Time Course of Thallium-201 Redistribution After Transient Myocardial Ischemia

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SUMMARY The mechanism and time course of thallium-201 (201Tl) redistribution after transient myocardial ischemia was investigated in 27 anesthetized dogs given 1.5 mCi of 201Tl intravenously 10 minutes after occlusion of the left anterior descending coronary artery. Coronary reperfusion (RP) was accomplished 10 minutes after 201Tl administration. Transmural myocardial biopsies were obtained in situ from normal (N) and ischemic (IS) regions during occlusion and 5 minutes (four dogs), 20 minutes (eight dogs), 90 minutes (six dogs), 4 hours (five dogs) and 6 hours (four dogs) after RP. There was a twofold rise in 201Tl activity (counts/10 min/mg) in the IS region after only 5 minutes of reflow with as yet no detectable change in 201Tl concentration in the N zone. In dogs undergoing 90 minutes of RP, 201Tl activity was 700 ± 150 (SEM) in the IS zone during occlusion and markedly increased (p < 0.001) to 3200 ± 100 at 90 minutes of reflow. During this period 201Tl activity in the N region decreased only slightly, from 7000 ± 800 to 6000 ± 450 (NS). In dogs that underwent 6 hours of RP, 201Tl activity in the IS zone increased from 1700 ± 500 during occlusion to 3300 ± 200 (p < 0.001) after RP. In this group, 201Tl activity in the N zone significantly decreased, from 6400 ± 1200 to 3900 ± 400 over the 6 hours of reflow, reflecting the magnitude of thallium washout after ischemia. This near-equalization of 201Tl activity between N and IS zones was already apparent by 4 hours of RP.

These data indicate that 201Tl redistribution after transient myocardial ischemia is related to both delayed accumulation of 201Tl into ischemic myocardial segments and to a more rapid washout of the radionuclide from normal segments. Qualitatively, the serial changes in myocardial 201Tl activity in ischemic and normal myocardium before and after flow restoration in this study, and the time course of thallium redistribution, are similar to the serial scintigraphic changes in patients who receive thallium during exercise stress or spontaneous rest angina.

DEFECTS in thallium-201 (201Tl) uptake appear in myocardial scintigrams in patients during exercise stress,1-7 during pain accompanying spontaneous angina6, 9 and in the presence of acute10 or prior myocardial infarction.9 The initial myocardial distribution of i.v. 201Tl is dependent on regional blood flow and the myocardial extraction fraction for TI.5, 11 Originally, 201Tl was thought to remain fixed in myocardial cells for several hours after initial uptake and that subsequently there was little change in distribution. This assumption was based upon the observation that the half-time for net myocardial TI clearance after intravenous injections was found to be approximately 7 hours.12 More recently, however, in anesthetized dogs, early TI defects appeared to fill in with 201Tl activity after 2 hours of reperfusion after the radionuclide was administered during transient left anterior descending coronary artery (LAD) occlusion.5

Clinical studies have demonstrated that this redistribution of TI is observed on delayed images after exercise in patients with stress-induced myocardial perfusion defects.5, 7 In the presence of myocardial infarction or scar, initial defects on myocardial scintigrams persist on delayed images and no significant redistribution is evident. From these preliminary observations, it appeared that serial imaging after a single dose of 201Tl might be useful in differentiating transient ischemia and/or underperfusion from myocardial infarction or scar.

The purpose of this investigation was to determine both the mechanism and time course of TI redistribution after transient myocardial ischemia in an animal model in which absolute TI concentration in ischemic and nonischemic regions could be serially measured with an in vivo biopsy technique. In prior studies of the kinetics of TI uptake and redistribution during acute ischemia, only relative TI activity, expressed as percent normal activity, was measured. Little information is available about what causes "filling in" of defects on delayed images. Equalization of activity between ischemic and normal myocardial zones could result from delayed accumulation of 201Tl in the previously ischemic regions, more rapid washout of 201Tl from normal myocardium or a combination of both mechanisms.

Methods

Canine Experimental Ischemic Model

The canine model used in these experiments has been described in detail.3 In these experiments, transient ischemia was produced in 27 open-chest dogs. The dogs were anesthetized with i.v. pentobarbital (30 mg/kg) and ventilated with a Harvard respirator. By using a mixture of room air and 40% oxygen, the arterial Po2 in all dogs was maintained between

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80–120 mm Hg. Arterial blood pressure was continuously monitored after a catheter was inserted into the central aorta via a cutdown on one of the femoral arteries. Lead 2 of the ECG was continuously recorded.

