THALLIUM-201 FOR MEDICAL USE.

II: BIOLOGIC BEHAVIOR

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Thallium-201 has been evaluated for myocardial imaging by determining its distribution and assessing its imaging properties.

Organ distribution with time was studied in goats, chosen for their large size and easy operability. Myocardial imaging was performed in living and sacrificed goats and also in two anesthetized dogs, without infarction. Infarcts were made by ligature at open chest surgery on the goats and the infarcts subsequently confirmed histologically. The myocardium of normal and infarcted, young and old goats was cut into blocks and the isotope distribution measured and compared with that in the lungs, liver, spleen, and kidney in normal goats. The renal medulla-to-cortex concentration ratio in goats was studied and is approximately five. The heart uptake exceeds 3% for 100 min whereas contiguous organs have less than one-half of the myocardial concentration, and blood clearance is rapid.

One problem may prove to be inhomogeneity of uptake of thallium in the "normal" myocardium, showing a standard deviation of 11% in a young goat and 29% in an old goat.

In view of the good myocardial uptake, however, this work strongly suggests the trial of ^{201}Tl in patients.

Thallium-201 has been suggested as a suitable agent for trial as a myocardial scanning agent because of its physical characteristics and biologic properties (*1,2*).

The half-life of 73 hr provides a shelf-life useful for availability in emergencies. The energies of the gamma emissions (135 and 167 keV) are excellent for efficient collimation and detection. Mercury x-rays (69–80 keV) are also emitted. Biologically, the distribution of the thallous ion (Tl^+) following intravenous administration is primarily intracellular and has been shown to be similar to that of the potassium ion (K^+) in its concentration in the heart (*3,4*). A number of myocardial imaging agents have been discussed, chosen on the basis of their similarity to potassium, the main intracellular cation (*2*). Studies were performed to determine the biologic distribution of ^{201}Tl in normal organs and its relation to myocardial and infarct imaging.

MATERIALS AND METHODS

Thallium-201 is prepared by the (p,3n) reaction on pure stable thallium metal using the Brookhaven 60-in. cyclotron. This isotope can be separated from stable thallium carrier and from chemical and radiochemical impurities and made sterile and pyrogen-free (*2*).

The organ distribution of intravenously administered ^{201}Tl was determined in seven normal goats and in two goats following coronary artery ligation by sacrificing the animals at intervals up to 7 days and assessing radioactivity in the organs with scintillation counting. Variation in distribution with time was studied as well as the variability of distribution within the heart muscle.

Scintillation camera monitoring of a rabbit was performed for 2 hr following intravenous administration of ^{201}Tl in order to evaluate relative organ concentration over the short term.

Homogeneity of distribution in goats was determined in the right and left ventricles, the septum, around infarcts, and in the liver, lungs, and spleen by cutting entire organs into small pieces, all between 1 and 3 gm (*5*) and counting the sections individually. Myocardial specimens were mostly

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TABLE 1. ^{201}Tl DISTRIBUTION WITH TIME IN GOATS

