Impact of Regional Ventricular Function, Geometry, and Dobutamine Stress on Quantitative $^{99m}$Tc-Sestamibi Defect Size

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**Background.** Serial myocardial perfusion imaging with $^{99m}$Tc-sestamibi (MIBI) was used to evaluate infarct risk area and salvage after thrombolysis. The purpose of this investigation was to determine whether changes in MIBI defect size observed after reperfusion may result in part from distortion of regional and global left ventricular geometry.

**Methods and Results.** Twenty-five open-chest dogs were subjected to either 15 minutes (groups 1A and 1B) or 3 hours (group 2) of left anterior descending coronary artery occlusion followed by 3 hours of reperfusion. MIBI was injected before occlusion (group 1A) or during occlusion (groups 1B and 2), and serial ECG-gated planar imaging was performed. Dobutamine was infused after 3 hours of reperfusion (groups 1B and 2) to transiently alter left ventricular size and function. Perfusion defect magnitude (DM) and extent (DE) were serially quantified with circumferential profile analysis of end-systolic (ES), end-diastolic (ED), and summed images. Flow was assessed with radio-labeled microspheres and correlated with myocardial MIBI activity. Myocardial thickening was assessed in the risk area with sonomicrometers. In group 1A dogs, ischemic dyskinesis produced large artifactual quantitative MIBI defects on ES images (DM, $9.3 \pm 1.3$; DE, $27.8 \pm 6.0$) that were significantly smaller on ED images (DM, $4.5 \pm 0.9$, $P<.05$; DE, $4.4 \pm 2.3$, $P<.05$). In addition, DM and DE correlated inversely with myocardial thickening on ES images (DM, $r=-.84$; DE, $r=-.78$) and summed images (DM, $r=-.72$; DE, $r=-.61$) but not ED images (DM, $r=-.12$; DE, $r=-.15$). An index of defect reduction derived from summed images correlated well with thickening fraction in infarcted dogs (group 1B, $r=.89$) but poorly in infarcted dogs (group 2, $r=.41$) subjected to dobutamine stress.

**Conclusions.** $^{99m}$Tc-MIBI defect size may be affected by alteration of left ventricular geometry. Changes in regional function may confound analysis of risk area and myocardial salvage with serial $^{99m}$Tc-MIBI imaging and may also affect defect size during pharmacological stress with dobutamine. Dobutamine $^{99m}$Tc-MIBI imaging may be useful for distinguishing viable and nonviable myocardium. (Circulation. 1993;88[part 1]:2224-2234.)

**KEY WORDS** perfusion, scintigraphy

Serial myocardial perfusion imaging with $^{99m}$Tc-labeled methoxyisobutyl isonitrile ($^{99m}$Tc-sestami-bi) has been used to evaluate both the initial "area at risk" and the degree of myocardial reperfusion after thrombolysis. Initial studies in humans suggest that $^{99m}$Tc-sestamibi defect size does not change in the presence of an occluded artery but decreases if coronary reperfusion is successful. From this decrease in defect size, myocardial salvage has been inferred. In addition, some patients with reperfusion of infarct arteries demonstrate an unexplained serial decrease in defect size during the first week after myocardial infarction.

In 1979, it was recognized that distortion of global and regional left ventricular geometry could cause artifactual defects in perfusion images obtained with $^{201}$TI or intracoronary administration of $^{99m}$Tc-labeled albumin microspheres. Therefore, it is conceivable that changes in $^{99m}$Tc-sestamibi defect size observed after reperfusion may also result, at least in part, from changes in ventricular geometry.

The purpose of this investigation was to evaluate the effect of altered left ventricular function and geometry under varying conditions on the quantification of $^{99m}$Tc-sestamibi defect size. Canine models of myocardial stunning and infarction were used to address this issue.