The experimental protocol is summarized in figure 1. After a left thoracotomy, the mid-left anterior descending coronary artery (LAD) was dissected free of the epicardial surface and occluded by a snare placed around the vessel. After 10 minutes of LAD occlusion, 1.5 mCi of $^{201}$TI chloride were injected intravenously. Ten minutes after $^{201}$TI injection, duplicate transmural myocardial specimens were obtained from the biopsy drill (24.0 × 2.0 mm) from the center of the regions of myocardium perfused by the occluded vessel and from normal myocardial regions perfused by the left circumflex coronary artery. The drill bit was attached to a Sears Rotary-Tool (model 758-25161) and samples were obtained at a rotary speed of 2400 rpm. In no dog in this study were arrhythmias produced by this technique, and the arterial blood pressure remained stable during the biopsy procedure. Bleeding from the biopsy site was contained by gentle pressure over the site of entry. Within several minutes, bleeding from the area usually ceased.

In all 27 dogs, coronary reperfusion was instituted by release of the occluding snare, 10 minutes after TI administration (20 minutes after occlusion). The duration of reperfusion was 5 minutes in four dogs, 20 minutes in eight dogs, 90 minutes in six dogs, 4 hours in five dogs, and 6 hours in four dogs.

Serial venous blood specimens were withdrawn during both occlusion and reperfusion periods in all dogs to determine blood clearance curves for the radionuclide. At the end of the reperfusion periods, a second set of duplicate transmural biopsies were obtained from ischemic and normal myocardium. As with the postocclusion specimens, all myocardial specimens were blotted dry on filter paper, weighed and counted in a multichannel gamma well scintillation counter (Packard Instrument Company, Chicago, Illinois). Thallium activity was expressed as counts/10 min/mg of wet weight. The myocardial samples weighed 10–25 mg. Blood $^{201}$TI activity was expressed as counts/10 min/mg of blood.

**Statistical Analysis**

All data are presented as mean ± sem. The significance of differences was assessed by the paired $t$ test using a two-tailed distribution.

**Results**

Figures 2–5 show the changes in myocardial $^{201}$TI activity in ischemic and normal zones in the dogs undergoing 5 minutes, 20 minutes, 90 minutes or 6 hours of coronary reperfusion after a 20-minute period of LAD occlusion. Thallium was injected intravenously 10 minutes before reperfusion. Values for the 4-hour reperfusion group were comparable to the values observed in the 6-hour group and are only shown in figure 6, which normalizes and summarizes the experimental data for all 27 dogs.

The change in myocardial TI concentration from the end of the 20-minute occlusion period to 5 minutes of reperfusion for four dogs are shown in figure 2. There was almost a twofold rise in TI activity in the ischemic zone over this brief period of reflow. There was no detectable change in TI concentration in the normal region at 5 minutes of reflow. In the eight dogs that underwent 20 minutes of reperfusion (fig. 3), TI activity was 500 ± 200 (SEM) counts/10 min/mg in the ischemic zone during occlusion and markedly increased ($p < 0.001$) to 1750 ± 450 counts/10 min/mg at 20 minutes of reflow. As was observed in the 5-minute group, there still was no detectable change in TI concentration in the normal zone at this time. Thallium activity was 4200 ± 800 and 4150 ± 700 counts/10 min/mg in the normal zone at 20 minutes of occlusion and 20 minutes of reperfusion, respectively.

Qualitatively similar changes appeared in the dogs
occluded for 20 minutes and reperfused for 90 minutes (fig. 4). Thallium concentration in the ischemic zone rose from 700 ± 150 counts/10 min/mg to 3200 ± 100 from occlusion to 90 minutes of reflow ($p < 0.001$). This change was significantly greater than that observed in the 5- or 20-minute groups. Thallium concentration in the normal zone fell from 7000 ± 800 to 6000 ± 450 counts/10 min/mg by 90 minutes of reperfusion (NS).

In contrast to these early reflow periods, changes in myocardial Tl concentration in ischemic and non-ischemic myocardium in the 6-hour reperfused dogs demonstrated a significantly greater decrease in Tl activity in the normal zone. In this group (fig. 5), near-
equalization of activity between ischemic and normal zones can be observed and is related to a significant early accumulation of Tl into the ischemic region and the more rapid washout of Tl from normal myocardium. Myocardial Tl activity increased from 1700 ± 500 counts/10 min/mg after 20 minutes of occlusion to 3300 ± 200 counts/10 min/mg at 6 hours of reperfusion (fig. 5). During this period, Tl activity in the normal region fell from 6400 ± 1200 to 3900 ± 400 counts/10 min/mg.

