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Effect of Duration of Regional Myocardial Ischemia and Degree of Reactive Hyperemia on the Magnitude of the Initial Thallium-201 Defect

THOMAS P. WHARTON, JR., M.D., WILLIAM A. NEILL, M.D., JOHN M. OXENDINE, B.S.,
AND LUCY N. PAINTER, B.A.

SUMMARY Thallium-201 and microspheres were injected into the blood simultaneously during left circumflex (LC) occlusion in open chest dogs. The dogs were sacrificed 6–8 minutes later and regional myocardial ²⁰¹Tl and microsphere concentrations determined. In dogs with permanent LC occlusion the myocardial ²⁰¹Tl distribution approximated blood flow distribution as judged by the microsphere concentrations. Release of LC occlusion 45 seconds after ²⁰¹Tl injection almost obliterated the myocardial ²⁰¹Tl deficit in the area of the LC without changing the microsphere results, presumably a result of deposition of ²⁰¹Tl during reactive hyperemia. Either delaying the onset of reflow until 3 minutes or attenuating the magnitude of reactive hyperemia by LC stenosis markedly decreased the change in ²⁰¹Tl distribution due to reflow. We conclude that for a given degree of reversible regional myocardial ischemia at the time of ²⁰¹Tl injection, the perfusion deficit observed on the initial scintigram will be influenced by the subsequent duration of ischemia and by the magnitude of post-ischemic reactive hyperemia.

THE CLINICAL USE of thallium-201 (²⁰¹Tl) scintigraphy for detecting reversible myocardial perfusion defects requires injecting the isotope during a state of temporary heterogeneity in coronary flow; for example, during exercise or coronary artery spasm. The heterogeneity may be so brief that it ends or even reverses its direction (due to postischemic reactive hyperemia) while isotope is still being actively removed from the blood by the myocardium. Thallium-201 uptake is greatest immediately after injection, when the blood level is highest, but continued uptake by myocardium can be detected by coronary arteriovenous sampling for at least 10 minutes after injection in animals.¹

Though it is customary to relate the pattern of myocardial ²⁰¹Tl deposition to the distribution of coronary blood flow that existed at the time of injection, this pattern might also be influenced by changes in flow distribution within several minutes after injection, when blood levels are still high. For any degree of initial ischemia, regional flow distribution during the first few minutes after injection is determined by at least two factors: duration of ischemia after injection (i.e., the interval between injection and cessation of exercise) and the degree of subsequent reactive hyperemia (i.e., degree of coronary stenosis or spasm). Either early restoration of flow to normal or marked reactive hyperemia might mask a profound but brief period of focal ischemia at the time of injection. In these experiments we examined the influence of these two factors on the formation of an initial ²⁰¹Tl perfu-

sion defect during reversible coronary ischemia in dogs. The ²⁰¹Tl defect was determined by tissue isotope analyses.

Methods

Preparation

Twenty-eight fasting mongrel dogs that weighed 20–25 kg, pretreated with acetyl salicylic acid 300 mg to limit platelet aggregation, were anesthetized with halothane gas after premedication with acepromazine 10 mg and methohexital 100 mg induction. They were endotracheally intubated and connected to a Bird respirator using 1% halothane in oxygen. Standard ECG leads were attached, and catheters were inserted into a peripheral vein for ²⁰¹Tl administration and a carotid artery for recording aortic pressure. A left thoracotomy was performed through the fifth intercostal space and a catheter was introduced into the left atrium for microsphere administration. A segment of the proximal left circumflex artery (LC) was dissected free and encircled by a Satham electromagnetic flowmeter transducer and, 5 mm distally, by a balloon cuff occluder (Barger) containing mercury. There were no arterial branches between the transducer and the occluder.

