Quantitation of size of relative myocardial perfusion defect by single-photon emission computed tomography

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ABSTRACT The purpose of this study was to validate a semiautomatic method for quantitating the size of relative myocardial perfusion defects from single-photon emission computed tomographic (SPECT) images. We compared the size of the image defect in vivo, expressed as percent of involved left ventricle, as determined by this method with the anatomic size of the defect in vitro in 19 dogs. To test the method under optimal conditions, we first labeled the left ventricular myocardium in nine dogs by left atrial injection of $^{99m}$Tc-labeled macroaggregated albumin particles after acute occlusion of one coronary artery. The “defect volume” was defined as the volume of the left ventricular myocardium for which counts fell 2 or more SDs below the distribution of counts in the myocardium supplied by a normal coronary artery in a series of animals. The relative in vivo defect volume by SPECT occupied 26.46 ± 12.7% of the left ventricular volume (mean ± SD), compared with a relative defect size in vitro of 33.3 ± 13.7% (p = NS) of left ventricular volume as determined by well counting of myocardial samples. There was a close correlation between the two measurements ($r = .92$). However, myocardial relative defect volumes involving less than 5% of myocardium were not identified by SPECT. The defect volume weighted for the relative reduction in flow within the defect zone or the relative “reduced perfusion volume” was also determined. The correlation between the estimates by SPECT and those made in vitro for relative reduced perfusion volume was also high ($r = .94$). The method was then evaluated under conditions simulating the clinical imaging situation by injecting $^{201}$Tl intravenously into 10 resting dogs. Relative defect volume in vivo by SPECT was 29.38 ± 13.3% of left ventricular volume compared with a relative defect volume in vitro of 35.09 ± 10.73% of left ventricular myocardial volume ($p = .09$). The correlation between the two was .70. The tomographic relative reduced perfusion volume occupied 11.4 ± 7.8% of the left ventricular volume compared with 16.9 ± 9.3% ($p = .003$) for the measure in vitro. Correlation between the SPECT and anatomic estimates of relative reduced perfusion volume was high ($r = .88$). We conclude that the size of a relative myocardial perfusion defect can be accurately quantitated by single-photon tomography. The techniques described may prove useful in the assessment in vivo of interventions directed at altering myocardial infarct size, in the determination of extent of ischemic myocardium, or in the diagnostic evaluation of patients with suspected coronary artery disease.

Circulation 70, No. 6, 1048–1056, 1984.

THE SEARCH FOR accurate noninvasive methods for determining the size of myocardial infarction has been the aim of many investigations.1–10 The use of therapeutic interventions designed to decrease infarct size has been an impetus for the development of measurements of size that might be applied clinically. Several imaging modalities have been proposed to define myocardial perfusion defects.5–6,10 In this study, we employed single-photon emission computed tomography (SPECT) to externally quantitate myocardial perfusion defects. For imaging of this type a standard gamma camera that rotates about the subject and readily available radionuclides are used, and it is thus relatively inexpensive and potentially widely applicable. A prior study in our laboratory has established that the visual analysis of SPECT images improves the ability to detect myocardial infarction when compared with conventional planar imaging.11 The purpose of this study was to test, in instrumented dogs, a semiautomatic method for quantitating relative myocardial perfusion...
abnormalities and to validate it by direct tissue counting. We studied both an idealized preparation using intra-atrial $^{99m}$Tc-labeled particles and a more clinically relevant preparation in which intravenous $^{201}$Tl was used.

Methods

Animal preparation

Myocardial labeling with $^{99m}$Tc particles. Nine mongrel dogs (25 to 45 kg) were instrumented with a left atrial catheter. Alternate dogs had a hydraulic coronary artery occluder placed on either the left anterior descending or circumflex coronary artery. The occluder was placed so that a wide size range of myocardial perfusion defects would be created. The amount of hydraulic pressure needed to produce complete occlusion of the coronary artery was determined. After a 10-day recovery period, each dog underwent baseline imaging without occlusion, and 1 week later imaging was performed after occlusion.

