Myocardial thallium-201 kinetics during coronary occlusion and reperfusion: influence of method of reflow and timing of thallium-201 administration

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ABSTRACT  Thallium-201 (201Tl) uptake and redistribution kinetics were examined in an open-chest canine preparation of occlusion and reperfusion. Seven dogs (group I) underwent 3 hr of sustained occlusion and received 1.5 mCi of 201Tl after 40 min of occlusion of the left anterior descending coronary artery (LAD). Group II (n = 18) underwent 60 min of LAD occlusion followed by sudden and total release of the ligature. Group IIIa (n = 8) received intravenous 201Tl during occlusion of the LAD, whereas group IIIb (n = 10) received intravenous 201Tl at the time of peak reflow. Group III dogs (n = 26) also underwent 60 min of LAD occlusion that was followed by gradual reflow through a residual critical stenosis. Animals in this group also received 201Tl either before (IIIa; n = 16) or after reflow was established (IIIb; n = 10). In group I, the relative 201Tl gradient (nonischemic minus ischemic activity) decreased from 88 ± 8% (mean ± SEM) to 59 ± 6% during 3 hr of coronary occlusion (p = .034). After rapid and total reperfusion (group IIa), this gradient decreased from 71 ± 6% during occlusion to 26 ± 5% after reflow (p < .001). After slow reperfusion through a residual stenosis (group IIIa), the gradient decreased from 81 ± 5% to 31 ± 5% (p < .001) (p = .56 compared with group IIa). In rapidly reperfused dogs receiving intravenous thallium during peak reflow (IIb), initial 201Tl activity in the ischemic zone was 155 ± 20% of initial normal activity and fell to 93 ± 13% of normal after 2 hr of reperfusion. Similarly, in dogs reperfused slowly through a critical stenosis (IIIb), which received 201Tl during reflow, 201Tl activity soon after reflow was 94 ± 4% of initial normal and decreased to 80 ± 6% at 2 hr of reperfusion (p = .10). Histochemical evidence of necrosis was present in the biopsy region in 80% of the 20 dogs subjected to triphenyl tetrazolium chloride (TTC) staining. Microsphere-determined transmural blood flow was similar in all groups during LAD occlusion and final flows after 2 hr were comparable in all subgroups undergoing reflow. Ischemic zone flow (% normal) was significantly higher at the time of 201Tl administration in groups IIIb (192 ± 25%) and IIIb (110 ± 5%), which received 201Tl during reflow, than in groups IIa (31 ± 9%) and IIIa (22 ± 5%), which received 201Tl during occlusion. These differences in flow at the time of administration of 201Tl explain the different thallium uptake patterns observed. These data suggest that after 1 hr of LAD occlusion there is no difference between rapid reperfusion through a totally patent vessel and slow reperfusion through a critical stenosis with regard to ultimate degree of flow restoration or magnitude of 201Tl redistribution in instances in which 201Tl is given before reflow. With both methods of reperfusion a residual 201Tl gradient is seen. Administration of 201Tl during reflow, however, probably overestimates the degree of myocardial salvage as reflected by final 201Tl uptake values. In dogs rapidly reperfused, a relative "hot spot" of 201Tl activity was observed in the ischemic zone when 201Tl was administered at peak reflow, despite histochemical evidence of necrosis. These results have clinical implications with respect to the timing of 201Tl administration and interpretation of serial 201Tl scintigrams in patients with acute myocardial infarction undergoing thrombolysis.


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THALLIUM-201 (201Tl) myocardial scintigraphy is being used increasingly as a noninvasive method for the assessment of myocardial ischemia and infarction. Initial 201Tl distribution after intravenous injection has been shown to be dependent on regional myocardial perfusion1-3 and the myocardial extraction for thallium.4,5 Delayed redistribution of 201Tl in a myocardial
region over 2 to 4 hr has been thought to be an indication of underperfused but viable myocardium. In contrast, a pronounced defect in 201Tl uptake that remains persistent over 2 to 4 hr after 201Tl administration is suggestive of irreversibly injured and salvage after coronary reperfusion. With the recent availability of thrombolytic agents for clinical use, several groups have begun to employ 201Tl myocardial scintigraphy to assess the extent of reflow and salvage after coronary reperfusion. The mode and times of 201Tl administration and the approach to the analysis of myocardial distribution of thallium have varied considerably in both experimental and clinical protocols assessing the efficacy of coronary reperfusion.

In experimental preparations of reperfusion, rapid reflow through a totally patent vessel has been shown to be associated with myocyte swelling, myocardial hemorrhage, and edema. These consequences of microvascular damage may not only limit the amount of reperfusion achieved in the ischemic bed, but may also be associated with significant alterations in myocardial extravascular compartments that could influence 201Tl uptake and washout kinetics. Clinical reperfusion with thrombolytic agents usually occurs as clot lysis progresses over 20 to 30 min and is frequently associated with a residual critical stenosis in the infarct vessel. Under these conditions, 201Tl uptake and washout patterns, changes in regional myocardial blood flow, and the degree of myocardial salvage may not reflect the situation of total coronary occlusion followed by rapid reflow through a totally patent vessel.

