

Quantitative Relationship Between Global Left Ventricular Thallium Uptake and Blood Flow: Effects of Propranolol, Ouabain, Dipyridamole, and Coronary Artery Occlusion

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The quantitative relationship between fractional myocardial thallium uptake and radioactive microsphere-determined flow was studied in 33 open chest dogs under baseline conditions during increased coronary flow (dipyridamole), decreased coronary flow (propranolol and coronary artery stenosis), inhibition of Na-K ATPase (ouabain), and regional infarction. Myocardial contents of thallium and microspheres were compared in left ventricular (LV) biopsies taken 5, 10, 15, 30, and 60 min after thallium injection, expressed as fractions of injected dose. Maximal LV thallium uptake occurred 10 min after injection and the 10-min values were therefore used for subsequent comparisons. Combining all dogs, fractional LV thallium content (% injected dose) correlated well with fractional LV blood flow (% cardiac output) ($r = 0.95$). However, for fractional LV flows in the low, normal, or moderately elevated range (LV flow/cardiac output $<9\%$), thallium content consistently exceeded flow by about 15%. This relationship was not altered by ouabain or regional ischemia or infarction. For greatly elevated fractional LV flows ($>9\%$), thallium content was not significantly different from flow. To explain these differences, myocardial and systemic extraction fractions for thallium were determined in eight dogs with a dual tracer method. At baseline, myocardial extraction fraction was significantly greater than systemic ($88 \pm 0.4\%$ compared with $75 \pm 1\%$, $p < 0.001$). During dipyridamole, myocardial extraction fraction decreased and myocardial and systemic values were no longer significantly different ($82 \pm 1\%$ compared with $79 \pm 1\%$). These results show that the fraction of injected thallium dose taken up by the LV myocardium exceeds the delivered fraction of cardiac output over a wide range of LV flows, and is not altered by ouabain-induced inhibition of sodium-potassium ATPase or regional myocardial infarction. This difference is explained by a greater myocardial than systemic extraction fraction for thallium. During high LV flows produced by dipyridamole, fractional LV thallium uptake and flow become similar as myocardial and systemic extraction fractions equalize.

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Thallium-201 (^{201}Tl), a cationic potassium analog, has become widely accepted as the tracer of choice for myocardial perfusion scintigraphy in man. Although the regional myocardial uptake of thallium has been

shown to be an accurate representation of regional perfusion (1-6), the quantitative relationship between global left ventricular (LV) thallium uptake and blood flow has not been examined.

The use of potassium analog agents for measuring myocardial blood flow is based on the indicator fractionation principle described by Sapirstein (7,8). According to this principle, the fractional uptake of injected tracer by an organ equals the fraction of cardiac output perfusing that organ during the measurement.

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This is true at any time for nonrecirculating indicators such as microspheres since virtually all the radioactivity that reaches the organ is trapped in the first circulation (9). This principle can also apply to recirculating indicators as long as organ extraction and total body extraction of the indicator are the same. While this assumption has been verified in animals with potassium-42 (^{42}K) (8), rubidium-86 (^{86}Rb) (10) and in patients with ^{86}Rb (11) for the first 1–2 min after i.v. injection, ^{201}Tl has not been studied and time periods postinjection more comparable to those used for imaging in patients (10 min) have not been examined. After i.v. injection, the time course of myocardial uptake of ^{201}Tl involves sequentially the first-pass extraction, the extraction of recirculating tracer, and the washout (12,13). We examined this time course to determine the maximal myocardial uptake after injection.

In order to provide further insight into the quantitative relation between myocardial perfusion and thallium uptake under conditions of high and low flow rates, sodium-potassium ATPase inhibition and regional myocardial necrosis, we compared in vitro measured myocardial thallium content as a percent of injected dose, and myocardial blood flow as a percent of cardiac output, at different times after i.v. thallium injection in the anesthetized dog. Parallel to these experiments, a comparison of the extraction fraction of thallium by the heart and the rest of the body was made under control conditions and after dipyridamole infusion.

MATERIALS AND METHODS

Measurement of Thallium Uptake

Thirty-three adult mongrel dogs (mean weight 23 kg) were anesthetized with sodium pentobarbital (30 mg/kg), intubated and maintained on a Harvard pump respirator. The heart was exposed through a left lateral thoracotomy and suspended in a pericardial cradle. Polyethylene catheters were inserted into the left atrium, the aortic arch, the pulmonary artery, the coronary sinus, and the jugular vein. Electrocardiographic lead 2, systemic arterial pressure, and left atrial pressure were monitored at regular intervals throughout the experiment and recorded on paper.[†]

In four other dogs, after control hemodynamics and ECG measurements, 2–4 million microspheres labeled with scandium-46 (^{46}Sc) were injected into the left atrium. For calculation of cardiac output, the syringe used for microsphere injection was counted before and after injection in a well counter with application of appropriate geometric corrections. Starting 10 sec before injection and continuing for 2 to 3 min afterwards, blood was withdrawn from the aortic arch using a

Harvard pump (2.16 ml/min). These collections served as a reference for calculating myocardial blood flow.

Figure 1A shows the main experimental protocol. Five animals received neither drug nor intervention and served as controls. Three additional groups of dogs were studied after drug administration. Five dogs received i.v. propranolol, 1 mg/kg bolus, in order to selectively decrease myocardial blood flow. Six dogs received an i.v. injection of ouabain, 0.030 mg/kg, followed by a second injection of 0.010 mg/kg 30 min later in order to block the sodium-potassium ATPase. This dose was sufficient to provoke arrhythmias in all dogs, decrease heart rate by 3% and increase blood pressure by 16%.

Ten dogs received an infusion of dipyridamole which started at a rate of 0.2 mg/min/kg and was decreased in a stepwise manner until a 15% decrease in mean aortic pressure was obtained. At that point, a constant infusion rate of 0.015 to 0.020 mg/kg/min was maintained. Four of the dogs with dipyridamole infusion were killed at 10 min with direct measurements of myocardial and lung activities; the remaining six dogs underwent the 60-min protocol with biopsies.

