Effects of dipyridamole-induced vasodilation on myocardial uptake and clearance kinetics of thallium-201

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ABSTRACT Myocardial thallium-201 (201Tl) uptake and clearance after intravenous administration of dipyridamole (150 μg/kg) were determined in 12 open-chest anesthetized dogs with a partial coronary artery stenosis. 201Tl (1.5 mCi) was injected intravenously and myocardial biopsy specimens were obtained 10 min, 60 min, and 2 hr after injection. Serial changes in 201Tl activity in the normal zone and in the zone of partial stenosis were correlated with microsphere-determined regional blood flow and distal coronary pressure. Another nine dogs with equivalent stenosis not given dipyridamole before 201Tl served as controls. In the 12 dogs given dipyridamole, 201Tl activity at 10 min in the zone of stenosis was reduced to 42 ± 5% of initial normal zone activity (p < .001) and remained at 44 ± 3% of initial normal zone activity at 2 hr. There was a good correlation (.81) between the percent reduction in myocardial 201Tl activity and the percent reduction of peak hyperemic flow as determined by measuring the percentage difference in peak coronary flow after a transient 10 sec occlusion under control and stenotic conditions. In contrast, 201Tl clearance was rapid in the normal zone, with 201Tl activity decreasing to 55 ± 3% of initial normal zone activity by 2 hr. A redistribution pattern was produced because of the disparate clearance rates from hyperperfused and relatively hypoperfused myocardial regions. The relative 201Tl defect decreased from 58% to 11% from 10 min to 2 hr. In the normal zone dipyridamole increased epicardial flow from 1.03 ± 0.09 (SEM) to 3.52 ± 0.36 ml/min/g (p < .0001) and endocardial flow from 1.19 ± 0.09 to 2.96 ± 0.20 ml/min/g (p = .0001). In the zone of partial stenosis the increase in epicardial flow after dipyridamole was less marked (1.01 ± 0.10 to 1.55 ± 0.15 ml/min/g; p = .009) and endocardial flow decreased (0.84 ± 0.11 to 0.64 ± 0.15 ml/min/g; p = .04). Coronary perfusion pressure distal to the stenotic zone fell from 65 ± 3 to 50 ± 3 mm Hg after dipyridamole. In the nine control dogs with equivalent stenosis, 201Tl uptake and washout were not significantly different in the stenotic zone compared with the normal zone. These data indicate that dipyridamole-induced vasodilation in the presence of a partial stenosis results in diminished uptake and delayed clearance compared with increased uptake and more rapid clearance in normally perfused myocardium producing an initial 201Tl defect with delayed redistribution. Our data further demonstrate that the magnitude of the initial decrease in 201Tl uptake after dipyridamole correlates well with the percent reduction in coronary flow relative to the peak hyperemic flow response.

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SYMPTOM-LIMITED EXERCISE is routinely used in conjunction with thallium-201 (201Tl) myocardial imaging for detection and evaluation of coronary artery disease. Adequate stress is essential, since coronary artery disease will reduce the reserve capacity of the stenotic vessel long before there is significant reduction in resting blood flow. An abnormal perfusion image will be obtained only if the level of exercise stress is sufficient to produce an abnormal distribution of myocardial blood flow.

Recently, intravenous infusion of dipyridamole has been suggested as an alternative to physical exercise for myocardial perfusion imaging with 201Tl. It is presumed that the powerful coronary vasodilatory effect of this drug will greatly increase the myocardial blood flow in regions served by normal coronary vessels but not in myocardial regions served by diseased vessels, producing an inhomogeneity of blood flow that would be evident by 201Tl scintigraphy. This pharmacologic method to induce maldistribution of blood flow may be most useful in patients who are physically

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unable to perform adequate exercise. In addition, if maximal vasodilation can be achieved, then the magnitude of the resulting myocardial defect may reflect the physiologic severity of the disease independent of the level of exercise achieved.