Accordingly, we sought to compare the effects of slow reperfusion through a critical stenosis with rapid reflow through a totally patent vessel on regional myocardial blood flow and 201Tl uptake and washout kinetics. Using these models, we administered 201Tl intravenously either during the period of coronary occlusion or soon after reflow, and then assessed the changes in 201Tl activity in nonischemic and ischemic myocardial regions for 2 hr after reperfusion.

Methods

Animal preparation. Experiments were performed in mongrel dogs (20 to 30 kg) that were fasted for 24 hr before surgery. Animals were anesthetized with pentobarbital sodium (30 mg/kg iv), after which intubation was accomplished. The dogs were then placed on a Harvard Apparatus respirator, set at a rate of 13/min and a tidal volume of 500 ml. Arterial blood gases were frequently monitored and the respirator was adjusted as necessary to maintain the arterial PO2 and pH within the normal physiologic range. Small additional doses of pentobarbital were periodically administered when necessary. Care was taken to ensure that pentobarbital was not given during or near the time of administration of microspheres or 201Tl or at the time of hemodynamic recording. A limb lead of the electrocardiogram was monitored continuously, with 18-gauge stainless steel needles inserted subcutaneously used as leads. A femoral vein was isolated and a polyethylene catheter (Intramedic No. 7450) was inserted for administration of fluids and 201Tl. This intravenous line was kept open with a 5% dextrose, 0.9% saline solution infused at a rate sufficient to maintain the left atrial filling pressure and arterial blood pressure at constant levels during the control state.

Catheters were introduced into both femoral arteries after cutdowns and were advanced to the aortic arch. These catheters were used to withdraw simultaneous reference blood samples for microsphere analysis as well as for monitoring central aortic pressure.

A thoracotomy was performed in the fifth left intercostal space of each dog, the pericardium was opened, and a “cradle” was established for suspension of the heart. The proximal portion of the left anterior descending coronary artery (LAD) was then dissected free of the epicardium and a hydraulic occluder (Rhodes Medical Instruments, Model VO-3) was placed around the vessel. An appropriately sized electromagnetic flow probe (Carolina Instruments) was fitted distal to the occluder in each animal. A 22-gauge angiographic catheter (Desseret) was inserted into a distal branch of the LAD and connected to a Hewlett-Packard 1280 pressure transducer to continuously monitor the distal coronary perfusion pressure throughout the experiments. A flared polyethylene tube was placed in the left atrial appendage for pressure measurement and for the injection of radiolabeled microspheres. Zero calibration for the electromagnetic flowmeter (EMF) was performed by brief occlusion of the LAD.

Experimental design

Instrumentation. In 18 dogs undergoing slow reperfusion, a partially tightened ligature was placed around the vessel just distal to the hydraulic cuff occluder. This ligature was progressively tightened to produce a critical stenosis as defined by the absence of the reactive hyperemic response after a 10 sec occlusion with the snare. In another eight dogs also selected to undergo slow reperfusion, a ligature-type stenosis was not used. Instead, the hydraulic cuff occluder was calibrated such that it opened no further than the previously defined critical stenosis. These dogs had reflow patterns and peak reflow values by EMF that were identical to those measured in dogs instrumented with a ligature-type stenosis. Both groups of dogs had LAD stenosis gradients and hemodynamics that were identical. The 18 dogs undergoing rapid reperfusion through a patent vessel and the seven dogs undergoing a sustained 3 hr occlusion were only instrumented with an occlusive snare.

Before occlusion. A summary of the experimental protocol is outlined in figure 1. After hemodynamic stabilization following the induction of anesthesia and surgical preparation, all dogs were pretreated with lidocaine (1 mg/period) administered by a slow-push intravenous and method 1 mg/min drip and heparin (200 units/kg iv). Additional lidocaine was administered as needed through the course of the experiments to control ventricular arrhythmias. Control hemodynamics were recorded and the first set of radioactive microspheres injected into the left atrium. Each dog was the subject to a 1 hr total occlusion of the LAD just after the first or second diagonal branch.

Sustained occlusion: group I. Seven dogs underwent 3 hr of sustained LAD occlusion and no reperfusion and are designated as group I. In this group 1.5 mCi of 201Tl was administered intravenously at 40 min of occlusion.

Rapid reperfusion: group II. Eighteen dogs were selected to undergo rapid reperfusion through a totally patent vessel and comprise group II. In these dogs, after 1 hr of occlusion, the
occlusive snare was suddenly released, allowing rapid reflow through a totally patent vessel. In eight dogs (group IIa), 1.5 mCi of $^{201}$TI was administered intravenously after 40 min of coronary occlusion. In another 10 dogs (group IIb), 1.5 mCi of $^{201}$TI was administered intravenously after reperfusion during peak reflow as assessed by the EMF, which was continuously recording phasic and mean total LAD flow. Peak reflow occurred by 5 min after the onset of reperfusion.

**Slow reperfusion: group III.** Twenty-six dogs were selected to undergo slow reperfusion through a critical stenosis and comprise group III. In these dogs, after 1 hr of occlusion, the hydraulic occluder was gradually released over a 30 min period, allowing restoration of flow through the previously created critical stenosis. In 16 dogs (group IIIa) 1.5 mCi of $^{201}$TI was administered intravenously after 40 min of coronary occlusion. In 10 dogs (group IIIb) 1.5 mCi of $^{201}$TI was administered intravenously after the 30 min gradual opening of the occluder. This time was chosen to ensure that the $^{201}$TI dose would be given at peak flow recovery, similar to that achieved in rapidly reperfused dogs.