Approximately 30–40 min after drug administration, ECGs and pressures were recorded and microspheres labeled with niobium-95 (^{95}Nb) were injected to measure myocardial blood flow and cardiac output. Immediately after the withdrawal of ^{95}Nb microsphere reference blood sample, 500 μCi of ^{201}Tl was injected intravenously as a bolus. The syringe used for the ^{201}Tl injection was counted before and after injection in the well counter. To avoid count losses associated with high counting rates and increased deadtime, the pre-injection syringe was counted at a higher elevator sitting. A correction factor was derived from pipetted aliquots of the injectate, diluted until correct count rates (deadtime ~ 0) were obtained, and counted at different elevator settings.

Sampling from the aorta, pulmonary artery, and coronary sinus was started 1 min after ^{201}Tl injection and continued every minute for 15 min, and every 10 min thereafter. All samples were placed in preweighed vials and reweighed to determine the amount of blood added. Transmural myocardial drill biopsies weighing ~ 20 mg were obtained at 5, 10, 15, 30, and 60 min after ^{201}Tl administration. The myocardial specimens were blotted dry on gauze, weighed and counted for ten minutes in a well counter.[‡] At 60 min after thallium injection the dogs were killed. The hearts were excised and washed free of blood. The left ventricle was isolated, weighed and cut into 1–2 g pieces and counted in a well counter. The lungs were also excised and cut into small pieces, which were placed in vials for counting.

A different protocol (Fig. 1B) was applied to seven dogs with coronary occlusion. In three dogs the left circumflex coronary artery was partially occluded with a variable screw occluder. Just proximal to the occluder

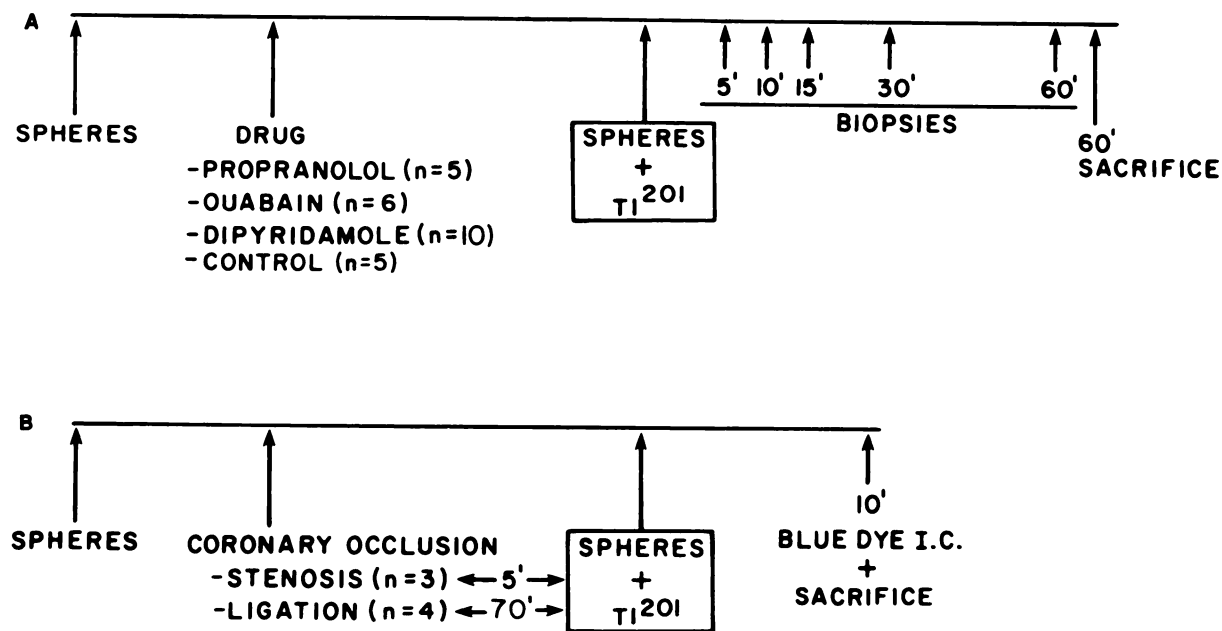


FIGURE 1
Experimental protocol for 33 dogs that received i.v. administration of ^{201}Tl and left atrial injection of microspheres

an electronic flow probe was placed around the artery. The occluder was tightened until resting coronary flow was compromised by 70% as determined by the flow meter. Five minutes after the stenosis was performed, myocardial blood flow and cardiac output were measured with microspheres. Immediately following these measurements, ^{201}Tl was injected.

After the control microsphere injection, the left circumflex coronary artery was acutely ligated in four dogs. Seventy minutes after ligation the second injection of microspheres was performed followed by injection of ^{201}Tl .

In these seven dogs, no biopsies were performed because of the risk of lethal arrhythmias produced by this technique under ischemic conditions. Dogs were killed at 10 min after injection of ^{201}Tl , as maximum LV ^{201}Tl uptake was observed to occur at this average time in the control dogs and the dogs with drug interventions. Just before excision of the hearts, monastral blue was injected into the left circumflex coronary artery near the site of stenosis. This injection allowed visualization of the perfused ischemic zone (stained blue) and the unstained nonischemic zone. The hearts were sectioned parallel to the atrioventricular groove forming five slices 1–1.5 cm thick. In the group of dogs with partial coronary stenosis, multiple transmural samples were taken from the ischemic and nonischemic zones. In the group of dogs with permanent coronary occlusion, the slices were placed in a solution of triphenyl tetrazolium chloride (TTC) at 37°C for 30 min. The TTC solution consisted of 5 mg/ml TTC, 1M Sorenson's PO_4 buffer and H_2O in 1:1:8 ratio. TTC separates the viable myocardium (stained dark red)

from the infarcted myocardium (stained pale grey). Three to four samples were taken from infarcted and normal areas.

