Comparative Myocardial Extraction of Two Technetium-Labeled BATO Derivatives (SQ30217, SQ32014) and Thallium

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The transcapillary exchange of a new class of ^{99m}Tc-labeled compounds (BATO) were compared to ^{201}Tl in isolated, blood perfused rabbit hearts. During variable blood flow (0.15-2.44 ml/min/g), peak and net extraction (E_{max} and E_{net}, respectively), and capillary permeability-surface area product (PS_{cap}) were determined with paired indicator-dilution techniques. Serial bolus injections of ^{201}Tl, [^{111}In]albumin, and [^{99m}Tc]BATO; chloro[tris(cyclohexanedionedioxime)methyl boronic acid]Tc (SQ30217, n = 8) and a hydroxy-substituted derivative (SQ32014, n = 5) were given to a total of 13 hearts. Mean (± s.d.) SQ30217 E_{max} and E_{net} were 0.72 ± 0.09 and 0.55 ± 0.18, respectively, which were higher than thallium values of 0.57 ± 0.10 and 0.46 ± 0.17 (p < 0.03). Mean SQ30217 PS_{cap} was 1.1 ± 0.4 ml/min/g and was also higher than corresponding thallium determinations (0.7 ± 0.3; p < 0.001). SQ32014 E_{max}, E_{net}, and PS_{cap} were all significantly less than thallium values (p <0.001). Thallium and SQ30217 values for E_{max} and PS_{cap} were closely correlated with blood flow (r ≥ 0.73), whereas those for SQ32014 were weakly correlated (r = 0.09). A small clinical pilot study (n = 3) was performed, which showed that SQ32014 was a poor myocardial perfusion agent in man. In summary, transcapillary exchange of SQ30217 is greater than thallium, which in turn, is greater than SQ32014. Therefore, SQ30217 appears to have good clinical potential, but SQ32014 does not.

J Nucl Med 1990; 31:67-74

$\mathbf{T}$hallium-201 (^{201}Tl) is presently the most common myocardial perfusion imaging agent, but several technetium-99m- (^{99m}Tc) labeled agents (1-6) have been proposed as possible alternatives because of better photon statistics, Anger camera imaging properties, cost, and clinical availability. One class of the technetium-labeled agents are the "BATO" compounds, which are boronic acid adducts of technetium dioxime (BATO) complexes that are stable, neutral, and lipid soluble (7,

8). Two such BATO compounds have been developed for possible use as myocardial perfusion agents: SQ30217 (teboroxime, Cardiotec, Squibb Diagnostics), [bis[1,2-cyclohexanedione dioximato(1-)-O]-[1,2-cyclohexanedione-ioximato(2-)-O]methylborato(2-)-N,N', N'',N''',N'''',N'''''']-chlorotechnetium and SQ32014, which has a hydroxy substituted for the methyl group. In preliminary clinical trials, SQ30217 has been favorably compared to thallium (5). In this study the goals were to compare myocardial transport of the technetium-labeled BATO compounds SQ30217 and SQ32014 to thallium during variable levels of coronary flow in an isolated rabbit heart preparation. In addition, the clinical utility of SQ32014 was also evaluated.

METHODS

Experimental Model

All experiments utilized an isolated isovolumetrically contracting rabbit heart as previously described (9) utilizing whole blood perfusion. The hearts (New Zealand white rabbits) were quickly removed and mounted on a perfusion apparatus already primed with 70-100 cc of heparinized (600 IU/kg) rabbit blood. A constant flow pump was set at a control rate that produced a mean coronary perfusion pressure of 100-125 mmHg, and the blood was recirculated between tracer injections. This typically resulted in a coronary flow of 2 ml/min/g and these hearts are quite stable for 60-90 min (10), which more than overlaps the complete experimental time of the present protocols. A thermistor and pacing catheter were placed in the right ventricle via the right atrium to monitor tissue temperature (37 ± 1°C) and maintain a heart rate of at least 180 bpm. A vinyl catheter was also placed in the right ventricle via the pulmonary artery to collect coronary sinus drainage for all isotope sample determinations and to measure coronary flow. A soft latex balloon catheter was also inserted into the left ventricle via the left atrium and filled with saline to an end-diastolic pressure of 5-10 mmHg for isovolumic contractions. Coronary perfusion and left ventricular pressures were continuously measured and recorded. In addition, the first derivative of left ventricular pressure was obtained by electronic differentiation of the pressure signal. The blood passes through a filter and membrane oxygenator which is gassed with a 3% CO_2 and air mixture. Blood gas measure-

ments were made every 30–40 min and appropriate adjustments were made to maintain blood pH, P_{O2}, and P_{CO2} in the physiologic range. The glucose level was also monitored and adjusted as needed to a level of 80–120 mg/dl. It is important to note that the use of a blood-perfused preparation may result in permeability disruption due to release of blood cell components. During the protocol, hearts that became hemodynamically unstable or had apical drainage exceeding 5% of coronary flow were removed from the study.