All dogs in groups II and III were subject to 2 hr of reperfusion. Microsphere injections and myocardial biopsies for $^{201}$TI activity were performed as described in figure 1.

**Determination of regional myocardial blood flow.** Serial changes in regional blood flow were determined by the radioactive microsphere technique as previously described. Microspheres (8 to 10 μm) were labeled with $^{85}$Sc, $^{99}$Nb, $^{103}$Ru, or $^{111}$Sn (New England Nuclear Corp.), and each aliquot was calibrated to contain approximately $2 \times 10^6$ spheres. Each dose of spheres was diluted to a volume of 5 ml with normal saline containing 0.01% polysorbate 80 (Tween 80). Before injection, the spheres were agitated vigorously by passing them back and forth between two 10 ml syringes connected by a stopcock. Microscopic examination of a drop of the sphere suspension showed no significant clumping with this technique, and duplicate reference arterial samples drawn simultaneously were similar in counts per milliliter per minute. Thus, excellent dispersion of the spheres was consistently achieved.

The microsphere suspension was injected as a bolus over 5 to 10 sec into the left atrium, after which the injection catheter was flushed with 3 to 5 ml of 0.9% saline with constant monitoring of arterial pressure, coronary blood flow, distal coronary pressure, and heart rate. This procedure was repeated for each dose. Duplicate timed withdrawals from the two femoral artery catheters were begun 10 to 15 sec before the microsphere injection and continued for a total of 90 sec. Blood samples from each withdrawal were divided among three or four tared tubes.

At the end of the experiment, the animal was killed by inducing ventricular fibrillation and the left ventricle and septum were separated from the remainder of the heart, trimmed of epicardial fat and vessels, and divided into four layers from apex to base. Each layer was then cut into eight transmural specimens. Each specimen was further subdivided into epicardial, midwall, and endocardial sections. The resulting 96 samples were weighed and counted, together with the duplicate withdrawals and pure isotope samples, for 500 sec in a Packard Gamma Auto scintillation counter. A multichannel analyzer was used with the following four windows: $^{40}$Sc = 740 to 1300 keV; $^{99}$Nb = 650 to 818 keV; $^{103}$Ru = 450 to 570 keV; $^{111}$Sn = 340 to 440 keV.

Myocardial blood flow was calculated with the equation $Q_m = (C_m \times 100 \text{ Qt})/Cr$, where $Q_m = \text{ myocardial blood flow (ml/min)}$; $C_m = \text{ tissue counts (counts/min)}$; Qt = withdrawal rate of the arterial samples (ml/min); Cr = counts in reference arterial sample. Flow per gram of myocardium was calculated by dividing blood flow by the sample weight. Separation of isotopes and myocardial blood flow calculations were calculated by computer according to the method of Heyman et al. With this method, the counts per minute recorded in each window from myocardial and reference blood samples are corrected for background activity and spill activity contributed by the isotopes of higher energy. $^{201}$TI activity in myocardial tissue samples was counted in the 50 to 100 keV window. Because of the relatively high radioactivity of $^{201}$TI (1.5 mCi), all myocardial samples were held for 2 weeks before counting to avoid excessive spill into the microsphere windows.

**Determination of $^{201}$TI activity.** Transmural myocardial biopsies were performed with a Travenol Tru-Cut needle. Biopsies samples from the nonischemic zone were obtained from the high lateral wall in a region supplied by the left circumflex artery. All ischemic zone biopsy samples were taken at the central LAD region as delineated by the area of central cyanosis after the total LAD occlusion. Final biopsy samples were obtained in duplicate. We have previously shown that with this biopsy method little variation in $^{201}$TI activity in the center of the ischemic region is observed. These biopsies usually yield samples weighing 15 to 25 mg. The samples were immediately blotted dry on filter paper, weighed, and placed in scintillation tubes for counting. All samples were analyzed in a Packard auto-gamma scintillation spectrometer. In many instances, bleeding from the biopsy site was prevented by gentle pressure applied to the epicardial site of entry. Occasionally a suture was required to prevent further bleeding.
Histochemical staining. In 20 dogs the heart was divided into four longitudinal slices of myocardium that were incubated in either nitro blue tetrazolium or triphenyl tetrazolium chloride (TTC) dissolved in 3% Sorensen's buffer at 38°C for 20 min. The infarcted area was measured by a videoplanimeter (Zeiss). Infarct area was multiplied by the weight of each slice to yield grams of infarcted tissue. Infarct size was then expressed as a percent of left ventricular weight.

Data analysis. Myocardial 201TI time-activity curves were plotted with the use of values obtained from the serial biopsies. 201TI activity was expressed as percent of the initial normal 201TI activity as measured in the initial biopsy sample obtained in the nonischemic region. "Nonischemic" myocardium was defined as an area on the posterior wall of the left ventricle in an area supplied by the circumflex artery. 201TI uptake and washout rates were determined by calculating the slopes of the 201TI time-activity curve between biopsy points for each experiment. Mean uptake values or washout rates were then calculated for each group.