**Methods**

**Surgical Preparation**

Experiments were performed in 25 fasting adult mongrel dogs anesthetized with sodium pentobarbital (30 mg/kg IV). Animals were intubated and mechanically ventilated on a respirator (Harvard Apparatus, South
Natick, Mass) supplemented with 95% oxygen. The ECG was monitored continuously with a limb lead. A femoral vein and both femoral arteries were isolated and cannulated for administration of fluids, drugs, and \( ^{99m} \text{Tc-sestamibi} \); pressure monitoring; and arterial blood sampling. Arterial pH, partial pressure of carbon dioxide (\( \text{PCO}_2 \)), and partial pressure of oxygen (\( \text{PO}_2 \)) were measured serially, and the ventilator was adjusted to maintain these parameters within the physiological range. A thoracotomy was performed in the fifth intercostal space, and the heart was suspended in a pericardial cradle. A flared polyethylene catheter was placed in the left atrium for the injection of radiolabeled microspheres. An 8F high-fidelity pigtail micromanometer (model SPC-484A, Millar Instruments, Inc, Houston, Tex) was passed retrogradely through the carotid artery into the left ventricle for the measurement of left ventricular pressure and the calculation of \( \text{dP/dt} \). The proximal left anterior descending coronary artery (LAD), after the first major diagonal branch, was isolated for placement of a hydraulic occluder (model VO-3, Rhodes Medical Instruments). A Doppler flow probe (Crystal Biotech, Hopkinton, Mass) was placed on the LAD just proximal to the occluder. Ten-megahertz Doppler transducers (Crystal Biotech) were attached to the epicardium of the left ventricle in the anterior left ventricular wall within the central perfusion territory of the LAD (distal to the site of occlusion) for measurement of regional myocardial thickening, as previously reported. All experiments were performed with approval of the Yale Animal Care and Use Committee in compliance with the guiding principles of the American Physiological Society on research animal use.

**Experimental Protocols**

Dogs were separated into three groups (see Fig 1). Sixteen dogs were subjected to 15 minutes of LAD occlusion followed by at least 3 hours of reperfusion (groups 1A and 1B). This canine model of brief LAD occlusion produces myocardial "stunning," characterized by reversible myocardial dysfunction. Four additional dogs were subjected to 3 hours of LAD occlusion and 3 hours of reperfusion (group 2), providing a model of myocardial infarction.

All dogs were injected intravenously with \( ^{99m} \text{Tc-sestamibi} \) (30 mCi) and then underwent serial ECG-gated planar imaging. Ten of the "stunned" dogs were injected with \( ^{99m} \text{Tc-sestamibi} \) before occlusion (group 1A), and 6 dogs were injected during coronary artery occlusion, 5 minutes before reperfusion (group 1B). The group 2 dogs with myocardial infarction were injected with \( ^{99m} \text{Tc-sestamibi} \) 2.5 hours after coronary occlusion and 30 minutes before reperfusion.

For purposes of imaging, the hearts were isolated from surrounding structures with flexible lead shielding. This facilitated analysis of changes in myocardial activity independent of changes in background. Serial planar imaging was performed during occlusion and reperfusion. Regional blood flow was assessed with radiolabeled microspheres in 6 of the 10 group 1A dogs during baseline, coronary artery occlusion, and reperfusion. Regional microsphere blood flow was assessed during baseline, occlusion, and after reperfusion in all the groups 1B and 2 dogs.

**STUNNED GROUPS**

In both groups 1B and 2 dogs, dobutamine was infused intravenously after 3 hours of reperfusion. The dobutamine infusion was increased from 2.5 to 10 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in increments of 2.5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) every 10 minutes. Dobutamine was administered to transiently improve left ventricular function and alter left ventricular size. These dogs were observed for 30 minutes after discontinuation of the dobutamine infusion and normalization of the hemodynamic parameters.

**Measurement of Myocardial Thickening**

Regional function in the central ischemic region was assessed with a pulsed Doppler epicardial transducer. This single-crystal system provides a nontraumatic technique of assessing myocardial thickening. This technique has been validated previously in experimental canine models. The beginning and end of the systolic interval were determined from the onset of the initial upstroke of left ventricular \( \text{dP/dt} \) and peak negative \( \text{dP/dt} \), respectively. Regional left ventricular wall function was estimated as net systolic thickening, defined as the amount of systolic wall thickening minus the amount of paradoxical systolic thinning if present and persisting >50% of the duration of systole. Thickening fraction was calculated by dividing the transmural net systolic
thickening by the end-diastolic wall thickness estimated by the range depth.

**Postmortem Analysis**

The hearts were rapidly excised and the LAD reocluded for postmortem dual perfusion staining to define the anatomic risk area and myocardial viability as previously reported. Both the left main coronary artery and LAD distal to the point of occlusion were cannulated. Dual perfusion was performed by simultaneous infusion of a buffered solution of monastral blue into the left main coronary artery and triphenyl tetrazolium chloride (TTC) into the distal LAD under physiological pressures for 5 minutes at 38°C, and hearts were incubated for an additional 15 minutes.