Experimental Protocol

The experimental protocol involved an initial stabilization period for each heart prior to the bolus injection of multiple-tracer cocktail, which consisted of a mixture of ^{201}Tl, Tc-labeled SQ30217 or SQ32014, and indium-111-(^{111}In) labeled albumin, into the aortic inflow. These tracer mixtures were diluted to 1.5 ml by addition of heparinized whole rabbit blood prior to injection. A total of eight hearts received 17 tracer bolus injections containing SQ30217 at variable levels of coronary perfusion, while five other hearts received 16 injections containing SQ32014. After an initial control injection, subsequent injections were made over a 30–40-min time period, during which flows were randomly varied by adjusting mean perfusion pressure. The coronary venous effluent was collected into preweighed plastic tubes at 1.2- to 5-sec intervals depending on the flow rate over a 1–7-min collection time. When the sampling was completed, coronary flow was again determined. The full sample weights were measured and counted along with an aliquot (0.1 ml) of each injectate in a gamma well counter. Appropriate correction for energy crossover, time, background and physical decay during the counting process was made for each curve (9).

Myocardial Transport Analysis

For each injection, the plasma flow (F_s, ml/min), the time of collection (t), the isotopic activity of each sample [$C(t)$, cpm/ml], and the injected dose of each isotope (q_o, cpm) is known. Consequently, the normalized dilution curves for albumin [$h_R(t)$] and the diffusible tracers [$h_D(t)$] can be calculated from the general equation: $h(t) = F_s \cdot C(t)/q_o$ (11,12).

Thallium and the BATO compounds are diffusion-limited substances and capillary membrane permeability can be estimated from these normalized curves. Specifically, an instantaneous fractional extraction, $E(t)$ was calculated at each point assuming that albumin (reference tracer) does not leave the vascular space: $E(t) = 1 - [h_D(t)/h_R(t)]$ (11,12).

If both tracers are equally dispersed in the arterial inflow and tracer backflux from the extra- to intravascular space is negligible, then fractional extraction can be used to determine the permeability and surface area product (PS_{cap}): $PS_{cap} = -F_s \cdot \log_e(1-E_{max})$ (13), where F_s is the flow of plasma in ml/min/g. E_{max} represents the peak value during the early plateau phase of $E(t)$ up to the peak of the albumin curve and represents the best estimate of average fractional extraction. An additional analysis is employed to evaluate net extraction (E_{net}) which is an integral extraction, defined as: $E_{net} = \int_o^t [h_R(t)-h_D(t)]d\tau / \int_o^t h_R(t)d\tau$, where t was defined as the time (sec.) when 99.99% of the albumin reference had emerged in the venous effluent (1 to 6.5 min), and τ was the dummy variable for integration. This function differs from E_{max} and is used to estimate the net myocardial extraction or retention of each diffusible tracer over the course of the experimental observation (11,12,14).

Clinical Protocol for SQ32014

Three normal male volunteers between the ages of 21 and 40 yr were studied after obtaining an institutionally approved consent form. Each subject was determined to be free of previous or present heart disease as evidenced by a negative medical history, physical examination and stress electrocardiogram. In addition, subjects were free of any condition requiring medical therapy. All subjects were studied in a fasted state and were injected at rest. Continuous anterior views (30 sec/frame) were collected utilizing an Anger gamma camera (Picker 501) for the first 60 min and stored in a dedicated computer system (Picker 512). Subsequent head, chest and abdominal views were recorded at 1, 2, 3, and 4 hr after SQ32014 administration. Serial blood, urine and stool collections were made prior to SQ32014 injection and over the first 24 hr. In all cases no abnormal blood chemistry (SMA-12 and CBC), urinalysis (gross and microscopic) or adverse reactions were noted.

BATO Preparation

The BATO agents were supplied as a lyophilized powder in sterile vials (7). Drug labeling was achieved by first reconstituting the vial contents with 1 ml of sterile, pyrogen-free ^{99m}Tc generator eluate containing not more than 50 mCi technetium pertechnetate for human studies and 5–10 mCi for animal experiments, and then heated in a water bath for 15 min at 100°C. The resulting solution was cooled to room temperature and diluted with 0.9% sodium chloride to a volume of 1 ml. The reconstituted product was used within 3 hr of preparation and stored at room temperature. The three clinical subjects (SQ32014) received ⅓, ⅔, ⅓ of the reconstituted vial contents, respectively, to characterize any effects of the chemical dose. No such effects were observed.