Organ	10 min		25 min		105 min		130 min		20 hr		2 days, 16 hr		7 days	
	%/ organ	% gm × 10^2	%/ organ	% gm × 10^2	%/ organ	% gm × 10^2	%/ organ	% gm × 10^2	%/ organ	% gm × 10^2	%/ organ	% gm × 10^2	%/ organ	% gm × 10^2
Heart	3.65	4.3	3.7	2.8	3.0	2.2	2.96	2.3	0.58	0.69	0.27	0.14	0.08	0.20
Liver	11.6	1.9	15.4	1.8	12.0	1.4	12.0	2.0	1.84	0.40	0.80	0.10	0.56	0.21
Spleen	1.26	1.2	2.4	2.7	1.6	1.7	—	—	0.20	0.29	0.17	0.058	0.04	0.015
Kidney	3.4	3.6	3.5	5.6	1.6	2.5	1.62	2.5	1.18	2.20	1.07	0.58	0.018	0.16
Lung	2.1	2.1	2.6	0.5	2.0	0.8	0.75	0.5	0.78	0.70	0.28	0.15	0.063	0.15
Skeletal muscle	—	0.6	—	1.3	—	1.5	—	2.0	—	0.81	—	0.21	—	0.17
Diaphragm	0.25	0.5	—	—	0.15	0.82	—	—	0.11	0.62	—	0.09	0.030	0.002
Gonads	0.34	0.3	—	—	—	—	—	—	—	—	0.02	0.40	—	—
Whole body	100%	—	—	—	—	—	—	—	60%	—	28%	—	—	—
Kidney														
Medulla	—	3.17	—	—	—	—	—	—	—	4.60	—	5.56	—	1.20
Cortex	—	0.92	—	—	—	—	—	—	—	0.84	—	0.560	—	0.28
Ratio, medulla/ cortex	3.45	—	—	—	—	—	—	—	—	5.40	—	9.95	—	4.20

TABLE 2. HEART/ORGAN RATIO (%/GM) AS FUNCTION OF TIME

	10 min	25 min	105 min	20 hr	64 hr
Liver	2.3	1.6	1.6	1.7	1.4
Spleen	3.6	1.0	1.3	2.4	2.4
Kidney	1.2	0.5	0.9	0.3	0.24
Lung	2.0	5.6	2.8	1.0	0.91
Skeletal muscle	7.2	2.1	—	0.85	0.65
Diaphragm	9.6	—	2.6	1.1	1.5
Whole body	21.5	—	—	5.3	2.3

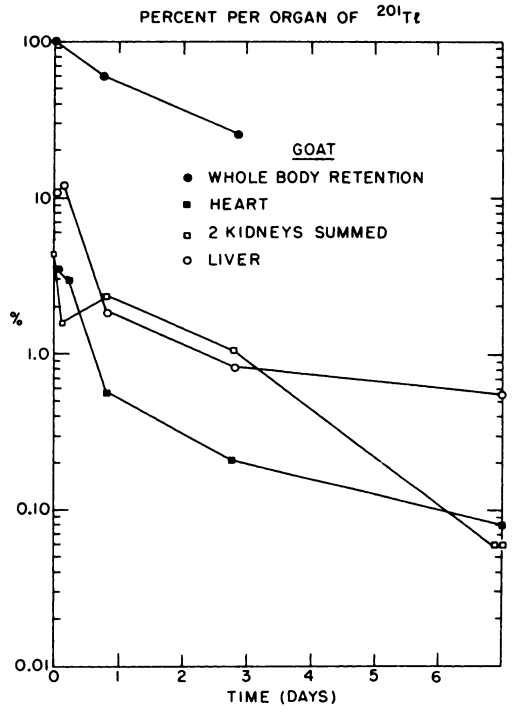

FIG. 1. Time distribution of ^{201}Tl in goats in selected organs and whole body is shown. Amount adequate for imaging is in heart for up to 2 hr.

transmural. The kidneys were sliced 1-mm thick prior to further accurate subdivision into medulla and cortex.

When a heart, infarcted 50 days previously, is removed, the extent of the infarct is difficult to identify visually. Therefore, blocks were taken in pairs, one for counting, the other for histology to determine the extent of the infarct.

Imaging of goats with and without infarcts was also performed at several intervals after administration of 100–700 μCi of the isotope. The spectrometer window was chosen to utilize the emissions of approximately 69–80 keV. Imaging was performed in two dogs employing the approximately 135–167-keV gamma emissions of ^{201}Tl.

Evidence of toxicity was not observed in the 14 goats or the 2 dogs given ^{201}Tl containing up to 7 μg of stable thallium. Another goat was also injected intravenously with 1,000 μg of stable thallium in solution with observation for gastrointestinal or neurologic symptoms for over a 3-month period.

