The use of preintervention and postintervention thallium imaging for assessing the early and late effects of experimental coronary arterial reperfusion in dogs

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ABSTRACT To determine if thallium-201 imaging of myocardial perfusion can be used as an early predictor of myocardial salvage after reperfusion, 24 adult dogs were subjected to complete occlusion of the left anterior descending coronary artery with release of the snare 2 hr later. Separate doses of thallium (1 mCi) and microspheres were given 15 min before, 5 min after, and 1 hr after release of the snare. Gamma camera images of the heart were obtained after each injection of thallium. Preinjection images were also acquired before the second and third doses and were subtracted from the postinjection images to eliminate the counts due to residual activity from the prior injections. The chest was then closed and the dog allowed to recover. The chest was reopened 48 hr later, final doses of thallium and microspheres were administered, and the heart was imaged. After the dog was killed, the left ventricle was sliced from apex to base, and any infarct was outlined with triphenyltetrazolium (TTC) staining. The slices were then subdivided into pieces of approximately 1 g each and then well counted for microsphere determination of regional myocardial blood flows. Thallium images were interpreted qualitatively and quantitatively. Fifteen dogs with myocardial infarctions, as assessed by TTC staining, all had thallium image defects during coronary arterial occlusion. Thallium scans obtained immediately after reperfusion demonstrated increased anterior wall thallium activity in nine dogs, normal activity in four dogs, and decreased activity in two dogs. In 14 of the 15 dogs, relative thallium activity correlated with the occlusion:normal zone flow ratios. Thallium scans 1 hr after reperfusion were normal in 10 dogs and demonstrated a defect in five. All thallium scans obtained 48 hr after reperfusion demonstrated an anterior wall defect. Six dogs with no myocardial infarction identified by TTC staining had thallium image defects during coronary arterial occlusion. Immediately after reperfusion, three dogs had increased anterior wall thallium activity and three had normal activity. One and forty-eight hours after reperfusion all thallium scans were normal. In conclusion, after a 2 hr coronary arterial occlusion, a thallium defect immediately or 1 hr after reperfusion indicates myocardial infarction. However, normal or increased thallium activity in the involved area does not rule out the possibility of myocardial infarction. At these early times after reperfusion, thallium uptake is more related to flow than to myocardial viability. Results of thallium imaging 48 hr after reperfusion do correlate with the presence or absence of myocardial infarction.

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MYOCARDIAL REPERFUSION in patients with acute myocardial infarction has been accomplished with emergency coronary artery bypass grafting, and more recently with percutaneous transluminal angioplasty or intracoronary streptokinase.1-5 However, the reestablishment of epicardial coronary arterial blood flow does not always prevent the completion of the myocardial infarction. In fact, in experimental animal preparations, restoration of coronary blood flow after a period of occlusion may actually be detrimental in some cases.6,7 The benefits or detriments of successfully restoring myocardial perfusion in patients can be assessed by the electrocardiography, determination of cardiac enzyme levels, and radionuclide ventriculography over the several days after the procedure. However, the early assessment of successful myocardial salvage has been more difficult. Several groups of investigators have used thallium uptake early after re-
perfusion as an indicator of successful myocardial salvage. Accordingly, the purpose of our canine study was to determine if results of thallium imaging of perfusion before, early, and late after successful experimental myocardial reperfusion correlate with the ultimate development, or lack thereof, of a myocardial infarction.

Methods

**Canine preparation.** Twenty-four adult mongrel dogs (mean weight 20 kg, range 17 to 24 kg) were anesthetized with chloralose (140 mg/kg iv) and urethane (1400 mg/kg iv). Each dog was intubated and placed on a respirator (Harvard Apparatus, South Natick, MA) with 5 cm of positive end-expiratory pressure. By a sterile technique the heart was exposed via a left thoracotomy and suspended in a pericardial cradle. A 20 cm vinyl catheter was inserted into the right atrium for administration of fluids. A second vinyl catheter was inserted into the left atrium for monitoring left atrial pressure and for injecting microspheres for determination of regional myocardial blood flow. A No. 7 National Institutes of Health catheter was placed in the brachial artery and positioned in the aortic arch to monitor aortic pressure and to obtain specimens of blood for determination of arterial pH, Pco2, Po2, and to obtain microsphere reference samples. The proximal left anterior descending coronary artery was dissected free and a silk suture was placed loosely around the coronary artery. Six small copper-wire loops were placed around a small diameter latex tubing and the tubing was sutured in place over the area supplied by the left anterior descending coronary artery in such a way that the wires were secured to provide epicardial electrograms without artifact from damage due to the sutures. A similar set of wire loops were positioned over the area supplied by the left circumflex coronary artery.