The hearts were divided from base to apex into four slices of equal thickness (1 to 1.5 cm thick) and photographed. The outlines of the myocardial borders, risk area, and infarct area were traced from projected images of the slices (×2 to ×3 enlargement) for computer digitization. The mass of myocardium at risk and infarcted was computed from the planimetered images as previously described.

**Determination of Regional Myocardial Blood Flow and 99mTc Activity**

Each of the myocardial slices was cut into eight radial sections, which were subdivided into epicardial, mid-wall, and endocardial segments, resulting in a total of 96 segments per heart for quantification of myocardial 99mTc-sestamibi activity and blood flow. Gamma-well scintillation counting of the myocardial samples was performed at 48 hours for the measurement of 99mTc-sestamibi activity. The samples were counted again 5 days later for the determination of microsphere flow with an autoscintillation counter (Beckman 8000). Separation of isotopes by energy windows (99mTc-sestamibi, 130 to 170 keV; 113Sn, 340 to 440 keV; 103Ru, 450 to 550 keV; 95Nb, 650 to 840 keV; 48Sc, 850 to 1300 keV) was performed according to the methods of Heymann et al.9 with spill-up and spill-down correction. Myocardial 99mTc-sestamibi activity and regional flow were expressed as a percentage of nonischemic myocardium, as previously reported.10 This facilitated comparisons between dogs.

**Image Analysis**

ECG-gated planar 99mTc-sestamibi images were acquired in the lateral view, using a small field of view gamma camera (Technicare 420). Images were acquired with 16 frames per cardiac cycle and a 64×64 matrix size. A high-resolution collimator was used to optimize image quality. The camera head was positioned such that the collimator surface was <10 cm from the center of the heart. The extrinsic resolution measured by the full-width-at-half-maximum (FWHM) of the point spread function of the system was 5, 7.1, and 9.1 mm at distances of 0, 5, and 10 cm from the collimator surface, respectively.

Quantification of the planar perfusion images was performed by a modification of our standard circumferential profile analysis.11 A region of interest was drawn around the left ventricle. This region of interest was divided into 36 radial sectors centered on the left ventricle. Circumferential count distribution profiles were generated from the mean pixel counts in each sector. For the group 1A dogs injected with 99mTc-sestamibi before coronary artery occlusion, each image profile was compared with the baseline profile for that dog. For groups 1B and 2 dogs injected during coronary artery occlusion, each image profile was compared with the initial occlusion profile obtained 5 minutes after injection. We calculated the defect integral and radial extent of the defect (group 1A; Figs 2B and 2C) or the index of defect reduction (groups 1B and 2; Fig 2D). The "defect integral" is unitless and reflects both the extent and severity of the defect relative to a baseline profile. The "defect extent" represents the radial extent to which the relative image intensity decreases by >15% from baseline. A 15% threshold provided the most reproducible quantitative assessment of defect size.12 The "index of defect reduction" is computed by integrating the area between two normalized image profiles. This area provides an index of the change in relative defect size. This quantitative image analysis was performed on standard static images derived by summing together all 16 frames acquired per cardiac cycle. Additional analysis was performed on the end-diastolic and end-systolic frames. The first frame of the gated sequence was assumed to represent end-diastole. The systolic and diastolic time intervals were defined from a simultaneously acquired left ventricular pressure signal (method outlined above) to determine the proportion of the cardiac cycle occupied by systole. The 16-frame image sequence was divided into the same systolic and diastolic portions. The end-systolic frame was defined as the last frame of the systolic portion of the cardiac cycle. In addition, heart size was estimated by analysis of the number of pixels in the area of interest manually drawn around the heart. The reproducibility of this method was established by redrawing the region of interest on 10 of the images (5 normal, 5 abnormal). The estimation of heart size by this method was highly reproducible (r= .99).

**Statistical Analysis**

All data are presented as mean±SEM. Normality of the distribution was verified with either the Wilk-Shapiro test or the Kolmogorov-Smirnov test, depending on the population size. Both univariate analysis of groups and ANOVA were performed (Statistical package, RS/1 Bolt, Beraneck, Newman, Cambridge, Mass). Dunnett's multiple comparison test was used when comparisons were made between multiple serial measurements and a control measurement. Selection of the statistical test was performed automatically on the basis of the results of normality testing. Differences between groups were considered significant at P<.05 (two-tailed).

