Relationship between myocardial perfusion and function following coronary reflow in the canine heart using single photon emission computed tomography and two-dimensional echocardiography

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Since DeWood et al.[1] described the occurrence of coronary thrombosis in acute myocardial infarction, there has been a renewed interest in thrombolytic therapy and the effects of subsequent reperfusion. Initial studies concerning reperfusion in animal models have demonstrated conflicting results.[2-10] Some investigators have described improvement in survival, infarct size, and left ventricular function following reperfusion;[2-4] others have described little or no effect;[5-7] still others have described deterioration and adverse effects.[8-10] Clearly, there are a number of reasons for these discrepancies including the animal model used, the state of anesthesia, the length of coronary occlusion and reperfusion, and the methodology of assessment of functional response. However, there is little doubt that reperfusion is a complex phenomenon with the potential for heterogeneous effects.

More recently, studies have focussed on the delay of functional recovery following coronary reflow—the "stunned" myocardium.[11-15] Although it is clear that this phenomenon occurs commonly, there are several animal[2,3] and clinical[16,17] reperfusion studies which have demonstrated early functional recovery following coronary reperfusion. We hypothesized that the coupling, or uncoupling, of myocardial perfusion and function may play an integral role in functional recovery.

Previous animal studies of reperfusion have used radioactive microspheres to assess myocardial perfusion and ultrasonic crystals to measure functional change. The recent development of the cardiac imaging techniques of single photon emission computed tomography and two-dimensional echocardiography has made it possible to make quantitative assessment of myocardial perfusion and function using methods that are applicable to man. In the present study, a canine model of coronary occlusion and reperfusion using single photon emission computed tomography and two-dimensional echocardiography to assess the effect of coronary reflow following prolonged occlusion on myocardial reperfusion and functional recovery was investigated.

METHODOLOGY

Eleven conditioned dogs were studied. Each dog was anesthetized with morphine, 3 mg per kg intramuscularly, and sodium pentobarbitol, 30 mg per kg intravenously. Artificial respiration was maintained with a Harvard respirator. Using sterile surgical techniques, a left thoracotomy was performed, and the circumflex branch of the left coronary artery was dissected free from surrounding tissue. A mercury-filled cuff occluder was implanted on the left circumflex coronary artery and was controlled externally by a piston screw device. Coronary occlusion was estimated from the number of turns of the screw

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following precallibration prior to implantation. Coronary occlusion was subsequently confirmed in-vivo after implanting the occluder by turning the screw the same number of times under direct visualization. Coronary occlusion was associated with typical ECG changes on test occlusion. In three of the dogs, an electromagnetic flow probe was implanted on the left circumflex coronary artery proximal to the cuff occluder. Indwelling catheters were placed in the ascending aorta and left atrium for pressure measurements and subsequent microsphere injection. An indwelling catheter was also implanted in the superior vena for pressure measurement and injection of drugs. The catheters were brought out of the chest through a subcutaneous tunnel to the back and were secured to the skin between the scapulae. The chest cavity was closed and the pneumothorax was evacuated. Catheters were flushed daily with 1000 U/ml of heparin. Antibiotics were administered intramuscularly prior to and following the surgery. The animals were kept in individual air-conditioned cages and were allowed to recover from surgery for 14 days.

Radionuclide imaging technique. For each imaging study, the animals were positioned within a rotating gamma camera tomograph. The detector was equipped with a high-resolution, low-energy, parallel hole collimator. The detector was positioned as close to the animal as possible while still permitting unobstructed rotation. For the thallium study, two mCi of thallium-201 were injected intravenously and imaging was begun 10 minutes later. Images were acquired over a 180-degree arc extending from the right lateral position to the left lateral position. Individual 30-second images were acquired every 5.8 degrees of rotation to provide 32 total images. Each image was digitized into a 64×64 matrix and was stored on a magnetic disk in a small computer. Tomographic sections encompassing the entire volume of the myocardium were then reconstructed using a filtered back projection algorithm without attenuation compensation.[18]

Immediately after the thallium-201 tomograms were completed, the camera was repeaked for technetium-99m and the study was repeated using technetium-99m labeled microspheres. Two mCi of tagged microspheres were injected into the left atrium and imaging was begun 2 to 3 minutes later. The same imaging parameters were used for the microsphere study as were used for the thallium study.