Electrocardiographic lead II and epicardial leads and pressures (P23Db transducers; Gould Inc., Oxnard, CA) were monitored continuously throughout the experiment and recorded on paper with a Hewlett-Packard Co. recorder (model 7788A, Palo Alto, CA). Specimens of arterial blood were obtained at frequent intervals to assess pH, Po2, and Pco2. Appropriate adjustments were made to maintain these parameters in the physiologic range (pH 7.35 to 7.45 and Pco2 30 to 40 mm Hg). Arterial Po2 was maintained at between 100 and 150 mm Hg throughout the experiment.

**Experimental protocol.** Figure 1 illustrates the experimental protocol. After baseline hemodynamic measurements were obtained, 1 g of procainamide (Pronestyl) was given intramuscularly. The silk suture snare around the left anterior descending coronary artery was tied, producing complete occlusion of the artery. One hundred and five minutes later thallium-201 chloride (1.0 mCi; New England Nuclear Corp., N. Billerica, MA) and 113Sn-labeled microspheres (30 μCi total dose, 4.5 million spheres, 15 μm size; New England Nuclear Corp., N. Billerica, MA) were injected into the left atrium. Arterial reference blood samples were collected for 2 min after the microsphere injection. A portable gamma camera (Siemens LEM, Needham, MA) equipped with an all-purpose parallel-hole collimator was then positioned directly over the lateral chest wall. Two 5 min images were collected 5 min after administration of thallium (thallium image 1). The left anterior descending coronary artery snare was then released (2 hr from time of occlusion). Five minutes later one 5 min gamma camera image was obtained (mask image 1). Ten minutes later a second dose of thallium (1.0 mCi) and a set of 109Ru-labeled microspheres were injected into the left atrium. Five minutes after administration of thallium, two 5 min images were collected (thallium image 2). One hour after the occlusion release a 5 min gamma camera image was obtained (mask image 2) and then a third dose of thallium (1.0 mCi) was given and a set of 59Nb-labeled microspheres was injected into the left ventricle and two 5 min gamma camera images were obtained (thallium image 3). All catheters, crystals, and electrocardiographic leads were then removed, the chest was closed, and the dog allowed to recover. Two days later, the dog was anesthetized and the chest opened. Catheters were placed in the left atrium and aortic arch as before. The gamma camera was positioned over the lateral chest wall and a 5 min image was obtained (mask image 3). The fourth dose of thallium (1.0 mCi) and a set of 46Sc-labeled microspheres were injected into the left atrium. Five minutes later two 5 min gamma camera images of the heart were obtained (thallium image 4). The dog was then killed.

After the dog was killed the heart was removed and rapidly frozen in liquid nitrogen. The entire left ventricle was sliced from apex to base into 5 mm slices parallel to the atrioventricular groove. Each slide was weighed and incubated in a 2% solution of triphenyltetrazolium (TTC). After TTC staining, the slices were photographed with a videodigitizer consisting of frame buffer, color monitor, and computer (VAX 11/780; Digital Equipment Corporation, Waltham MA). Infarct size by weight was calculated by planimetry of each slice and multiplication by slice weight. The percent of infarcted myocardium was calculated by dividing the infarct weight by the total weight of all slices. After the left ventricular slices were stained with TTC and videodigitized, they were placed on the surface of the gamma camera and imaged for 5 min.