During baseline imaging coronary blood flow was increased by intravenous injection of dipyridamole (0.4 mg/kg), which was used to maximize delivery of radionuclide to the myocardium and thus increase the target to background counts for imaging purposes. This dose of dipyridamole has previously been shown to increase coronary flow by three to fivefold over resting levels by 5 min after injection. To assess myocardial perfusion, 2 to 3 million macroaggregated albumin (MAA) particles labeled with $^{99m}$Tc (mean dose 19.2 mCi, range 17 to 23) were injected into the left atrium 5 min after the dipyridamole infusion. The animals were lightly sedated with xylazine (0.5 mg/kg) and placed on the imaging table. Baseline SPECT images of the distribution of normal blood flow were acquired (see below).

One week later, hyperemia was again induced with dipyridamole as before. The coronary artery of each dog was occluded by applying 50% more pressure to the occluder than was needed to produce occlusion at the time of surgery. The myocardium was then labeled by an identical left atrial injection of $^{99m}$Tc-MAA particles as used for the baseline study. After particle distribution, the coronary occluder was released and tomographic images were acquired. The animal was then heparinized, anesthetized, and killed.

Intravenous myocardial labeling with $^{201}$Tl. A second series of 10 dogs was studied with use of intravenous $^{201}$Tl injected into animals at rest, simulating clinical imaging in patients with myocardial infarction. Dipyridamole was not used. For the baseline study, 1.0 to 1.5 mCi of $^{201}$Tl was injected intravenously into animals standing quietly. They were then sedated and 20 min later, baseline tomographic imaging was begun. One week later the animals were sedated, intubated, anesthetized, and ventilated. After pretreatment with intravenous lidocaine, each heart was exposed through a left thoracotomy and in alternate dogs either the left anterior descending or circumflex coronary artery was ligated. The chest was closed, an identical amount of $^{201}$Tl as used for the baseline study was injected intravenously, and 20 min after injection, acquisition of tomographic images was begun. Upon completion of the experiment the animals were killed.

Preparation in vitro. In both series of experiments the hearts were excised and washed free of blood with 37°C saline and a polyurethane resin was introduced into the right and left ventricular chambers simultaneously. This resin hardens, allowing pathologic sectioning as previously described. With the use of the apex of the left ventricle as a reference, each heart was cut into a series of 18 mm thick cross-sectional slices perpendicular to the long axis of the left ventricle. The slice thickness of 18 mm approximated the in-air, full-width-at-half-maximum reso-

![FIGURE 1. The four anatomic slices, each 1.8 cm thick, of the left ventricular myocardium, from one of the study animals. The slices have been positioned to be as close as possible to the orientation in vivo as viewed from the apex of the heart. Both atria and the right ventricle have been dissected off of the left ventricle. Superimposed on the base slice is the template used to cut each slice into 32 myocardial segments, 11.25 degrees each.](image-url)

LUNATION of the imaging system being used. Right ventricular and atrial tissue was removed as shown in figure 1. Since the slice located at the base frequently included connective tissue structures (i.e., mitral apparatus), which variably affects definition of the normal counts per gram of myocardium (see below), only the four apical slices were analyzed.

Each slice was oriented so the position of its external structures corresponded to its position in vivo and each was cut into a series of 32 segments as shown in figure 1. These samples were then weighed and $^{99m}$Tc or $^{201}$Tl activity was measured in a well counter and expressed as counts per minute per gram of myocardium after correction for decay.

Data analysis

Anatomic slices (analysis in vitro). Analysis of the anatomic slices was performed in the same way for both series of animals. Left ventricular weight for each animal was determined by summing the weights of the 128 samples (four cross-sectional anatomic slices × 32 samples per slice). To define the segments with a normal distribution of activity, we identified on each slice the location of that segment containing the coronary artery that was occluded. A segment 180 degrees away in the opposite wall was considered to be in the center of the normal zone for that slice. Five samples on either side of the reference normal segment were identified, the counts per minute per gram as measured by well counting for these 11 normal samples were summed, and the mean and SD counts per minute per gram were determined. This was considered to be the normal value for the slice under consideration. The counts from all 32 myocardial samples for each slice were then examined and those samples in which activity fell below 2 SDs of this mean normal value were defined as abnormal. This statistical definition was employed to correspond to our analysis of tomographic images (see below). Since no attenuation correction is available for thoracic SPECT imaging, only a relative comparison of counts in a perfusion defect to a normal zone is possible; hence our analysis of the data in vitro.
The total relative defect volume was calculated by summing the volumes (sample weight in g/1.05 g/cm³) of all myocardial samples that had count activities more than 2 SDs below normal. Relative defect volume was also expressed as the percent of the left ventricle involved by dividing it by the total volume of left ventricular myocardium.