Regional myocardial blood flow is expressed as a percent of flow in the nonischemic or normal zone. Regional myocardial blood flow values in four to five adjacent segments on the posterior wall were averaged for each microsphere injection. Regional flow in each segment that was biopsied for 201TI activity was then divided by the mean nonischemic value to yield regional myocardial blood flow as a percent of normal.

All computations were done on a VAX 11/750 computer. Data are expressed as mean ± SEM. Statistical comparisons between groups were performed by analysis of variance with Duncan's multiple-range testing to determine points of significance. Paired t testing was used for comparisons within groups.

Results

Hemodynamics. Figure 2 summarizes the serial hemodynamic measurements made during the experiment in groups I, IIa, and IIIa. Dogs receiving 201TI during reflow (groups IIb and IIIb) had a similar hemodynamic profile. While the heart rate remained similar and constant in animals undergoing either rapid or slow reperfusion, dogs with a 3 hr sustained occlusion (group I) had a significantly higher heart rate at the end of the experiment (p < .001). Mean arterial pressure was similar in all three groups. LAD flow by the EMF was undetectable throughout the period of the 3 hr occlusion in group I dogs. Rapid reperfusion (group II) resulted in peak flows 5 min after reflow rising to three times control (p < .0001), whereas slow reperfusion through a critical stenosis (group III) was associated with early reflow values that were not higher than baseline LAD flow measured before occlusion. In dogs receiving 201TI during LAD occlusion (groups I, IIa, and IIIa), LAD flow during administration of 201TI was zero by electromagnetic flow probe. In groups IIb and IIIb, which received thallium after reflow, total LAD flow was 91 ± 6 and 47 ± 6 ml/min (p < .0001), respectively, during administration of 201TI.

![Graph showing hemodynamic changes](image_url)
after rapid reflow when $^{201}\text{TI}$ was injected). In group IIb, the intermediate flow measurement was made at $t = 65$ min (5 min after rapid reflow). In this group, flow in the ischemic bed was 192 ± 25% of normal at the time when $^{201}\text{TI}$ was administered.

**Group III: slow reperfusion through a critical LAD stenosis.** Figure 3 also shows that the reduction in transmural regional flow produced by coronary occlusion was similar in slow reperfusion groups IIIa and IIb at 22 ± 5% and 24 ± 4% of normal, respectively. Final transmural flows at the end of reperfusion were not significantly different at 79 ± 6% in group IIIa and 65 ± 5% in group IIIb. Intermediate flow values were again determined at different times. In group IIIa, transmural flow was 103 ± 15% of normal at $t = 120$ min (30 min after completion of slow reflow.) In group IIIb, the intermediate transmural flow was obtained at $t = 95$ min (after completion of slow reflow when $^{201}\text{TI}$ was injected) and was 110 ± 5% of normal.

**Myocardial $^{201}\text{TI}$ activity**

**Group I: 3 hr sustained LAD occlusion.** Figure 4 shows the myocardial $^{201}\text{TI}$ time-activity curves from the transmural biopsies obtained in the central ischemic and normal myocardial regions in dogs undergoing 3 hr of sustained LAD occlusion. After 55 min of LAD occlusion $^{201}\text{TI}$ activity in the ischemic region was reduced to 12 ± 2% of normal and remained low (10 ± 3%) at 3 hr of occlusion. During this time period, the relative gradient in $^{201}\text{TI}$ activity between nonischemic and ischemic zones (nonischemic minus ischemic activity) decreased from 88 ± 8% after 55 min of occlusion to 59 ± 6% after 3 hr of coronary occlusion ($p = .034$). Initial nonischemic activity was normalized to 100%. As depicted in figure 4, this reduction was primarily due to $^{201}\text{TI}$ washout from normal myocardium, which decreased the gradient between the two

**Regional myocardial blood flow**

**Group I: 3 hr sustained LAD occlusion.** Figure 3 shows the regional blood flow in the ischemic zone expressed as a percent of nonischemic flow. After 55 min of LAD occlusion, transmural ischemic bed flow was reduced to 23 ± 5% of normal. During the subsequent 2 hr of sustained coronary occlusion, blood flow in this region remained reduced at 20 ± 5% and 23 ± 5% of normal at 90 and 180 min of coronary occlusion, respectively.

**Group II: rapid reperfusion through a totally patent LAD.** Figure 3 shows that the reduction in regional blood flow produced by coronary occlusion in groups IIa and IIb, which were rapidly and totally reperfused, was not significantly different at 31 ± 9% and 26 ± 5% of normal, respectively. Similarly, the ultimate degree of restoration of flow determined at the end of the reflow period was comparable in groups IIa and IIb at 82 ± 9% and 84 ± 6% of normal, respectively. Intermediate flow values were obtained at different times in groups II and IIb. In group IIa transmural coronary flow was 103 ± 18% of normal at $t = 90$ min (30 min

![Graph](http://circ.ahajournals.org/)

**FIGURE 3.** Transmural myocardial blood flow (% normal flow) for all groups of animals. $t =$ time of experiment after initial coronary artery occlusion (see text for description of groups). Middle and right pairs of bars in groups II and III represent early and late reperfusion values.