After the experiment the biopsy samples were first counted for 10 min using a 60–200 keV window-width setting for ^{201}Tl . The whole left ventricle (1–2 g samples), lungs, and blood samples were then counted for thallium activity for 1 min each. The contribution of ^{46}Sc and ^{95}Nb to the thallium window was <1%. Thallium-201 activity in the biopsies was expressed as counts/min/g and multiplied by total LV weight. The accuracy of this method for calculating total left ventricular thallium activity was verified by comparing the results from the 60-min biopsy with the activity obtained from counting of the entire left ventricle after killing. In ten dogs, LV thallium activity from the 60-min biopsy averaged $9.06 \pm 8.64 \times 10^6$ (s.d.) cpm, compared with $8.50 \pm 6.43 \times 10^6$ cpm obtained by counting the whole left ventricle (N.S., $p = 0.50$). The mean difference between the two measurements was only $1.7 \pm 18.5\%$ (s.d.). After ^{201}Tl activity had decayed two half-lives, samples were recounted for microsphere activities (690–820 keV for ^{95}Nb , 850–1200 keV for ^{46}Sc). A computer program was used to correct for activity overlap between the two windows.

The following parameters were calculated:

1. Left ventricular blood flow determined by the microsphere method was calculated by the formula: $\text{LVBF} = \text{Cm} \times \text{R/Cr}$, where LVBF = left ventricular blood flow, Cm = total counts in left ventricle, R = reference blood flow, and Cr = total counts in reference blood sample.

2. Cardiac output determined by the microsphere

method was calculated by the formula: $CO = ID \times R / Cr$, where CO = cardiac output, ID = microsphere injected dose, R = reference blood flow, and Cr = total counts in reference blood sample.

3. Thallium-201 activity in the whole left ventricle was measured at 60 min after injection and calculated from the biopsy samples at 5, 10, 15, and 30 min.

4. Thallium-201 activity in the lungs was determined at 60 min after injection and back corrected to 10 min postinjection using sequential arteriovenous activity differences (aortic counts – pulmonary artery counts), according to the Fick principle, assuming a constant pulmonary flow equal to the cardiac output.

5. Thallium-201 injected dose was measured before and after i.v. injection and corrected by subtracting ^{201}Tl lung uptake at 10 min after injection. Thus, the corrected injected dose was the injected dose entering the systemic circulation and represents the amount available for distribution to the systemic organs.

6. In dogs with coronary occlusion, the ^{201}Tl and microsphere activity levels of samples taken from ischemic and infarcted myocardium were normalized by dividing these values by the corresponding mean non-ischemic zone activity levels.

Extraction Fraction of Thallium

Eight dogs weighing 18–25 kg were anesthetized with 30 mg/kg i.v. sodium pentobarbital. The dogs were intubated and placed on a Harvard respirator. Thoracotomy was performed in the fifth left intercostal space and the heart was suspended in a pericardial cradle. Polyethylene catheters were introduced in the aorta, left atrium, pulmonary artery, and coronary sinus. An isotope mixture of 50 μCi technetium-99m human serum albumin ($^{99\text{m}}\text{Tc}$]HSA) and 150 μCi ^{201}Tl in a volume of 5 ml was prepared and mixed in a vial. This mixture was injected as a bolus into the left atrium and at the same time withdrawal of blood from the aorta, coronary sinus, and pulmonary artery was initiated. Samples of 1 ml of blood were taken every 3 sec during the first 35 sec after ^{201}Tl injection. The 1-ml samples were withdrawn manually over 2 sec with a 1-sec interval to change the syringe. The experiment was repeated after 30 min with a double volume of isotope mixture injected. Blood samples were weighed and counted in a scintillation counter. Standards of each tracer were counted in each window. Thallium-201 was found to comprise <20% of the counts in the $^{99\text{m}}\text{Tc}$ window (124–170 keV) and $^{99\text{m}}\text{Tc}$ <1% of the counts in the ^{201}Tl window (58–96 keV). Appropriate ratio corrections were made for crossover of activity into each of the windows. From each set of three second blood samples collected from the coronary sinus and the pulmonary artery, the ratio of ^{201}Tl to $^{99\text{m}}\text{Tc}$ activity was calculated, and instantaneous extraction fraction was calculated using the following equation of the

double tracer method (14):

$$EF = \left[1 - \left(\frac{TL_v}{Tc_v} \right) \left(\frac{Tc_a}{TL_a} \right) \right] \times 100\%$$

where EF = extraction fraction; v is the concentration of the isotope in the venous sample (coronary sinus or pulmonary artery); a = the arterial sample; Tc = [$^{99\text{m}}\text{Tc}$] HSA used for the nonextractable reference isotope.

The instantaneous EF was calculated for each 3-sec interval from first appearance of the indicator until its concentration had decreased to one third of peak concentration. Results were expressed as an average of these values which usually varied <5%. Four dogs were studied as controls (six measurements). Four dogs were instrumented with an electromagnetic transducer implanted around the circumflex coronary artery. These dogs received an infusion of dipyridamole in order to increase the mean coronary blood flow by two- or threefold without decreasing mean arterial pressure by >15%. When an adequate increase in flow was obtained, extraction fraction measurements were performed in these four dogs (seven measurements).

Statistical Analysis

Student's t-tests for paired and unpaired data were utilized for statistical comparisons between groups. All results are presented as mean \pm s.e.m. One-way analysis of variance was used to test the difference between the lung thallium uptake of the five groups. Linear regression analysis was done by the least squares fit method.

RESULTS

Hemodynamic Changes During Interventions

Hemodynamics recorded before and after the various interventions are shown in Tables 1 and 2. Propranolol caused a significant decrease in heart rate (148 to 111 bpm, $p < 0.05$), LV flow (66 to 55 ml/min, $p < 0.05$) and cardiac output (1,316 to 1,183 ml/min, $p < 0.05$). With ouabain, mean arterial pressure increased by 16% (88 to 102 mmHg, N.S.); cardiac output increased slightly by 6% (1,613 to 1,706 ml/min; N.S.) and left ventricular flow decreased by 8% (98 to 90 ml/min; N.S.). With dipyridamole, mean arterial pressure fell from 112 to 95 mmHg (15%, $p < 0.05$) and left ventricular flow increased by 101% (89 to 179 ml/min; $p < 0.005$). After coronary occlusion, left ventricular flow decreased by 32% (85 to 58 ml/min; $p < 0.005$). Compared with the control group, the ratio of left ventricular flow/cardiac output was smaller after propranolol (4.6 compared with 6.4%, $p < 0.05$), ouabain (5.2 compared with 6.4%, $p < 0.05$), and coronary occlusion (4.3 compared with 6.4%, $p < 0.05$). This ratio increased after dipyridamole (11 compared with 6.4% in control, $p < 0.005$).