**Calculation of regional myocardial blood flow.** After the TTC-stained slices were photographed, they were subdivided into approximate 1 g pieces. The myocardial and blood microsphere reference samples were counted after thallium activity had decayed eight to 10 half-lives. All samples were counted in a well counter (Auto-Gamma Scintillation Spectrometer; Pack.
ard Instrument Co., Downers Grove, IL) for 5 min to collect at least 10,000 counts for each isotope. The thallium was counted within a 60 to 120 keV window, the tin-113 within a 350 to 435 keV window, the ruthenium-103 within a 450 to 550 keV window, the niobium-95 within a 600 to 800 keV window, and the scandium-46 within a 800 to 1200 keV window. A computer program was used to correct for activity spilling from one window into another. Regional myocardial blood flow was computer calculated (Vax 11 780; Digital Equipment Corp., Waltham, MA) from the sample activity and the activity in the reference blood samples obtained simultaneously with the administration of each isotope.13 Myocardial blood flow was expressed as milliliters per minute per gram of tissue. Myocardial blood flows for pieces from the anterior wall were averaged, as were those for pieces from the posterior wall.

**Analysis of thallium image.** Mask image 1 was subtracted from thallium image 2 to produce an image corresponding to the thallium distribution immediately after occlusion release (subtraction image 1), and mask image 2 was subtracted from thallium image 3 to produce an image corresponding to the thallium distribution 1 hr after occlusion release (subtraction image 2). Mask image 3 was subtracted from thallium image 4 to produce an image corresponding to the thallium distribution 2 days after occlusion release (subtraction image 3). Thallium image 1, the three subtraction images, and the slice images were reviewed by two observers who arrived at a consensus interpretation. The anterior wall was interpreted as demonstrating decreased activity (defect), increased activity (hot spot), or equal activity (normal) compared with the posterior wall.

Thallium image 1 and the three subtraction images were also analyzed with a computer-assisted technique. Briefly, the technique was as follows. An ellipse, defined by its width, length, and angle of rotation between the long axis and vertical plane, was placed by the operator around the left ventricular cavity of thallium image 1. Automatic realignment of the left ventricular cavities of the three subtraction images to fit into the drawn ellipse was performed by horizontal and vertical translation as well as rotation of the images by computer cross-correlation. Samples of the background were assumed to be pixels lying on the perimeter of a "background" ellipse, which was two pixels outside of the original ellipse. Actual background subtraction was then performed for each pixel within the original ellipse, taking into account the activity in the background ellipse and the distance between the pixel point and the background ellipse. Thallium activities in the four serial images were normalized to the hottest pixel in thallium image 1 after nine-point smoothing. The profile of curve thallium activity in the left ventricular myocardium in each image was then determined by the maximum mean peak activity of a running average in three pixels within the myocardium on a line perpendicular to the tangent of approximately 200 equally spaced points on the elliptical perimeter. Myocardial portions of the ellipse were subdivided into five equal segments along the perimeter and designated segments 1 to 5 in a clockwise manner. Mean normalized regional thallium activities in each of the five segments in each image were then calculated and plotted in graphic form. A defect was defined as at least a 75% reduction in counts in any one segment compared with the most normal segment defined in thallium image 1. A hot spot was defined as at least a 25% excess in counts in any one segment compared with the most normal segment defined in thallium image 1.

The image-subtraction technique was validated in a separate study. Separate thallium doses were administered during an intervention and after its reversal. Images were obtained after each injection and a difference image was obtained by subtracting the first from the second image to correct for residual isotopes from the first injection. Interventions on coronary blood flow included transient occlusion and then reperfusion, subcritical stenosis with dipyridamole infusion, and permanent occlusion. The first images showed defects corresponding to the occlusion or stenosis while the difference images correlated with myocardial perfusion at the time of the second injection.

**Data analysis.** Dogs were grouped according to whether they had or had not had an infarct, as determined by TTC staining. The ratio of occlusion/normal zone regional myocardial blood flow was calculated for each of the four times that blood flow was determined. This flow ratio was compared with the results of the thallium scan at each of the four times. Since small differences in radioactivity between adjacent myocardial walls cannot be detected by external imaging, ratios of occlusion/normal zone flow greater than 0.75 and less than 1.25 were arbitrarily defined as consistent with homogeneous myocardial thallium activity.16 A ratio of occlusion/normal zone flow less than or equal to 0.75 was defined as consistent with decreased perfusion to the anterior wall. A ratio greater than or equal to 1.25 was defined as consistent with increased perfusion to the anterior wall.

