Thallium-201: Non-Invasive Determination of the Regional Distribution of Cardiac Output

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Sapirstein (1) employed cationic radiopotassium to determine the fractional distribution of cardiac output to several organs. Thallium-201 can substitute for radiopotassium in myocardial imaging, and was evaluated in the present studies to determine the distribution of cardiac output in the anesthetized dog in comparison with tracer microspheres, both under control circumstances and following the infusion of norepinephrine in a dose sufficient to raise the blood pressure 20 mm Hg above control levels. The concentrations of thallium-201 and microspheres were similar in the heart, kidney, thyroid, and skeletal muscle in both control and norepinephrine-treated animals ($r = 0.93$). Thallium concentration in the liver and lung exceeded that of microspheres, however, and probably is not related solely to the regional distribution of arterial perfusion.

These data suggest that in the heart, kidney, thyroid, and skeletal muscle, thallium-201 distribution reflects the fractional distribution of cardiac output.

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In 1958, Sapirstein described a method for determining the regional distribution of cardiac output using the fractional distribution of monovalent cationic indicators (potassium-42) that were rapidly extracted from the blood stream (*1*). He noted that only organs with an extraction of tracer close to that of the total body could have their blood flow measured by this technique, whereas organs with a relatively low extraction of tracer (such as the brain) could not be evaluated. The initial flow-related distribution of these cationic tracers was altered as the nuclide equilibrated with the total-body potassium pool, so that measurements of the distribution of cardiac output had to be made very rapidly following injection.

Thallium-201 has biologic properties that are similar to those of tracer potassium. In 1963 in vitro studies by Gehring and Hammond (*2*) revealed that thallium could substitute for potassium in the activation of the sodium-potassium ATPase pump. Recent work by Weich et al. (*3,4*) indicates that 88% of thallium entering the coronary and renal arteries is extracted by the heart and kidneys, whereas Love et al. (*5*) found that only 70% of potassium was so extracted. In addition, the secondary re-equilibration time for cardiac thallium has been found to be longer than that for potassium (*6*). The present study compares the fractional distribution, in dogs, of tracer microspheres, delivered into the left ventricle, with organ concentrations of thallium-201 administered intravenously. In addition, three normal volunteers underwent whole-body imaging to determine the total-body distribution of thallium-201.

MATERIALS AND METHODS

Thallium-201 was obtained as a sterile pyrogen-free radiochemical with a specific activity of 1 mCi per microgram of thallium.

Human albumin microspheres, mean size 20 microns, were labeled with technetium-99m using the tin reduction method. The preparation was checked

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for the presence of unbound technetium-99m by ascending acetone-methanol chromatography, being considered acceptable if less than 3% of activity was unbound. The microspheres were labeled to achieve a specific activity of 500 μCi technetium-99m on 750,000 particles. This relatively low specific activity was desired to assure that organs receiving less than 0.05% of cardiac output would have an adequate number of particles to assure a precision of measurement of 10%.

Twelve adult mongrel dogs, 20–30 kg, were anesthetized with 25–30 mg/kg of sodium pentothal. A left femoral arteriotomy was performed and a catheter advanced retrograde through the aortic valve into the apex of the left ventricle for pressure recording.

In the control group of six dogs, 100 μCi of thallium-201 was administered intravenously, followed 3 min later by 500 μCi of Tc-99m-labeled microspheres through the left arterial catheter. Multiple blood samples were obtained, and 3 to 5 min later the animals were killed; liver, heart, lungs, kidneys, thyroid, 10 cc of blood, and a sample of skeletal muscle from the right thigh, were removed, weighed and counted with a 5-inch diameter sodium iodide well detector. (In three dogs, samples of stomach, duodenum, jejunum, ileum, colon, and spleen were also counted.) Samples were counted long enough to record at least 10,000 counts per sample. Technetium-99m was counted with a 130 to 150-keV window. The samples were then allowed to decay for 24 hr and thallium-201 was counted with a window of 70–90 keV. Standards of both tracers were counted in a similar fashion and correction made for crossover of activity into each of the windows.

In six additional dogs, a 30-min i.v. infusion of norepinephrine was administered in a dose sufficient to increase systolic blood pressure at least 20 mm Hg over control values. This was followed by injection of the tracers as described above. The animals were then killed and tracer distribution determined.

The activity of each tracer in each organ was compared with the dose administered and expressed as a percentage of the injected dose per organ. The kidney was subdivided into cortex and medulla, and activity in each portion expressed as percentage dose/gram. For blood, the total blood volume of the dog was assumed to be 6% of body weight, and total blood activity was estimated from that measured in 10 cc of whole blood.