Radiochemical purity was determined by the percentage of ^{99m}Tc pertechnetate and complexed SQ30217 or SQ32014 immediately after dilution by paper chromatography methods. Approximately 20–25 μCi of activity for each BATO compound was placed on two strips of Whatman 31 ET-Chrom chromatography paper. The strips were placed into one of two chromatography chambers; one with 0.9% NaCl solution and the other with 50:50 (by volume) 0.9% NaCl/Acetone solution and allowed to develop. Subsequent radioactivity determinations were used to calculate the percentage of noncomplexed and reduced hydrolyzed [99m]Tc. In all measurements labeling efficiency was greater than 92%.

All data are expressed as the mean ± s.d. Comparisons between groups of a single numeric variable were performed by an analysis of variance and appropriate t-statistic (15,16).

RESULTS

The mean hematocrit in the SQ32014 hearts was 35 ± 4% which was higher (p < 0.01) than the average of 28 ± 5% noted in the SQ30217 hearts and the fraction of water content was slightly lower in the SQ32014 hearts compared to the SQ30217 hearts (0.73 ± 0.03 vs. 0.77 ± 0.02, respectively; p < 0.03). The mean heart weight was 6.0 ± 0.8 g in the SQ32014 experiments and 5.6 ± 1.6 g in the SQ30217 protocols.

The average hemodynamic determinations from all experiments are shown in Table 1 for the seven

TABLE 1
Hemodynamics[*]

	SQ30217	SQ32014	p
Heart rate (bpm)	197 ± 11	182 ± 11	0.001
Aortic pressure (mm Hg)	107 ± 40	102 ± 44	N.S.
LV peak systolic pressure (mm Hg)	80 ± 33	46 ± 17	0.01
LV end-diastolic pressure (mm Hg)	13 ± 16	10 ± 8	N.S.
Coronary blood flow (ml/min/g)	1.3 ± 0.6	0.8 ± 0.5	0.02

[*] All results are mean ± s.d.
LV = left ventricular; N.S. = not significant.

SQ30217 and five SQ32014 hearts. The aortic pressure and left ventricular end-diastolic pressures were similar in both groups of hearts during each bolus injection of isotopes. The coronary flow and heart rate were significantly higher in the SQ30217 hearts and consequently the left ventricular peak systolic pressure was also higher. This suggests that the flow variations selected for the SQ30217 group resulted in higher perfusion rates over the entire range of injections when compared to the selected flow variations used in the SQ32014 group.

Transport Analysis

The h(t) transport functions represent the fraction of injected tracer emerging from the heart per second and are used to calculate the other exchange estimates. A close examination of the plots (Fig. 1) reveal important differences among the tracers. The shape of the h(t) curve, which characteristically has a rapid rise to a relatively sharp peak followed by a gradually decreasing "tail" portion, is caused by several factors. The general shape results from the dispersion caused by heterogenous flow in the cardiac vasculature as well as laminar flow in the system. Because albumin is assumed to be confined to the vascular space [appropriate for the time frame of the experimental period (17)], the shape of the albumin h(t) curve (solid lines, Fig. 1A and B) reveals this overall dispersive affect. However, the shape of the h(t) curves for the diffusible tracers result from not only this global dispersion, but also from the escape of tracer from the vasculature into extravascular compartments (interstitium, membranes, and parenchymal cells). Therefore, the difference between the h(t) of albumin and the h(t) of thallium or BATO compounds indicates an escape of diffusible tracer from the perfusate as it passed through the heart. This is the fractional extraction, E(t), plotted for SQ30217 and thallium (Fig. 1A) and for SQ32014 and thallium (Fig. 1B). The thallium and SQ30217 overall E(t) patterns are typical for cations (rapid rise and rapid fall during the h(t)

peaks) despite the fact that SQ30217 is a neutral lipophilic compound.

A further comparison of the h(t) curves reveals important differences in the myocardial exchange and retention of the diffusible tracers. When the albumin curve is above the diffusible h(t) curve (thallium, dotted line; SQ30217, dashed line; Fig. 1A), a net blood-to-tissue transport is indicated. When the albumin h(t) curve is less than the diffusible h(t) curve, such as during the tail portion for thallium or for SQ30217, a net clearance of tracer from the extra- to intra-vascular space is indicated (14). Thallium and SQ30217 have a net blood-to-tissue exchange only during the early portion of the h(t) curve, but a net tissue-to-blood exchange during the tail portion.

In contrast, the h(t) curve for SQ32014 was always closer to albumin than the simultaneous h(t) peak for thallium and the tail portion was always lower. These observations confirm the lower extraction for SQ32014 and suggests that the back diffusion of this Tc-labeled compound is relatively less than thallium. The instantaneous extraction curves for thallium and SQ32014 are also shown. In contrast to thallium and SQ30217 E(t) curves, SQ32014 shows a slow rise in extraction with a relatively long and low plateau phase. This suggests that the extraction mechanism for SQ32014 is quite different than thallium or SQ30217 and appears to have a much slower exchange process.

