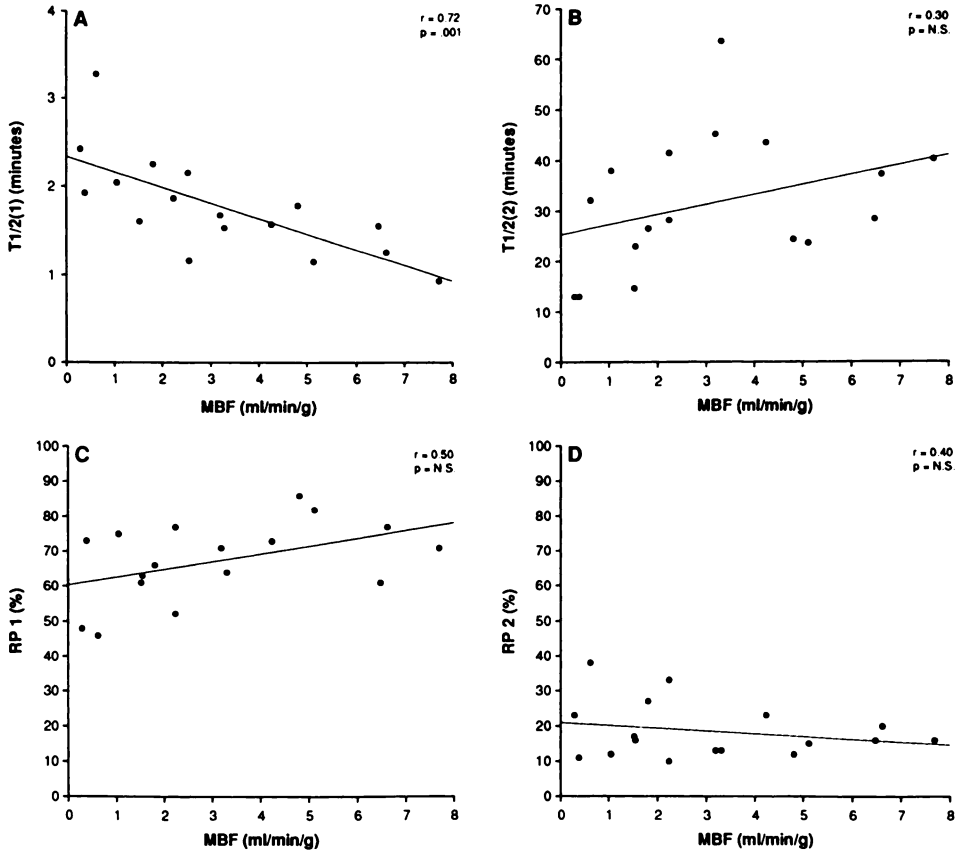

FIGURE 6
(A) Clearance half-time of the early "rapid" component ($T_{1/2\,(1)}$) and (B) late "slow" component ($T_{1/2\,(2)}$) versus mean myocardial tissue blood flow. The relative size of the early and late phases (RP_1, RP_2) versus myocardial blood flow is shown in panels C and D.