Radionuclide image quantification. The reconstructed tomographic sections were displayed on a computer terminal. Using the computer display, the operator identified an appropriate starting point within the perfused volume of myocardium. An automatic program then traced out the total volume corresponding to perfused myocardium on all contiguous tomographic sections (Fig. 1). The algorithm used was based on a region growing technique that determined the border of the perfused zone based on threshold and rate-of-change criteria. The method was previously validated on phantom studies and was found to be accurate over the range of 20 to 400 cc. The total volume of the perfused region was then calculated by multiplying the volume of a single pixel (0.25 cc) by the total number of pixels within the computer-defined perfused volume.

Two-dimensional echocardiographic studies. Two-dimensional echocardiograms were performed as previously described,[19] with the animal in the right lateral decubitus position on a specially constructed table with a cutout allowing transducer positioning below the right lateral precordium. The best acoustic window was determined and marked externally with ink to insure reproducible external positioning of the transducer. Hard copies of end-diastolic and end-systolic freeze frames were generated in the short-axis projection at the midpapillary muscle level for quantitative analysis. Using these freeze frames, the endocardial border was manually digitized and the area ejection fraction was calculated as: end-diastolic area − end-systolic area/end-diastolic area $\times$ 100%. Regional area ejection fraction was calculated using computer-aided processing as previously described.[20] In brief, an automatic program calculates the center of mass of the diastolic endocardial border, the rotation angle, and translation coordinates for alignment of the systolic borders over the diastolic borders. Using a fixed end-diastolic center of mass, our program divides each frame into 16 to 24 radial segments for calculations of the regional area ejection fraction. Specific regions of interest for regional analysis were selected by superimposing the functional map over the corresponding pathologic slab using the papillary muscles as landmarks.

We have previously validated the accuracy of quantitative two-dimensional echocardiography (2DE) measures in our laboratory.[21] In the present study, interobserver variability for the area ejection fraction was determined by dividing the difference between observers by the means of their observations. Variability of the area ejection fraction measurements ranged from 4.4% to 10.4%. This degree of variability is acceptable and is comparable to that reported by Moynihan et al.[22]

Specific protocol. At 14 days following surgery,

each conscious dog was studied. After baseline echocardiographic imaging, constriction of the circumflex coronary artery was achieved in the conscious, sedated animal by a few turns of the screw-driven piston on the occluder. Coronary occlusion was estimated from the number of turns of the screw following precallibration prior to implantation. Coronary occlusion was associated with typical ECG changes, regional wall motion, and wall thickening abnormalities on 2DE. Beginning 3 hours after occlusion, each animal underwent echocardiographic, thallium-201, and technetium-99m microsphere imaging studies. Circumflex coronary artery flow was then reestablished after 4.7 ± 0.3 hours by completely releasing the occluder under echocardiographic monitoring. At 7 days after occlusion, the seven surviving animals again underwent echocardiographic, thallium-201, and technetium-99m microsphere radionuclide imaging studies.

Pathologic quantitation. Following the second set of images, the dogs were killed and the excised hearts were rinsed with saline and were then attached to a perfusion apparatus.[23] The coronary circulation was flushed by perfusing the aorta with 1 L of warm saline. Next, the left circumflex coronary artery was cannulated at the point of previous occlusion and was perfused with warm, buffered triphenyltetrazolium chloride (TTC), while buffered 0.13% Evans blue dye was delivered at equal pressure (100 mm Hg) into the aorta. Differential perfusion of the left circumflex coronary artery and remaining vasculature under these conditions delineated the anatomic area at risk, as well as the infarcted myocardium, based on the ability of dehydrogenases present in viable, perfused myocardium to react with TTC. With this staining technique, the myocardium that was not part of the area at risk was stained dark blue. Within the boundaries of the area at risk, normal tissue was stained brick red by the TTC, while infarcted myocardium appeared pale yellow. After approximately 15 minutes, the perfusion-stained hearts were sliced transversely into five or six 1 cm thick sections. The outlines of the infarcted and risk areas were traced on transparent overlays, and the fraction of the risk area in the left ventricle occupied by infarcted tissue was determined by manually digitizing these tracings and computer processing. The perfused myocardium (area not at risk), risk area, and infarcted tissue were then expressed as a percentage of the total left ventricular mass. The perfused myocardial (non-risk) mass during coronary occlusion was calculated as: total left ventricular mass − (risk + infarct) mass. The perfused myocardial (non-risk) mass at 7 days was considered: total left ventricular mass − infarct mass.