The balloon cuff was inflated for temporary occlusion of the LC. To achieve LC stenosis, sufficient mercury was injected into the balloon cuff until hyperemia after a 10-second occlusion was nearly obliterated, with minimal change in baseline LC blood flow as determined by the flowmeter. The stenosed LC could then be completely occluded by manual compression of the exposed tubing leading to the balloon. Release of the compression terminated the occlusion but maintained the original degree of stenosis. Two hundred fifty millicuries of ²⁰¹Tl (New England Nuclear) were injected into a peripheral vein as a bolus, followed by 10 ml of saline. One million microspheres 15 μ in diameter (3M Co.) labeled with ⁸⁶Sr were injected

From the Cardiology Section, Boston Veterans Administration Medical Center and the Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts.

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Address for correspondence: Thomas P. Wharton, Jr., M.D., Cardiology Section, Boston Veterans Administration Medical Center, 150 South Huntington Avenue, Boston, Massachusetts 02130.

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simultaneously via the left atrial catheter over a 10-second period.

Protocols

Group 1: No Reflow (Five Dogs)

Thallium-201 and microspheres were injected simultaneously 3 minutes after the onset of LC occlusion. Occlusion was maintained for another 6 minutes, and the dogs were sacrificed. No reperfusion was allowed.

Group 2: Early Reactive Hyperemia (Seven Dogs)

Thallium-201 and microspheres were injected 3 minutes after LC occlusion. Occlusion was released 45 seconds after injection and free reactive hyperemia was allowed. The dogs were sacrificed 5 minutes after release of occlusion.

Group 3: Late Reactive Hyperemia (Eight Dogs)

Thallium-201 and microspheres were injected 45 seconds after LC occlusion. Occlusion was released 3 minutes after injection, allowing free reactive hyperemia. The dogs were sacrificed 5 minutes after release of occlusion.

Group 4: Stenosis (Eight Dogs)

The LC was initially stenosed in the manner described above and 10 minutes were allowed for stabilization. Thallium-201 and microspheres were injected 3 minutes after subsequent total LC occlusion, and the occlusion (but not the stenosis) was released 45 seconds after injection. The dogs were sacrificed 5 minutes after release of the occlusion.

Observations

Lead II of the ECG, aortic pressure sensed by a P23Gb Statham transducer, and mean and phasic LC blood flow were recorded continuously throughout the procedure on a Brush Mark 200 four-channel ink recorder. The LC flowmeter transducer was calibrated in vitro using dog blood at 38°C, and zero blood flow

during the experiments was determined by temporary LC occlusion. Blood samples for measurement of ^{201}Tl concentration were obtained from the aortic catheter at 1-minute intervals, starting 1 minute after injection of the isotope. At the end of the protocol, the dog was killed by i.v. injection of pentobarbital. The heart was immediately removed and within 15 minutes the left ventricular free wall was divided into three approximately equal regions on the basis of distribution of the epicardial arteries: (1) myocardium supplied by the left anterior descending (LAD) artery; (2) myocardium supplied by the LC distal to the cuff occluder; and (3) myocardium in a marginal area intermediate between the LAD and LC regions. The marginal region was excluded from further analysis. Myocardial and blood samples were placed in 15-mm-diameter glass tubes and weighed. Their ^{201}Tl and ^{85}Sr contents were determined by gamma emissions counted in a Packard 5230 automatic spectrometer system set at a window 130-80 keV for ^{201}Tl and 560-460 keV for ^{85}Sr , calibrated using ^{137}Ce before each run. The LC/LAD ^{201}Tl and LC/LAD microsphere ratios were calculated from the mean concentrations of ^{201}Tl and ^{85}Sr , respectively, for the LC and LAD regions.

Statistics

Statistical significance was judged by a two-tailed *t* test, paired (table 1) or unpaired (tables 2 and 3).

Results

Mean arterial blood pressure and heart rate during control, at the end of LC occlusion, and 4 minutes after release of occlusion are shown in table 1. Arterial pressure fell slightly in all groups during LC occlusion. Arterial pressure returned nearly to baseline in groups 2-4 after the occlusion was released (including group 4, with persistent LC stenosis) but remained low in group 1, in which occlusion was maintained. The ST segment in ECG lead II rose during LC occlusion and returned to baseline within 1 minute after release of the occlusion.