In the human subjects, whole-body imaging of the distribution of thallium-201 was accomplished with a dual-probe whole-body imager. Images were recorded following injection at rest with a scan speed of 2.5 cm/min, beginning at the subject's head.

RESULTS

In the dogs, thallium-201 clearance from the blood followed an exponential curve, and at the time of killing residual blood activity averaged 12.7 ± 2.5% in the control animals and 8.0 ± 3% in the norepinephrine-treated animals.

The distributions of thallium-201 and microspheres in the control animals and in the norepinephrine-treated animals are shown in Tables 1 and 2.

It can be seen that organs with a single circulation—for example heart, thyroid, skeletal muscle, and total kidney—there was no significant difference between the distribution of microspheres/organ and percentage thallium/organ either in the control or the norepinephrine-treated animals. On the other hand, in organs with a dual circulation (such as liver and lung), there was a significant difference between percentage thallium/organ and percentage microspheres/organ in both groups of dogs. This led us to subdivide the kidney, which has an internal portal-type circulation of its own into cortex and medulla, and the activity in each portion was determined (Table 3).

Typical anterior and posterior whole-body human scans are shown in Fig. 1.

TABLE 1. PERCENTAGE DOSE/ORGAN IN CONTROL AND NOREPINEPHRINE-TREATED ANIMALS

	Percentage dose/organ					
	Heart	Kidney	Thyroid	Skel musc*	Liver	Lung
Control (n = 6)						
Thallium	5.6 ± 1.1	12.9 ± 4.0	0.06 ± 0.02	0.009	12.4 ± 5.4	10.3 ± 1.4
Microspheres	5.0 ± 1.3	12.8 ± 4.4	0.09 ± 0.05	0.008	5.6 ± 6.1	5.0 ± 1.4
	pns	pns	pns	pns	$p < 0.05$	$p < 0.10$
Norepinephrine (n = 6)						
Thallium	9.0 ± 2.4	7.2 ± 0.4	0.05 ± 0.02	—	16.5 ± 3.9	7.4 ± 1.4
Microspheres	9.0 ± 1.4	6.0 ± 0.9	0.05 ± 0.02	—	5.9 ± 3.0	1.6 ± 0.05
	pns	pns	pns		$p < 0.01$	$p < 0.01$

* % Dose/gram.

TABLE 2. PERCENTAGE DOSE/ORGAN IN SELECTED VISCERA*

	Microspheres	Thallium
Spleen	2.3	3.3
Stomach	1.5	1.5
Duodenum and jejunum	2.9	3.0
Ileum	2.3	2.5
Colon	2.5	2.3

* n = 3 dogs; r = 0.82 (stomach, duodenum & jejunum, ileum & colon).

TABLE 3. UPTAKE IN KIDNEY

	Uptake in kidney (% dose/gram)	
	Cortex	Medulla
Control (n = 6)		
Thallium	0.22 ± 0.07	0.034 ± 0.016
Microspheres	0.27 ± 0.11	0.003 ± 0.002
	pns	$p < 0.05$
Norepinephrine (n = 6)		
Thallium	0.14 ± 0.05	0.02 ± 0.02
Microspheres	0.12 ± 0.03	0.002 ± 0.001
	pns	$p < 0.05$

DISCUSSION

Myocardial perfusion imaging with thallium-201 has been shown to be useful for the noninvasive detection of regional myocardial ischemia, infarction, and hypertrophy of both the right and left ventricular chambers (*6*). Previous work has shown thallium-201 uptake by the heart is related to regional myocardial blood flow (*7*). The results of the present study suggest that thallium-201 may also be useful in evaluating the body distribution of cardiac output.

In organs with a single circulation—such as the heart, skeletal muscle, thyroid, stomach, colon, and whole kidney—there is no significant difference between the percentage of thallium/organ and percentage of microspheres/organ, either in the control or norepinephrine-treated animals. The data in these experiments in the basal state are similar to those found by Kaihara et al. using microsphere distribution (*8*). In organs with a dual circulation—such as the lung and liver—there was, however, a significant difference between percentage of thallium/organ and percentage of microspheres/organ both in the control and norepinephrine-treated animals. Similarly, in examining an organ such as the kidney, in which there is a double circulation, there was a significant difference between distribution of thallium and microspheres in both the renal medulla and cortex.