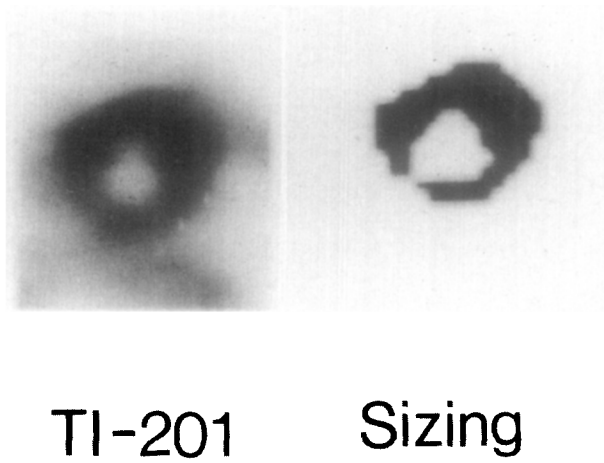

Fig. 1. Reconstructed short-axis view of Tl-201 tomograph *(left panel)* with sizing program outlining volume corresponding to perfused myocardium *(right panel)*. See text for details. *Tl-201* = thallium-201.

Table I. Perfused myocardial mass measurement during acute occlusion

Dog no.	*Thallium 201 perfused mass (gm)*	*Tc-99m microsphere perfused mass (gm)*	*Nonischemic myocardial mass at pathology (gm)*
1	79	—*	76
2	140	151	128
3	59	65	92
4	85	85	80
5	86	—*	78
6	83	80	76
7	93	116	100
8	142	136	137
9	98	117	103
10	94	107	103

Tc-99m = technetium-99m.
*Technically inadequate study.

Statistical analysis. Multiple comparisons were performed using a two-way analysis of variance with Tukey's test for multiple differences. In addition, paired, or unpaired, *t* tests were performed for analysis of changes in reperfused groups. Correlations were calculated using least squares linear regression. All data are expressed as mean ± standard deviation of the mean.

OBSERVATIONS

A total of 11 dogs weighing 31 ± 3 kg underwent surgery and chronic instrumentation. Following left

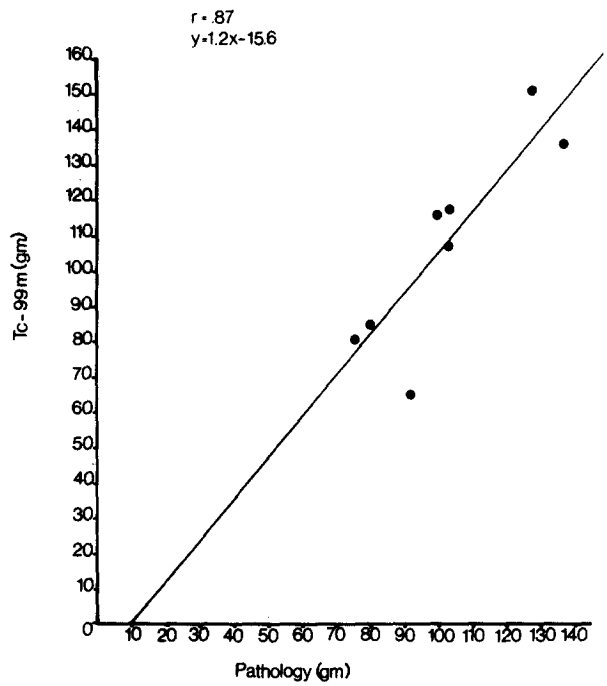

Fig. 2. Correlation between Tc-99m-derived perfused myocardial mass (during occlusion) and actual perfused mass measured pathologically. *Tc-99m* = technetium-99m microsphere.