TABLE 1
Hemodynamics in Five Groups of Dogs

Item	Mean arterial pressure (mmHg)		Heart rate (beats/min)	
	Pre	Post	Pre	Post
Controls (n = 5)	—	98 ± 7	—	157 ± 8
Propranolol (n = 5)	104 ± 9	90 ± 6	148 ± 15	111 ± 11*
Ouabain (n = 6)	88 ± 5	102 ± 11	154 ± 15	149 ± 9
Occlusion (n = 7)	112 ± 7	95 ± 9†	151 ± 6	155 ± 9
Dipyridamole (n = 10)	106 ± 9	104 ± 8	143 ± 10	136 ± 6

* p < 0.05, Compared with values before intervention.
† p < 0.005, Compared with values before intervention.

Time Course of LV Thallium Uptake

Figure 2 shows the time course of total LV thallium content as a percent of the injected dose calculated from the myocardial sequential biopsies. In the control group as well as in the groups receiving drugs, maximum LV thallium uptake occurred 10 min after the i.v. injection of thallium. However, the ratios at 5 and 15 min after injection were not statistically different from the ratios at 10 min, and the ratios at 30 min were also not significantly different except for the dipyridamole group. The average time of maximal thallium uptake obtained from the biopsies was corroborated by noting the time at which the myocardial arteriovenous difference (aorta-coronary sinus) in thallium counts became negative (control 9.2 ± 1.7 min; propranolol 10.2 ± 1.3 min; ouabain 11 ± 1.4 min; dipyridamole 8.4 ± 1.3 min).

Lung Thallium Uptake

Lung thallium uptake at 10 min after injection was calculated in order to obtain the true injected dose available to the systemic circulation (total injected dose minus lung content). There was no difference in lung uptake among the five groups of dogs with mean values ranging from 6.2 to 10.2% of injected dose (Table 3). Correction for lung uptake resulted in a small but

significant increase in the mean LV thallium content/injected dose ratios in each group ($p < 0.05$) (Table 3).

Comparison of LV Blood Flow/Cardiac Output and LV Thallium Content/Corrected Injected Dose

The average values for each group of LV flow/cardiac output and LV thallium content/corrected injected dose are shown in Fig. 3. Ten-minute postinjection LV thallium content was chosen for this comparison because 10 min represents the time of maximal thallium content. Table 3 shows the average values and the ranges for the two ratios, as well as for LV thallium content/*uncorrected* injected dose. LV thallium content/injected dose slightly overestimated LV flow/cardiac output in the control group (7.6 ± 0.3 compared with 6.4 ± 0.3 , $p = 0.02$) in the propranolol group (5.3 ± 0.4 compared with 4.6 ± 0.4 , $p = 0.004$) in the ouabain group (5.8 ± 0.4 compared with 5.2 ± 0.4 ; N.S.) and after coronary occlusion (4.7 ± 0.4 compared with 4.3 ± 0.4 , $p < 0.1$). Conversely, in the dipyridamole group, LV thallium content/injected dose slightly underestimated LV flow/cardiac output (10.2 ± 0.9 compared with 11 ± 1.5 , N.S.). The values of these ratios for the individual dogs are plotted in Fig. 4. By linear regression analysis, there was a significant rela-

TABLE 2
Microsphere-Determined LV Blood Flow Cardiac Output for Five Groups of Dogs

Item	LV flow (ml/min)		Cardiac output (ml/min)		LV flow/cardiac output (%)	
	Pre	Post	Pre	Post	Pre	Post
Control (n = 5)	—	108 ± 14	—	1,656 ± 126	—	6.4 ± 0.4
Propranolol (n = 5)	66 ± 18	55 ± 7*‡	1,316 ± 125	1,183 ± 85*‡	4.9 ± 1.1	4.6 ± 0.3‡
Ouabain (n = 6)	98 ± 18	90 ± 15	1,613 ± 106	1,706 ± 224	5.9 ± 0.7	5.2 ± 0.2‡
Dipyridamole (n = 10)	89 ± 8	179 ± 28*‡	1,601 ± 87	1,665 ± 147	5.6 ± 0.1	11 ± 1.5*‡
Coronary occlusion (n = 7)	85 ± 7	58 ± 8*‡	1,444 ± 149	1,336 ± 145	5.9 ± 0.3	4.3 ± 0.4*§

* p < 0.05, Compared with values before intervention.
† p < 0.005, Compared with values before intervention.
‡ p < 0.05, Compared with values in control groups.
§ p < 0.005, Compared with values in control groups.

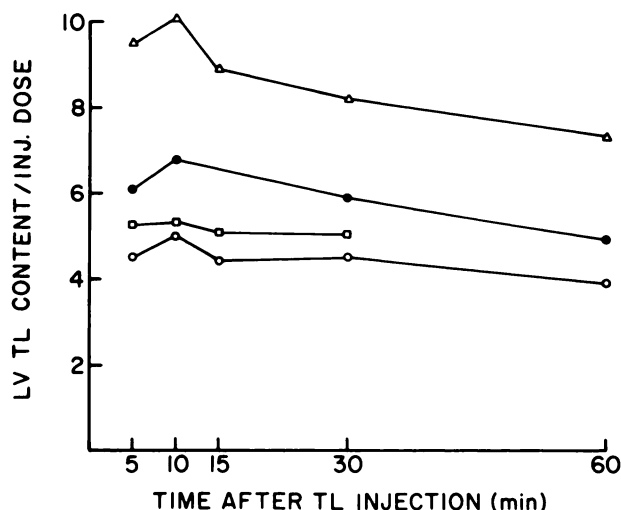


FIGURE 2

Time course of LV thallium content as percent of injected dose, determined from myocardial biopsies. Ratios at 5 and 15 min after injection were not statistically different from ratios at 10 min in the four groups of dogs. (Δ) Dipyridamole; (●) Controls; (□) Ouabain; (○) Propranolol