**Statistical methods.** All results are expressed as mean ± SD. Differences were analyzed by a one-way analysis of variance and the Newman-Keuls multiple-comparison test or by a paired t test.

**Results**

**Electrocardiographic and hemodynamic results.** Fifteen dogs had acute myocardial infarctions, as defined by TTC staining. Mean ST segment elevation was 0.7 ± 2.0 mm before occlusion, 7.6 ± 7.6 mm during occlusion, and 0.4 ± 0.6 mm 1 hr after release of the occlusion. Heart rate and mean arterial blood pressure were 137 ± 22 beats/min and 92 ± 15 mm Hg before occlusion, 135 ± 27 beats/min and 93 ± 18 mm Hg during the occlusion, 133 ± 27 beats/min and 92 ± 23 mm Hg 1 hr after release of the occlusion, and 140 ± 15 beats/min and 80 ± 17 mm Hg 2 days later.

In six dogs there was no evidence of acute myocardial infarction, as defined by TTC staining. Mean ST segment elevation was 0.2 ± 0.9 mm before occlusion, 6.4 ± 3.7 mm during occlusion, and 0.4 ± 0.4 mm 1 hr after release of the occlusion (p = NS compared with dogs with infarcts. Heart rate and mean arterial blood pressure were 116 ± 12 beats/min and 96 ± 15 mm Hg before occlusion, 109 ± 9 beats/min and 98 ± 15 mm Hg during the occlusion, 114 ± 25 beats/min and 92 ± 6 mm Hg 1 hr after release of the occlusion, and 125 ± 5 beats/min and 93 ± 3 mm Hg 2 days later.

**Regional myocardial blood flow and results of thallium scanning.** Table 1 lists the ratios of occlusion/normal zone flow and results of thallium scanning for the 15 dogs found by TTC staining to have had acute myocardial infarctions. Qualitative and quantitative interpretations of thallium images produced identical results with only one exception: the anterior wall of dog No. 4 on subtraction image 2 was qualitatively interpreted as
normal, whereas quantitative analysis demonstrated only 72% of normal counts, which is consistent with a defect. Four of the 15 dogs died after their chests had been closed on the first experimental day and before chests could be reopened 2 days later. Thus, for these four dogs there were no 48 hr flow determinations or thallium scans. All 15 dogs had anterior wall defects during coronary occlusion that appeared on the thallium scan and ratios of occlusion/normal zone flow less than or equal to 0.75. However, subtraction thallium scans obtained 10 min after coronary snare release demonstrated increased thallium activity in the anterior wall in nine dogs and normal activity in four. Ratios of occlusion/normal zone flow were all greater than 1.25 for dogs demonstrating increased activity and were all greater than 0.75 and less than 1.25 (except in dog 14) for dogs demonstrating normal activity. In only two dogs was an anterior wall defect noted on the thallium scan taken 10 min after release of the coronary snare. Subtraction thallium scans obtained 1 hr after release of the coronary snare were normal in 10 dogs and demonstrated a defect in only five dogs. The ratios of occlusion/normal flow were greater than 0.75 and less than 1.25 for all but two dogs (Nos. 8 and 13) in which normal thallium activity was demonstrated. All subtraction thallium scans and images of left

<table>
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Pre = during left anterior descending coronary artery (LAD) occlusion; Immed = immediately after LAD release; 1 hr = 1 hr after LAD release; 48 hr = 2 days after LAD release; LV slices = left ventricular slices; D = defect; N = normal thallium activity; HS = hot spot representing greater than normal thallium activity.

Quantitative analysis was consistent with a defect (anterior wall = 72% of normal wall).

FIGURE 2. Thallium images from one dog (No. 5) with an infarction, as determined by TTC staining. The image obtained during occlusion of the left anterior descending coronary artery demonstrated an anterior wall defect (ratio of anterior/posterior wall flow 0.30). Immediately after release of the stenosis, the anterior wall thallium activity was greater than that for the posterior wall, which is consistent with hyperemic blood flow to the anterior wall (flow ratio of 1.40). One hour after release of the stenosis, myocardial thallium activity was homogeneous consistent with a flow ratio of 1.05. Forty-eight hours after release of the stenosis there was an anterior wall defect consistent with a flow ratio of 0.60.
ventricular slices obtained at 48 hr demonstrated anterior wall defects. Figures 2 through 4 are examples of serial thallium images from the dogs with myocardial infarctions.