**Results**

A total of 25 dogs underwent either 15 minutes (n=19) or 3 hours (n=6) of coronary occlusion followed by 3 hours of reperfusion. Five dogs were excluded from the analysis because of arrhythmic death (n=3) or technical complications (n=2). Analysis was restricted to the remaining 20 dogs, which included 10 group 1A dogs (mean weight, 19.9±0.5 kg), 6 group 1B dogs (mean weight, 19.2±0.3 kg), and 4 group 2 dogs (mean weight, 21.4±0.6 kg).
Postmortem Analysis

The postmortem "area at risk," expressed as a percentage of the left ventricular area (%LV), was comparable among the three groups of dogs (group 1A, 30±2%LV; group 1B, 33±2%LV; group 2, 33±3%LV). There was no evidence of myocardial necrosis in any of the group 1A or 1B dogs by TTC staining. Among the group 2 dogs, infarct size was 44±4% of the risk area.
TABLE 1. Hemodynamics and Risk Area Myocardial Thickening

<table>
<thead>
<tr>
<th>Group</th>
<th>Base</th>
<th>Occ</th>
<th>Rep 15 Min</th>
<th>Rep 1 Hour</th>
<th>Rep 2 Hours</th>
<th>Rep 3 Hours</th>
<th>Dobutamine Dose, μg · kg⁻¹ · min⁻¹</th>
<th>Post Dobut</th>
<th>2.5</th>
<th>5.0</th>
<th>7.5</th>
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<tr>
<td>HR (bpm)</td>
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<td>147±7</td>
<td>146±7</td>
<td>148±6</td>
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<td>120±5</td>
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<td>-10±1*</td>
<td>-8±2*</td>
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<td>3±5*</td>
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<td>22±5‡</td>
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<tr>
<td>HR (bpm)</td>
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<td>142±9</td>
<td>141±9</td>
<td>152±6</td>
<td>155±5</td>
<td>135±8</td>
<td>147±10</td>
<td>155±9</td>
<td>166±7</td>
<td>170±10</td>
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<tr>
<td>AoP (mm Hg)</td>
<td>134±9</td>
<td>121±10</td>
<td>103±5</td>
<td>108±5</td>
<td>106±7</td>
<td>85±3</td>
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<td>98±10</td>
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<tr>
<td>%TF RA</td>
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<td>-10±1*</td>
<td>-11±1*</td>
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<td>-10±1*</td>
<td>-8±1*</td>
<td>-3±4*</td>
<td>-1±5*</td>
<td>-2±5*</td>
<td>-10±1*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Base indicates baseline; Occ, occlusion; Rep, reperfusion; Dobut, dobutamine; Post Dobut, 30 minutes after dobutamine infusion; HR, heart rate; bpm, beats per minute; AoP, mean aortic pressure; and %TF RA, percent thickening fraction in risk area.

*P<.05 vs baseline.
†P<.05 vs 3 hours of reperfusion.

Hemodynamics and Risk Area Myocardial Thickening

Heart rate and aortic pressure remained stable during coronary occlusion and reperfusion among all three groups of dogs (Table 1). During dobutamine administration in groups 1B and 2, heart rate increased progressively. Dobutamine caused an initial increase in mean aortic pressure; however, aortic pressure decreased slightly at the maximum dose of dobutamine (10 μg · kg⁻¹ · min⁻¹) in both groups.

The “stunned” dogs (groups 1A and 1B) developed dyskinesis as expected in the ischemic area during coronary occlusion, reflected in the negative percent thickening fraction (Table 1). Thickeniong fraction partially improved after 3 hours of reperfusion in these “stunned” dogs. The administration of dobutamine in group 1B dogs caused a transient normalization of thickening fraction in the postischemic region.

The infarcted dogs (group 2) demonstrated a decrease in percent thickening fraction in the ischemic region comparable to the “stunned” dogs (groups 1A and 1B) (Table 1). In contrast to the “stunned” dogs, infarcted dogs did not demonstrate a significant improvement in risk area thickening fraction with dobutamine administration.

Regional Myocardial Blood Flow and ⁹⁹mTc-Sestamibi Activity

Myocardial ⁹⁹mTc-sestamibi activity and serial microsphere flow were assessed in the risk area in 7 of the 10 group 1A dogs injected with ⁹⁹mTc-sestamibi before coronary occlusion (Table 2). In these dogs, no significant change in myocardial ⁹⁹mTc-sestamibi activity was seen in the ischemic risk area, despite subsequent coronary artery occlusion and reperfusion. Myocardial ⁹⁹mTc-sestamibi activity in the ischemic risk area was 106±4% nonischemic, which was not significantly different from relative microsphere blood flow (111±3% nonischemic) at the time of the ⁹⁹mTc-sestamibi injection.