RESULTS

The greatest concentration of ^{201}Tl in goats is in kidney, heart, and liver (Table 1). The concentration remains high in these organs for at least the first 2 hr. Maximum myocardial and renal concentration is achieved by 10 min. The relative concentration of ^{201}Tl with respect to neighboring organs such as liver and lung (Table 2) is optimal between 10 and 25 min. The maximum total organ content of thallium in the myocardium is approximately 3.7% of injected dose at 10–25 min.

The change in distribution of ^{201}Tl with time in the various organs is seen in Fig. 1. These data provide information concerning biologic half-time in the various organs. The $T_{1/2}$ for residence of ^{201}Tl in the heart muscle is in two components of 4.4 hr (78%) and 40 hr (22%); in liver 3.8 hr (33%) and 38.3 hr (67%); in kidney 40 min (72%) and

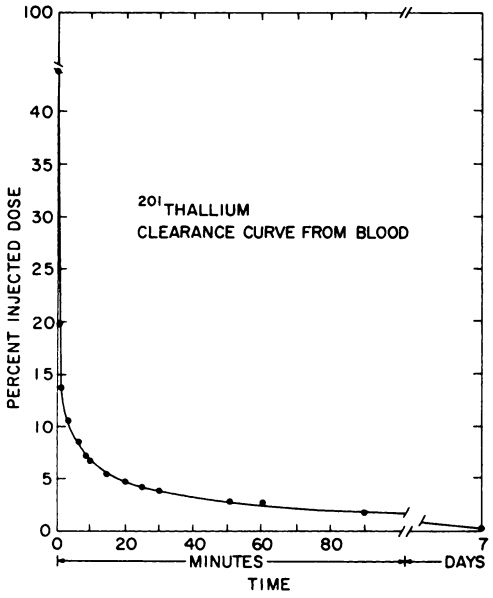

FIG. 2. ^{201}Tl clearance from whole blood of goat is shown here to be rapid, indicating that harmful background from imaging of blood in heart chambers should not be a problem.

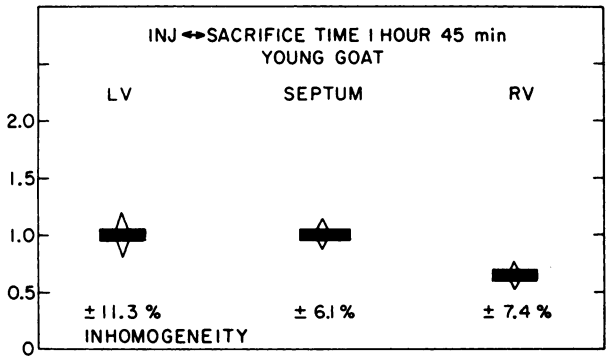

FIG. 3. Homogeneity of ^{201}Tl in young goat (Goat No. 7 control) myocardium is shown. Multiple small samples of myocardium from left ventricle, right ventricle, and septum were counted. Data are normalized to left ventricle as 1.0.

140 hr (28%); and in the whole body 24 hr. For dosimetric purposes, a single effective $T_{1/2}$ of 24 hr was used (*6*).

Of importance to myocardial imaging is the quantity of radioactivity in the heart blood pool. The disappearance half-time in the blood is less than 1 min (Fig. 2), thus assuring minimal interference with imaging of the myocardium.

Examination of the variability of concentration of ^{201}Tl in the myocardium (Fig. 3) indicates about 11% s.d. in the left ventricle and lesser degrees in the interventricular septum and right ventricle. This should be compared with a decrease of 60% in an infarcted region (Fig. 4). Of interest is the increase in radioactivity at the edges of a 50-day-old infarct. In an older goat, the degree of inhomogeneity in noninfarcted myocardium is considerably greater (up to 29% in the left ventricle) than in a younger goat.

Sequential imaging of the rabbit distribution showed the relative concentrations of radioactivity in heart, liver, and kidneys (Fig. 5). At 15 min the myocardial concentration was considerably greater than in liver and kidneys but at 2 hr the myocardial activity had faded relative to the other two organs.