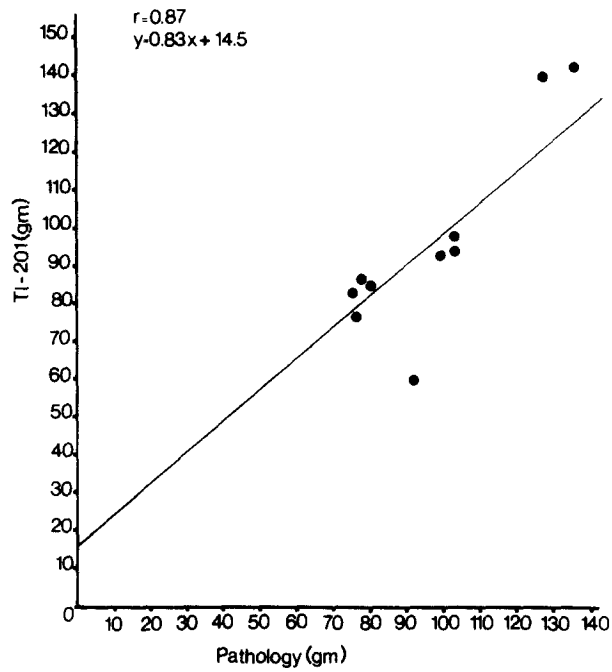

Fig. 3. Correlation between Tl-201 SPECT-derived perfused myocardial mass (during occlusion) and actual perfused mass measured pathologically. *Tl-201* = thallium-201.

Table II. Perfused myocardial mass measurement at 7 days

Dog no.	*Thallium 201 perfused mass (gm)*	*Tc-99m microsphere perfused mass (gm)*	*Noninfarcted myocardial mass at pathology (gm)*
1	118	121	113
2	143	157	161
3	—*	—*	148
4	89	98	109
5	—*	—*	78
6	83	73	109
7	—*	—*	136
8	197	218	205
9	121	116	166
10	148	—†	154

Tc-99m = technetium-99m.
*Dog died.
†Technically inadequate study.

circumflex coronary occlusion, one dog fibrillated and died approximately 20 minutes following occlusion. The remaining 10 dogs underwent circumflex occlusion for an average of 4.7 ± 0.3 hours followed by abrupt and complete release of the occlusion. In the three dogs with electromagnetic flow probes, coronary release was associated with immediate restoration of coronary flow to baseline values which were maintained on repeat study at 7 days.

Of the 10 dogs surviving coronary occlusion and reflow, one dog died suddenly 24 hours post occlusion, one dog died on day 3, and one dog died on day 4. The remaining seven animals survived the full 7-day study period.

SPECT data. The individual data from the single photon emission computed tomography studies with thallium-201 and technetium-99m microspheres, and the pathologic data are summarized in Tables I and II. The pathologically measured risk area was 37 ± 6%, and infarct size was 11 ± 9% of the total left ventricle. Infarct/risk ratio was 32 ± 31%.

The average perfused myocardial mass during coronary occlusion determined by technetium-99m microsphere single photon emission computed tomography (SPECT) was 107 ± 25 gm, and by thallium-201 SPECT it was 96 ± 25 gm. These values correlated well with the actual nonischemic myocardial (non-risk) mass of 97 ± 22 gm as measured at pathology ($r = 0.87$) (Figs. 2 and 3). In addition, the perfused myocardial mass by SPECT using the two radiopharmaceuticals correlated well with each other ($r = 0.93$) (Fig. 4). At 7 days, thallium-201 SPECT measured 128 ± 36 gm and correlated well with pathology (145 ± 34 gm, $r = 0.90$) and technetium-99 microsphere SPECT (130 ± 47, $r = 0.98$).

2DE data. The individual area ejection fraction data from the two-dimensional echocardiography (2DE) studies are presented in Table III. With coronary occlusion, area ejection fraction decreased from 57 ± 13% to 36 ± 16% ($p < 0.01$). Following coronary release, there was an improvement in area ejection fraction (36 ± 16% to 44 ± 16%, $p < 0.05$) which remained constant (47 ± 12%, p = NS) at 1 week. There was no change in regional ejection fraction in the nonischemic segment from baseline (58 ± 19%) to occlusion (48 ± 19%) to immediate reperfusion (52 ± 22%) to 1 week (47 ± 27%, all p = NS). Regional ejection fraction in the central ischemic zone fell significantly with coronary occlusion (69 ± 22% to 26 ± 35%, $p < 0.05$), remained depressed with immediate reperfusion (35 ± 28%, $p < 0.05$), but recovered by 1 week (48 ± 19%, p = NS vs control).