The mean E_{max}, PS_{cap} and E_{net} values are shown in Figure 2. Mean SQ30217 extraction was 0.71 ± 0.09 and was 27% higher than the mean thallium E_{max} of 0.57 ± 0.10 over a flow range that varied from 0.30 to 2.44 ml/min/g. It is important to note that the mean values in this figure are not constants, but rather represent an average of determinations that vary widely (as expressed by the relatively large s.d.) over a range of coronary flow levels. The mean PS_{cap} for SQ30217 was 1.1 ± 0.4 ml/min/g and this was also higher (46%) than mean thallium PS_{cap} of 0.7 ± 0.3.

Although a relatively high extraction and PS_{cap} value are regarded as important attributes of a perfusion tracer (11,14), it is equally important that the initial extraction of the radionuclide remain stable in the tissue during the period of imaging. Therefore, E_{max} and PS_{cap} values must be combined with E_{net} calculations to account for both the first-pass transcapillary permeation as well as net tissue clearance (backdiffusion) of the initially-extracted tracer. The mean E_{net} for SQ30217 was 0.55 ± 0.19 which was only 20% higher than the average thallium values. Despite a higher net retention than thallium, SQ30217 has a relatively smaller disparity than might have been expected based on the observed initial differences in E_{max} and PS_{cap}. It is important to note that E_{net} measurements were collected over 1 to 6.5 min and strongly suggests that the relatively high first-pass extraction for SQ30217 results in an
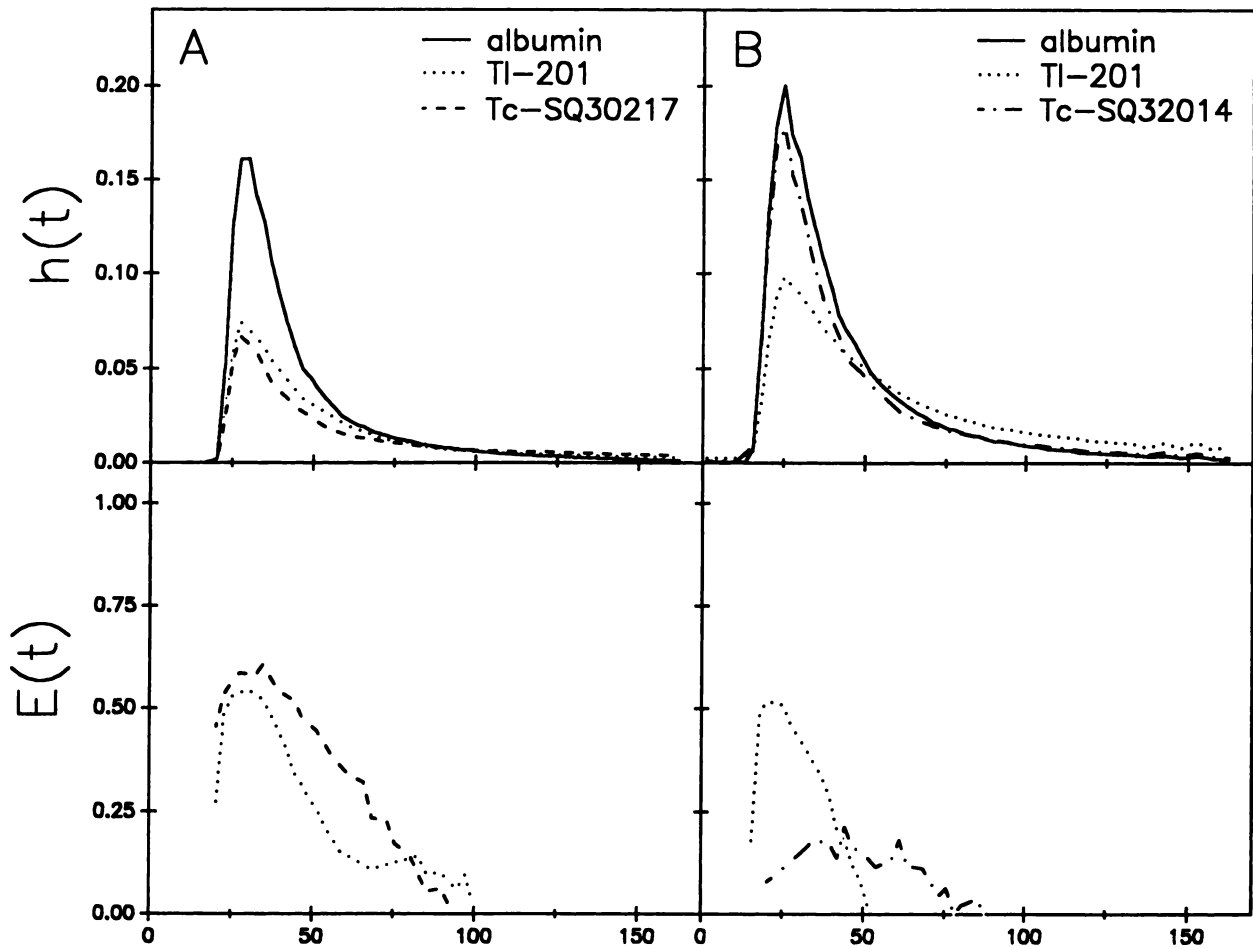
FIGURE 1