* $p < 0.001$

Compared to IIa

**FIGURE 4.** Myocardial $^{201}\text{TI}$ time-activity curves in dogs undergoing 3 hr of sustained coronary artery occlusion.
regions and not delayed $^{201}$Tl accumulation in the ischemic zone.

**Group II:** rapid reperfusion through a totally patent LAD

**IIa:** Intravenous administration of $^{201}$Tl during coronary occlusion. In this group of dogs $^{201}$Tl was given intravenously during the occlusion phase before reflow. Figure 5 shows the $^{201}$Tl time-activity curves from ischemic and normal myocardium for this group before and after sudden and total release of the LAD occlusion. After 55 min of occlusion $^{201}$Tl activity in the central ischemic zone was $29 \pm 8\%$ of initial normal activity, a value not significantly different from that measured during LAD occlusion in groups undergoing sustained occlusion and slow reperfusion. After reperfusion, $^{201}$Tl activity in the ischemic zone rose to $39 \pm 4\%$ of initial normal ($p = NS$). The relative $^{201}$Tl gradient decreased from $71 \pm 6\%$ after 44 min of occlusion to $26 \pm 5\%$ after 2 hr of reflow ($p = .001$, compared with group I; $p = NS$ compared with group IIIa). This diminution in the relative $^{201}$Tl gradient after reperfusion can be attributed to both delayed accumulation of $^{201}$Tl in the ischemic region and $^{201}$Tl washout in the normal region.

**IIb:** Intravenous administration of $^{201}$Tl during peak reflow. Figure 6 shows the myocardial $^{201}$Tl time-activity curves from ischemic and normal myocardium when $^{201}$Tl was administered intravenously soon after total release of the LAD ligature. Ten minutes later, $^{201}$Tl activity in the central ischemic region was $155 \pm 20\%$ of the initial normal activity ($p < .0001$ when compared with groups I, IIa, and IIIa). After 2 hr of reperfusion, $^{201}$Tl activity in the central ischemic zone fell to $93 \pm 13\%$ of the initial normal activity, which is significantly higher ($p < .001$) than the final 2 hr reperfusion values observed in the groups that received $^{201}$Tl before reflow. This method of administration of $^{201}$Tl actually produced a relative "hot spot," with early $^{201}$Tl activity in the ischemic zone significantly exceeding that in the normal zone. This increased uptake was followed by rapid washout of $^{201}$Tl (figure 6). Because of this rapid washout, no significant difference between $^{201}$Tl activity in the normal and ischemic zone was ultimately observed after 2 hr of reflow. Thus, the configuration of these $^{201}$Tl activity curves (figure 6) were quite different than the curves obtained when $^{201}$Tl was given during occlusion and partial redistribution was observed (figure 5).

**Group III:** slow reperfusion experiments through a critical stenosis

**IIIa:** Intravenous administration of $^{201}$Tl during coronary occlusion. Figure 7 shows the myocardial $^{201}$Tl time-activity curves from ischemic and normal myocardium in dogs undergoing 1 hr of LAD occlusion followed by slow reperfusion through the residual critical stenosis. In these dogs $^{201}$Tl was given after 40 min of LAD occlusion, similar to the protocol followed for the rapid and totally reperfused group. After 55 min of LAD occlusion, $^{201}$Tl activity in the central ischemic region was $19 \pm 3\%$ of normal, comparable to the degree of diminution in $^{201}$Tl seen in the dogs undergoing sustained occlusion (group I) or rapid reperfusion (group II). After reperfusion, $^{201}$Tl activity in the ischemic zone rose to $40 \pm 4\%$ of normal ($p = .003$). The relative $^{201}$Tl gradient between ischemic and normal regions decreased from $81 \pm 5\%$ after 55 min of occlusion to $31 \pm 5\%$ after 2 hr of reperfusion ($p = .003$).

![Graph](attachment:graph.png)
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reflow.

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FIGURE 8. Group IIb. Myocardial $^{201}$TI time-activity curves in 10 dogs undergoing 1 hr of coronary occlusion followed by slow reperfusion through a residual critical stenosis. $^{201}$TI was administered at peak reflow.

.001). The decrease in the gradient is due to a combination of delayed $^{201}$TI accumulation in the ischemic region and washout of $^{201}$TI from the normal myocardium, as was observed in the rapid and totally reperfused groups. This final gradient was similar to that measured in dogs in group IIa that underwent rapid and total reperfusion.

IIIb: Intravenous Administration of $^{201}$TI During Peak Reflow. Figure 8 shows the $^{201}$TI time-activity curves from ischemic and normal myocardium in dogs undergoing slow reperfusion through a critical stenosis and given $^{201}$TI intravenously after completion of the 30 min reflow period. The first biopsy values showed only a 5% difference in $^{201}$TI activity between nonischemic and central ischemic zones. $^{201}$TI activity in the ischemic zone in these dogs was significantly lower (p < .03) than observed in rapidly and totally reperfused dogs that received $^{201}$TI after complete release of the coronary occlusion. After 2 hr of reperfusion in group IIIb, $^{201}$TI activity fell in the normal zone to 94 ± 4% of the initial normal activity and in the ischemic zone it fell to 80 ± 6% of initial normal activity, resulting in a mild residual $^{201}$TI gradient at the end of the reflow period. No such final gradient was seen at 2 hr in group IIb dogs receiving $^{201}$TI after reflow. Once again, the configurations of the $^{201}$TI time-activity curves were quite different than those obtained when $^{201}$TI was given during occlusion and partial redistribution was observed (figure 7).