There are several questions concerning the use of myocardial $^{201}$TI scintigraphy with dipyridamole as an alternative to exercise. First, substantially increasing myocardial blood flow by vasodilation could alter the myocardial extraction of $^{201}$TI so that uptake would not correctly indicate the resulting distribution in myocardial blood flow. Second, the effect of dipyridamole on blood flow in myocardial regions supplied by stenotic vessels is not well understood. Finally, the amount and significance of $^{201}$TI redistribution on delayed images may be significantly altered by the administration of intravenous dipyridamole. Evidence of redistribution of $^{201}$TI in delayed images after exercise stress has been suggested to indicate viable muscle that was hyperperfused during exercise. Redistribution has also been reported after dipyridamole infusion and one might expect the mechanism of redistribution to be the same. However, the induced maldistribution of blood flow is maintained for some time by the persistence of the vasodilatory effect of dipyridamole, whereas the abrupt termination of exercise may allow a more rapid renormalization of myocardial blood flow distribution. This may influence redistribution, although we have previously suggested that redistribution is rate limited by cell membrane exchange and should not be primarily dependent on the rate of renormalization of myocardial blood flow. If this model is correct, the process of redistribution after dipyridamole infusion would be similar to that after exercise.

The following experiments were performed to address these questions in the animal preparation. In this canine preparation, a stenosis was produced on the left anterior descending artery, which maintained normal or near-normal resting blood flow but eliminated most of the capacity for reactive hyperemia. Initial uptake and net clearance of intravenously administered $^{201}$TI were then determined in a control group of dogs with stenoses that were not given dipyridamole and in a similar group of dogs receiving dipyridamole. We tested the hypothesis that the magnitude of a $^{201}$TI defect produced by dipyridamole infusion can be used as an indicator of the physiologic severity of a coronary artery narrowing. We also sought to determine the redistribution kinetics of myocardial $^{201}$TI when the radionuclide was administered intravenously during dipyridamole-induced vasodilation. Finally, alterations in $^{201}$TI uptake and clearance were correlated with changes in regional myocardial blood flow as determined by the microsphere technique.

**Methods**

**Animal preparation.** Experiments were performed in mongrel dogs (20 to 30 kg) that had been fasted for 24 hr before surgery. All 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 cc. Arterial blood gases were serially monitored and the respirator was adjusted as necessary to maintain the arterial Po$_2$ and pH within the normal physiologic range. Small additional doses of pentobarbital were periodically administered when necessary. 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 $^{201}$TI. 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 and advanced to the aortic arch after cut-downs over both femoral fossae. These catheters were used to withdraw simultaneous reference blood samples for the microsphere technique as well as for monitoring central aortic pressure.

A thoracotomy was performed in the fifth left intercostal space, the pericardium was opened, and a “cradle” was established for suspension of the heart. The proximal portion of the left anterior descending 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 proximal to the occluder in each animal. Another snare was placed distal to the flow probe and occluder and was used for the transient occlusions in determining reactive hyperemic responses. A 22-gauge angiographic catheter (Deseret) 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 flow meter was performed by brief occlusions of the LAD.

**Determination of regional myocardial blood flow.** Serial changes in regional myocardial blood flow were determined by the radioactive microsphere technique as previously described. Microspheres were labeled with $^{46}$Sc, $^{99}$Nb, $^{103}$Ru, or $^{113}$In (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 6 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 cath-
eters 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 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. The sites from which myocardial biopsy specimens were taken were recorded on a map of the epicardial surface of the left ventricle, and the specific specimens used for needle biopsies were identified for subsequent correlations between flow and $^{201}$Tl activity. 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: $^{46}$Sc = 740 to 1300 KeV; $^{95}$Nb = 650 to 818 KeV; $^{103}$Ru = 450 to 570 KeV; $^{113}$Sn = 340 to 440 KeV.

Myocardial blood flow was calculated with the equation $Q_{m} = (C_{m} \times 100\ Qr)/Cr$, where $Q_{m} = \text{myocardial blood flow (ml/min)}, C_{m} = \text{tissue counts (counts/min)}, Qr = \text{withdrawal rate of the arterial samples (ml/min)},$ and $Cr = \text{counts in reference arterial sample.}$ Flow per gram of myocardium was calculated by dividing blood flow by the weight sample. Separation of isotopes in myocardial blood flow calculations was calculated by computer (TRS 80; Radio Shack) 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 contribution isolated by the isotopes of higher energy. $^{201}$Tl activity in myocardial tissue samples was counted in the 50 to 100 KeV window. All myocardial samples were held for 2 weeks before counting to permit decay of the $^{201}$Tl to appropriate levels.

**Experimental design.** A summary of the experimental protocols for dogs in the control and dipyridamole groups is outlined in figure 1.