The counts per cubic centimeter for individual myocardial segments within the defect volume were not uniformly reduced because of anatomic variations, collateral blood supply, and/or sampling artifact, and ranged from slightly below the 2 SD value to substantially lower. Because of this, we also calculated a defect volume based on the relative reduction in counts within the defect volume. We have termed this the relative reduced perfusion volume, which was determined in the following manner. The magnitude of the count reduction within the defect volume was calculated from the sum of the counts per cubic centimeter in the normal zone minus the counts per cubic centimeter in the abnormal zone divided by the counts per cubic centimeter in the normal zone. This ratio defined the average reduction in counts in the abnormal zone compared with that in the normal zone. This ratio, multiplied by the volume of the defect volume, defined the relative reduced perfusion volume. The relative reduced perfusion volume was also expressed as a percent of the left ventricle by dividing the volume of the relative reduced perfusion volume by the total volume of left ventricular myocardium.

Tomographic images (analysis in vivo). For the MAA studies, 128 projection images were acquired (128 × 128 format) about the entire circumference of each dog’s chest at 10 sec/view. Maximal counts per second over the entire field of view ranged from 15,000 to 20,000 and maximal counts per pixel in the projection image ranged from 150 to 200. For the 201TI studies, 64 projection images were collected at 20 sec per image over the anterior 180 degrees centered about the animal’s sternum. Maximal count rates were approximately 2000 counts/sec, similar to those in human studies in our laboratory. Maximal counts per pixel ranged from 20 to 40. The projection images from both the baseline and the occlusion studies were reconstructed into a series of 6 mm thick transaxial slices with use of filtered back-projection techniques. Details of the system resolution, performance, and image reconstruction process used have been described. These transaxial slices were then reoriented into a series of short-axis slices perpendicular to the long axis of the left ventricle. Quantitative analysis was initiated by summing all of the short-axis slices to form a composite image. Then, as shown in figure 2, the approximate geometric center in this image was estimated by technician placement of a cross-hair. The two orthogonal long-axis images defined by the cross-hair for the three-dimensional data set were then displayed as shown in figure 2. These two images were used to define the final three-dimensional volume in which data would be analyzed. Non-left ventricular activity was excluded by operator placement of a rectangular region of interest on these images. The apex was defined by a threshold value of 45% of the overall maximal counts per pixel for the left ventricle (figure 2), based on results of phantom experiments and those of Tauxe et al. The twelfth slice (7.2 cm from the apex) was chosen as the base to correspond to the measured anatomic long axis of the excised heart (see above).

Outer myocardial edges for each short-axis slice were defined by a threshold value of 45% of the maximal count value for a given slice. The maximal count value of each slice, rather than the maximal value for the entire heart, was used to partially correct for attenuation losses. Thus, although absolute count values were lower in the slices at the base of the heart because of attenuation, the relative thresholding per slice was the same for all slices. If, because of a perfusion defect, no outer edge was found, the location of the edge for the prior slice was used. In the case of a large defect with no previous slice for comparison, symmetry of the slice about the long axis was assumed and the radial distance out from the centerline to the opposite wall was used. These edges, as shown in figure 2, were used to define the major and minor diameters of an elliptical region of interest to be applied subsequently to each raw short-axis image. When summed for all slices, these ellipses represented the three-dimensional volume in which activity was quantitated and included both myocardium and blood pool. For 201TI imaging, resolution of the edges of small blood pool chambers has not been reliable and we therefore chose not to attempt to identify the endocardial border on any of the studies. An example of a 201TI image in a dog (figure 3) demonstrates this point.