SPECT-2DE relationship. Two subgroups of dogs who survived the protocol were identified during the reperfusion imaging studies at day 7. Three of seven animals showed evidence of adequate reperfusion (>20%) by both thallium-201 and technetium-99m microsphere SPECT (Fig. 5). In these animals, there was a mean increase in the measured perfused mass of 47.7%. Four animals showed evidence of inadequate reperfusion (<20%) by both thallium-201 and technetium-99m microsphere SPECT (Fig. 6). In this group, the mean increase in the perfused mass was only 6.5%. Comparing those animals with adequate reperfusion to those with inadequate reperfusion, there was no difference in occlusion times (4.7 ± 0.7 hours vs 4.5 ± 0.6%, p = NS) or infarct size (7.8 ± 3.5% vs 10.0 ± 5%, p = NS). However, the change in area ejection fraction determined by 2DE was significantly greater in those animals who had SPECT evidence of adequate reperfusion (34 ± 19% vs 4 ± 16%, $p < 0.05$). After 7 days, the change in area ejection fraction determined by 2DE was similar in both subgroups (44 ± 31% vs 32 ± 92%, p = NS).

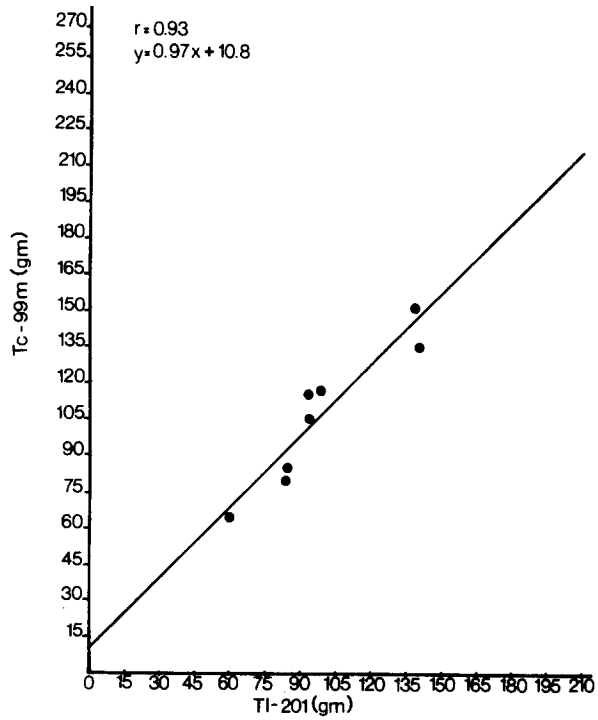

Fig. 4. Correlation between Tl-201 derived myocardial mass (during occlusion) and Tc-99m myocardial mass (during occlusion). *Tc-99m* = technetium-99m microsphere; *Tl-201* = thallium-201.

Table III. Area ejection fraction by 2DE

Dog no.	*Baseline EF (%)*	*Occlusion EF (%)*	*Release EF (%)*	*7 days EF (%)*
1	60	47	63	60
2	52	48	39	56
3	42	23	39	—*
4	65	22	28	48
5	71	46	70	—*
6	80	54	53	—†
7	53	14	41	—*
8	35	19	31	34
9	65	59	62	30
10	50	38	42	48

2DE = two-dimensional echocardiography; EF = ejection fraction.
*Dog died.
†2DE study not done.

COMMENTS

Our data indicate that the mass of perfused myocardium estimated by thallium-201 or technetium-99m microsphere SPECT corresponds well to the actual viable perfused myocardial mass during acute coronary occlusion. However, after a lengthy coronary occlusion of almost 5 hours, significant reperfusion by thallium-201 uptake occurred in only three of seven dogs. Conversely, in the remaining four surviving animals, there was evidence of decreased perfusion to the histologically defined at-risk zone, suggesting either infarction or severe persistent ischemia. Since the histologic staining demonstrating triphenyltetrazolium chloride staining of much of this zone implied tissue viability, the lack of thallium-201 and technetium-99m microsphere uptake most likely indicated severe persistent hypoperfusion. Furthermore, the 2DE studies suggested that the degree of reperfusion predicted the early change in left ventricular function; those animals with good reperfusion had significantly