Figure 6 demonstrates myocardial visualization in a normal dog, using the gamma photons at 135–167 keV ungated. Clear delineation of the myocardium is present.

No adverse reactions or evidence of toxicity were noted in any of the animals studied.

DISCUSSION

The importance of imaging the myocardium lies in the possible benefit to patients in the diagnosis and management of coronary artery disease. The characteristic changes in the electrocardiogram may be delayed or may be such that they cannot be interpreted because the size of the infarct is too small or there may be changes on another wall of the heart, masking the infarct, (*7–9*). Blood enzymes provide no indication of the infarction site and changes relating to them may be delayed. Thus, information from imaging may be necessary for the determination of appropriate therapy.

There is need for a noninvasive method of obtaining information concerning myocardial perfusion in patients, especially in those who are critically ill. Intravenous ^{201}Tl in combination with physiologic gating, a scintillation camera, and a computer, is a potentially useful aid in diagnosing and following infarcts and areas of ischemia and in evaluating their site and size. With this method, the visualization of

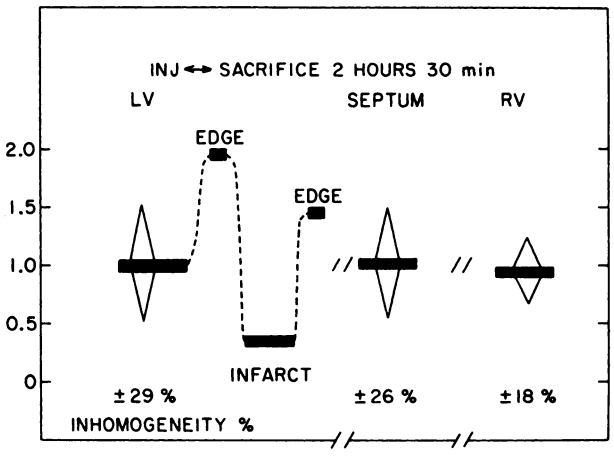

FIG. 4. Inhomogeneity of distribution of ^{201}Tl in myocardium of old goat No. 6 (infarct after 50 days) and distribution at edge and center of operatively produced infarct are shown. This shows greater inhomogeneity in old goat compared with young goat.

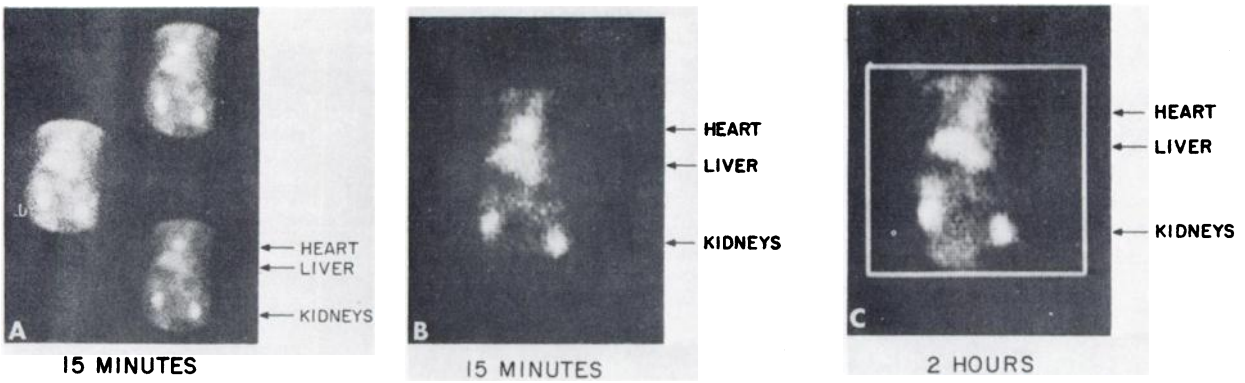

FIG. 5. Time distribution of ^{201}Tl in anesthetized rabbit is shown. Ratio of heart/liver content is seen to start high (A and B) and falling (C).