**Control group.** A group of nine dogs prepared in the manner described above served as control animals for the dipyridamole experiments. At baseline conditions, after instrumentation was completed, measurements of heart rate, phasic and mean aortic blood pressure, phasic and mean distal coronary perfusion pressure, left atrial mean pressure, and electromagnetically determined flow were recorded. The first set of radioactive microspheres was then injected into the left atrium. A critical stenosis was then placed in place by inflation of the hydraulic occluder. The end point for severity of stenosis was inflation or marked attenuation (<20% increase) of the reactive hyperemic response to a transient 10 sec total coronary occlusion. When the desired degree of stenosis was achieved, repeat hemodynamic measurements were made and another set of radioactive microspheres was injected. Immediately thereafter, 1.5 mCi of $^{201}$Tl was administered intravenously. Ten minutes after $^{201}$Tl administration, transmural myocardial microsphere specimens (Tru-Cut biopsy needle; Travenol Laboratories) were obtained from the center of the region perfused by the critically stenosed LAD and from the nonischemic region perfused by branches of the left circumflex vessel. This method is similar to that described previously by our group. These biopsies usually yielded specimens weighing from 15 to 25 mg. The samples were immediately blotted dry on filter paper, weighed, and placed in scintillation tubes for gamma well scintillation counting. In almost all instances, bleeding from the biopsy sites was prevented by gentle pressure applied to the epicardial sites of entry. Occasionally a suture was required to prevent further bleeding. At 1 hr after $^{201}$Tl injection, hemodynamic recordings were again made. Immediately thereafter a second set of transmural needle biopsy specimens were obtained from the same regions. This entire procedure was repeated 2 hr after $^{201}$Tl administration. The third set of microspheres was injected, and immediately thereafter the final biopsy specimens were obtained, this time in duplicate, from stenotic and nonischemic regions. The animals were then killed and the hearts were removed for examination as described above.

**Dipyridamole group.** Another 12 dogs underwent production of the partial coronary stenosis in the manner described for control animals. The severity of stenosis was assessed by the percent reduction in peak hyperemic flow after a 10 sec transient occlusion of the LAD achieved with the snare placed distal to the hydraulic occluder and flow meter. Hemodynamic measurements and blood flow determinations were obtained with the stenosis in place. Dipyridamole was then infused in the femoral vein at a dose of 0.15 mg/kg over a period of 1 min. During the infusion, aortic pressure, heart rate, distal LAD pressure, left atrial pressure, and electromagnetically determined coronary flow were continuously monitored. Four minutes after dipyridamole infusion the second set of microspheres was injected and femoral reference samples were withdrawn. Immediately thereafter a dose of 1.5 mCi of $^{201}$Tl was administered intravenously. Ten minutes later, transmural biopsy specimens were obtained from the central LAD region and from the nonischemic zone perfused by branches of the unstenosed circumflex area.

This procedure was again repeated at 2 hr after $^{201}$Tl administration just before the animal was killed. Duplicate biopsy specimens of the stenotic and nonischemic regions were obtained in 11 of the 12 dogs at this final stage. In the remaining dog, single biopsies were performed. As described for control dogs, the hearts were excised and multiple myocardial specimens from the left ventricle were processed for gamma well scintillation counting for determinations of blood flow by the microsphere technique.

**Data analysis.** Myocardial $^{201}$Tl time-activity curves were

![FIGURE 1. Summary of experimental protocol. Bx = biopsy; DP = dipyridamole.](http://circ.ahajournals.org/)}
plotted for each animal from control and dipyridamole groups with the values obtained from the serial biopsies. For both groups of animals, all myocardial 201TI values were expressed as a percent of the initial normal 201TI activity as determined from the 10 min biopsy sample obtained from the nonischemic region. In dogs with LAD stenoses receiving dipyridamole, myocardial 201TI activity from the central LAD region (expressed as a percent of normal) at 10 min was plotted against the percent reduction in peak hyperemic flow. To determine the peak flow reduction, the maximum blood flow capacity of the vessel in the unstented state was first measured with the electromagnetic flowmeter at peak reactive hyperemic flow after a 10 sec temporary occlusion. Peak hyperemic flow was then measured after a transient 10 sec occlusion with the stenosis in place. The ratio of these two values was recorded and compared with the magnitude of the 201TI defect obtained after dipyridamole vasodilation with the same stenosis in place. This value for defining severity of stenosis was adopted to characterize the actual hemodynamic impact of the obstruction independently of its anatomic structure.