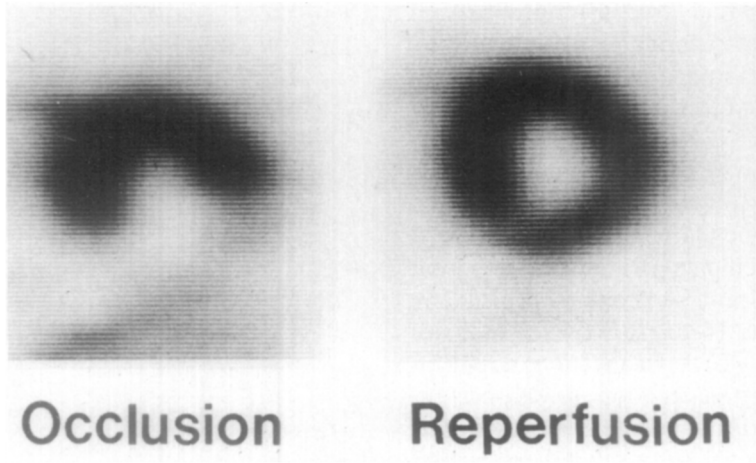

Fig. 5A. Reconstructed short-axis thallium tomograph demonstrating a large posterior perfusion defect during left circumflex coronary occlusion *(left panel)* and marked improvement in perfusion in the posterior region *(right panel)*. Quantitatively, the improvement in perfusion was 49%.

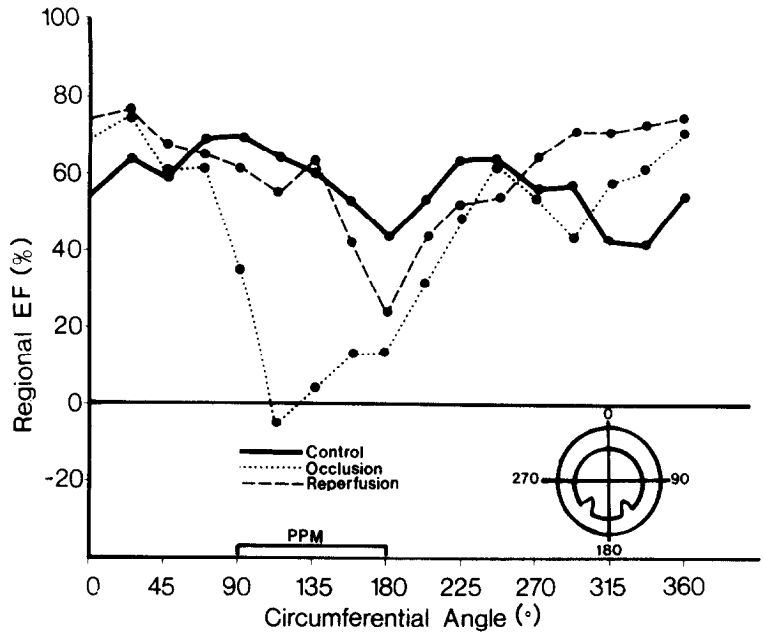

Fig. 5B. Corresponding functional data in the same animal as in Fig. 5A. The regional area ejection fraction is measured at 22.5-degree intervals and mapped circumferentially over 360-degrees. Note the marked wall motion abnormality in the region of the PPM corresponding to the thallium-201 perfusion defect during coronary occlusion. With coronary release, there is good functional recovery, corresponding to the reperfusion noted on thallium-201 tomography. *PPM* = posterior papillary muscle.

better early functional recovery than those with poor reperfusion. However, by day 7 further improvement in functional recovery was apparent in both groups despite the degree of reperfusion.

The "no-reflow" phenomenon. Two well described reperfusion phenomena may help explain these findings: (1) the "no-reflow" phenomenon,[24-26] and (2) the delayed functional recovery of myocardial tissue—the "stunned" myocardium.[11-15] The no-reflow phenomenon is thought to be related to microvascular injury occurring with coronary occlusions greater than 90 minutes. Swollen perivascular and endothelial cells develop during ischemia and contribute to the obstruction of capillaries in the ischemic zone. Although the no-reflow phenomenon is usually most apparent in the central ischemic

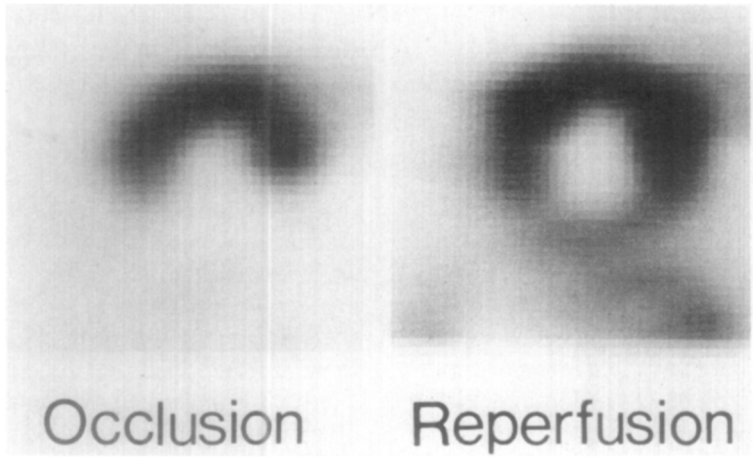

Fig. 6A. Reconstructed short-axis thallium tomograph demonstrating a large perfusion defect during left circumflex coronary occlusion *(left panel).* Following coronary reflow *(right panel),* there is little improvement in myocardial perfusion, which was quantitatively 5%.