Thallium-201 uptake by an organ depends on the presence of an active sodium-potassium ATPase transport system, organ blood flow/organ, and tissue permeability to the ion. The most important of these factors appears to be blood flow/organ under control conditions and in situations such as norepinephrine-induced hypertension. Previous studies in our laboratory have shown that thallium is extracted rapidly from the blood. The extraction fraction for the heart is 88% (*3*), and for the kidneys 85% (*4*). Because of this, thallium-201, in its initial distribution, "tags" organs with high extraction rate much as microspheres do, since the initial distribution is related to regional blood flow. Microspheres have the advantage of being large enough (20 μ) to be totally extracted by organs in one passage, so that their distribution reflects only arterial flow. On the other hand, microspheres suffer from a distinct disadvantage in comparison with soluble tracers such as thallium-201: being trapped on their initial circulation, they cannot reflect total blood flow to organs that receive a dual blood supply—such as the liver, in which portal flow provides an important contribution to total hepatic flow, and the renal medulla,

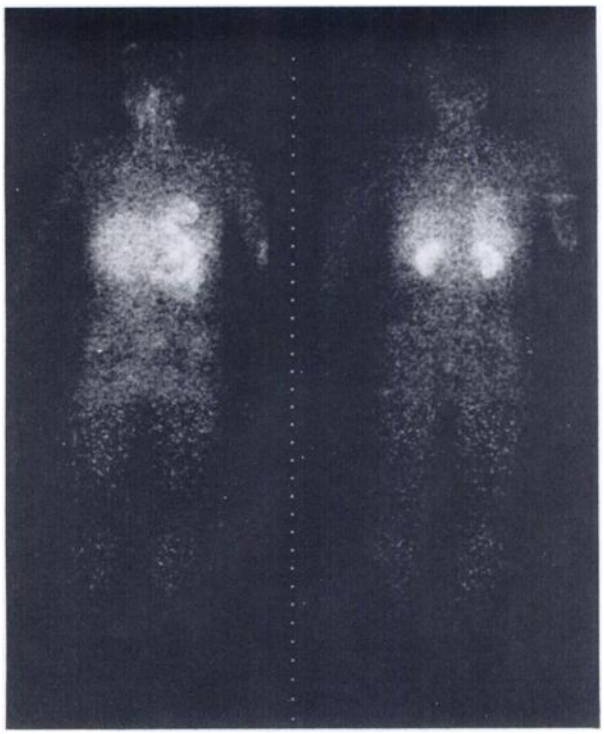

FIG. 1. Human whole-body scan views, anterior (left) and posterior (right), following i.v. administration of thallium-201 to a healthy volunteer. Heart, liver, stomach, and salivary glands can be seen clearly defined on anterior view. Kidneys, spleen, and liver are shown on posterior view. There is significant tracer concentration in muscles of lower extremity, even though patient was injected while in basal state. There is no significant tracer concentration in brain area.

whose blood must first pass through the capillary bed of the renal cortex. Results of the present study show that, although there is no significant difference between the percentages of thallium and of microspheres in the total kidney, there is a significantly lower value for percentages of microspheres/gram of renal medulla and a higher percentage of microspheres/gram of renal cortex. Thallium, on the other hand, is not "trapped" exclusively in the renal cortex, and thus can follow more closely the normal distribution of blood flow. This, we think, is why our cortex-to-medulla ratio for thallium-201 (6:1) closely parallels the ratio of five or six to one found by Hollenberg et al. (*9*) using a xenon-133 clearance technique.

Thallium-201 has several advantages over isotopes of potassium for the study of the distribution of cardiac output. In previous potassium studies, measurements of relative distribution of the blood flow had to be made within 30–60 sec (*1*), while in the present study with thallium-201, measurements could be made 5–10 min after injection. The difference is due to the slower loss of thallium from organs in comparison to potassium (*7*) or other cationic tracers, such as rubidium-81. Significant redistribution of thallium does occur over an interval of 24 hr following administration, as demonstrated by Atkins et al. (*10*) with whole-body thallium scans performed at multiple times following i.v. administration of the tracer. Their data suggest that tracer concentrations in the heart and kidneys on initial measurements were significantly greater than at 24 hr, while the activity in the limbs increased during the same time period. After 24 hr, however, the decay of thallium in multiple organs followed the same exponential time course as that in the entire body. This biologic difference is of practical importance in the consideration of an agent for the study of the distribution of cardiac output in man; so are the physical characteristics of Tl-201—in particular the 80-keV x-rays, which can be imaged easily by contemporary gamma cameras.

There is relatively little information on the distribution of cardiac output in man under normal conditions, and even less in pathologic states. Total-body imaging after injection of thallium-201, such as shown in Fig. 1 could be useful in a variety of situations—for example in detecting peripheral vascular disease or renal ischemia. It is expected that after further experience and validation in man, the relative distribution of thallium-201 will be of clinical value, supplementing its usefulness in the detection of regional myocardial ischemia. The ultimate value of this technique, however, will not be achieved until absolute flow measurements are made.

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