Myocardial $^{201}$TI Gradients. Figure 9 compares the initial and final $^{201}$TI gradients (nonischemic activity minus ischemic zone activity) for each of the experiments. As can be seen from figure 9, the initial $^{201}$TI gradient was similar in groups I, IIa, and IIIa in which $^{201}$TI was administered intravenously during LAD occlusion. After reperfusion, in groups IIa and IIIa there was a reduction in $^{201}$TI gradient that was significantly smaller than the residual $^{201}$TI gradient that was seen in dogs undergoing sustained LAD occlusion (group I). When $^{201}$TI was administered after reflow, different $^{201}$TI gradients became apparent. In dogs reperfused rapidly through a patent vessel (group IIb), the initial $^{201}$TI gradient was reversed, with ischemic zone $^{201}$TI activity exceeding that of the normal zone. With further reperfusion, this gradient diminished to the point that $^{201}$TI activities in the ischemic and normal zones were nearly identical. In dogs reperfused slowly

FIGURE 7. Group IIIa. Myocardial $^{201}$TI time-activity curves in 16 dogs undergoing 1 hr of coronary occlusion followed by slow reperfusion through a residual critical stenosis. $^{201}$TI was administered during occlusion.

FIGURE 9. Relative $^{201}$TI gradient (nonischemic minus central ischemic activity) between normal and ischemic myocardium in all groups of dogs. A "negative" gradient denotes that $^{201}$TI activity in the ischemic zone is higher than activity in the normal zone (group IIb). Nonischemic $^{201}$TI activity would be designated as 100%. Statistical comparisons of final $^{201}$TI activities between group I and groups IIb and IIIb are not shown.

CIRCULATION
through a critical stenosis (group IIb) only a small $^{201}$TI gradient was initially noted between ischemic and normal myocardium. With further duration of reperfusion, this gradient increased slightly but not to the point seen when $^{201}$TI was administered before reflow. Thus, in identical preparations of occlusion and reperfusion, differences in the timing of $^{201}$TI administration may result in vast differences in initial and final myocardial $^{201}$TI gradients.

**Myocardial $^{201}$TI uptake and clearance rates.** The slope of the myocardial time activity curve is related to net myocardial uptake or clearance rate. Table 1, lists the slope of the $^{201}$TI time-activity curve between each biopsy point for all groups. Positive slopes represent $^{201}$TI uptake, whereas negative slopes represent $^{201}$TI washout. In the normal zone, there was a slight but significant difference in the early washout of $^{201}$TI between group IIa at $-0.0070 \pm 0.002\%$ activity/min and group IIIa at $-0.0020 \pm 0.001\%$ activity/min ($p = .01$). Normal zone washout was comparable in all groups during the latter portion of the reflow period. Ischemic zone washout rates varied considerably during the early portion of reperfusion. Groups IIa and IIIa received $^{201}$TI during occlusion and exhibited net $^{201}$TI uptake during the early reperfusion period at rates of $+0.0032 \pm 0.003\%$ and $+0.0024 \pm 0.002\%$ activity/min. This is in distinct contrast to group IIb and IIIb dogs, which received $^{201}$TI during reperfusion and exhibited net $^{201}$TI washout in the ischemic zone during the early reperfusion period at rates of $-0.0020 \pm 0.002\%$ and $-0.0020 \pm 0.003\%$ activity/min ($p = .0003$). There was no significant difference in ischemic zone $^{201}$TI clearance rates in the late reperfusion period.

**Histochemical staining.** In group I (3 hr of sustained occlusion), histochemical evidence of myocardial necrosis was seen in the biopsy region in all five dogs. Necrosis involved most of the endocardium and mid-epicardium, and was frequently transmural. Infarct size averaged $31 \pm 3\%$ of the left ventricle by weight. In group II dogs (rapid reperfusion), histochemical evidence of myocardial necrosis in the biopsy region was evident in six of seven samples stained. The area of necrosis was usually confined to the endocardial regions and frequently showed signs of gross hemorrhage. Infarct size averaged $4.2 \pm 1\%$ of the left ventricle. Similarly, in the group III dogs that underwent slow reperfusion through a critical stenosis, histochemical evidence of myocardial necrosis was seen in the region biopsied in nine of the 13 cases ($p = NS$ compared with group II). Infarct size in this group averaged $3.2 \pm 1\%$ of the left ventricle by weight. Again, the area of necrosis was usually confined to the endocardial region and gross hemorrhage was readily apparent.