The amount of ^{201}Tl remaining in the arterial blood, expressed as the percent of that present 1 minute after

TABLE 1. Arterial Blood Pressure and Heart Rate

Group	Mean arterial pressure (mm Hg)			Heart rate (beats/min)		
	Control	LC occlusion (4 min.)	LC release (4 min.)	Control	LC occlusion (4 min.)	LC release (4 min.)
1 (n = 5)	93 ± 6	75 ± 5†	(73 ± 6)†	103 ± 5	108 ± 4	(96 ± 2)
2 (n = 7)	92 ± 4	79 ± 6*	83 ± 6	110 ± 5	114 ± 5	112 ± 5
3 (n = 8)	81 ± 3	66 ± 6*	84 ± 3	91 ± 6	104 ± 7*	96 ± 8
4 (n = 8)	78 ± 4	70 ± 4†	78 ± 4	106 ± 6	111 ± 4	105 ± 8

LC occlusion was not released in group 1 dogs.

Values are mean ± SEM; values in parentheses are at 8 minutes of occlusion.

**p* < 0.05 vs control.

†*p* < 0.01 vs control.

Abbreviations: LC = left circumflex artery; n = number of dogs.

TABLE 2. Effect of Duration of Left Circumflex Occlusion After Thallium-201 (^{201}Tl) Injection on Myocardial ^{201}Tl Distribution

Group	Duration of LC occlusion after ^{201}Tl injection	$\frac{\text{LC}}{\text{LAD}}$ (microspheres)	$\frac{\text{LC}}{\text{LAD}}$ (^{201}Tl)
1 (n = 5)	LC occlusion not released	0.10 \pm 0.03	0.13 \pm 0.03*
2 (n = 7)	45 sec	0.14 \pm 0.03	0.69 \pm 0.05*
3 (n = 8)	3 min	0.13 \pm 0.03	0.34 \pm 0.03*

Values are mean \pm SEM.

* $p < 0.01$ vs both other groups.

Abbreviations: LAD = left anterior descending artery; LC = left circumflex artery.

TABLE 3. Effect of Postocclusion Reactive Hyperemia on Myocardial Thallium-201 Distribution

Group	Reactive hyperemia		$\frac{\text{LC}}{\text{LAD}}$ (microspheres)	$\frac{\text{LC}}{\text{LAD}}$ (^{201}Tl)
	Peak flow (multiple of control)	Mean flow 5 min (multiple of control)		
1 (n = 5)	LC occlusion not released		0.10 \pm 0.03	0.13 \pm 0.03*
2 (n = 7)	4.70 \pm 0.44	2.80 \pm 0.23	0.14 \pm 0.03	0.69 \pm 0.05*
4 (n = 8)	1.20 \pm 0.09	1.23 \pm 0.10	0.15 \pm 0.02	0.35 \pm 0.03*

* $p < 0.01$ vs. both other groups.

Abbreviations: LC = left circumflex artery; LAD = left anterior descending coronary artery.

i.v. administration, was $31 \pm 1.3\%$ (mean \pm SEM) at 3 minutes and $20 \pm 0.8\%$ at 5 minutes after injection.

Postocclusion reactive hyperemia data are shown in figure 1. In dogs without LC stenosis (groups 2 and 3), peak blood flow occurred during the first minute after occlusion release. Peak flows were 4.7 ± 0.44 and 5.9 ± 0.68 times control flow in groups 2 and 3, respectively; mean flows integrated over the 5-minute period after occlusion release were 2.8 ± 0.23 and 3.5 ± 0.34 times control flow in these groups. In group 4, which had residual LC stenosis after occlusion release, peak and mean postocclusion flows were only 1.2 ± 0.09 and 1.2 ± 0.10 times control flow. The postocclusion reactive hyperemia was significantly less in group 4 than in groups 2 or 3 ($p < 0.01$).

