critically ill patients and can be incorporated into the management of these patients in an intensive care unit setting.

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References


Early Redistribution of Thallium-201 after Temporary Ischemia

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SUMMARY To define the time course of redistribution of thallium-201 (201TI), ischemia was induced in seven pigs by temporary occlusion of the circumflex coronary artery. After 1½ min of occlusion 201TI and labeled microspheres were injected into the left atrium. Flow was re-established 4 min after occlusion. Prior to reflow, the relative activities of 201TI and microspheres in the ischemic area were similar, but as early as 5 min after reflow the relative 201TI activity was considerably higher than the relative microsphere activity and from 15 to 105 min after reflow, relative 201TI activity (average 65% of that in normal myocardium) continued to be higher than relative microsphere activity (average 6% of normal). Myocardial arteriovenous differences for 201TI were followed sequentially after 201TI injection in normal dogs and in dogs with temporary coronary occlusions. The results suggested both loss of 201TI from normal myocardium beginning 10 min after 201TI injection and increased extraction of 201TI from the blood pool immediately after release of a transient occlusion. Redistribution of 201TI therefore begins very soon after relief of myocardial ischemia and even a short delay in initiating myocardial imaging may decrease the sensitivity of the technique for detecting transient ischemia.

Because of its favorable physical and biologic properties 201TI appears to be the best myocardial perfusion imaging agent presently available for intravenous use. Resting 201TI images have been used for the detection of myocardial infarction, and stress images have been used for the detection of myocardial ischemia. The initial distribution of 201TI has been shown to reflect regional myocardial perfusion. There has been recent clinical evidence, however, that a perfusion defect on a stress image fills in over several hours.

Redistribution has also been demonstrated clinically in patients with variant angina. Thallium-201 injected during angina resulted in large defects in images performed within 10–20 min of injection. Two or three hours later, after relief of angina, the defects had filled in.

Redistribution has been studied in the experimental animal by occluding coronary arteries of dogs for 20 min during which 201TI and labeled microspheres were injected into the left atrium. After 100 min of reperfusion, the relative 201TI activity in the previously ischemic area was significantly higher than the microsphere activity indicating that redistribution of the 201TI had occurred.

The present study was undertaken to better define the time course and mechanism of 201TI redistribution. The pig was used as an experimental animal in the initial portion of this study because it has a less extensive and less variable collateral circulation than the dog.
Methods

Myocardial Distribution of Thallium and Microspheres in the Pig

Seven domestic pigs weighing from 25-32 kg were premedicated with intramuscular ketamine (15 mg/kg) and atropine (0.04 mg/kg) and were anesthetized with halothane and nitrous oxide administered via a cone-shaped face mask. After endotracheal intubation or tracheostomy, respiration was controlled with a Harvard volume respirator pump. The femoral artery and vein were isolated and cannulated for monitoring arterial pressure and for infusion of drugs.

Intramuscular procainamide (500-1,250 mg) and intravenous lidocaine (bolus of 50-100 mg and continuous infusion of 2 mg/min) were used for arrhythmia prophylaxis. Ventricular arrhythmias were treated with additional intravenous lidocaine. The chest of each pig was opened via a left lateral thoracotomy. The heart was exposed and the pericardium was incised. A snare was placed around the left circumflex coronary artery beyond the first large diagonal branch. A triple lumen catheter was placed in the left atrium for injection of microspheres and \(^{201}\)TI, and for monitoring of left atrial pressure. Carbonized microspheres (7-10 \(\mu\)m labeled with Scandium-46 (\(^{46}\)Sc) (3M Company) suspended in 0.05% Tween-80 (14-28 million microspheres) were used to assess regional blood flow. The microsphere solution was mixed in an ultrasonic bath for at least 25 min before injection.

The left circumflex coronary artery of each pig was temporarily occluded just beyond the first large diagonal branch. One and one-half minutes after occlusion 470-770 \(\mu\)Ci of \(^{201}\)TI,* and 14-28 million microspheres labeled with 2-4 \(\mu\)Ci of Scandium-46 were injected simultaneously through separate lumens of the left atrial catheter and flushed rapidly with normal saline. Simultaneously, a reference sample of arterial blood was obtained from the aortic catheter at a constant rate of 7.5 cc/min for 2 min so that absolute myocardial blood flow could be calculated. Two and one-half minutes after radionuclide injection (4 min after occlusion), the snare was released and flow was re-established. Aortic blood samples were obtained for \(^{201}\)TI levels at 1 min intervals for 5 min after \(^{201}\)TI injection; 2 min intervals for the following 6 min; then at 15 and 30 min.