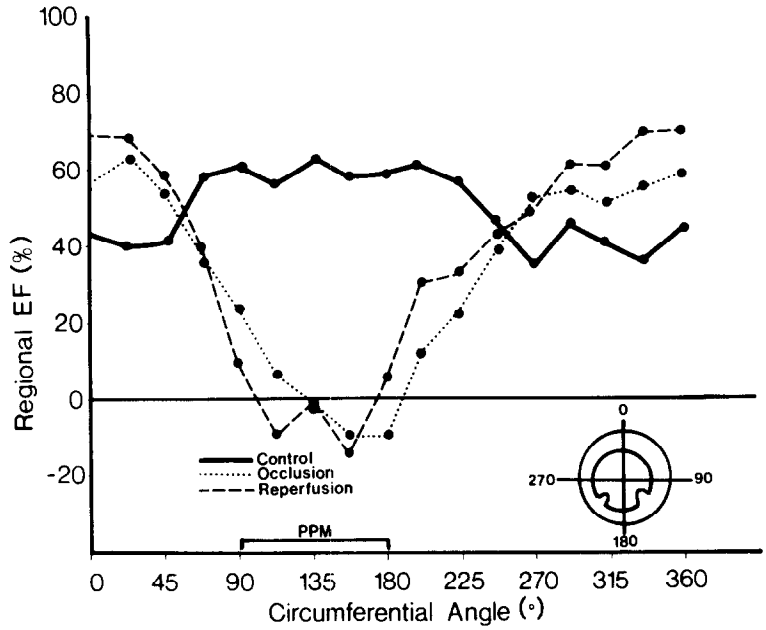

Fig. 6B. Corresponding functional data in the same animal as in Fig. 6A. The regional area ejection fraction is measured at 22.5-degree intervals and mapped circumferentially over 360 degrees. Note the marked wall motion abnormality in the region of the PPM corresponding to the thallium-201 perfusion defect during coronary occlusion. With coronary release, there is no functional recovery corresponding to poor reperfusion noted on the thallium-201 tomograph. *PPM* = posterior papillary muscle.

zone, hypoperfusion in ischemic but viable myocardial tissue has been described.[13] Recent clinical studies suggest that myocardial perfusion is reestablished following thrombolytic therapy;[27-29] however, the degree and significance of the no-reflow phenomenon in man is incompletely understood. A factor contributing to no-reflow may be the method and degree of reestablishment of coronary flow. In the present experiments, there was abrupt release of the coronary occlusion which may have contributed to microvascular damage. A slow, limited reestablishment of coronary flow, as may occur with strep-

tokinase thrombolytic therapy, may have different effects on tissue perfusion and viability.

"Stunned" myocardium. The "stunned" myocardium has been described by several investigators[11-15] as a delay in functional recovery of the myocardium following coronary reflow. Although the pathophysiology of this phenomenon is not completely understood, delay in recovery of high energy phosphates and abnormalities in calcium flux following reperfusion may be contributing factors. Our data suggest that some early myocardial functional recovery may occur and may be predicted by the degree of reperfusion. Those animals with persistent hypoperfusion following coronary reflow had poor early functional recovery, with gradual improvement of "stunned" myocardial tissue over the subsequent 7 days.

It is possible that the generally small size of the infarcts in the animals influenced our functional results, since only 32% of the risk region was infarcted. There are a number of possible explanations for the limited infarct size in our animals. First, all animals were pretreated with a beta blocker to reduce the incidence of occlusion arthythmas, and this may have limited infarct size.[30] Secondly, it is possible that collateral development was stimulated by the chronically applied occluder, which subsequently limited the degree of necrosis. Thirdly, it is possible that the risk region was overestimated by our in-vitro technique of dual perfusion staining, particularly in the setting of chronic collateral development. Whatever the mechanism, it is clear that our animals had limited infarctions despite 5-hour coronary occlusions, and this may have influenced the changes in left ventricular function which we observed.