The temporal relationships between ^{201}Tl blood concentration and postocclusion reactive hyperemia are shown in figure 2. In group 2, in which occlusion was released 45 seconds after isotope injection, peak reactive hyperemia (4.7 times control) occurred within 2 minutes of ^{201}Tl injection, when blood levels were still relatively high. In group 3, peak reactive hyperemia (5.9 times control) occurred when the blood ^{201}Tl content had fallen to 20–30% of the concentration 1 minute after injection, and the entire reactive hyperemia curve was shifted over to a period when blood ^{201}Tl content had fallen to lower values. In group 4, reactive hyperemia was blunted by continued stenosis of the artery after the occlusion was released. Although reflow began when blood ^{201}Tl content was high (as in group 2), the magnitude of peak reactive hyperemia was only 1.2 times control in this group.

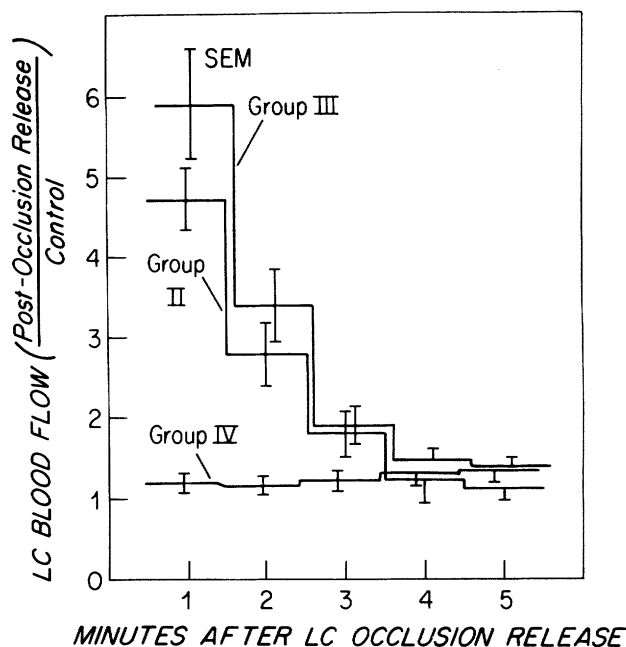


FIGURE 1. Blood flow in left circumflex (LC) artery as a function of time after LC occlusion release for groups 2, 3 and 4. Values are not shown for group 1, in which occlusion was not released. The flows are group means, expressed as multiples of flow during the control (preocclusion) period. Standard errors of the mean are shown by brackets. Postocclusion reactive hyperemia was maximal during the first minute for groups 2 and 3, without LC stenosis. Group 4, with residual LC stenosis, had a minimal hyperemic response.