One pig was sacrificed just prior to release of the snare. The other animals were sacrificed at different time periods after reflow was established: two pigs at 5 min of reflow and one pig each at 15 min, 35 min, 60 min and 105 min.

The heart was removed and the entire heart was divided into 1-2 cm thick transverse slices excluding the apex. Adjacent full thickness sample blocks of myocardium approximately 5 mm in length were taken across the entire left ventricular free wall. These myocardial samples included normal areas supplied by the left anterior descending coronary artery and areas supplied by the occluded left circumflex coronary artery. The radioactivity of all of these samples of myocardium was measured with a Picker scintillation well counter. The samples were numbered so that the anatomic location of a given sample was known. Since the myocardial samples counted included the entire free wall of the left ventricle except the apex, whether or not a given area was ischemic could be determined by looking at the microsphere activity in that area.

Differentiation of \(^{201}\)TI radiation from \(^{46}\)Sc radiation was accomplished by appropriate settings on the pulse height analyzer. There was insignificant crossover of counts from the higher energy radiation of \(^{46}\)Sc into the lower energy \(^{201}\)TI channel because of the high ratio of \(^{201}\)TI/\(^{46}\)Sc administered. The plasma samples were also assayed for \(^{201}\)TI radioactivity in the well counter.

To calculate the ratio of counts in ischemic compared with normal myocardium, the counts per weight of sections of normal myocardium were averaged as were those from the lowest count sections of ischemic myocardium. Absolute myocardial blood flow was calculated by using the reference sample obtained during the injection of microspheres. Knowing the rate of withdrawal of the reference sample (Qr) and the \(^{46}\)Sc radioactivity in the reference sample (Cr) and assuming that the ratio of flow and radioactivity should be identical in all organs because uniform mixing of microspheres with blood should occur during passage through the left ventricle, myocardial blood flow (Qm) was determined by measuring the myocardial \(^{46}\)Sc radioactivity (Cm) and calculating 

\[
Q_m = Q_r \cdot \frac{C_m}{C_r}.
\]

Myocardial Extraction of \(^{201}\)TI in the Dog

In order to better define the mechanism of redistribution of \(^{201}\)TI, the coronary arteriovenous difference for \(^{201}\)TI was determined in six dogs. These animals were anesthetized with pentobarbital (30 mg/kg). Their chests were opened and catheters were placed in the central aorta and the coronary sinus. Each animal received 0.5 to 4 mCi of \(^{201}\)TI intravenously after which simultaneous arterial and coronary sinus samples were withdrawn at frequent intervals for 40 min.

In five animals these studies were performed with the coronary circulation intact. In ten studies in six animals the left anterior descending coronary artery was occluded for 2 min prior to injection of thallium. In six of these studies the occlusion was released 10 min after it was applied or 8 min after thallium injection. In the other four studies the occlusion was released 20 min after it was applied or 18 min after thallium injection.

The order of performing the control study and the 10 and 20 min occlusions was varied in the six animals. A minimum of 45 min was allowed between \(^{201}\)TI injections. The dose of \(^{201}\)TI was doubled for each sequential study in a given animal. The blood samples were all analyzed in duplicate and the two values were averaged.

Results

Table 1 shows the percent of normal myocardial activity in the center of the ischemic area for both \(^{201}\)TI and microspheres at various times after reflow. In the animal sacrificed after 4 min of occlusion without reflow, the reduction of microspheres and thallium in the ischemic area was

![Table 1. Percent of Normal Activity in Ischemic Area](http://circ.ahajournals.org/)

*The thallium-201 was kindly supplied by the New England Nuclear Corporation.
similar, with thallium activity averaging 5.5% of normal myocardium and microsphere activity 1.5% of normal (fig. 1, table 1).

Two animals sacrificed 5 min after reflow showed considerable disparity between microsphere and thallium activity in the ischemic area (201TI 44.3% of normal; microspheres 15.4% of normal). In these animals microsphere activity in the ischemic area was higher than in other animals in the series, probably reflecting a somewhat higher collateral flow in these pigs. In animals sacrificed 15 to 105 min after reflow, thallium activity continued to be relatively high (average 69.1% of normal) whereas microsphere activity remained low (average 6.4% of normal) (fig. 2).

At the time of release of the occlusion (2.5 min after injection), 201TI activity in arterial plasma averaged 0.6% of the injected dose per 100 cc of plasma. At 15 min after injection, it had fallen to 0.1% per 100 cc and at 30 min, it was 0.07% per 100 cc.

The absolute flows in normal myocardium and in the center of the ischemic area were calculated for six of the seven pigs using the microsphere technique. Flow in the normal left ventricular myocardium averaged 0.77 ± 0.25 cc/min/g, whereas that in the center of the ischemic zone averaged 0.055 ± 0.034 cc/min/g.