Groups 1B and 2 dogs were injected with ⁹⁹mTc-sestamibi during coronary artery occlusion. Occlusion flow in the “stunned” dogs (group 1B) was 7±1% of nonischemic. The ⁹⁹mTc-sestamibi activity in this region was 46±3% of nonischemic (P<.05), suggesting that significant redistribution may have occurred in this model of myocardial stunning. In the infarcted dogs (group 2), flow in the risk area during occlusion was 17±4% of nonischemic, and myocardial ⁹⁹mTc-sestamibi activity in this region was 27±4% of nonischemic (P=NS).

Image Analysis: Alteration of Defect Size With Changing Left Ventricular Thickening and Geometry

Group 1A. The group 1A dogs demonstrated a perfusion defect in the risk area during occlusion and reperfusion, despite injection of the ⁹⁹mTc-sestamibi under resting basal conditions and initially normal images. The artifactual defect was evident on summed images and exaggerated further on the end-systolic images.

TABLE 2. Myocardial Blood Flow and ⁹⁹mTc-Sestamibi Activity in Risk Area

<table>
<thead>
<tr>
<th>Transmural Flow in Risk Area (% nonischemic)</th>
<th>Dobutamine Activity (% nonischemic)</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Occlusion</td>
</tr>
<tr>
<td>Group 1A (n=6)</td>
<td>111±3</td>
</tr>
<tr>
<td>Group 1B (n=5)</td>
<td>111±7</td>
</tr>
<tr>
<td>Group 2 (n=4)</td>
<td>117±9</td>
</tr>
</tbody>
</table>

*P<.05 vs baseline flow.
†P<.05 vs occlusion flow.
defect was minimized in some animals when analysis was restricted to the end-diastolic frame (Fig 3).

The observed changes in the defect integral and defect extent for group 1A “stunned” dogs are summarized in Fig 4. Both the defect integral and extent decreased after reperfusion. The defect integral and extent were largest when analysis was restricted to end systole. The average defect at end systole extended over 25% of the image profile. Average defect integral correlated inversely with thickening fraction for both summed ($r=-.72$) and end-systolic images (ES; $r=-.84$) but not end-diastolic images (ED; $r=-.12$). Similarly, the average defect extent correlated inversely with thickening fraction for both summed ($r=-.61$) and end-systolic images ($r=-.78$) but not end-diastolic images ($r=-.15$). Analysis of summed and end-systolic images demonstrated a direct correlation of the dilatation index with both average defect integral (summed, $r=.63$; ES, $r=.79$) and defect extent (summed, $r=.79$; ES, $r=.84$). Analysis of end-diastolic images revealed a poor correlation between the dilatation index and the defect integral ($r=.42$) or defect extent ($r=.44$).

The observed changes in heart size relative to the baseline images for group 1A dogs are summarized in Fig 5. The heart size increased approximately 11% on the summed images during coronary occlusion and slowly returned toward normal size (albeit not completely) after reperfusion (Fig 5).

Thus, an artifactual defect was created in group 1A dogs associated with coronary artery occlusion. The measured indices of defect size after reperfusion correlated with changes in both estimated heart size and regional myocardial thickening for both summed and end-systolic images. However, no correlation of defect size and the dilatation index or thickening fraction was observed when analysis was restricted to end-diastolic images.

**Group 1B.** A change in $\gamma$-TC-sestamibi defect size was also seen in the group 1B dogs. The average index of defect reduction on the summed images tracked with the change in thickening fraction in the central ischemic region (Fig 6). After reperfusion, there was a gradual decrease in defect size. Dobutamine stress caused an additional transient decrease in the defect integral. Changes in the defect size correlated linearly with
changes in regional thickening in the central ischemic region for both summed ($r=0.89$) and end-diastolic ($r=0.86$) images (Fig 7). Improvement in the thickening in the group 1B “stunned” dogs was associated with a reduction in the defect size.

Group 2. In contrast to the stunned dogs (groups 1A and 1B), the infarcted dogs (group 2) demonstrated no significant reduction in defect size after reperfusion or with dobutamine stress (Fig 8). In these dogs with myocardial infarction, no change in regional myocardial thickening was observed.