There have been conflicting clinical[16, 31, 32] and animal data[2-10] concerning the early recovery of global left ventricular function following thrombolysis. It is possible that these discrepancies may be related to the no-reflow phenomenon, producing severe hypoperfusion and subsequently a "stunned" myocardium. Of equal importance is the consideration of the type of analysis of left ventricular function performed. In this study, 2DE was used to provide tomographic information concerning regional function of a slice of myocardium. There have been previous reports that changes in global left ventricular function using traditional indices of left ventricular volumes and ejection fraction may minimize or mask changes that are only detected by regional assessment.[33]

Another possible explanation for our reperfusion findings is that the long period of tissue ischemia altered the uptake pattern of thallium in otherwise viable myocardial cells. This alternative hypothesis seems unlikely on theoretical grounds and is also refuted by the corollary experiments with technetium-99m microspheres. All of the animals demonstrating lack of reperfusion on the late studies by thallium-201 also demonstrated this phenomenon in the microsphere studies. Since the only common mechanism of distribution between these two tracers is tissue blood flow, this provides strong supporting evidence that persistent ischemia in a zone of still viable myocardium is indeed the reason for these findings.

SPECT imaging. In previous experiments, several investigators[34, 35] have demonstrated the usefulness of SPECT in localizing acute myocardial infarction as small as 2 gm in size using technetium-99m pyrophosphate in dogs. Subsequent studies[36] in the canine heart in vitro demonstrated the ability of SPECT with thallium-201 to accurately measure total and infarcted myocardial mass. Since thallium-201 is only distributed to viable myocardium, the definition of the infarcted myocardium required certain assumptions regarding endocardial and epicardial borders in regions lacking thallium-201 uptake. While these studies appear to give valid results in the nonbeating canine heart in vitro, it is recognized that assumptions of wall thickness and shape may not be valid in the beating in-vivo canine heart. In addition, the technique used to define the nonvisualized myocardial segment was not applicable to infarctions which encompass the area of the left ventricular apex. For these reasons, no attempts were made in the present study to directly measure infarct size. Rather, total perfused myocardial mass, as reflected by thallium-201 uptake or technetium-99m microsphere distribution, was quantified and changes in this mass over time were used to infer changes in the mass of myocardium at risk and total infarct mass. Thus, our data confirm the ability of SPECT to estimate myocardial mass in vivo and agree with the recent experience of others.[37, 38]

In summary, this study demonstrates that SPECT with both thallium-201 and technetium-99m microspheres has sufficient accuracy to quantitate perfused myocardial mass during acute ischemia and following completed infarction. Coronary reflow does not necessarily predict adequate myocardial reperfusion, since the "no-reflow" phenomenon may be a significant factor following prolonged occlusion. Regional assessment of left ventricular function using 2DE demonstrates early but incomplete functional recovery in those animals who were adequately reperfused, but poor functional recovery in those with inadequate reperfusion. These obser-

vations may have important clinical implications in patients who receive thrombolytic therapy. Furthermore, this study demonstrates the potential of using SPECT and 2DE in the clinical assessment of thrombolytic therapy.

CONCLUSIONS

To further understand the interrelationship of myocardial perfusion and function following coronary occlusion and reflow, 10 chronically instrumented closed-chest dogs were studied. Serial 2DE was performed at baseline, following occlusion, during early reperfusion, and at 7 days. Serial thallium-201 (TL-201) SPECT was done during coronary occlusion and at 7 days. Following coronary occlusion, there was a large perfusion defect on Tl-201 SPECT accompanied by a decrease in 2DE left ventricular area ejection fraction from 57 ± 13% to 36 ± 16% ($p < 0.01$). After 5 hours of coronary occlusion, coronary reflow produced an improvement in myocardial perfusion on Tl-201 SPECT (96 ± 25 to 128 ± 36 gm, $p < 0.05$), accompanied by an improvement in 2DE area ejection fraction (44 ± 16%, $p < 0.05$). However, animals with better reperfusion had significantly better functional recovery than those with a "no-reflow" phenomenon ($p < 0.05$). After 1 week, there was further functional improvement in both groups. Our data suggest that coronary reflow produces varying degrees of myocardial reperfusion which may affect early functional recovery.

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