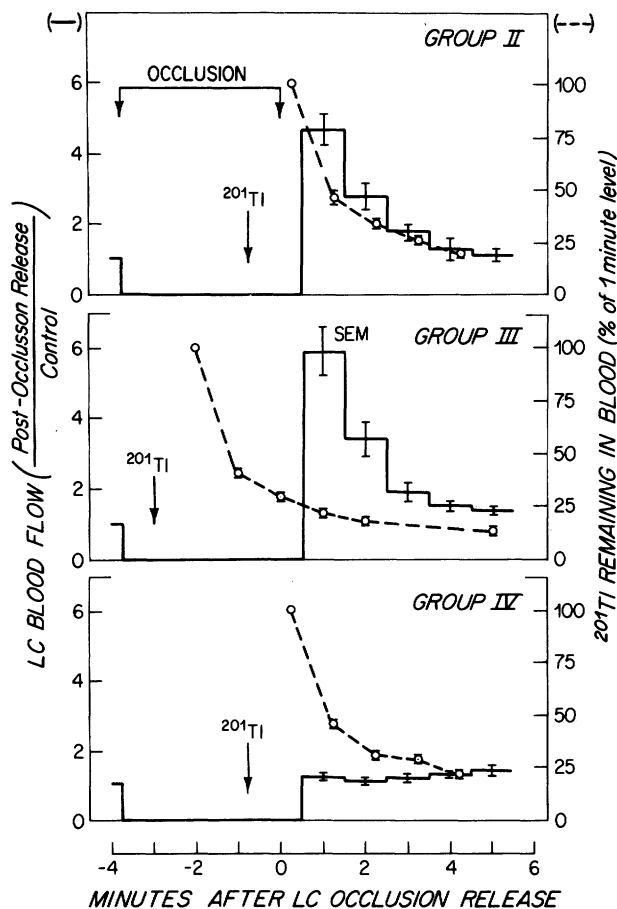


FIGURE 2. Schematic representation of experimental protocols, thallium-201 (^{201}Tl) blood levels, and postocclusion release left circumflex (LC) blood flows as function of time for groups 2 (top), 3 (middle), and 4 (bottom). Values are group means. Standard errors of the mean are shown as brackets. Thallium blood levels (dotted lines) are expressed as percent of the blood level at 1 minute. LC flows (solid lines) are as described in the legend for figure 1. In group 2 peak reactive hyperemia occurred near the time of the highest ^{201}Tl blood level; in group 3, peak reactive hyperemia occurred several minutes later than the peak ^{201}Tl blood level; and in group 4 there was only a minimal hyperemic response at the time of peak ^{201}Tl level.

Myocardial microsphere and ^{201}Tl data are listed in tables 2 and 3 and figure 3. The values are expressed as LC/LAD concentration ratios. Mean values for microsphere LC/LAD were comparable for the four groups (range 0.10–0.15), indicating similar degrees of ischemia at the time of ^{201}Tl injection. Thallium-201 and microsphere LC/LAD values were not significantly different from each other in group 1 (no reperfusion), 10 ± 0.03 and 0.13 ± 0.03 , respectively (fig. 3, tables 2 and 3).

The effect of the duration of ischemia after injection on myocardial ^{201}Tl distribution is demonstrated by comparison of groups 2 and 3 (fig. 3, table 2). The duration of coronary occlusion, the intensity of regional ischemia during occlusion and the duration

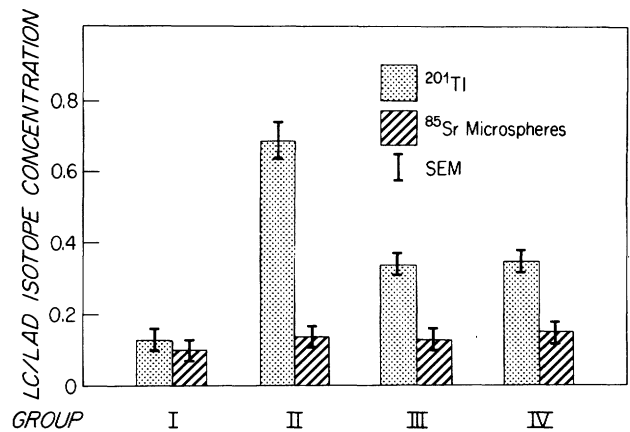


FIGURE 3. Isotope concentration ratios in myocardium supplied by the left circumflex (LC) and the left anterior descending (LAD) arteries. The concentration ratios of ^{201}Tl and ^{85}Sr -labeled microspheres are shown for the four groups, expressed as group means. Standard errors of the mean are shown by brackets. The ^{201}Tl and microsphere LC/LAD ratios are not different in group 1, which had no reflow. The ^{201}Tl LC/LAD is much higher in group 2, with early occlusion release. The rise in ^{201}Tl LC/LAD is significantly less marked when reperfusion is delayed (group 2) or attenuated by LC stenosis (group 4).

and magnitude of reflow before sacrifice were approximately the same for both groups. The temporal relationship between ^{201}Tl injection and reflow was the only factor that differed. Thallium-201 LC/LAD was 0.69 ± 0.05 in group 2 and 0.34 ± 0.03 in group 3 ($p < 0.01$).