tionship between the two ratios for the 33 dogs ($y = 0.71 \times +2.2$; $r = 0.95$; $p < 0.001$) but the intercept on the y-axis, thallium content/injected dose, was significantly ($p < 0.001$) >0 . Without the dipyridamole group, the relationship was also significant ($y = 1.11 \times +0.09$; $r = 0.91$; $p < 0.001$; $n = 23$) without difference between the slope and the line of identity or between the intercepts. For values of LV flow/cardiac output below 9%, LV thallium content/injected dose slightly overestimated LV flow/cardiac output. Above 9% (dipyridamole group) the inverse trend is noticed. The two ratios of left ventricular blood flow/cardiac output above 15% were consequences of both an increase in LV flow (131% and 140%) and a decrease in cardiac output (22

and 16%). The drop in mean arterial systemic pressure was greater in these dogs than in the others (22 compared with 13%).

Myocardial and Total Body Extraction Fraction

The instantaneous extraction fraction for thallium calculated from each 3-sec sample was maximal after 13 ± 1 sec in the myocardium and found to remain relatively constant thereafter (Table 4). As illustrated in Fig. 5, the mean extraction fraction of thallium by the heart under control conditions (six measurements in four dogs) was significantly higher than the average extraction fraction of thallium by the body ($87.7 \pm 0.5\%$ compared with $75.2 \pm 1.1\%$, $p < 0.001$). This difference appears to explain the slight overestimation of left ventricular blood flow by thallium observed in the first series of experiments. Dipyridamole was given to four dogs during an increase in mean coronary flow of $115 \pm 8\%$ as shown by an electromagnetic flow meter. Mean arterial pressure decreased by $12 \pm 4\%$ after dipyridamole. Myocardial thallium extraction fraction decreased in the dipyridamole group ($82.3 \pm 1.5\%$ compared with $87.7 \pm 0.4\%$; $p = 0.01$) while systemic extraction fraction increased slightly compared to controls (78.7 ± 1.2 compared with $75.2 \pm 1.1\%$, $p = 0.05$). In the dipyridamole group, the systemic and myocardial extraction fraction were not significantly different ($78.7 \pm 1.2\%$ compared with 82.3 ± 1.5).

Comparison of Regional Myocardial Blood Flow and Thallium Uptake After Coronary Occlusion

There was a significant linear relationship between thallium activity 10 min after injection and microsphere-determined regional myocardial blood flow both after partial coronary stenosis ($r = 0.98$, $p < 0.001$) and 70 min of coronary ligation ($r = 0.99$, $p < 0.001$). The relationships were similar and close to the line of identity despite the presence of acutely ischemic and/or infarcted areas (Fig. 6).

TABLE 3
Comparison of LV Blood Flow as Percent of Cardiac Output and LV Thallium Content as Percent of Corrected Injected Dose*

Item	LBBF/CO	LV TI content/ uncorrected injected dose	Lung TI content/ID	LV TI content/corrected LV TI injected dose
Controls (n = 5)	6.4 ± 0.3 (5.6–7.9)	6.9 ± 0.3 (6.1–7.8)	8.2 ± 0.4 (6.9–9.4)	7.6 ± 0.3 (6.6–8.5) [†]
Propranolol (n = 5)	4.6 ± 0.4 (3.3–5.5)	5.0 ± 0.4 (3.5–5.7)	6.2 ± 0.8 (4.0–7.6)	5.3 ± 0.4 (3.8–6.1) ^{‡§}
Ouabain (n = 6)	5.2 ± 0.4 (4.4–5.9)	5.3 ± 0.3 (4.4–6.4)	7.9 ± 0.5 (6.3–9.5)	5.8 ± 0.4 (4.8–7.1) [§]
Occlusion (n = 7)	4.3 ± 0.4 (3.3–6.3)	4.3 ± 0.4 (3.4–6.3)	8.4 ± 0.4 (7.5–10.0)	4.7 ± 0.4 (3.7–6.8) [§]
Dipyridamole (n = 10)	11 ± 1.5 (6.1–10.5)	9.1 ± 0.7 (7.0–13.6)	10.2 ± 1.6 (4.2–22.0)	10.2 ± 0.9 (7.5–17.4) [†]

* Values represent mean \pm s.e.m. Numbers in parentheses represent range.

[†] $p < 0.05$, versus LBBF/CO.

[‡] $p < 0.005$, versus LBBF/CO.

[§] $p < 0.05$, versus controls.

[†] $p < 0.005$, versus controls.

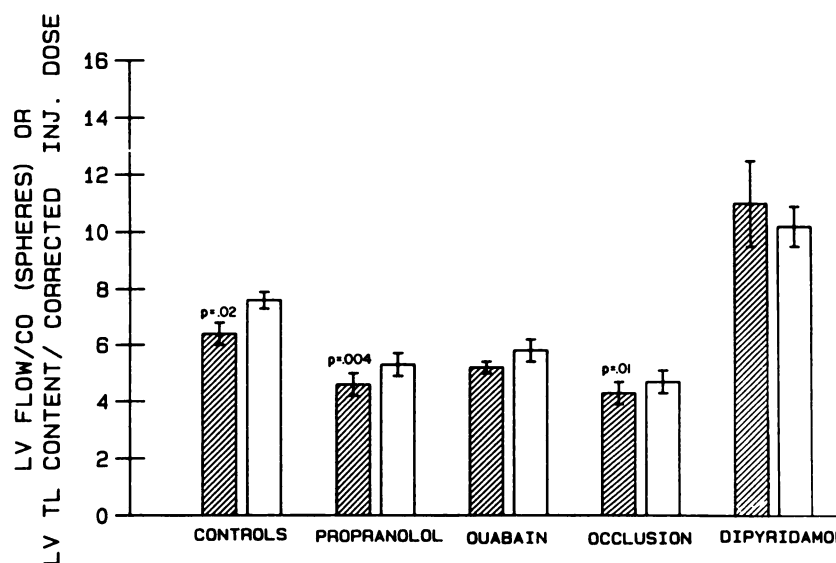


FIGURE 3

Comparison of mean values of LV flow/cardiac output (▨ spheres) and of LV thallium content/corrected injected dose (□ thallium) for five groups of dogs. Controls, n = 5; propranolol, n = 5; ouabain, n = 6; occlusion, n = 7; dipyridamole, n = 10