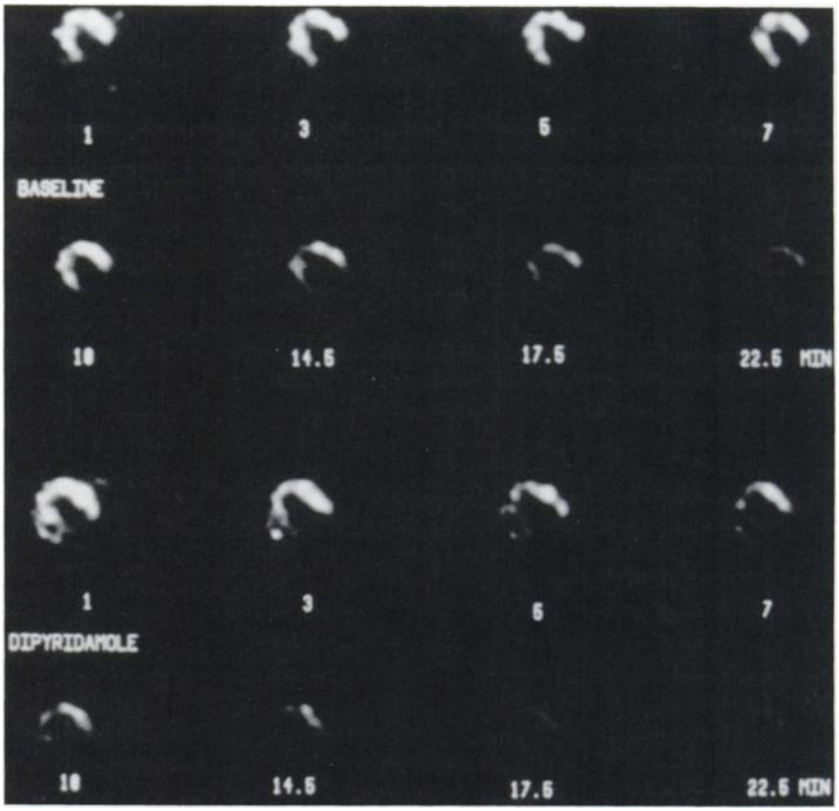

FIGURE 7
Reconstructed SPRINT images of canine left ventricle at various time points after i.v. injection of 10 mCi ^{99m}Tc-SQ30217. The upper images were acquired under baseline conditions, while the lower images were acquired after dipyridamole infusion (0.56 mg/kg). All images were standardized to counts/min. Please note the more rapid tracer clearance following dipyridamole.

indicate that SPECT imaging following i.v. injection of SQ30217 yields good image quality with high contrast between heart and blood activity. In addition to the qualitative assessment of regional tracer distribution, the kinetic information obtained by the tracer clearance may allow evaluation of flow independent of initial tracer retention assuming a tracer kinetic model can be developed to quantitatively describe the kinetics.

Tracer Characteristics

Technetium-99m-SQ30217 represents a lipophilic compound of the BATO class which diffuses rapidly across phospholipid membranes. It is not known, however, if this compound enters the myocardial cell or is incorporated into the phospholipid layers of cellular membranes. The physiologic properties defined in vitro are confirmed by the high initial myocardial retention and subsequent rapid clearance, as observed in our study. The kinetics of SQ30217 are strikingly different from ^{99m}Tc-MIBI, which has been recently introduced as a myocardial blood flow tracer (*7*). This latter compound is taken up by the myocardial cell and binds to cytosolic proteins resulting in a long biologic tissue half-life (*4*,*14*).

The initial retention fraction of SQ30217 averaged 90% and did not change significantly over a wide range of myocardial blood flow. Our findings are in contrast to studies by Meerdink et al. in the isolated rabbit heart (*14*). These studies indicate an inverse relationship between first-pass extraction fraction of SQ30217 and myocardial blood flow. The discrepancy may be related to possible species differences or to differences in the experimental model. We did not employ a multiple tracer technique to estimate first pass extraction frac-

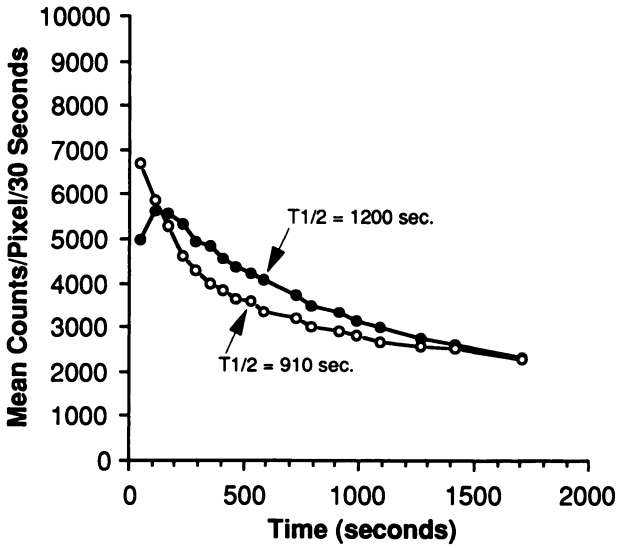

FIGURE 8
Representative example of ^{99m}Tc myocardial tissue clearance from one closed-chested dog, as assessed by SPRINT. Left ventricular ROI data are expressed as mean counts/pixel/30 sec under baseline conditions (●) and after a 4-min infusion of dipyridamole (0.56 mg/kg) (○).

tion, but measured the initial tissue retention fraction. This approach only approximates first-pass tracer extraction and may be less sensitive to flow changes. The observed first-pass retention fraction, however, is comparable to that of nitrogen-13 ammonia under baseline conditions in the same model, but remains considerably higher at high flow (*15*). The stable retention fraction over a wide flow range indicates a large permeability surface area product for SQ30217 in canine myocardium as expected by its lipophilic nature.