Table 2 lists the ratios of occlusion/normal zone myocardial flow and results of thallium scanning in the six dogs without acute myocardial infarctions, as determined by TTC staining. Qualitative and quantitative thallium interpretations produced identical results. All six dogs had defects of the anterior wall thallium during the occlusion and all but one (No. 20) had ratios of occlusion/normal zone flow less than or equal to 0.75 during occlusion. Ten minutes after release of the coronary snare, three dogs had increased anterior wall thallium activity and three had normal activity. One and forty-eight hours after release of the coronary snare thallium scans demonstrated homogeneous activity for all dogs. Figures 5 and 6 are examples of serial thallium images from dogs that did not have myocardial infarctions.

**Discussion**

Intracoronary thrombolysis with streptokinase has been described as an effective means of reestablishing coronary arterial blood flow in patients with acute myocardial infarction. Myocardial reperfusion has been shown to be beneficial in canine preparations of coronary occlusion followed by release. Furthermore, the beneficial effects of myocardial reperfusion have been demonstrated in patients during the several days after the event, as evidenced by preservation of the electrocardiographic R wave, improvement in the left ventricular ejection fraction, and decreased in-hospital mortality. However, in patients in whom epicardial coronary arterial blood flow is partially or completely restored, an early indicator of myocardial salvage would be helpful. For example, further therapeutic maneuvers might be considered if there were early indications of failure to salvage myocardium. $^{99m}$Tc-stannous pyrophosphate has been proposed as one such early marker of myocardial salvage. Parkey et al. found that reperfusion markedly increased uptake of $^{99m}$Tc-stannous pyrophosphate in infarcted myocardium. However, other investigators have proposed the use of thallium uptake as an early indicator of myocardial salvage.

In the present study, thallium defects were observed before reperfusion in all dogs, regardless of whether or not an infarct subsequently developed. However, this study demonstrates that thallium perfusion imaging

**FIGURE 3.** Thallium images from one dog (No. 2) with an infarction, as determined by TTC staining. The image obtained during occlusion of the left anterior descending coronary artery demonstrated an anterior wall defect (ratio of anterior/posterior wall flow 0.52). Immediately and 1 hr after release of the stenosis, myocardial thallium activity was homogeneous (flow ratios of 0.78 and 0.99). Forty-eight hours later an anterior wall thallium defect was again apparent.

**FIGURE 4.** Thallium images from one dog (No. 7) with an infarction, as determined by TTC staining. The images obtained before and immediately, 1 hr, and 48 hr after release of the left anterior descending coronary artery demonstrate anterior wall defects.
immediately after coronary arterial blood flow is reestablished is of limited value in predicting the ultimate presence or absence of infarction. Normal or increased thallium uptake in the previously ischemic area was observed early both in dogs who ultimately had and those that did not have an infarction, as assessed by TTC staining. However, a thallium defect even at this early imaging time was specific for the subsequent demonstration of an infarction. Melin et al.\textsuperscript{22} also demonstrated thallium uptake in reperfused necrotic regions early after reperfusion in a canine preparation. In our study, 1 hr after release of the coronary arterial occlusion thallium imaging demonstrated normal uptake of tracer in all dogs without infarctions. However, most of the dogs with infarctions also had normal thallium images at 1 hr. As with the early thallium images, a defect at 1 hr was specific for the subsequent development of an infarction. Forty-eight hours after release of the coronary arterial occlusion all dogs without infarcts had normal thallium images and all dogs with infarcts had defects on their thallium scans.

In our study thallium distribution early and at 1 hr after release of coronary arterial occlusion correlated best with regional myocardial blood flow as determined with microspheres. Dogs with infarcts and increased and normal thallium uptake in the previously ischemic region had, respectively, hyperemic and normal regional myocardial blood flow to these regions at the early and 1 hr imaging times. Forty-eight hours after the coronary arterial occlusion was released, the ratios of anterior/posterior wall flow were either normal (two dogs) or decreased (nine dogs), even though all dogs had decreased thallium uptake in the anterior wall. Thus, despite complete recovery of myocardial perfusion in two dogs with infarcts after 48 hr, thallium imaging was a good predictor of myocardial viability at this time.