Figure 6 combines the data from all five groups of dogs. Values for each group were normalized by expressing Tl concentration in ischemic regions as percent of initial normal values. Thallium concentrations for normal myocardium before reflow was designated as 100%. Changes in Tl concentrations in both normal and ischemic regions are represented as percentages of this initial normal activity. Normalizing values for all groups of dogs in this manner allows for a better appreciation of the pattern and time course of Tl redistribution after transient myocardial ischemia. The half-time for net Tl washout from normal myocardium for these groups of dogs was 7.2 hours, a value similar to that reported previously. From 5–90 minutes of reperfusion the rate of Tl accumulation in the ischemic zone is rapid, with little washout in normal regions (fig. 6). However, from 90 minutes to 6 hours of reperfusion, the difference in Tl activity between ischemic and normal zones narrows more gradually and is predominantly due to a more rapid washout of Tl from the normal zone compared with the ischemic zone. By 3 hours, the difference in Tl concentration between ischemic zones and normal zones is sufficiently decreased so that an in vivo scintigram obtained at this time and including the effects of background and imperfect sampling of the ischemic zone would probably have shown disappearance of the initial myocardial defect.

Figure 7 is a typical blood clearance curve for Tl after i.v. administration in a representative dog from this study. There is a rapid decline in blood Tl activity soon after tracer injection, and a plateau is ap-
approached 20 minutes after injection. Redistribution of TI observed over a 6-hour posts ischemic period in this study appeared in the presence of sustained low blood TI concentrations.

Discussion

These data demonstrate that when $^{201}$TI is administered intravenously during coronary artery occlusion, a large gradient in TI concentration between ischemic and normal zones appears. In this study, there was more than a fivefold decrease in TI concentration 20 minutes after coronary occlusion in ischemic myocardium. This decrease in initial TI concentration reflects the relative diminution in blood flow as demonstrated by an early study$^3$ that demonstrated a linear correlation between myocardial TI concentration and relative regional myocardial blood flow as determined by the microsphere technique. In the present study, when blood flow was restored to normal after 20 minutes of transient LAD occlusion, TI redistribution occurred so that over a period of time, normalization of TI activity appeared in the previously ischemic zone. From 5-90 minutes of reperfusion, the rate of TI accumulation in ischemic myocardium was relatively rapid, whereas the TI concentration in the normally perfused regions decreased quite slowly. By 90 minutes after flow restoration, the TI concentration in the normal myocardium decreased by 10%; however, there was more than a 300% increase in activity in the previously ischemic zone. During the period from 2-4 hours, the concentration of TI in the ischemic zone was approaching that of the normal myocardium at a slower rate, and by 4-6 hours the TI concentrations in both previously ischemic and normal zones were comparable.

These data are consistent with a compartmental model to explain the redistribution phenomena.$^{13}$ In this model, it is recognized that immediately after i.v. injection, TI is distributed throughout the body roughly in proportion to the distribution of cardiac output, with approximately 4% of the TI accumulated by the myocardium and more than 90% by extracardiac organs. After the initial distribution of TI, continual

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**Figure 6.** Serial determination of myocardial thallium-201 ($^{201}$TI) activity, expressed as percent of initial (before reflow) normal $^{201}$TI activity in all five groups of dogs occluded for 20 minutes and reperfused for 5, 20, 90, 240 and 360 minutes. The initial value of $^{201}$TI activity in the ischemic region was obtained before reflow and represents the mean ± SEM for all 27 dogs. Near-equalization of $^{201}$TI concentration in normal and previously ischemic myocardial regions appears by 4 hours.

**Figure 7.** Blood clearance curve for intravenously injected thallium-201 ($^{201}$TI) in a representative dog reperfused for several more hours. A plateau in blood $^{201}$TI concentration is reached by 20 minutes after radionuclide administration.
exchange of Tl occurs between the extracardiac organs and the myocardium. Myocardial regions that were initially deprived of Tl but have restored perfusion and that still have viable cell membrane function will continue to extract Tl, which is being recirculated through the blood from the extracardiac compartment so as to eventually normalize the intracellular Tl concentration. After enough time has passed, all of the viable myocardial cells will reach a stable value of intracellular Tl concentration. This delayed myocardial concentration thus reflects an exchange equilibrium that will be the same for all viable myocardial cells that later have equal perfusion regardless of the unequal initial concentration that reflected the unequal perfusion at the time of injection. The data from this study suggest that significant redistribution would occur within 30 minutes to 1 hour after injection and that normalization of activity would be observed 2-4 hours after injection.

The findings of this present study are comparable to those described by Schwartz et al., who showed that redistribution of Tl occurred in significant proportion beginning 5 minutes after reflow in pigs that underwent temporary occlusion of the circumflex coronary artery. In this latter study, however, coronary flow was reestablished after only 4 minutes of occlusion. At this time, our blood clearance data indicated that the blood concentration of Tl after injection was still high, so that much of the Tl accumulation in the transiently ischemic region occurred during the initial distribution phase. In the present study, Tl redistribution occurred even though 10 minutes elapsed between Tl administration and reperfusion at a time when blood levels of the tracer were markedly lower (fig. 7). Additionally, in the study by Schwartz et al., changes in Tl activity were only assessed up to 105 minutes of reperfusion, and longer periods were not examined; therefore, the time course of redistribution could not be accurately assessed.