DISCUSSION

The use of radioactive potassium analogs as quantitative flow indicators is based on the assumption that myocardial uptake of isotope is proportional to coronary flow as a fraction of cardiac output. Experimental validations of this assumption have been obtained for rubidium (10,11,15-19), although Moir (20) obtained less satisfactory results. Similar studies with thallium have been virtually absent from the literature. Using thallium and potassium time-concentration curves in patients, L'Abbate et al. (21) showed that the values of myocardial uptake of thallium at 2, 10, and 25 min after a pulmonary artery injection correlated positively with blood flow and with myocardial blood flow/cardiac output but these correlations were not observed

for potassium. Strauss et al. (22) found a similar fractional uptake of thallium and microspheres in the heart in anesthetized dogs studied at baseline and during norepinephrine infusion.

Our study was done to provide further insight into the quantitative relation between myocardial perfusion and thallium uptake under conditions of high and low flow rates, sodium-potassium ATPase inhibition with ouabain and regional myocardial necrosis. We initially examined the time course of thallium uptake in the myocardium using serial biopsies to determine whether the quantitative relation between thallium uptake and flow was significantly time-dependent within the first 30 min.

On average, maximum LV uptake occurred 10 min after injection in all experimental groups. Schwartz et al. (23) also found that the net uptake by the heart in dogs, measured by arteriovenous differences, was normally maximal by about 10 min. Using a miniature radiation detection device, Okada et al. (24) showed that myocardial thallium activity reached at least 80% of peak activity within 1 min and peaked at a mean

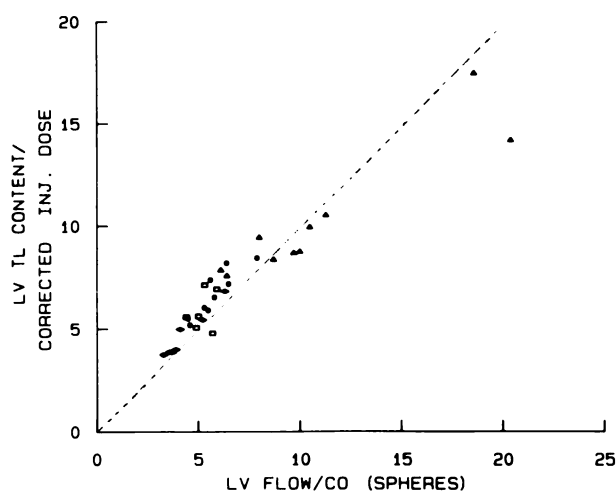


FIGURE 4

Comparison between LV flow/cardiac output and LV thallium content/corrected injected dose in individual dogs. Dotted line is line of identity. (●) Controls; (○) Propranolol; (□) Ouabain; (◆) Occlusion; (▲) Dipyridamole

TABLE 4
Total-Body and Myocardial Extraction Fraction for Thallium Calculated from Each 3-Sec Sample

Time (sec)	Controls (n = 6)		Dipyridamole (n = 7)	
	Total-body	Myocardium	Total-body	Myocardium
9	—	—	—	—
12	—	81 ± 6	—	68 ± 3
15	—	86 ± 5	—	74 ± 3
18	66 ± 2	87 ± 3	74 ± 4	76 ± 2
21	73 ± 3	88 ± 3	74 ± 4	79 ± 1
24	74 ± 4	89 ± 1	77 ± 2	81 ± 1
27	76 ± 4	87 ± 1	77 ± 2	82 ± 1
30	75 ± 3	88 ± 1	78 ± 1	82 ± 1
33	74 ± 3	87 ± 1	78 ± 1	83 ± 2
36	77 ± 3	87 ± 1	77 ± 2	83 ± 1

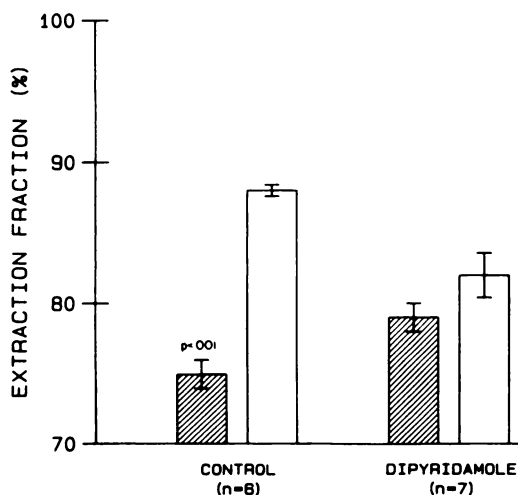


FIGURE 5

Comparison of total-body and myocardial extraction fraction in control and dipyridamole group. Note that vertical axis begins at 70%. (▨) Total-body extraction fraction; (□) Myocardial extraction fraction

time of 23 min in nonischemic myocardium. The longer time-to-peak activity in this study may have been due to a combined sampling of both blood and myocardial activity by the cadmium telluride detectors. Based on the available data, we used the 10-min myocardial thallium measurements to compare to microsphere measurements under the various experimental conditions of our study. Although 10 min represents

the average time of maximal uptake, considering the net balance between uptake of recirculating tracer and clearance of tracer from the myocardium, the measurements taken at 5, 15, and 30 min were not significantly lower except for the 30-min value in the dipyridamole group. The time period of 5 to 30 min postinjection represents the usual time when images are acquired clinically, and the quantitative relation we have found between early thallium uptake and flow should therefore be generally applicable to clinical studies. For images obtained after 30 min under resting conditions, or after 15 min under conditions of rapid tracer clearance such as after exercise or dipyridamole infusion, however, the fractional LV content of thallium would be expected to be less than the fractional distribution of cardiac output.