Representative transport function [h(t)] and instantaneous extraction [E(t)] curves from a heart which had sequential administrations of thallium (^{201}Tl), SQ30217 and labeled albumin followed by another mixture of ^{201}Tl, SQ32014 and albumin. This heart had constant flow (1.37 ml/min/g) during both injections and was performed as part of a pilot study (not included in this report) to evaluate transport of the two BATO compounds in the same heart. The left-sided curves show ^{201}Tl (dotted line), SQ30217 (dashed line), and albumin (solid line) data for transport (upper panel) and extraction (lower panel) while the right-sided curves show the SQ32014 (dashed line) comparative data.

equally rapid net clearance (especially in comparison to thallium).

In contrast, SQ32014 E_{max} and PS_{cap} values were significantly lower than corresponding thallium determinations (p < 0.0001) over a flow range of 0.15 to 1.63 ml/min/g. SQ32014 E_{max} averaged 0.21 ± 0.11, PS_{cap} was 0.12 ± 0.12 ml/min/g, and E_{net} was 0.21 ± 0.11, which represents a reduction of 68%, 74%, and 54%, respectively, compared to thallium. Mean thallium E_{max} was higher (p < 0.04) in the SQ32014 hearts (0.65 vs. 0.57) and PS_{cap} was lower (0.50 vs. 0.75; p < 0.01), which is due to the lower average flow in this group compared to the SQ30217 group.

The individual values for the E_{max} and PS_{cap} determinations for thallium and both BATO compounds are shown in Figures 3 and 4, respectively. The slopes, intercepts and correlation coefficients are shown in Table 2 for both E_{max} and PS_{cap} regression analyses.

Although the slopes are similar, it is clear that each SQ30217 E_{max} (Fig. 3) is higher than the simultaneously determined thallium value. In contrast, SQ32014 E_{max} determinations are always less than corresponding thallium values. Thallium and SQ30217 show an inverse linear relationship between E_{max} and coronary blood flow. However, myocardial extraction of SQ32014 does not demonstrate a linear relationship to blood flow.

The capillary flux (Fig. 4) for SQ30217 is always higher than simultaneously determined thallium values but both tracers show a plateau effect at coronary flows of greater than 1.5–2.0 ml/min/g. This probably represents diffusion limitation at the capillary level. There is a positive linear relationship between PS_{cap} and flow for SQ30217 and thallium, but SQ32014 shows a much weaker linear correlation. The higher mean PS_{cap} value and SQ30217 slope compared to flow, suggest that it has a more linear initial deposition of tracer than thal-
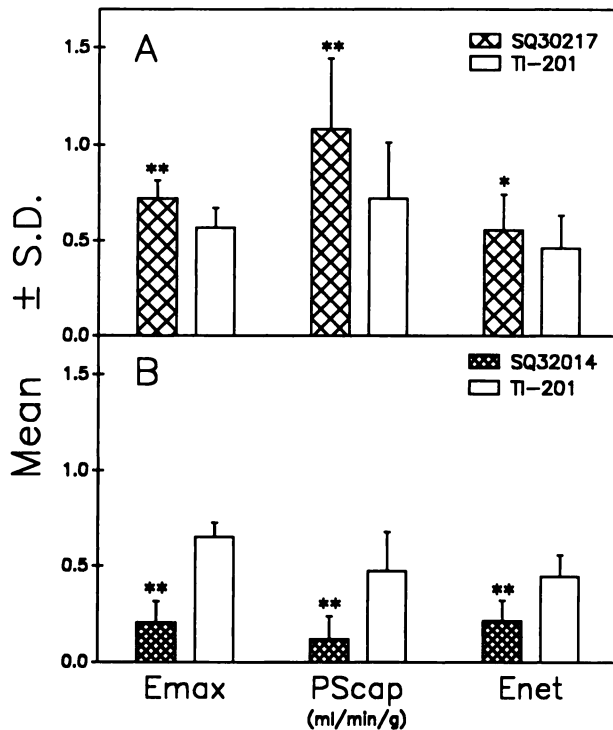
FIGURE 2
Mean (± s.d.) of all E_{max}, PS_{cap}, and E_{net} determinations for SQ30217 (wide cross-hatch) and SQ32014 (narrow cross-hatch) as well as corresponding ^{201}Tl values (open bars) for each group. The paired-t statistically significant differences between the BATO compounds and simultaneous ^{201}Tl values are shown as * ($p < 0.05$) or ** ($p < 0.01$).

lium. This predicts better initial clinical imaging properties for SQ30217, but the reverse for the other BATO compound.