**Discussion**

In the present study, we examined myocardial $^{201}$TI uptake and washout kinetics in two separate preparations of experimental reperfusion after intravenous administration of $^{201}$TI. When $^{201}$TI was given during coronary occlusion and before reflow the initial myocardial $^{201}$TI activity in the ischemic zone was low, reflecting the reduction in transmural blood flow. In dogs undergoing either rapid (group IIa) or slow (group IIIa) reperfusion that received $^{201}$TI at 40 min of occlusion, reflow instituted 10 min later resulted in a comparable degree of delayed $^{201}$TI redistribution. After 2 hr of reperfusion both rapid and slow reperfusion groups had final $^{201}$TI gradients between normal and ischemic zones that were significantly lower than the gradients measured during coronary occlusion. This improvement in the initial $^{201}$TI gradient was due to delayed accumulation of $^{201}$TI in the previously ischemic zone combined with a net washout of $^{201}$TI from the normal zone. These changes in $^{201}$TI activity over

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**TABLE 1**

Slopes of early and late portions of myocardial $^{201}$TI time-activity curves (% activity/min) in normal and central ischemic zones

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal zone</th>
<th>Ischemic zone</th>
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<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
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<tr>
<td>I</td>
<td>$-0.0050 \pm 0.002$</td>
<td>$-0.0019 \pm 0.004$</td>
</tr>
<tr>
<td>IIa</td>
<td>$-0.0070 \pm 0.002^a$</td>
<td>$-0.0014 \pm 0.005$</td>
</tr>
<tr>
<td>IIIa</td>
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<td>$-0.0021 \pm 0.004$</td>
</tr>
<tr>
<td>IIb</td>
<td>$+0.0009 \pm 0.001$</td>
<td>$-0.0012 \pm 0.005$</td>
</tr>
<tr>
<td>IIIb</td>
<td>$+0.0005 \pm 0.002$</td>
<td>$-0.0009 \pm 0.004$</td>
</tr>
</tbody>
</table>

Minus sign denotes net washout of $^{201}$TI; plus sign denotes net uptake of $^{201}$TI.

^ap < .05 group IIa vs IIIa.

^bp < .001 group IIb vs IIIb.
time suggest the presence of viable myocardial tissue in the central ischemic zone that could perhaps be salvaged by reperfusion.

There are at least two possible explanations for the fact that only partial redistribution was observed after reperfusion in these experiments. It has previously been shown that when \(^{201}\text{TI}\) is given after 10 min of occlusion, and reflow is instituted 10 min later, complete normalization of the \(^{201}\text{TI}\) gradient is observed after only 360 min of reflow.\(^{23}\) With further observation and sampling after 2 hr in the present study, more complete normalization of \(^{201}\text{TI}\) gradients might have occurred. The more likely explanation for partial redistribution, however, is that the biopsy samples from the central ischemic zone contained a mixture of ischemic and infarcted myocardium. It is well known that after 40 min of coronary occlusion irreversible myocardial injury is present.\(^{16}\) Irreversible injury begins in the endocardium and spreads toward the epicardium as a wavefront of myocardial necrosis.\(^{24}\) One hour of occlusion followed by reperfusion has been shown not to result in complete salvage of the myocardium at risk.\(^{25}\) Differences in the amount of \(^{201}\text{TI}\) redistribution seen between persistently occluded dogs and the reperfused groups can be attributed to differences in the amount of infarction present in each group. This hypothesis is supported by our histochemical analysis confirming that reperfused dogs (groups II and III) had much smaller infarctions than those experiencing a sustained LAD occlusion (group I).

A difference in the configuration of the time-activity curves between fast and slowly reperfused dogs receiving \(^{201}\text{TI}\) before reflow is apparent (figures 5 and 7). This difference is primarily due to the slope of the early portion of the nonischemic \(^{201}\text{TI}\) washout curve. There was no significant difference in the latter portion of the curves from the second to the final biopsy point. Caution must be exercised in making inferences from linear fits of three points to what is probably an exponential process.\(^{3}\) The slopes of the early portion of the nonischemic \(^{201}\text{TI}\) time-activity curves for groups of dogs receiving \(^{201}\text{TI}\) during reperfusion (figures 6 and 8) are different from the slopes in dogs receiving \(^{201}\text{TI}\) during occlusion (figures 5 and 7). Again, the latter points of the time-activity curves had similar slopes and the observed differences in the early washout rates may be random. In dogs receiving \(^{201}\text{TI}\) during the occlusion phase, the time-activity curves from the ischemic zone are upsloping and give some indication of the rate of delayed \(^{201}\text{TI}\) uptake after reperfusion. The slopes of the initial portions of the ischemic zone time-activity curves are different in dogs subjected to rapid reperfusion through a totally patent vessel (group IIa) and those undergoing slow reperfusion through a residual stenosis (group IIIa), implying that the rate and magnitude of reflow (soon after release of the occlusion) may have some effect on the rate of delayed \(^{201}\text{TI}\) uptake. It is interesting to note that despite these variable initial ischemic zone rates, final \(^{201}\text{TI}\) uptake after 2 hr of reflow was similar in both rapidly and slowly reperfused animal groups, as were the regional flow values.