Discussion

In experimental models of coronary artery occlusion and reperfusion, we have demonstrated that the $^{99m}$Tc-sestamibi defect size may be affected by alteration of left ventricular geometry often associated with myocardial stunning. Coronary occlusion produces regional ischemia, which in turn produces systolic thinning (dyskinesis) and distortion of left ventricular geometry. This regional dysfunction can create artificial perfusion defects on planar $^{99m}$Tc-sestamibi images. This artifact is apparent on static images but is maximal on end-diastolic images. Gradual improvement in regional left ventricular function in the central ischemic area after reperfusion and transient augmentation of regional function with dobutamine were both associated with a quantitative reduction in $^{99m}$Tc-sestamibi defect size. Thus, transient changes in regional function may confound analysis of risk area with $^{99m}$Tc-sestamibi when delayed imaging is performed after injection. In addition, geometric factors could also lead to misinterpretation of myocardial salvage when serial images are compared. Myocardial viability and salvage may be underestimated by analysis of serial $^{99m}$Tc-sestamibi images because of
Fig 6. Graph showing average reduction in defect size over time relative to the change in percent thickening fraction (%TF) for group 1B dogs (n=6) injected with ⁹⁹ᵐTc-sestamibi during coronary occlusion. The quantitative index of defect reduction derived from summed planar images was compared with changes in regional thickening measured in the central ischemic area with sonomicrometers. Both defect size (left axis) and regional percent thickening fraction (right axis) were expressed relative to values obtained during occlusion (OC). At 3 hours of reperfusion, the defect reduction was significantly greater than the initial change after reperfusion. The slow reduction in defect size matched temporally with the improvement in percent thickening fraction. Dobutamine (DOB) caused a transient improvement in regional thickening, which was associated with a transient reduction in defect size. *P≤.05 versus value 5 minutes after reperfusion.

persistent yet ultimately reversible postischemic regional dysfunction.

The alteration of ⁹⁹ᵐTc-sestamibi defect size that we observed is in part related to partial volume effects. This partial volume effect has been observed previously with positron emission tomography (PET) and single photon emission computed tomography (SPECT). The partial volume effect is a result of the finite resolution of the gamma camera. Galt et al suggested that the accuracy with which regional activity can be derived with PET or SPECT is limited when the object is smaller than 2 FWHM of the point spread function of the system. Recorded activity of a thin object (<2 FWHM) is lower than that of a thick object (>2 FWHM), even though the concentration of activity may be identical. Thus, the partial volume effect refers to the underestimation of count density from a structure that is thinner than the resolution of the imaging system. The thinner the object, the more prominent the artifact.

FWHM of a typical gamma camera system ranges from 12 to 20 mm. Thickness of myocardium falls within this range. Therefore, ⁹⁹ᵐTc-sestamibi myocardial perfusion defects can be observed even when the distribution of activity is uniform.

Assuming uniform distribution of ⁹⁹ᵐTc-sestamibi, one would expect the most apparent artifactual defects on end-systolic images. This phenomenon is caused by systolic thinning of the ischemic region at a time of maximal systolic thickening in the normal region. Thus, differences in wall thickness between normal and ischemic regions will be most prominent at end systole. In fact, a compensatory increase in thickening may occur in the normal region, resulting in an increased magnitude of the artifact. In the absence of aneurysm formation (defined by diastolic deformity), wall thickness at end diastole is relatively uniform. Therefore, analysis of end-diastolic images may minimize this effect. The partial volume effects may also be seen on static images, although the effect may be reduced by averaging systolic and diastolic images.

Myocardial ⁹⁹ᵐTc-sestamibi activity remains fixed within the myocardium during each cardiac cycle. Con-
sequentially, during systolic thickening, count density per volume of myocardium decreases, whereas during diastolic relaxation, count density per volume increases. This “thickening effect,” although in opposition to the “partial volume effect,” is far less important. Analysis of ECG-gated $^{99m}$Tc-sestamibi images demonstrates cyclic changes in image brightness (count density). These changes in image brightness are predominantly related to the partial volume effect and may provide a means of assessing regional thickening.\(^\text{17}\)

Parodi et al\(^\text{15}\) demonstrated that regional wall motion abnormalities can create artifactual segmental defects on PET images of the heart. They also suggested that heart rate and contractility may play a role in the quantification of myocardial tracer concentration. Heart rate and regional myocardial contractility will influence the mean wall thickness during an entire cardiac cycle. Changes in mean wall thickness will induce changes in measured regional myocardial activity.