The effect of the degree of reactive hyperemia after occlusion release on the myocardial ^{201}Tl distribution is demonstrated by groups 2 and 4 (fig. 3 and table 3). The duration of occlusion, the timing of isotope injection, the initial intensity of ischemia and the duration of the reflow period before sacrifice were the same in both groups. The magnitude of reflow was the only factor that differed. Thallium-201 LC/LAD was 0.69 ± 0.05 in group 2 and 0.35 ± 0.03 in group 4 ($p < 0.01$).

Discussion

Intravenously administered ^{201}Tl is rapidly cleared from the blood by the myocardium and other body tissues. Therefore, the distribution of coronary blood flow during the period soon after ^{201}Tl injection, when blood levels are still high, should exert the greatest influence on the pattern of myocardial ^{201}Tl deposition. Net uptake by the heart in dogs normally appears to be complete in about 10 minutes.¹ Thereafter, near-equilibrium conditions ensue, with much slower exchange of ^{201}Tl ions between a small extracellular pool and a large intracellular pool. By this slow exchange, ^{201}Tl ions can leave one intracellular compartment, recirculate via the blood, and enter a new intracellular compartment.² There is evidence that reversal of temporary myocardial ischemia favors later ^{201}Tl entry

into the previously ischemic region. Experiments in dogs have shown that when focal myocardial ischemia at the time of ^{201}Tl administration is subsequently terminated by release of coronary occlusion, the difference in ^{201}Tl concentration between previously ischemic and normally perfused myocardium decreases over a 100-minute period.³ Furthermore, sequential scintigraphy after ^{201}Tl injection during exercise in coronary patients often shows, over several hours, a gradual resolution of perfusion defects that were apparent on the initial scintigram.³⁻⁵ This process, which reflects exchange of tissue ^{201}Tl via the blood over time, is known as redistribution.

Our investigation, however, does not concern the phenomenon of redistribution as applied to the slow exchange of ^{201}Tl during near-equilibrium conditions. Our aim is to define certain factors that influence the pattern of initial uptake of ^{201}Tl into myocardium by the time the first clinical scintigram would be taken. Specifically, we chose to investigate (1) how variations in the timing of ^{201}Tl injection with relation to the cessation of ischemia, and (2) how the presence of reactive hyperemia after ischemia reversal would influence the formation of the initial ^{201}Tl defect. The dogs were sacrificed for LC/LAD ^{201}Tl determinations 6-8 minutes after injection. The myocardial concentration ratios, therefore, were obtained at approximately the time when initial scintigrams would be obtained in a patient after ^{201}Tl injection.^{3, 6, 7}

The degree of regional ischemia in myocardium supplied by the LC at the time of ^{201}Tl injection was determined by the microsphere LC/LAD ratio. The ^{85}Sr -labeled microspheres, which were injected into the left atrium simultaneously with ^{201}Tl injection into a peripheral vein, were trapped in the myocardial microcirculation proportionately to regional blood flow and mostly cleared from the blood in one circulation. LC/LAD microsphere ratios did not differ among the groups. Therefore, all groups had comparable degrees of ischemia in the LC region at the time of injection. The degree of regional ischemia caused by the acute occlusion of the LC was severe but not complete. Coronary blood flow in the myocardial region supplied by the LC during occlusion was 10-15% of that supplied by the LAD.

The purpose of the experiments in group 1 was to determine how closely the myocardial ^{201}Tl distribution reflects the degree of regional ischemia when reflow does not occur. Under these conditions the ^{201}Tl LC/LAD ratio was similar to the LC/LAD ratio for coronary blood flow as judged by the microsphere method. Therefore, the ^{201}Tl distribution was not influenced significantly either by the decrease in extraction coefficient for ^{201}Tl caused by myocardial hypoxia⁸ (presumably related to impaired function of the $\text{Na}^+\text{-K}^+$ ATPase membrane transport system) or by possible passive diffusion of ^{201}Tl into the ischemic region before the LC and LAD myocardial tissue could be separated post mortem. Without reflow, the ^{201}Tl LC/LAD ratio satisfactorily reflected the degree of ischemia. Thus, differences between ^{201}Tl and

microsphere LC/LAD ratios in groups 2-4 can be attributed to the effects of reflow.