Under control conditions, myocardial thallium activity, expressed as percent of injected dose, slightly but consistently overestimated LV blood flow expressed as percent of cardiac output. To explain this difference, we determined thallium extraction fraction in the myocardium and in the systemic circulation with the double tracer method described by Chinard et al. (25) and modified by Crone (26) and Lassen and Crone (27). These extraction fractions should, in fact, be equal in order for recirculating indicators to precisely measure myocardial blood flow. In these experiments the myocardial extraction fraction was of the same magnitude as reported by Weich et al. (28) and Grunwald et al.

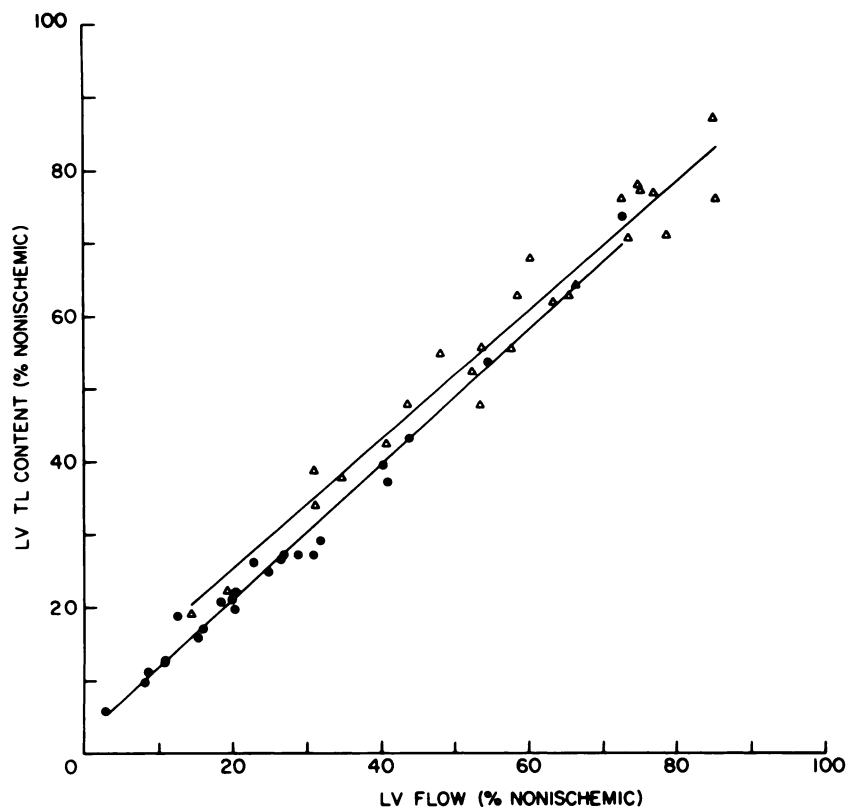


FIGURE 6

Comparison between flow and thallium uptake in individual samples from dogs with coronary stenosis and occlusion. (Δ) Coronary stenosis (25 samples, 3 dogs), $[TL] = 0.88$ [spheres] + 7.6, $r = 0.977$, $p < 0.001$; (●) Coronary ligation (24 samples, 4 dogs) $[TL] = 0.92$ [spheres] + 2.4, $r = 0.992$, $p < 0.001$

(29) but was significantly higher than the extraction fraction of the whole body. These findings are different from those of Sapirstein (7,8) using ^{42}K in animals and Donato et al. (11) using ^{86}Rb in patients. They showed that for the first 2 min after tracer injection, myocardial extraction was similar to that for the average of the body. Using a constant infusion technique, Mymin and Sharma (30) showed that myocardial and whole-body extraction of ^{84}Rb was similar in normal individuals, but that myocardial extraction was significantly reduced in patients with coronary and noncoronary heart disease (49.5% compared with 55.3%, 52.4% compared with 59.3%, respectively). These different results confirm that, despite some similarities, thallium does not have identical properties to potassium and its analogs (31–34). Myocardial extraction fraction for thallium, for example, appears to be higher than for rubidium, potassium, or cesium (13,28,30,32). In addition, clearance of thallium from the myocardium after initial uptake (“washout”) appears to be much slower for thallium than potassium (21).

The explanation for the higher myocardial than total-body extraction fraction for thallium is uncertain. Since extraction is inversely related to flow, the inclusion of a large high flow compartment, such as the renal circulation, may result in a relative lowering of the whole-body estimate. Weich et al. (14) found an average renal extraction fraction for thallium of 81%, compared with a myocardial extraction fraction of 88% measured with the same method in another series of studies (28). Alternatively, the lower average whole-body extraction could be due to a lack of uptake of thallium by the brain because of an inability of the cation to cross the blood-brain barrier (35).

Our results indicate generally good agreement between fractional myocardial thallium uptake and perfusion. At moderately elevated, normal, or low myocardial blood flows (<9% of the cardiac output), fractional thallium uptake exceeded fractional myocardial blood flow by ~9–19% depending on the experimental group. This discrepancy can be directly related to the higher myocardial than average body extraction fraction for thallium. Despite this overestimation of flow by thallium, there was a strong linear relationship between 10-min thallium uptake and myocardial blood flow over this flow range, not only under normal metabolic conditions, but also after metabolic changes induced by ouabain and regional myocardial necrosis.

Reduced myocardial blood flow conditions were experimentally provoked by coronary stenosis and by beta-adrenergic blockade. Propranolol caused an average 17% decrease in LV blood flow but also caused a 10% decrease in cardiac output; as a result, the fractional LV flow fell only from 4.9 to 4.6% of the cardiac output. Nevertheless, fractional thallium uptake de-

creased proportionately. The previously reported decrease in thallium uptake (36,37) after propranolol was probably also a result of the reduction in coronary flow following beta-blockade. We could not identify a flow-independent reduction of thallium uptake as shown by the preliminary data of Schelbert et al. (38) in mouse hearts in organ culture.

Our study confirms previous reports that under ischemic conditions, the initial myocardial uptake of thallium is proportional to regional perfusion (4,5,22,23,39,40). We have extended these observations by determining that the fractional uptake of thallium by the whole left ventricle remains proportional to fractional perfusion despite the presence of a large region of ischemia. A slight excess of thallium in regions with very low flow was also observed, as initially reported by Becker et al. (41) with rubidium. This relative excess is thought to be related to more efficient extraction of monovalent cations with more prolonged circulatory exposure (20,42) or possibly to uptake of tracer directly from the LV cavity by the most ischemic subendocardial regions.