In our study, dobutamine caused a transient reduction in quantitative defect size only in “stunned” dogs, which was associated with an improvement in regional thickening. The observed reduction in defect size with dobutamine probably resulted from an improvement in regional thickening (improved contractility) and an increase in heart rate. As would be predicted, we observed the most dramatic changes in defect size when analysis was restricted to end-systolic frames, since “stunned” myocardium will demonstrate maximal regional thinning during systole.

In group 1A dogs, regional dysfunction created an artifactual perfusion defect. Defect size was inversely correlated with regional thickening in both summed and end-systolic images. However, this correlation was not observed for the end-diastolic images. In group 1A dogs, mild improvement in thickening after reperfusion did not produce corresponding changes in end-diastolic defect size. The improvement in function did, however, alter defect size on the summed and end-systolic images. Coronary occlusion produces changes in global heart size in addition to regional dysfunction. Changes in global geometry are more likely to produce changes in end-diastolic defect size than would changes in regional function. Under these conditions, end-diastolic defect size would be significantly altered independent of changes in regional thickening.

In contrast, in group 1B dogs, the change in thickening fraction correlated with the change in defect size for end-diastolic images. The group 1B dogs were infused with increasing doses of dobutamine after reperfusion. The graded infusion of dobutamine produced progressive changes in contractility, regional thickening, and global left ventricular geometry. Under these conditions, changes in defect size would be related to serial changes in both regional thickening and global geometry. The correlation of defect size and regional thickening for end-diastolic images among group 1B may in part be related to serial changes in geometry produced with dobutamine.

In group 1A dogs, we created an initial change in global geometry, followed by serial changes in regional dysfunction. In group 1B dogs, we created serial concomitant changes in regional dysfunction and global geometry. Analysis of the group 1B dogs suggests that serial changes in global left ventricular geometry may not be corrected by analysis of only end-diastolic frames. However, the data from our group 1A dogs do support the potential for end-diastolic analysis to minimize the partial volume effect associated with changes in regional thickening. These data also suggest that the partial volume effects may be only partially reduced by restricting analysis to end-diastolic frames.

**Effect of Redistribution on $^{99m}$Tc-Sestamibi Defect Size**

Our study also demonstrates no redistribution after reperfusion in the presence of myocardial necrosis (group 2) and significant redistribution after transient ischemia (group 1B). $^{99m}$Tc-Sestamibi was injected 5 and 30 minutes before reperfusion in group 1B and group 2 dogs, respectively. Reperfusion in group 1B dogs 5 minutes after injection of $^{99m}$Tc-sestamibi could theoretically result in early redistribution. However, early redistribution of $^{99m}$Tc-sestamibi is unlikely, since previous studies suggest that blood levels of $^{99m}$Tc-sestamibi are already low 5 minutes after injection.\(^\text{19}\) In addition, changes in defect size among group 1B dogs was slow, suggesting that early redistribution did not occur. Thus, difference in time to injection probably does not account for the observed differences in redistribution. Our data suggest that the degree of myocardial salvage after reperfusion and the timing of imaging after injection may be critical when $^{99m}$Tc-sestamibi is used for the assessment of risk area in acute myocardial infarction. This is consistent with some, but not all, studies evaluating the phenomenon.\(^\text{8,18-20}\)

**Clinical Implications**

**Acute myocardial infarction.** Serial $^{99m}$Tc-sestamibi imaging has been used clinically for the assessment of the area at risk and myocardial salvage after thrombolyis.\(^\text{1,2,4}\) Injection of $^{99m}$Tc-sestamibi before intervention in the setting of acute myocardial infarction has been used to identify the myocardial risk area. Initial imaging is frequently delayed several hours, assuming that the distribution of $^{99m}$Tc-sestamibi will not change significantly even if reperfusion occurs. This approach has been supported by experimental studies\(^\text{8,20,21}\) that used canine models of occlusion and reperfusion in which extensive myocardial infarction was present. Differences in $^{99m}$Tc-sestamibi defect size observed clinically in the presence of comparable anatomic coronary occlusions\(^\text{2}\) have been attributed in part to differences in collaterals at the time of occlusion. Our data suggest that initial $^{99m}$Tc-sestamibi defect size may also be influenced by changes in regional and global left ventricular function and geometry and potentially $^{99m}$Tc-sestamibi redistribution. These effects may be significant in the acute phase of myocardial infarction.