To define count activity within the volume of myocardium, the 12 tomographic cross-sectional slices were compressed into four sequential slices of equal thickness beginning with the apical slice. This was done so that the tomographic and anatomic slices were comparable. Equally spaced radians were project ed from the center of each short-axis slice to create 32 sectors, as was done for the anatomic slices (figure 4). The number of pixels, the number of counts, and the maximal counts in each

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sector were then computed for each slice. A composite normal baseline (i.e., no occlusion) image was formed from the mean maximal counts per pixel per sector values that were obtained by summing the value from the corresponding sector of each slice from all nine animals. Count values were normalized to the sector in the four slices analyzed with the maximum counts per pixel.

For the individual occlusion studies, the maximum counts per pixel in each of the sectors within the volume of interest were similarly obtained. For the individual animals, each sector was compared with the corresponding sector in the composite normal image. Those sectors for which activity was below 2 SDs of the mean normal value were considered abnormal.

The tomographic definition of defect size was identical to that used for the data obtained in vitro. That is, relative defect volume was calculated by summing the volume of all abnormal sectors for each animal (volume in cm$^3$ = number of pixels per abnormal sector $\times$ pixel volume in cm$^3$). Tomographic relative reduced perfusion volume was similarly determined as follows. The mean maximal counts per pixel per sector in the baseline normal study minus the maximal counts per pixel per sector in each abnormal sector divided by the mean maximal counts per pixel per sector in the normal sector were multiplied by the volume of each abnormal sector. The tomographic relative defect volume and the relative reduced perfusion volume were also expressed as a percent of total tomographic left ventricular volume.

**Display of three-dimensional data.** To allow display of all of the three-dimensional data in an anatomically appropriate and easily assimilated format, the following was done. All count data were visually presented in image format and scaled to the maximal counts per pixel per sector such that 0% was black and 100% was white — intermediate values were gray. The slice data were then displayed as a series of concentric rings in which the apex was represented by the center ring and subsequent slices by the adjacent, larger rings, as shown in figure 4. This format preserves the traditional left anterior oblique orientation used in coronary angiography that best separates the anatomic beds of the left anterior descending, circumflex, and right coronary arteries. Perfusion defects in the anterior septal region appear to the left, the right coronary artery appears inferiorly, and the circumflex is on the right of the image. Defects at the apex appear in the center of the image and those at the base are located peripherally. A defect with 100% reduction of flow will

**FIGURE 4.** A schematic representation of the image analysis and display format. Left. A single short-axis left ventricular slice. Radians are projected from the center to define 32 myocardial sectors, 11.25 degrees each. The number of pixels and the maximum counts per pixel for each sector are determined for each slice from apex to base. The corresponding sectors are aligned as shown in the center. The maximal counts per pixel for each sector in the left ventricular region of interest is then scaled to the sector with the maximal counts. For purposes of display, the distribution of normalized maximum counts per pixel per sector per slice is then reformatted into a series of concentric circles as shown on the right, maintaining the normal left anterior oblique anatomic orientation of the image data. The apical slice is located at the center of the image and the basal slice at the edge. Activity from the inferior wall is located at the bottom of the image, from the septum on the left and from the free wall on the right. This display format has been termed the bullseye image. This single bullseye image displays all of the quantitative data for the entire heart.
appear black and an entirely normal heart will appear nearly uniformly white (figure 5). Both the anatomic location and the percent of left ventricular involvement and relative reduction of flow can be ascertained visually from this format. Figures 5 to 7 illustrate this display format under both normal conditions and those of occlusion.

Reproducibility. To define the intraobserver variability of the tomographic analysis technique, one technician analyzed each postocclusion study on two separate occasions 3 months apart. Interobserver variability was tested by two technicians (one experienced in the analysis algorithm and one inexperienced) analyzing the postocclusion images separately in a blinded manner.

Statistical analysis. Defect size as determined by tomography was compared with the defect size in the anatomic samples by both paired t testing and linear regression analysis. Interobserver and intraobserver variability were tested by the same statistical approach.

FIGURE 5. Four representative short-axis tomographic slices from the baseline $^{99}$Tc-MAA study of one of the dogs in this series. The tomographic slices have been chosen to correspond to the anatomic slices. Displayed on the right in the bullseye format is the scaled maximum counts per pixel per sector data for all of the tomographic slices described in figure 4. Maximal counts are shown in white and minimal counts in black. The relatively uniform distribution of activity can be appreciated. In this and subsequent figures, the term "maximal counts % global maximal" refers to the use of the maximum count per pixel per sector value scaled to that sector with the highest count value.