Several studies have suggested that the sodium-potassium pump plays an important role in the initial uptake of thallium by the myocardium (31,43–45). We have examined this possibility under two different conditions: after ouabain (which inhibits the pump) and in infarcted myocardium (in which sodium-potassium ATPase activity is lacking). With a dose of ouabain which is known to inhibit potassium transport (46) a small decrease in the ratio of myocardial blood flow over cardiac output was observed and was reflected by a parallel decrease in thallium uptake. This decrease may be explained by the neurogenic coronary vasoconstrictor effect of digitalis, demonstrated by Hamlin et al. (47) and Garan et al. (48). The lack of a flow-independent effect of ouabain on early thallium uptake in our study is consistent with the results obtained with rubidium by Schelbert et al. (50) and Goldstein et al. (13). For thallium, preliminary studies in cultured fetal mouse hearts by Costin and Zaret (36) in dogs and by Schelbert et al. (38) have shown decreases in thallium uptake of 22 and 31%, respectively, after digitalis administration. However, Krivokapich and Shine (50) reported that in the isolated perfused rabbit septum, the influx of thallium was not inhibited by acetylcholinesterase and was, thus, not dependent on the sodium-potassium pump. Similarly, thallium extraction fraction during the first pass of tracer remained unchanged after strophanthidin in the study of Weich et al. (28).

In the myocardium made necrotic by 70 min of ischemic injury, our study indicates continued good agreement between thallium uptake and myocardial blood flow. In a previous study (51), we showed the same good correlation between thallium uptake and

myocardial flow after a permanent coronary occlusion of 70-min and of 5-hr duration. Di Cola et al. (2), Chu et al. (5), and Khaw et al. (52) also observed that the reduction in regional thallium uptake correlated well with microsphere estimates of blood flow in 24- to 96-hr canine infarct models. A flow-independent effect of ischemic-like injury on cellular extraction of thallium has been suggested by Goldhaber et al. (53). In a fetal mouse heart preparation, these authors showed that extraction of thallium from the medium was depressed only when irreversible cell damage existed. These results, however, may pertain more to late thallium uptake during the redistribution phase than to initial uptake.

In order to assess the effects of an increase in coronary blood flow on myocardial thallium uptake, we used dipyridamole, a potent small-vessel coronary vasodilator. LV blood flow doubled, without any significant change in cardiac output. Only a slight and nonsignificant underestimation of myocardial blood flow by myocardial thallium content was noted for myocardial blood flow over cardiac output ratios above 9%. This finding may be directly explained by the observed equality of myocardial and systemic extraction fractions after dipyridamole. As already shown by Weich et al. (28) and Winkler et al. (54), an increase in coronary flow in excess of myocardial demands results in a progressive decrease in thallium myocardial extraction due to the marked rise in capillary and venular blood flow velocity (55). In our extraction fraction experiments, coronary flow was increased by 115%, and the associated decrease in myocardial extraction fraction from 88 to 82% resulted in an equality between myocardial and systemic extraction fractions. For even larger increases in coronary flow, myocardial extraction fraction would have probably dropped more drastically and would have caused an underestimation of flow by thallium as was seen in our study for fractional LV blood flows of ~20%. Gould (56) obtained three- to fourfold coronary flow increases after dipyridamole, and at these high flows, thallium uptake increased by approximately one half of the increase in coronary flow. Nielsen et al. (3) found a close linear relationship between initial thallium uptake and regional coronary flow in exercising dogs in which circumflex coronary flow was restricted with a mechanical snare. Blood flow increased three- to sevenfold in the region with unrestricted flow. A study from the same laboratory (6) showed that the relationship between the distribution of ^{201}Tl and myocardial blood flow during dipyridamole infusion was similar to that observed in animals subjected to treadmill exercise; there was a slight rolloff of thallium activity as blood flow increased. In patients, Nichols et al. (57) found that the relative spatial distribution of thallium activity during pacing accurately reflects the distribution of myocardial blood flow meas-

ured with intracoronary xenon-133 injection (flow ranges 46–130 ml/min). In our experiments, the good correlation between thallium uptake and myocardial blood flow was probably due to the fact that the increase in coronary flow with dipyridamole was not great (two-fold rise on average). This flow increase is comparable to the rise obtained in man during treadmill testing: 139% (58), 177% (59) and 252% (60) of control values.

Clinical Implications

The results of the present study indicate that under different flow and metabolic conditions, the early fractional uptake of thallium by the left ventricle is a reasonably good approximation of myocardial blood flow as a fraction of cardiac output. The relation between early thallium uptake and flow was not altered by beta-adrenergic blockade, ouabain-induced inhibition of sodium-potassium ATPase activity, or by myocardial ischemia or infarction. The commonly held belief that thallium uptake depends on both myocardial perfusion and viability therefore appears to be incorrect, at least for early uptake (within the first 15–30 min). It remains possible, however, that myocardial thallium content at later times is critically dependent on cellular viability, either because of an altered thallium clearance or abnormal cellular cationic milieu associated with impaired cellular metabolism. The results reported here should provide a rationale for the use of myocardial thallium uptake as a quantitative index of myocardial blood flow. The *in vivo* application of this concept has been reported in patients during exercise (21,61) and after vasodilating drugs (62). However, an adequate measurement of absolute coronary flow by thallium uptake assumes a simultaneous measurement of cardiac output and accurate quantification of thallium uptake with proper corrections for background and attenuation of activity by the chest wall. Preliminary data (63) have shown that a noninvasive scintigraphic technique (using two 180° opposed views) can accurately determine the uptake of thallium by the left ventricle and kidneys. Tomographic imaging has shown promise for good spatial localization and quantitation of myocardial perfusion defects. However, it is as yet unclear whether it will also be able to provide accurate quantitation of absolute radionuclide content in the heart.

FOOTNOTES

[†] Gould, Inc., Rolling Meadows, IL.

[‡] Packard Instrument Co. (5986), Downers Grove, IL.

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