The clinical relevance of these experimental data pertain to the redistribution of Tl after the radionuclide is administered intravenously during exercise stress or during an episode of variant angina pectoris. In these clinical situations, there is heterogeneous perfusion of the left ventricular myocardium when Tl is injected. In the instance of exercise stress, flow is significantly enhanced to regions of myocardium supplied by nonobstructed coronary vessels, but areas perfused by arteries with significant stenoses demonstrate little or no increase in flow. Since myocardial Tl uptake is proportional to flow, more Tl will be delivered to normal than to underperfused regions, causing a relative defect. After cessation of exercise and restoration of the resting flow state, the relative defect may normalize within 2-4 hours after exercise and redistribution is considered to have occurred, presumably by the mechanism described above. In the presence of prior infarction and scar, initial defects remain persistent in the postexercise period.

In conclusion, this study demonstrates that when 201 Tl is administered during transient coronary occlusion in dogs, near-equalization of activity between normal and ischemic zones occurs by 4 hours, although significant redistribution occurs by 20 minutes after flow restoration. The mechanism of Tl redistribution in this model is related both to delayed accumulation of Tl into previously ischemic myocardial segments and to more rapid net Tl washout from normal segments. In this model, the differing rates of accumulation and/or washout are observed at a time when perfusion has been restored to its normal level, and are therefore presumed to be caused by the different concentration gradients between previously ischemic and normal zones that favor net influx or net efflux. The changes in regional myocardial Tl activity in ischemic myocardium before and after flow restoration in this canine study, and the time course of Tl redistribution, are similar to the serial scintigraphic changes observed in patients with coronary artery disease who undergo exercise stress or spontaneous rest angina.

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References

Linear Relationship Between the Distribution of Thallium-201 and Blood Flow in Ischemic and Nonischemic Myocardium During Exercise

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SUMMARY The purpose of this study was to compare the myocardial distribution of thallium-201 and regional myocardial blood flow during ischemia and the physiologic stress of exercise. Studies were carried out in six dogs with chronically implanted catheters in the atrium and aorta and a snare on the circumflex coronary artery distal to the first marginal branch. Regional myocardial blood flow was measured during quiet, resting conditions using 7–10 μ of radioisotope-labeled microspheres. Each dog was then exercised on a treadmill at speeds of 5–9 mph at a 5° incline. After 1 minute of exercise the circumflex coronary artery was occluded and thallium-201 and a second label of microspheres were injected. Exercise was continued for 5 minutes. The dogs were then sacrificed and the left ventricle was sectioned into approximately 80 1–2-g samples to compare thallium-201 activity and regional myocardial blood flow.

The maximum increase in blood flow ranged from 3.3–7.2 times resting control values. Each dog had myocardial samples in which blood flow was markedly reduced, to less than 0.10 ml/min/g. In each dog there was a close linear relationship between thallium-201 distribution and direct measurements of regional myocardial blood flow. Linear regression analyses demonstrated a correlation coefficient of 0.98 or greater in each dog. These data indicate that during the physiologic stress of exercise, the myocardial distribution of thallium activity is linearly related to regional myocardial blood flow in both the ischemic and nonischemic regions.

THALLIUM-201 is the most frequently used radioisotope tracer to evaluate regional myocardial perfusion. Although thallium-201 scintigrams of the heart during rest and exercise stress testing have been useful for diagnosing coronary artery disease, a number of patients with significant coronary artery disease by cardiac catheterization do not demonstrate deficits on thallium scintigrams.1–3 This apparent insensitivity to significant disease may be related to several variables, including limitation of available imaging equipment,4 inability to resolve small perfusion deficits,4 early redistribution of radioisotope,5 variable interpretation of significant anatomic disease, variable relationship between anatomic disease and clinical manifestation of ischemia,6 and inconsistent relationship between thallium-201 distribution and myocardial blood flow.6–8,9 Although experimental studies have demonstrated a close linear relationship between thallium-201 activity and direct measurements of regional myocardial blood flow after acute coronary artery occlusion,4–7 certain studies have indicated that the thallium-201 distribution may not be linearly related to myocardial perfusion when blood flow is increased above control values.6–8,9 The relationship between the myocardial distribution of thallium-201 and regional myocardial perfusion during ischemia and the physiologic stress of exercise has not been reported.

In this study we compared the myocardial distribution of thallium-201 and regional myocardial blood flow during exercise and ischemia. Direct measurements of regional myocardial blood flow were made using the radioisotope-labeled microsphere technique.10,11

Methods

Six mongrel dogs were trained to run on a motorized treadmill using positive reinforcement techniques. Each dog was anesthetized with thiamyal
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