FIGURE 6. Images from the same dog as in figure 5 acquired after the creation of a perfusion defect. The large septal perfusion defect involving the three apical slices is readily appreciated in both the tomographic image and the bullseye format. The size of the defect relative to the overall size of the left ventricle at risk is also apparent in the bullseye display.
Results

Analysis of $^{99m}$Tc-labeled hearts in vitro. The mean volume (weight of the myocardium/1.05 g/cm$^3$) of the left ventricular myocardium for the nine animals was 101 ± 22 cm$^3$ (mean ± SD). Mean myocardial relative defect volume was 33.6 ± 15.56 cm$^3$, with a range from 7.6 to 57 cm$^3$. This relative defect volume is the sum of all sectors identified for which counts were more than 2 SDs below the normal range. Expressed as a percent of total left ventricular volume, the relative defect volume was 33.3 ± 13.7% of the left ventricle. When the defect size was expressed as the relative reduced perfusion volume, it was 20.78 ± 9.28 cm$^3$ and it involved 21.35 ± 10.27% of the left ventricular volume. The relative reduced perfusion volume was much smaller than the defect volume, as would be expected since there was some residual flow in most abnormal sectors. (The in vitro and the SPECT results are summarized in Table 1.)

Tomographic analysis of $^{99m}$Tc images. The tomographic estimate of relative defect volume was 73.68 ± 38.86 cm$^3$ (p < .001 compared with anatomic defect volume). This represented 26.46 ± 12.7% of the total left ventricular volume measured tomographically (p < .001 compared with results in vitro). The relative reduced perfusion volume in these zones was 13.67 ± 7.88% of left ventricular volume and was significantly less than the same anatomically defined value (p < .001 compared with in vitro).

When expressed as a percent of left ventricular vol-

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Perfusion defect size</th>
<th>In vitro</th>
<th>SPECT</th>
<th>$p$ value*</th>
<th>r value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defect volume (cm$^3$)</td>
<td>33.60 ± 15.56</td>
<td>73.68 ± 38.86</td>
<td>&lt;.001</td>
<td>.93</td>
<td></td>
</tr>
<tr>
<td>Defect volume as % total LV</td>
<td>33.30 ± 13.70</td>
<td>26.46 ± 12.70</td>
<td>&lt;.001</td>
<td>.92</td>
<td></td>
</tr>
<tr>
<td>Reduced perfusion volume (cm$^3$)</td>
<td>20.78 ± 9.28</td>
<td>38.17 ± 23.44</td>
<td>&lt;.001</td>
<td>.94</td>
<td></td>
</tr>
<tr>
<td>Perfusion volume as % total LV</td>
<td>21.35 ± 10.27</td>
<td>13.67 ± 7.88</td>
<td>&lt;.001</td>
<td>.90</td>
<td></td>
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<tr>
<td>$^{201}$TI studies</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Defect volume (cm$^3$)</td>
<td>30.51 ± 9.88</td>
<td>78.14 ± 40.69</td>
<td>.003</td>
<td>.55</td>
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</tr>
<tr>
<td>Defect volume as % total LV</td>
<td>35.09 ± 10.73</td>
<td>29.38 ± 13.34</td>
<td>.094</td>
<td>.70</td>
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</tr>
<tr>
<td>Reduced perfusion volume (cm$^3$)</td>
<td>14.57 ± 8.43</td>
<td>30.37 ± 22.51</td>
<td>.012</td>
<td>.88</td>
<td></td>
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<tr>
<td>Perfusion volume as % total LV</td>
<td>16.87 ± 9.29</td>
<td>11.38 ± 7.79</td>
<td>.003</td>
<td>.88</td>
<td></td>
</tr>
</tbody>
</table>

LV = left ventricle.

* Determined by paired t test.
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cm³ (p = .003 compared with anatomic relative defect volume). This represented 29.38 ± 13.34% of the
tomographically measured left ventricular volume (p = .09 compared with in vitro; table 1). The relative
reduced perfusion volume in these zones represented
11.38 ± 7.79% of left ventricular volume and was
significantly less than the corresponding anatomically
defined value (p = .003 compared with in vitro).