Statistical analysis. In control and dipyridamole groups, a t statistic from paired observations was used to test for differences between experimental conditions. An unpaired t statistic was calculated to identify differences between mean values in groups or between means of myocardial zones within a group under different treatment conditions. The average R^2 was calculated from linear regression for the duplicate myocardial biopsies of the stenotic and normal regions to determine the percentage of variation held in common for the two measurements of 201TI activity. This provided a “reliability percentage” of the technique.

Results

Control group. Serial changes in mean aortic pressure and mean distal LAD coronary perfusion during baseline conditions, 10 min after 201TI administration with the LAD stenosis in place, and 2 hr after 201TI administration, are shown in figure 2. In these nine animals there was no significant change in mean aortic pressure with the LAD stenosis. However, there was a slight but significant fall in mean aortic pressure 2 hr after 201TI administration. The mean distal LAD coronary perfusion pressure fell from 102 ± 4 (SE) to 74 ± 4 mm Hg with the stenosis in place in these animals. At 2 hr the distal coronary pressure was unchanged at 72 ± 4 mm Hg. Mean electromagnetically determined coronary flow was 58 ± 8 and 50 ± 8 ml/min at baseline and stenotic conditions, respectively (NS). Mean heart rate was 143 ± 4 beats/min at baseline conditions and was unchanged at 143 ± 4 beats/min after production of the stenosis. At 2 hr the heart rate was slightly lower at 136 ± 5 mm Hg (p = .017).

Serial changes in myocardial 201TI activity in normal and stenotic regions are shown in figure 3. No diminu-

FIGURE 2. Serial changes in mean aortic pressure and mean distal LAD coronary perfusion pressure during control conditions (open bars), 10 min after 201TI administration with the stenosis in place (solid bars), and 2 hr after 201TI administration (hatched bars) are shown for the nine control dogs receiving 1.5 mCi 201TI intravenously.

FIGURE 3. Serial changes in myocardial 201TI activity in normal (solid lines) and stenotic (dotted line) myocardial regions of control dogs. Values are expressed as percent of initial normal 201TI activity, which is designated as 100%.
tion in $^{201}$TI uptake in the central LAD region 10 min after injection was apparent compared with $^{201}$TI activity in the normal region. The net clearance rates of $^{201}$TI over the ensuing 2 hr were also comparable in normal and stenotic myocardial regions.

Figures 4 and 5 summarize regional values for myocardial blood flow in epicardial and endocardial layers in normal and stenotic regions in the nine control dogs. Epicardial and endocardial flow in both regions were similar before inflation of the hydraulic occluder around the LAD. After production of the stenosis, endocardial flow in the stenotic region fell slightly from 0.98 ± 0.11 to 0.85 ± 0.11 ml/min/g (p = .10). Epicardial flows were comparable at baseline and stenotic conditions (1.05 ± 0.15 to 1.03 ± 0.11 ml/min/g) in the stenotic region. In both normal and stenotic regions, epicardial and endocardial flows tended to fall at 2 hr compared with the 10 min values. Thus the coronary stenosis did not significantly alter either regional blood flows or uptake and clearance of $^{201}$TI despite the fact that a significant gradient across the stenosis was hemodynamically evident and the reactive hyperemic response to a 10 sec transient occlusion was eliminated or greatly attenuated.

**Dipyridamole group.** Figure 6 summarizes the values for mean aortic pressure, mean distal coronary perfusion pressure, and electromagnetically determined flow in the 12 dogs receiving 0.15 mg/kg dipyridamole before $^{201}$TI administration. As shown, the stenosis resulted in a slight but significant fall in mean aortic pressure (110 ± 3.6 to 100 ± 3.9 mm Hg; p = .001). A further fall in mean aortic pressure to 86 ± 3.2 mm Hg (p < .0001) was evident after dipyridamole infusion. Two hours after dipyridamole, aortic pressure rose to 91 ± 3.9 mm Hg (NS).

The mean distal coronary perfusion pressure before stenosis (control) was 104 ± 4 mm Hg and fell significantly to 64 ± 3 mm Hg after production of the stenosis (p < .0001). With dipyridamole infusion, the distal coronary perfusion pressure fell even further to 48 ± 3 mm Hg (p < .0001). Two hours after the 1 min dipyridamole infusion, the distal pressure returned to 62 ± 3 mm Hg. The mean LAD perfusion pressure with the stenosis in place, and before dipyridamole, was not significantly different from that in the nine control dogs, indicating that severity of the stenosis was comparable in the two groups. As expected, dipyridamole-induced vasodilation resulted in decreases in both mean aortic and coronary perfusion pressure in the 12 dogs receiving the infusion. Despite this diminution in
pressures, flow was not significantly altered after dipyridamole infusion (55 ± 5 vs 50 ± 6 ml/min). Similarly, the mean heart rate was not significantly altered after dipyridamole infusion compared with that under stenotic conditions before infusion (140 ± 4 vs 140 ± 5 beats/min).