Clinical Observations with SQ32014

Each subject (n = 3) received a single intravenous injection of SQ32014 in a dose range of 20 to 25 mCi (mean, 21.8). Myocardial uptake was rapid (Fig. 5), but images were quickly degraded post injection. In all cases, the images were rated as poor in quality and extensive non-target organ uptake was noted in the liver. Myocardial clearance was rapid and blood clearance was relatively slow with an average of 29% and 15% of the administered dose remaining 15 and 120 min, respectively, postinjection. Cumulative urinary excretion averaged 23% and stool excretion averaged 18% through the first 24 hr. These results suggest that SQ32014 is a safe agent, but is not a potentially effective myocardial imaging agent in clinical practice. These clinical observations confirm the isolated heart results that showed SQ32014 had poor capillary permeation and was not a flow-limited diffusible myocardial tracer.

DISCUSSION

A series of first-pass extraction determinations were performed in isolated rabbit hearts having variable

(0.15–2.44 ml/min/g) coronary flow. Bolus injections (n = 33) or radiolabeled albumin, thallium, and either SQ30217 (n = 17) or SQ32014 (n = 16) were made in the aortic root and myocardial capillary transport was evaluated. In addition, a small clinical trial failed to demonstrate adequate myocardial perfusion images with i.v. SQ32014 administration.

Critiques of Methodology

The model utilized is a standard one for our laboratory (9) and represents an attempt to precisely control coronary perfusion levels during multiple indicator-dilution determinations of myocardial isotope transport. This experimental preparation had levels of blood flow and tissue water content that represent a more physiologic model than buffer perfused hearts (18). Although rate constants in this in vitro heart may not provide an exact correlation to in vivo determinations, it is assumed that relative differences and overall transport analysis will be a meaningful measurement. Specifically, our results imply that SQ30217 has significantly higher capillary permeation than thallium which is, in turn, significantly higher than SQ32014. The observed difference in perfusion level between the two heart groups would tend to elevate the calculated extraction of SQ32014 compared to SQ30217. This was, in fact, observed for thallium because relatively lower blood flow levels typically elevate calculated E_{max} values for diffusible tracers. Therefore, myocardial SQ32014 extraction is clearly depressed despite undergoing protocols that should enhance this measurement. The observed hemodynamic differences in these two groups can be directly attributed to the different level of coronary perfusion utilized.

Transport Function Analysis

The results of the transport function curve analysis [h(t), E_{max}, PS_{cap}, and E_{net}] demonstrate that SQ30217 has higher initial capillary permeation than thallium. Both tracers show an inverse linear relationship between flow and E_{max} and a direct linear relationship between capillary flux (PS_{cap}) and coronary perfusion. However, SQ30217 and thallium also show a diffusion limitation to capillary transport when flow exceeds 1.75 ml/min/ g. Although SQ30217 is a neutral, lipid soluble compound (7,8), the extraction curves for thallium and SQ30217 are remarkably similar and quite typical for cation-type transport (18,19). The high SQ30217 extraction is somewhat offset by a relatively rapid back-diffusion of tracer into the vascular space as demonstrated by the consistent observation that the "tail" portion of this tracer was always higher than the thallium curve. This results in a relatively small (but significant) disparity in E_{net} values between thallium and SQ30217.