The findings of normal or even increased thallium uptake in the ischemic zone immediately after reperfusion, when the cells must still be ischemic, is in agreement with previous reports. Myocardial thallium uptake depends on myocardial blood flow and extraction by the cell.\textsuperscript{23, 24} Although some studies have demonstrated an active sodium/potassium pump-like uptake of thallium by the cell,\textsuperscript{25, 26} others have reported a passive mechanism.\textsuperscript{27} Such a mechanism could explain

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FIGURE 5. Thallium images from one dog (No. 16) with no infarction, as determined by TTC staining. The image obtained during occlusion of the left anterior descending coronary artery demonstrated an anterior wall defect (ratio of anterior/posterior wall flow 0.33). Immediately after release of the stenosis, thallium activity in the anterior wall was greater than that in the posterior wall, which is consistent with a flow ratio of 3.90. One and forty-eight hours after release of the stenosis, images demonstrated homogeneous thallium activity consistent with flow ratios of 1.01 and 0.98.
the uptake of thallium by ischemic cells that have been reperfused. An alternate explanation for the normal or increased thallium activity in the irreversibly damaged reperfused zone is that there is uptake into an interstitial edema space. We have previously observed increased thallium uptake into lung interstitial edema space in dogs and patients with left ventricular failure.28, 29

The results of our study may apply only to 2 hr occlusions. The results may be different when shorter or longer occlusion times are used before reperfusion. Further studies are indicated since in the clinical situation a variety of time periods between the onset of symptoms and the reestablishment of coronary blood flow are observed.

Previous studies have reported the use of thallium perfusion imaging for assessing the effects of coronary arterial thrombolysis with streptokinase.8-14 Markis et al.8 reported nine patients with acute myocardial infarctions. Images acquired before streptokinase after intracoronary thallium demonstrated a defect in the area of the involved coronary artery. Coronary arterial blood flow was then reestablished 2.3 to 4.3 hr after the onset of chest pain. Poststreptokinase images after a second dose of thallium (10 times initial dose) demonstrated resolution of the defects. Maddahi et al.9 also performed experiments using intracoronary thallium after streptokinase. These investigators reported normal or improved thallium uptake after streptokinase in two patients in whom the interval since the onset of chest pain was less than $2\frac{1}{2}$ hr. Images were still abnormal in three patients with 5 hr intervals since the onset of chest pain. In our study, administration of intracoronary thallium was not used for the following reasons. First, it is difficult to inject intracoronary thallium at a rate just sufficient to replace coronary arterial blood flow. Second, streaming of the thallium solution selectively down one branch of the left main coronary artery may occur despite the fact that there is no difference in flows. Third, it is difficult to detect abnormalities in right coronary arterial perfusion since the relative amounts of the total thallium dose to be injected into the right and left coronary arteries can only be approximated. For these reasons, we used intravenous thallium.

Other reports have described a thallium redistribution technique for assessing the effects of myocardial reperfusion. Reduto et al.10 gave intracoronary thallium before streptokinase. Four hours after reperfusion, thallium redistribution images were acquired without a second thallium injection. These investigators reported significant thallium redistribution into the prior defect after successful thrombolysis. Simoons et al.13 and Maddahi et al.14 gave intravenous thallium before streptokinase. Delayed redistribution thallium images were acquired after successful thrombolysis and demonstrated transient thallium defects in most patients. However, some patients demonstrated persistent thallium defects despite successful thrombolysis. This method, in which redistribution images are used, is promising for assessing the effects of reperfusion on myocardial viability, but further studies correlating the thallium findings to other markers of myocardial salvage are indicated.

In conclusion, after a 2 hr coronary arterial occlusion, a thallium defect immediately or 1 hr after reperfusion indicates a myocardial infarction. However, the finding of normal or increased thallium activity in the involved area does not rule out the possibility of myocardial infarction. At these early times after reestablishment of blood flow, thallium uptake is related more to flow than to myocardial viability. Results of thallium imaging 48 hr after reperfusion do correlate with the presence or absence of myocardial infarction.
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