As shown in figure 7, in the 12 dogs receiving dipyridamole 201Tl activity at 10 min in the stenotic zone was reduced to 42 ± 5% of initial normal zone activity (p < .001) and remained at 44 ± 3% of initial activity in the normal zone at 2 hr. In contrast, the 201Tl clearance was rapid in the normal zone, with 201Tl activity decreasing to 55 ± 3% of initial normal activity by 2 hr. Thus there was a 45% decrease in 201Tl activity in the normal myocardial region as compared with no net change in activity in the stenotic region (flat clearance). This inhomogeneous early uptake and differential clearance from the two regions produced a redistribution pattern in which near-normalization of activity was achieved. These myocardial time-activity curves differ markedly from those plotted for the nine control dogs (figure 3), in which no initial decrease in 201Tl activity was observed in the stenotic region and clearance patterns were identical in normal and stenotic regions.

Epicardial and endocardial regional flow values in normal and stenotic regions before dipyridamole infusion, at peak dipyridamole effect and at 2 hr after dipyridamole infusion, are summarized in figures 8 and 9. In the normal region, dipyridamole increased epicardial flow from 1.03 ± 0.09 to 3.52 ± 0.36 ml/min/g (p < .0001) and endocardial flow from 1.19 ± 0.09 to 2.96 ± 0.20 ml/min/g (p = .0001). In contrast, in the stenotic region, epicardial flow after dipyridamole increased to a lesser extent, from 1.01 ± 0.10 to 1.55 ± 0.15 ml/min/g (p = .009). Endocardial blood flow in the stenotic region significantly decreased with dipyridamole infusion from 0.84 ± 0.11 to 0.64 ± 0.15 ml/min/g (p = .04). At 2 hr after infusion, regional myocardial blood flow in epicardial and endocardial zones of both regions returned toward the baseline prevasodilatory state with the stenosis still in place. The only exception was that endocardial blood flow in the stenotic region 2 hr after dipyridamole (0.69 ± 0.06 ml/min/g) was not significantly different from that at peak dipyridamole effect.

**FIGURE 8.** Epicardial blood flow (ml/min/g) in normal and stenotic regions during control conditions (open bars), 4 min after dipyridamole infusion (solid bars), and 2 hr after dipyridamole administration (hatched bars) in 12 dogs receiving the vasodilator.

**Relationship between 201Tl uptake and percent reduction in maximum hyperemic flow.** We sought to determine whether or not the magnitude of 201Tl diminution in the stenotic region after dipyridamole correlated quantitatively with the physiologic or functional severity of the partial obstruction. Figure 10 demonstrates that good correlation exists (r = .81) between the percent reduction in 201Tl uptake at 10 min and the percent reduction of peak hyperemic flow, as determined by measuring the percentage difference in peak flow after a transient 10 sec occlusion under control and stenotic conditions. The horizontal axis on this plot (figure 10) represents the ratio of peak hyperemic flow with the partial stenosis to the peak hyperemic flow of the vessel at baseline.

**FIGURE 7.** Serial changes in myocardial 201Tl activity in normal (solid line) and stenotic (dotted line) regions in 12 dogs receiving intravenous dipyridamole before 201Tl administration. Values are expressed as percent of initial normal myocardial 201Tl activity designated as 100%.
before the graded occlusion. The vertical axis represents $^{201}$TI activity measured in the 10 min biopsy of the stenotic region (expressed as a percent of uptake in normal myocardium) when the radionuclide was administered during dipyridamole-induced vasodilation. Thus the data in the 12 dogs receiving dipyridamole suggest that early myocardial $^{201}$TI distribution after intravenous dipyridamole infusion provides a reasonable estimate of the functional significance of this stenosis in terms of diminished reserve capacity.