Several other investigators have administered \(^{201}\text{TI}\) immediately after reperfusion rather than during occlusion.\(^{7,8,10}\) These studies demonstrated a striking restoration of \(^{201}\text{TI}\) uptake in the previously ischemic zone with the implication that substantial myocardial salvage occurred as a result of reperfusion. Our data suggest that similar durations of occlusion and reperfusion, administration of \(^{201}\text{TI}\) during reperfusion results in significantly different \(^{201}\text{TI}\) uptake and washout patterns compared with those seen when \(^{201}\text{TI}\) is given before reflow (figures 6 and 8 vs figures 5 and 7). When \(^{201}\text{TI}\) is administered at peak reflow after rapid reperfusion through a totally patent vessel, an actual "hot spot" of \(^{201}\text{TI}\) activity is apparent in the ischemic zone. This is because the initial uptake of \(^{201}\text{TI}\) is proportional to myocardial blood flow and 5 min after reperfusion in this preparation, substantial hyperemia is present. The early rapid washout component of \(^{201}\text{TI}\) observed in this ischemic and reperfused zone may indicate that much of the \(^{201}\text{TI}\) was in the noncellular spaces and not transported intracellularly into intact viable myocytes. With respect to the administration of \(^{201}\text{TI}\) through a critical stenosis after slow release of the LAD occlusion, \(^{201}\text{TI}\) activities were identical in normal and reperfused zones and quite different from the residual defect seen in dogs reperfused in a similar manner but in which \(^{201}\text{TI}\) was injected during the occlusion phase, 20 min before reflow.

Our observation and those of others\(^{14,26-28}\) imply that when \(^{201}\text{TI}\) is administered immediately after reperfusion, excessive \(^{201}\text{TI}\) activity in the reperfused area may mask the presence of nonviable myocardium. Melin et al.\(^{27}\) have recently shown that in experimental myocardial infarcts, as verified by histochemical and electronmicrographic techniques, \(^{201}\text{TI}\) activities are as high as 50% of normal when the radionuclide is injected after reflow. Similarly, Forman and Kirk\(^{28}\) have recently reported that after reperfusion, infarcted myocardium may have detectable \(^{201}\text{TI}\) activity. Okada and Pohost,\(^{14}\) using a method of sequential administration of \(^{201}\text{TI}\) and subtraction of occlusion from reperfusion images, showed that \(^{201}\text{TI}\) scans obtained shortly after
reperfusion failed to delineate defects that were apparent on scintigraphy 48 hr later. Necrosis in the zones corresponding to the demonstrated defects was documented by TTC staining. Also, if coronary reperfusion is instituted too soon after intravenous administration of 201Tl, “excess” 201Tl uptake followed by rapid washout may be observed in the ischemic zone since blood levels of 201Tl have not yet appreciably declined to a plateau. Rapid washout of 201Tl has been observed after either reactive or vasodilator-induced hyperemia, and in reperfused myocardial infarcts. In spite of an accelerated early 201Tl washout from the reperfused ischemic zone in our study (figure 6), final 201Tl activity at 2 hr remains high and is not significantly different from the activity in the normal zone. This normalization of 201Tl activity in the ischemic zone certainly masked the extent of myocardial injury since the amount of necrosis was comparable to that seen in the group of dogs undergoing a similar duration of occlusion and reperfusion but receiving 201Tl before reflow in which a final 201Tl gradient (partial redistribution) was observed.

Clinical implications. This study has clinical implications with regard to the administration of 201Tl and subsequent imaging techniques for assessing efficacy of coronary reperfusion with thrombolytic therapy. This work provides experimental validation of the methods of Reduto, Simoons, and DeCoster and their colleagues, who administered 201Tl intravenously during acute coronary occlusion followed by clinical thrombolysis. Each of these studies has shown that successful thrombolysis is associated with 201Tl redistribution and smaller 201Tl defect size.

Our data suggest that after 1 hr of coronary occlusion there is no significant difference in degree of restoration of regional blood flow and final myocardial 201Tl activity in the central ischemic zone between dogs undergoing rapid reperfusion through a patent vessel and those undergoing slow reperfusion through a critical stenosis at 2 hr of reflow. Our data further indicate that administration of 201Tl immediately after reperfusion results in excessively high 201Tl uptake with subsequent rapid washout. This may explain normal 201Tl uptake in infarct zones seen on scintigrams obtained soon after thrombolysis with direct intracoronary administration of thallium. Our data and those of others suggest that the amount of viable tissue present after reperfusion could be overestimated when 201Tl is given for the first time immediately after reperfusion, whereas intravenous administration of 201Tl during occlusion results in uptake and washout patterns that allow the observation of 201Tl redistribution after reperfusion. The greater the degree of redistribution and defect resolution, the more likely myocardial salvage was accomplished.

In human coronary reperfusion, a smaller 201Tl defect after reperfusion may not always represent salvage secondary to successful reflow. Enhanced collateral blood flow and alterations in left ventricular volume have been shown to affect size of the 201Tl defect. Finally, prolonged cellular metabolic abnormalities consequent to ischemia in the absence of necrosis (“stunned” myocardium) might adversely influence 201Tl uptake and washout patterns soon after reperfusion such that repeat imaging 2 to 3 weeks later could show a substantially smaller 201Tl defect. Knowledge of the diverse 201Tl uptake and washout kinetics seen with different methods of reperfusion and different modes of administration of thallium should assist in the interpretation of clinical scintigrams when this radionuclide technique is employed for serial assessment of perfusion and viability in patients undergoing thrombolytic therapy.

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