Overall, E_{net} represents the net retention of tracer remaining in the hearts once the reference tracer has
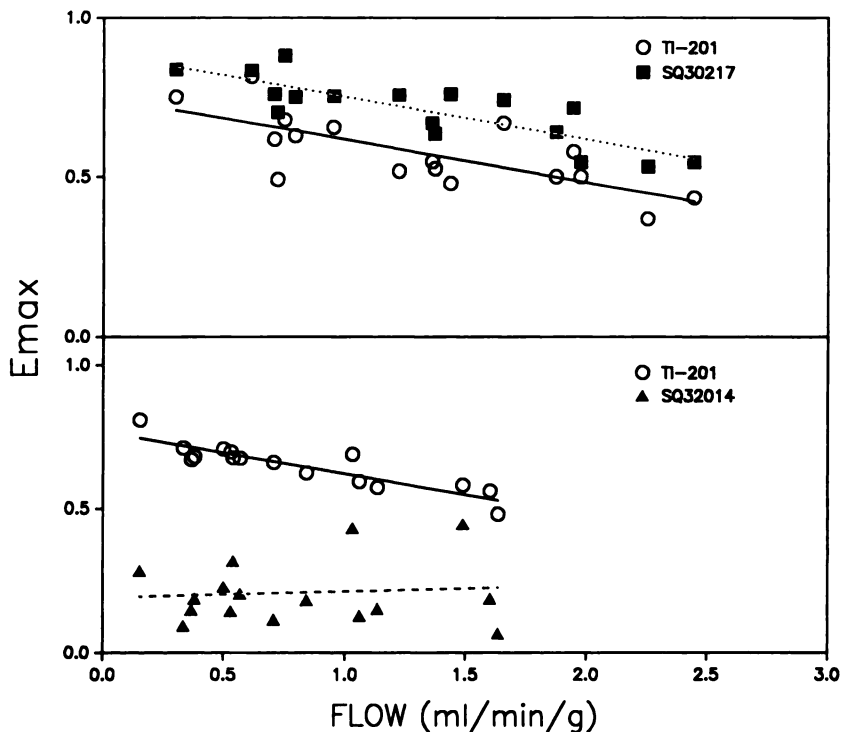
FIGURE 3
The individual values for each ^{201}Tl and ^{99m}Tc E_{max} determination in the SQ30217 (top panel) and SQ32014 (bottom panel) hearts are shown. Thallium values are shown as circles, SQ30217 as boxes and SQ32014 as triangles. The least squares linear regression lines (^{201}Tl, solid; SQ30217, dotted; and SQ32014, dashed) are also displayed. The slopes, intercepts and correlation coefficients (r) for these regression analyses are shown in Table 2.

been collected and needs to be evaluated along with initial tracer permeation estimates (E_{max} and PS_{cap}). Specifically, a perfusion agent should have both high extraction properties as well as a stable cellular volume of distribution during the time it takes to collect the cardiac images. Therefore, a myocardial perfusion agent should be flow-limited over a physiologic range of flow and remain stable until diagnostic images can be ac-

quired. One must also note that capillary recruitment, which is noted for both thallium and SQ30217 (Fig. 4) is typical for most diffusible tracers (20), because the increase in surface area available for exchange is greater than changes in permeability (independent of surface area).

It is important to note that this experimental model correctly predicted that cardiac transport of SQ30217
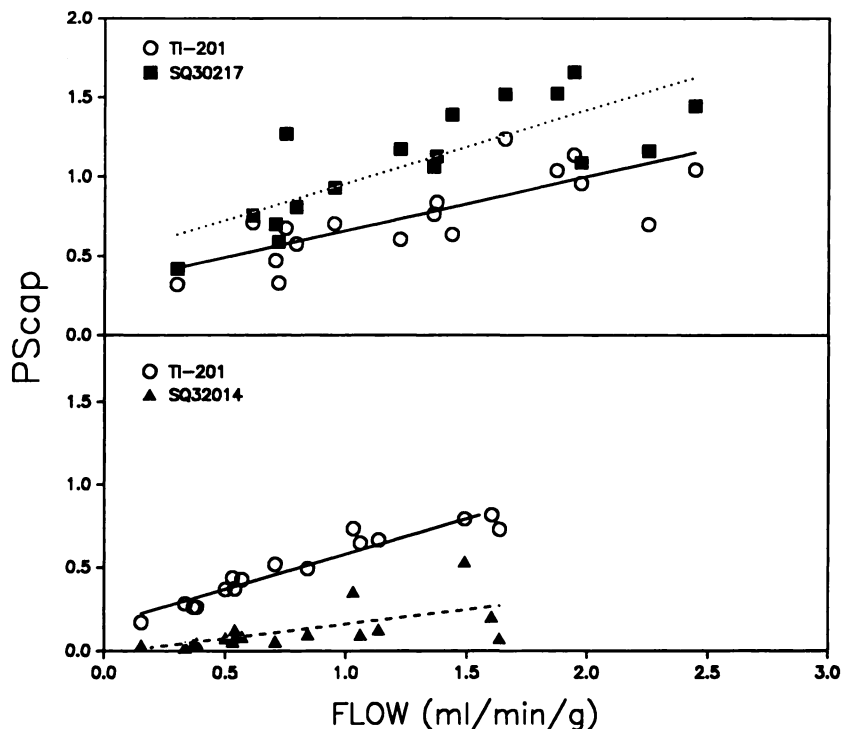
FIGURE 4
The individual values for each ^{201}Tl and ^{99m}Tc PS_{cap} determination in the SQ30217 and SQ32014 hearts are shown. The data presentation is the same as noted above in Figure 3 and the regression analyses are also shown in Table 2.
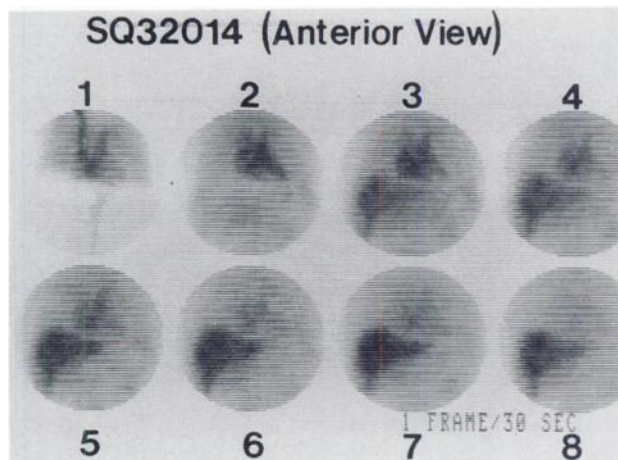
FIGURE 5
Serial anterior (chest) views of a normal volunteer after receiving 25 mCi of SQ32014. Each frame represents 30 sec so that a summary of the first 4 min (frames 1-8) is shown.