Effect of Duration of Ischemia After Injection

In group 2, with early reactive hyperemia, ^{201}Tl uptake into the LC region during reflow made up for most of the deficit in uptake incurred during the 45 seconds when the vessel was occluded. The mean ^{201}Tl LC/LAD concentration ratio was 0.69 8 minutes after isotope injection, which is approximately the time when the first scintigram would be performed in clinical testing. This represents almost a fivefold increase in uptake in the LC region during the reflow period. In group 3, in which the reactive hyperemia occurred later relative to injection, ^{201}Tl uptake into the LC region during reflow was considerably less. The mean ^{201}Tl LC/LAD ratio was 0.34, intermediate between groups 1 and 2. Reversal of ischemia before ^{201}Tl uptake was completed resulted in at least partial resolution of the defect. The earlier the reversal, the more complete the resolution.

When considering clinical exercise testing in light of these findings, the duration of exercise after injection might be expected to have a similar qualitative influence on ^{201}Tl distribution for similar degrees of ischemia at the time of injection. If so, in order to compare one patient to another or to test a patient before and after an intervention, it would be necessary to standardize the duration of exercise after isotope injection.

In our animal models, the termination of ischemia was abrupt. In humans, the rate of resolution of insufficient coronary flow after stopping exercise is not well known, but is certainly somewhat more gradual. Heart rate normally returns more than halfway to baseline within 1 minute.⁹ Chest pain and/or electrocardiographic changes may persist for several minutes, but these symptoms may represent persisting chemical results of previous insufficient coronary flow rather than continuing low blood flow. Thus, our models necessarily differ from the clinical situation. They were designed not to show quantitatively what happens in humans, but rather to demonstrate qualitatively the changes in ^{201}Tl uptake that may be produced by changing the variables under study.

Effect of Reactive Hyperemia After Injection

In group 4, reactive hyperemia was blunted by residual coronary stenosis. Even though LC flow was restored promptly when blood ^{201}Tl was high, as in group 2, ^{201}Tl uptake into the LC region during reflow was considerably less than in group 2. The mean ^{201}Tl LC/LAD ratio was 0.35. This difference is presumably because LC blood flow did not rise much above normal during the reflow period. A smaller degree of regional reactive hyperemia after ischemia resulted in a greater ^{201}Tl defect at the time the first scintigram would be taken in clinical testing.

In patients, the magnitude of reactive hyperemia for a given degree and duration of ischemia is presumably

greater when the coronary stenosis is less severe, and may be greatest in patients with coronary spasm. (In dogs, coronary stenoses that reduce luminal diameter by 50–60% still permit considerable reactive hyperemia.¹⁰) Postischemic reactive hyperemia can be expected to deposit ²⁰¹Tl in the previously ischemic region of the heart. A patient with coronary spasm or only moderate stenosis and high reactive hyperemia after exercise might demonstrate a smaller scintigraphic defect than a patient with more severe stenosis, even though both had the same degree of ischemia during exercise (at different work loads) when the ²⁰¹Tl was injected.

In conclusion, we find that two variables in reversal of ischemia may exert important influences on the initial deposition of ²⁰¹Tl within the myocardium. The first variable is the length of the interval between isotope injection and the reversal of ischemia. For a given degree of regional ischemia at the time of injection, a shorter duration of ischemia after injection will result in a smaller defect. This may have important implications with regard to how long exercise should be continued after ²⁰¹Tl injection in clinical testing. The second variable is the magnitude of reactive hyperemia. A larger degree of postischemic reactive hyperemia will result in a smaller defect. This effect presumably will be related inversely to the degree of coronary stenosis, and should be maximal in patients with coronary spasm.

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