The favorable characteristics of ^{99m}Tc-SQ30217 promise a linear relationship between tracer retention and blood flow over a wide range. Most currently used tracers, such as ^{201}Tl and ^{99m}Tc-MIBI, demonstrate a decreasing retention fraction with increasing blood flow, limiting the accurate assessment of blood flow at high flow states (*4*).

The high first-pass retention of ^{99m}Tc-SQ30217 is somewhat offset by the rapid clearance rate of the tracer from myocardium. Rapid image acquisition is necessary to avoid early redistribution which cannot be achieved with single head SPECT imaging. Therefore, the use of this tracer as a flow agent based on the static imaging protocols as employed for ^{201}Tl and ^{99m}Tc-MIBI, appears limited. However, this study indicates that the rapid clearance kinetics can be used to estimate myocardial blood flow using dynamic image acquisition.

The flow dependency of tracer clearance is expected for freely diffusible tracers and has been used for quantitative assessment of organ blood flow for other radiopharmaceuticals such as xenon-133 (^{133}Xe) and oxygen-15- (^{15}O) water. Kety et al. developed tracer kinetic models which have been successfully employed to assess cerebral and myocardial blood flow using ^{133}Xe (16). However, ^{133}Xe has to be injected into the coronary artery for quantitation of myocardial blood flow, limiting this approach to clinical investigations in the catheterization laboratory (*17*). Further kinetic studies with SQ30217 are required to define the feasibility of quantitative flow measurements using the clearance kinetics of this tracer.

The biexponential washout of SQ30217, as observed in the open-chest probe studies, suggest that kinetics of this compound represent both blood flow as well as non-flow related cellular binding. However, because this agent is not a simple inert diffusible tracer, the first component of the washout is not only related to flow, but also influenced by other kinetic processes. A four-fold increase in blood flow produced only a two-fold decrease in the half-time of the first component of the washout. Tracer kinetic modeling may allow the differentiation of flow parameters from processes determining tissue binding of this tracer.

As expected, the tissue clearance half-times determined by dynamic SPECT imaging were longer than those following intracoronary tracer injection. The differences in half-times are best explained by the recirculation of tracer following i.v. injection and continuing tracer uptake during the first 5–10 min following injection. After i.v. infusion of dipyridamole in the closed-chested animals, the half-time of this early rapid clearance decreased to 13 min, confirming the results obtained in open-chested animals. Seldin et al. recently obtained dynamic planar images in patients injected with ^{99m}Tc-SQ30217. The authors observed an increased clearance of the activity following exercise testing, suggesting a similar flow dependence of ^{99m}Tc SQ30217 kinetics in human myocardium (*6*).

Currently employed single- and dual-head tomography does not provide the necessary temporal resolution to delineate the kinetics of SQ30217 in the human heart. The newer multi-head SPECT systems may provide sufficient temporal resolution for the clinical application of ^{99m}Tc-SQ30217 (*18*). Since estimates of regional myocardial blood flow require stable flow conditions during the acquisition, the use of pharmacological coronary vasodilation appears to be the preferred approach for the delineation of the regional coronary reserve using ^{99m}Tc-SQ30217. Since the cessation of exercise produces rapid changes in myocardial perfusion, flow measurements during exercise would require prolonged exercise during image acquisition. The effects of dipyridamole on myocardial flow are prolonged, and provide stable hemodynamic conditions to delineate the tracer kinetics of SQ30217.

CONCLUSION

The kinetics of ^{99m}Tc-SQ30217 challenge conventional static imaging approaches for the evaluation of regional myocardial blood flow using SPECT. Flow dependence of the early washout phase of activity may lead to early redistribution of perfusion defects, and may therefore decrease the sensitivity of static image acquisition for detection of regional perfusion abnormalities. However, advanced SPECT technology will allow the definition of uptake and washout rates of this tracer with high temporal resolution. This promising flow agent may permit the clinical assessment of regional myocardial blood flow under various conditions. Due to the rapid clearance of SQ30217, flow estimates in short-time intervals will be possible, allowing the assessment of coronary reserve in a clinically practical time frame.

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