would be sufficient to permit clinical imaging (5), but not with SQ32014. It is clearly easier to screen prospective perfusion tracers in this experimental manner rather than mounting large scale, in-vivo animal or clinical trials. Clearly, more experience is needed and comparison of species differences should be done, but the initial observations and methodology appear promising.

The transport analysis showed that SQ32014 blood-tissue exchange was slower and fundamentally different than that noted for thallium or SQ30217. Despite the apparently simple appearing substitution of hydroxyl for a methyl group on the boron atom, the consequences on myocardial transport are impressive. This may be due in part to nonspecific binding of SQ32014 with serum proteins (thereby decreasing its availability

for transcapillary exchange) or inhibition of capillary and cellular membrane permeability. Further studies involving the nonspecific binding capacity of human and rabbit serum proteins should be performed in order to document these intriguing comparative observations.

Clinical Implications

The ideal clinical myocardial perfusion agent would be an intravenous injection of a chemical microsphere. Specifically, it would have very high first-pass extraction from the coronary circulation and remain constant in the tissue during gamma camera imaging such as described by Bassingthwaighte et al. (21). However, such a compound has not yet been developed for widespread clinical applications. Thallium has many important characteristics, but SQ30217 has greater capillary permeation and has a more flow-limited relationship between myocardial capillary flux and blood flow. However, the apparent cellular volume of distribution of SQ30217 appears to be significantly smaller than thallium, which implies that relatively rapid image collection times should be utilized. The fairly small disparity in E_{net} between SQ30217 and thallium suggests that back diffusion is a prominent feature of SQ30217 cardiac transport. In contrast, the basic characteristics of SQ32014 appear to make it unsuitable as a myocardial perfusion agent which has been confirmed by a phase I human trial.

Overall, SQ30217 has myocardial transport properties that suggest it has good potential as a diffusible perfusion agent and appears to have faster capillary exchange than thallium. Initial clinical trials have been successful (5) and further trials should be done that might take advantage of its relatively high capillary permeation. It is also possible that its relatively rapid back-diffusion (and the factors controlling such tracer movement) can be related to regional flow and may,

TABLE 2
Least-Squares Linear Regression Analysis

	Slope		Intercept		
	mean	s.e.	mean	s.e.	r
SQ30217 hearts					
^{99m}Tc E_{max} vs. Flow	−0.14	0.02	0.89*	0.03	−0.83
^{201}Tl E_{max} vs. Flow	−0.13	0.03	0.75	0.05	−0.73
^{99m}Tc PS_{cap} vs. Flow	0.43*	0.09	0.52*	0.13	0.78
^{201}Tl PS_{cap} vs. Flow	0.32	0.02	0.33	0.10	0.76
SQ32014 hearts					
^{99m}Tc E_{max} vs. Flow	0.02*	0.06	0.19*	0.06	0.09
^{201}Tl E_{max} vs. Flow	−0.15	0.02	0.77	0.02	−0.89
^{99m}Tc PS_{cap} vs. Flow	0.17*	0.06	−0.01*	0.06	0.60
^{201}Tl PS_{cap} vs. Flow	0.42	0.03	0.16	0.03	0.96

* $p < 0.01$ from corresponding thallium mean.

therefore, offer serial "washout" imaging studies in a similar fashion to xenon (22). Clearly, SQ30217 is the BATO compound that will be clinically developed and additional studies should focus on imaging this compound in a different way than thallium.

ACKNOWLEDGMENTS

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