**Methodologic considerations.** An $R^2$ value was computed for the duplicate $^{201}$TI biopsy specimens by linear regression analysis. This value depicts the covariation among the determinations and reflects a "reliability percentage" of the biopsy technique. The $R^2$ value for the $^{201}$TI count determinations from duplicate samples obtained from the nonischemic region in the dogs receiving dipyridamole was .97 and the correlation coefficient was .98. The intercept of the regression line was not significantly different from zero. Similarly, the $R^2$ value was .96 for the duplicate $^{201}$TI biopsy samples obtained from the stenotic region 120 min after dipyridamole administration and the correlation coefficient was .98. As with the regression line observed for the nonischemic samples, the intercept of the regression for samples from the stenotic region was not significantly different from zero. Thus these data indicate that the mean variation between the duplicate $^{201}$TI determinations at biopsy was between 3% and 4%.

To determine whether regional blood flow was relatively homogeneous within the regions examined at biopsy, the final 120 min transmural flow values for the myocardial specimens containing the 10, 60, and 120 min needle biopsy sites were compared. Table 1 shows that the regional flow at 120 min after $^{201}$TI administration was comparable in the myocardial specimens with needle-puncture sites and not significantly different from the flow in the immediately adjacent samples. This homogeneity of flow was observed within both the nonischemic and stenotic regions, although absolute flow was lower in myocardium perfused by the critically stenosed LAD as expected. If trauma or hemorrhage had occurred with the 10, 60, or

### TABLE 1

<table>
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<tr>
<th>Myocardial specimen</th>
<th>Nonischemic region (n = 14)$^a$</th>
<th>Stenotic region (n = 14)$^a$</th>
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<tr>
<td></td>
<td>(ml/min/g)</td>
<td>(ml/min/g)</td>
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<tr>
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<td>0.79 ± 0.05</td>
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<tr>
<td>Adjacent</td>
<td>0.90 ± 0.09</td>
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$^a$Flow values within regions not significantly different.

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**FIGURE 9.** Endocardial blood flow (ml/min/g) in normal and stenotic regions during control conditions (open bars), 4 min after dipyridamole infusion (solid bars), and 2 hr after dipyridamole administration (hatched bars) in 12 dogs receiving the vasodilator before $^{201}$TI administration.

**FIGURE 10.** Relationship between the percent reduction in initial $^{201}$TI uptake (vertical axis), shown as percent of initial normal myocardial uptake, in the stenotic region and the percent reduction of peak hyperemic flow, as determined by measuring the percentage difference in peak electromagnetically determined flow after a transient 10 sec occlusion under control and stenotic conditions. The horizontal axis represents the ratio of peak hyperemic flow with the partial stenosis in place to the peak hyperemic flow at baseline before the graded occlusion.
120 min needle biopsies, one might have expected the flow at 120 min to have been altered in the transmural specimens from which the biopsy samples were acquired in vivo.

Discussion

The results of this study demonstrate that dipyridamole-induced vasodilation in the presence of a partial coronary stenosis resulted in diminished uptake and delayed clearance of intravenously administered $^{201}$Tl, compared with increased uptake and more rapid clearance of the radionuclide in normally perfused myocardium, producing an initial $^{201}$Tl defect with delayed redistribution. Percent reduction of initial $^{201}$Tl uptake with dipyridamole infusion was proportional to the diminution in coronary reserve capacity as gauged by the percent reduction in peak hyperemic flow produced by the given coronary stenosis. In a group of control animals with coronary stenoses of physiologic severity similar to that in the dogs receiving dipyridamole, no initial defect in $^{201}$Tl uptake was observed and net clearance rates were identical from myocardium perfused by the patent circumflex coronary artery and myocardium perfused by the stenotic LAD.