After acute myocardial infarction, a reduction in $^{99m}$Tc-sestamibi defect size on subsequent follow-up studies after intervention (ie, thrombolysis or percutaneous transluminal coronary angioplasty) has been equated with reperfusion and myocardial salvage.\(^\text{1,2,4}\) Our data would also suggest that the assessment of myocardial salvage by analysis of serial images may be influenced by changes in regional left ventricular function and geometry. The progressive decrease in $^{99m}$Tc-sestamibi defect size observed between 2 and 7 days after thrombolytic therapy of myocardial infarction may
be related to the functional recovery of stunned myocardium. Experimental data suggest that these changes are probably not related to differences in myocardial uptake. In an experimental model of myocardial stunning, the uptake of $^{99m}$Tc-sestamibi was proportional to flow in the postischemic myocardium.

We have demonstrated that partial volume effects may be significant for the quantitative assessment of defect size when planar cardiac imaging is used. Since the resolution of SPECT imaging is generally less than that of planar imaging, these effects may be even more dramatic for SPECT imaging. Recent preliminary experimental data suggest that changes in regional function can also create artifactual SPECT $^{99m}$Tc-sestamibi defects. Differences in quantitative $^{99m}$Tc-sestamibi SPECT defect size have been observed when analysis was restricted to end-diastolic images versus gated images.

The effect of geometry on $^{99m}$Tc-sestamibi defect size in humans may be better understood with attention to volume status of the patient and simultaneous analysis of left ventricular volume and function. $^{99m}$Tc-Seastamibi permits the unique assessment of perfusion, function, and volume if first-pass analysis of the left ventricular bolus is performed. Restricting the quantitative analysis of defect size to end-diastolic images may only partially compensate for the effect of regional dyskinesis and changing left ventricular geometry.

**Exercise scintigraphy.** The effect of changing left ventricular function and geometry and associated partial volume effects may also have important implications for exercise perfusion scintigraphy. Exercise echocardiography and radionuclide angiography have demonstrated that regional left ventricular dysfunction is generally short-lived after exercise, although it may persist for as long as 40 minutes after exercise. This phenomenon has been called postexercise stunning. Scintigraphic imaging immediately after exercise may be affected by transient regional left ventricular dysfunction or left ventricular dilatation. Changes in $^{201}$TI defect size observed after exercise have been attributed to redistribution of the tracer within the myocardium. Our data would suggest that the reduction in defect size between initial and delayed $^{201}$TI imaging after exercise or pharmacological stress also may be partially related to changes in left ventricular function and size. Perhaps less clinical reversibility has been observed with $^{99m}$Tc-sestamibi after exercise than $^{201}$TI because initial $^{99m}$Tc-sestamibi imaging has been delayed 60 to 120 minutes. This delay in imaging with $^{99m}$Tc-sestamibi would permit recovery of exercise-induced left ventricular dysfunction and reduce potential partial volume effects.

**Dobutamine stress.** Dobutamine has been used as a pharmacological stress agent for use in conjunction with perfusion scintigraphy. The effect of dobutamine on heart rate and contractility may influence the assessment of regional myocardial activity. Experimental models demonstrate that dobutamine produces pronounced heterogeneity in function in the presence of a critical stenosis, whereas the differential effects on regional flow may be minor. Clinical differences observed in regional perfusion with dobutamine pharmacological stress may in fact represent residual effects on heart rate and regional thickening. These confounding effects may be minimized by restricting analysis to selected frames in the cardiac cycle and careful attention to timing of imaging relative to the stress. Evaluation of true changes in myocardial perfusion during pharmacological stress would necessitate delaying imaging until left ventricular size and function have returned to baseline. Perhaps analysis of end-diastolic images will facilitate earlier imaging.

Conversely, these geometric effects may be capitalized on for the assessment of myocardial viability after coronary reperfusion. Our data suggest that $^{99m}$Tc-sestamibi scintigraphy before and during dobutamine stress may be useful in distinguishing "stunned" from reperfused infarcted myocardium. However, clinical implementation of this approach may be complicated by a residual coronary artery stenosis and the presence of a mixture of viable and nonviable myocardium. In this study, the effects of dobutamine were evaluated in the two most extreme conditions: (1) "stunning" in the absence of necrosis (group 1B) and (2) the presence of extensive necrosis (group 2). In addition, both groups of dogs had open arteries at the time of dobutamine stress. Further studies are warranted to evaluate the clinical implications of the observed effects of changing left ventricular geometry on perfusion scintigraphy. The potential of dobutamine scintigraphy for the assessment of myocardial viability also warrants further investigation.

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