Figure 3 shows the average myocardial extraction ratios for 201TI during the three experimental protocols in dogs. With an intact coronary circulation myocardial arteriovenous difference fell progressively and became negative at 10 min after thallium injection. When coronary occlusion was produced two minutes before injection, arteriovenous differences were nearly identical to those in the control animals until the time of release (8 and 18 min after thallium injection) when arteriovenous differences increased and remained at higher levels. Extraction ratio changes did not reach statistical significance in this small number of experiments.

Discussion

This study demonstrates quantitatively that there is very rapid redistribution of 201TI after reperfusion of ischemic myocardium. In the animal sacrificed after coronary occlusion without reflow, the relative thallium activity was only slightly higher than microsphere activity, a finding in agreement with the results obtained by Polost et al. in dogs. Within 5 min, however, the previously ischemic area already had accumulated considerable thallium and by 15 min...
thallium levels appeared to have reached a plateau of approximately 70% of normal concentration that did not change appreciably over the ensuing 1½ hours. As Maseri et al. have pointed out, only the initial distribution of $^{201}$TI appears to reflect regional flow at the time of injection.

In our animal model, we chose to reperfuse the myocardium 1½ min after $^{201}$TI injection. This protocol was selected so that the timing would be similar to clinical exercise $^{201}$TI studies during which exercise usually is stopped 1 to 3 min after radionuclide injection.

Two possible mechanisms could account for the redistribution of $^{201}$TI after ischemia is relieved. Diffusion of $^{201}$TI from normal to ischemic myocardium is unlikely to be contributory since it would probably affect only several millimeters at the border and because of the rapidity of the redistribution in our studies. Another possibility is that the defect may be filled in by gradual extraction of the $^{201}$TI from the blood pool. This latter mechanism would require that blood levels of $^{201}$TI remain high enough at the time of relief of ischemia to provide adequate radionuclide for myocardial uptake.

Since myocardial arteriovenous thallium difference became negative an average of 10 min after injection in the control studies, myocardial concentration would be expected to reach its peak at that time. Thereafter myocardial release of thallium should occur. When a coronary occlusion was released after thallium injection, the sustained increase in myocardial extraction suggests the uptake of radionuclide from the blood pool in the previously ischemic area. Therefore if a transient occlusion is released in the first 10 min following thallium injection, the relative increase in activity in the previously ischemic area is likely to represent more radionuclide uptake by this low activity zone as compared to the normal myocardium. After 10 min, the relative increase in the previously ischemic zone can be attributed to simultaneous loss from normal myocardium and uptake by the ischemic area. This latter situation can be viewed as a true redistribution of thallium from normal to previously ischemic myocardium via the blood pool.

In the pig studies, at the time of release of the occlusion 2½ min after $^{201}$TI injection, the plasma level of $^{201}$TI was 0.6% of the injected dose per 100 cc of plasma. This plasma level continued to fall, reaching 0.07% per 100 cc 30 min after injection. The rate of thallium accumulation in the previously ischemic myocardium might therefore be expected to be highest immediately after release of occlusion while blood activity is highest. This phenomenon may account for the rapid increase in activity in the ischemic area within 5 min after reperfusion and the relative plateau that is reached at 15 min. If the artery had been occluded for a longer period of time so that reflow occurred at a time when the plasma $^{201}$TI level was lower, it is likely that the amount of $^{201}$TI taken up during the first minutes after reflow would have been lower.

An important difference between our model and clinical exercise-induced ischemia is the state of the coronary artery in the postischemic period. At that time, the artery in our model was normal and significant reactive hyperemia probably occurred. In contrast, in exercise-induced ischemia, the artery supplying the ischemic area should remain narrowed and reactive hyperemia may be limited or absent. If reactive hyperemia had been prevented in our model, the rate of $^{201}$TI uptake by the ischemic area after reflow might have been slower since less radioactivity would have been delivered to the ischemic area per unit time after relief of ischemia.

Although the hemodynamics of this model are not completely analogous to exercise-induced ischemia, our results demonstrate that redistribution of $^{201}$TI can occur very quickly after reperfusion of a previously ischemic area. The sensitivity of exercise perfusion imaging depends on the ratio of radioactivity in the normal area to that in the ischemic area and on the size of the ischemic area. If uptake of $^{201}$TI in the ischemic area begins soon after the relief of ischemia, the ratio of radioactivity in the normal area to that in the abnormal area may quickly decrease. Therefore, even a short delay between relief of ischemia and the start of imaging may decrease the sensitivity of the technique.

References

Early redistribution of thallium-201 after temporary ischemia.
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