In 1977, Strauss and Pitt injected microspheres radiolabeled with $^{201}$Tl after intravenous adenosine infusion to dogs with a subcritical left circumflex stenosis in which resting flow was not diminished. They demonstrated perfusion defects on images with vasodilator administration, which was associated with a fall in the left circumflex-to-LAD bed flow ratio. Several groups have further investigated the effects of coronary vasodilation on $^{201}$Tl kinetics in canine preparations. Strauer et al. showed that the dipyridamole-enhanced $^{201}$Tl uptake in normal myocardium was independent of an increase in myocardial oxygen demand. Gould reported that myocardial perfusion imaging during coronary vasodilation with dipyridamole was superior for identification of coronary stenoses of moderate severity than was exercise stress in conscious dogs. Leppo et al. showed that after $^{201}$Tl was administered during adenosine infusion in dogs with a left circumflex stenosis, delayed redistribution occurred secondary to a faster net loss of $^{201}$Tl from LAD-perfused myocardium than in circumflex-perfused myocardium, which cleared $^{201}$Tl at a slower rate. Okada et al. confirmed these observations and demonstrated that the net myocardial clearance rate of $^{201}$Tl after dipyridamole seemed to correlate with the severity of the stenosis. However, only minimal delayed $^{201}$Tl redistribution was apparent in their canine experiments in which a gamma probe was positioned on the endocardial surface of the left ventricle. Nishiyama et al. injected $^{201}$Tl intravenously during peak reactive hyperemia after a transient circumflex coronary occlusion and showed that subsequent myocardial $^{201}$Tl clearance was more rapid with a half-life of 3.4 hr compared with 11 hr in ischemic myocardial regions. The results of our experiments, as well as the results of those described above, show that dipyridamole infusion results in greatly increased blood flow in normal vessels but no increase in total coronary flow in the critically stenosed vessel. Although total coronary flow measured with the flowmeter was unaltered by dipyridamole, there was increased epicardial flow but decreased endocardial flow, producing an adverse endocardial/epicardial flow gradient in myocardium distal to the stenosis. This has been referred to as "coronary steal." The mechanism of "steal" in the setting of a single-vessel stenosis is not entirely clear. There was a striking reduction in perfusion pressure distal to the stenosis, perhaps related in part to the fall in aortic pressure produced by the drug. It may be that the reduced perfusion pressure is adequate to maintain increased blood flow in the epicardium but insufficient to provide adequate subendocardial flow.

For this study, the following definition of "physiologic severity" of a coronary stenosis was adopted. The maximum blood flow capacity of the vessel in the unobstructed vessel was first measured with the electromagnetic flowmeter at peak reactive hyperemic flow after a 10 sec temporary occlusion. This was considered to be the peak blood flow capacity of the unobstructed vessel. After the partial stenosis was established, peak flow was recorded after another 10 sec temporary occlusion. If, for example, this was one-half the value obtained for the unobstructed vessel, the stenosis was characterized by the value of 0.5, indicating that the effect of the stenosis was to reduce the peak blood flow capacity of this vessel in response to ischemic challenge to 50% of its original capacity. These values were compared to the biopsy-determined magnitude of the $^{201}$Tl defect obtained after dipyridamole-induced vasodilation with the same stenosis in place. This definition was adopted to characterize the actual hemodynamic impact of the obstruction independent of its anatomic structure. In addition, this ratio is independent of vascular tone or the absolute blood flow in the vessel, which would depend on the amount of myocardium supplied by the individual vessel.

The $^{201}$Tl activity in this study was determined from the results of transmural biopsies that averaged the epicardial and endocardial regions, as would be the case in most clinical imaging studies. For this type of
sampling, the initial uptake of $^{201}$TI would be expected to reasonably reflect the distribution of total coronary arterial flow as divided between the normal and stenosed vessels. The early uptake of $^{201}$TI with dipyridamole infusion in the present study was indeed shown to significantly diminish in the stenotic region sampled relative to nonischemic $^{201}$TI activity.

The observation of delayed net $^{201}$TI clearance in this and prior studies from a compromised vascular region after dipyridamole infusion is further evidence of physiologically significant hyperperfusion induced by the vasodilator. After dipyridamole infusion, the net $^{201}$TI clearance from myocardium perfused by the stenotic LAD was slower (see figure 7) than that in a similarly compromised myocardial region without dipyridamole (see figure 3). This occurred despite the fact that total coronary flow (measured electromagnetically) through the stenotic LAD was comparable in control dogs and dogs receiving dipyridamole when the $^{201}$TI was administered. The observation of slower net $^{201}$TI clearance in dogs receiving dipyridamole is inconsistent with a model which assumes that the cellular efflux of $^{201}$TI is directly proportional to a constant rate coefficient in product with the local intracellular $^{201}$TI concentration. If the rate transport coefficient remained constant, the total integrated efflux of $^{201}$TI throughout the transmural myocardial region would be independent of the manner in which $^{201}$TI was distributed within that region and thus would be independent of the endocardium-to-epicardium flow inhomogeneity induced by dipyridamole. If, in addition, it is assumed that the average extraction coefficient within the myocardial region is not significantly altered by dipyridamole, the net clearance of $^{201}$TI from myocardium perfused by the stenotic vessel should not be any slower than that from the similarly stenosed region without dipyridamole.