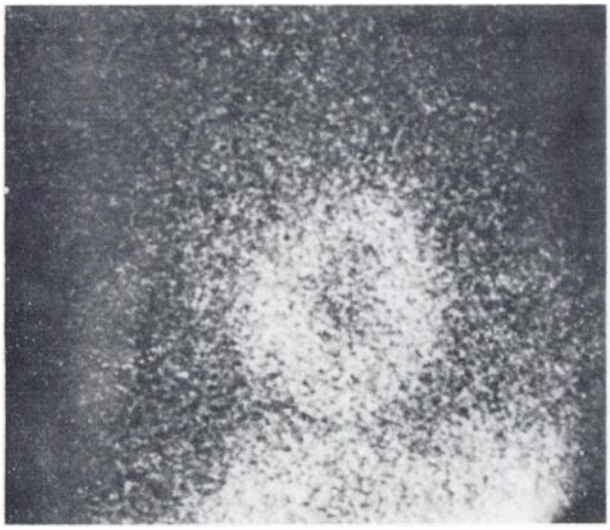

FIG. 6. Visualization of anesthetized dog's heart is obtained without physiologic gating, using a standard 5,000-hole collimator about 90 min after i.v. injection. Anterior view is shown. Gamma photons from approximately 135–167 keV are used. This figure demonstrates annular form usually noted in myocardial images.

an infarct might be quantifiable, its clinical course followed, and results of therapeutic agents evaluated.

The myocardium contains over 3% of the injected dose of ^{201}Tl (comparable to potassium and rubidium) for about 100 min after administration in goats and this amount is expected to be sufficient to visualize the heart, particularly as contiguous organs contain little ^{201}Tl and blood clearance is rapid.

On the basis of our data in goats, adequate images should be obtained in a reasonable time in man. For example, after administering 5 mCi of ^{201}Tl, we estimate an image would take about 1 min for 500,000 counts, using the x-rays of ^{201}Tl and about 12 min for 500,000 counts, using the 167-keV gamma ray of ^{201}Tl. With electronic gating, based on the electrocardiogram and respiration, imaging would take approximately ten times longer for a given number of collected counts.

W. S. Snyder of Oak Ridge National Laboratory has calculated the radiation dosages utilizing the Oak Ridge computer program and the biologic data obtained in this study (Table 1). The clearance data were fitted by a least-squares analysis, and the goat organ concentrations were multiplied by the ratio of human organ weight/goat organ weight since the proportional cardiac output to various organs is expected to be similar in humans and goats. Table 3 gives these expected radiation dosages of ^{201}Tl, which will be reassessed following clinical studies. The critical organ is the kidney whose average radiation dose is 0.52 rads/mCi (the renal medulla where thallium concentrates receives a radiation dose of 1.1 rads/mCi). The whole-body radiation dose is 0.07 rads/mCi (*6*).

Toxicity was not observed in this study either in the 16 goats given small amounts (under 7.0 μg) of thallium nor in the goat given 1,000 μg i.v. deliberately and watched for 3 months. This is in accordance with the literature and with toxicity figures for thallium (given subcutaneously) to rats in which an LD_{50} of between 13 and 20 mg/kg is found (*10*).

Toxicity in higher animals and man consists of depilation (approximately 0.1 mg/kg), gastrointestinal symptoms including hemorrhage at higher levels, and central nervous system syndromes with death at levels of approximately 2.8 mg/kg (*10,11*). Even for minimal toxicity, the required dose of thallium is

TABLE 3. ^{201}Tl DOSE (RADS/mCi)

Whole body	0.07
Gonads (testes)	0.25
Heart	0.32
Liver	0.17
Kidneys*	0.52
Medulla	1.1
Cortex	0.26

* Assuming per weight that cortex is twice the medulla in humans (12).

about 10,000 times greater than the dose of thallium given as a radiopharmaceutical.

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