From the above argument, it must be concluded that either the average extraction of $^{201}$TI must increase or the cellular efflux or intrinsic washout of $^{201}$TI must be slowed in the stenotic region in the presence of dipyridamole to explain the slower net clearance of $^{201}$TI in dogs receiving the vasodilator. The influence of hyperperfusion on initial extraction and subsequent intrinsic washout of $^{201}$TI was previously examined in a canine preparation by means of a graded reduction in transmural myocardial flow produced by a hydraulic occluder around the LAD. The intrinsic washout rate of $^{201}$TI was measured by loading the heart with $^{201}$TI via an intracoronary injection and monitoring residual myocardial activity over time. We demonstrated that the extraction fraction for $^{201}$TI did not increase with a decrease in distal coronary perfusion pressure but that ischemia resulted in a decrease in the rate of intrinsic efflux of intracellular $^{201}$TI. As coronary perfusion pressure fell to below 60 mm Hg, the intrinsic $^{201}$TI washout rate became progressively more prolonged. These ischemic regions continue to extract recirculating $^{201}$TI. The reduced efflux reduces the net loss of $^{201}$TI and even produces net accumulation of the radionuclide in cases where extraction exceeds efflux. The same mechanism is likely to be responsible for the observed delayed $^{201}$TI clearance with dipyridamole. In this instance, the coefficient of epicardial rate transport would probably remain at its normal value, but the transport coefficient in the subendocardial region may be modified as a result of local hyperperfusion to produce local accumulation of $^{201}$TI. This would produce a slower clearance rate (including loss of clearance or net accumulation) compared with that observed in the control experiments without dipyridamole. This could produce a flat net clearance pattern from the stenotic region, as demonstrated in figure 7.

Clinical implications. A number of clinical studies have been published that deal with the utility of myocardial imaging after dipyridamole for detection of coronary artery disease. As expected from the animal kinetic data, myocardial defects are observed on images in patients receiving intravenous dipyridamole before $^{201}$TI administration. Delayed redistribution, when sought for, has been reported to occur on subsequent images in those regions demonstrating initial defects as long as no myocardial scar is present. Some patients receiving dipyridamole even manifest clinical ischemia, reflected by the development of angina and ST segment depression. These latter manifestations of drug infusion surely must be related to the fall in subendocardial blood flow that is evident in the presence of a critical stenosis when maximum vasodilation is induced. Francisco et al. observed $^{201}$TI defects in the distribution of some mild stenoses of 30% to 50% diameter narrowing in patients by means of dipyridamole stress. These investigators, using a dose of dipyridamole in patients comparable to that used in these experiments, reported a 90% sensitivity and 90% specificity for tomographic $^{201}$TI imaging with dipyridamole in patients with chest pain who were being evaluated for the presence of coronary artery disease. Other clinical studies report comparable sensitivities between dipyridamole imaging and exercise imaging for detection of coronary narrowings of 50% or greater in diameter.

There are certain hypothetical advantages of dipyridamole stress over exercise testing. The maximum
coronary flow achieved may be greater than that achieved with exercise alone. Gould et al. demonstrated in an animal preparation that myocardial perfusion imaging with \(^{201}\text{Tl}\) during coronary vasodilation induced by intravenous dipyridamole was better for identifying moderate coronary stenoses than exercise. Based on the observations made in the present canine experiments, further clinical studies appear warranted to determine whether dipyridamole \(^{201}\text{Tl}\) scintigraphy can be used to measure the physiologic or functional severity of coronary stenoses in humans by means of imaging data obtained from both the initial distribution phase and the subsequent clearance phase.

Thus these experimental studies demonstrate that with a vasodilator-induced increase in coronary blood flow, the initial uptake of \(^{201}\text{Tl}\) is reduced in regions supplied by a coronary stenosis, whereas \(^{201}\text{Tl}\) uptake is enhanced in regions receiving an increase in flow. Subsequently redistribution occurs because of disparate clearance rates from hyperperfused and relatively hypoperfused myocardial regions. The near total delayed redistribution in these dogs was related to a more rapid clearance of \(^{201}\text{Tl}\) from the zone perfused by the patent left circumflex coronary artery and a delayed or flat clearance of \(^{201}\text{Tl}\) in the hypoperfused region perfused by the stenosed LAD. This abnormal net clearance of \(^{201}\text{Tl}\) may be related to an altered intrinsic cellular efflux rate of \(^{201}\text{Tl}\) in subendocardial regions rendered ischemic by the vasodilator. Our data further demonstrate that the magnitude of the initial decrease in \(^{201}\text{Tl}\) uptake after dipyridamole infusion correlates well with severity of stenosis.

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