When expressed as a percentage of left ventricular
volume, the tomographic relative defect volume corre-
lated reasonably well with the in vitro relative defect
volume (r = .70). The tomographic relative reduced
perfusion volume expressed as a percent of total left
ventricular volume correlated closely (r = .88) with
the anatomic relative reduced perfusion volume ex-
pressed as a percentage of total left ventricular volume
(figure 9). Small relative reduced perfusion volumes
(less than 5% of left ventricular volume) were not
identifiable tomographically.

Reproducibility. For the studies in which the radiolabeled
MAA particles were used the interobserver vari-
ability for determination of relative reduced perfusion
volume (in cm³) by the tomographic method was small
(r = .85, SEE = 12.81; p < .001). When expressed
as a percentage of left ventricular volume, this vari-
ability was similar (r = .85; SEE = 4.90; p < .001).
Intraobserver variability was also small both for rela-
tive reduced perfusion volume in cubic centimeters (r
= .96, SEE = 6.95; p < .001) and as a percentage of
left ventricular volume (r = .97; SEE = 1.96; p <
.001). The results were similar for relative defect
volume.

FIGURE 8. For the ⁹⁹ᵐTc-MAA study, tomographic relative defect
volume as a percentage of left ventricular volume was compared
with the anatomic defect volume as a percentage of left ventricular volume.

FIGURE 9. For the ²⁰¹TI study, tomographic relative reduced perfu-
sion volume as a percentage of left ventricular volume was compared
with the anatomic reduced perfusion volume as a percentage of left
ventricular myocardial volume.

Analysis of ²⁰¹TI-labeled hearts in vitro. The mean vol-
ume of the left ventricular myocardium for the 10
animals in the ²⁰¹TI study was 87.14 ± 14.02 cm³. 
Mean myocardial relative defect volume was 30.51 ±
9.88 cm³, with a range of from 13 to 41 cm³. Expressed
as a percentage of total left ventricular myocardial
volume, the relative defect volume was 35.09 ±
10.73% of the left ventricle. Defect size, expressed as
the relative reduced perfusion volume, was 14.57 ±
8.43 cm³ and involved 16.87 ± 9.29% of the left
ventricular volume.

Tomographic analysis of ²⁰¹TI images. The tomographic
estimate of relative defect volume was 78.14 ± 40.69

For the $^{201}$TI studies, interobserver and intraobserver variability for relative reduced perfusion volume were $r = .99$, SEE = 6.87, $p = .001$, and $r = .99$, SEE = 2.85, $p < .001$, respectively. The corresponding values for relative reduced perfusion volume as a percentage of left ventricular volume were $r = .98$, SEE = 3.43, $p = .004$ and $r = .99$, SEE = .94, $p < .001$.

Discussion

In this study we validated a method for quantitating myocardial perfusion images acquired by SPECT. Imaging conditions were initially idealized so that the optimal potential clinical utility of this technique could be determined. Subsequently the method was applied under conditions that approximated the clinical imaging situation, i.e., $^{201}$TI was injected intravenously into resting animals in doses that produced counting rates similar to those observed in humans.

Our results demonstrate that SPECT imaging can be used to quantify both the relative volume of underperfused myocardium and the relative defect volume weighted for flow reduction when expressed as a percentage of the left ventricular myocardial volume. Use of the relative reduced perfusion volume provides the most consistent and best results under clinical imaging conditions. These results suggest that relative quantitation of myocardial perfusion defects produced by either infarction or ischemia in patients may be possible with SPECT. However, our approach assumes that some portion of the myocardium is normal and thus would underestimate perfusion defects that involve the entire heart.

Second, we have devised a display format that presents all of the three-dimensional slice data in a single two-dimensional image with an anatomically familiar orientation. As previously discussed, a large volume of three-dimensional data is generated in any tomographic analysis and optimal utilization of the information content is essential. Our display format reduces the quantitative slice data for the entire heart to a single image. This image preserves the familiar left anterior oblique orientation used in most coronary arteriographic images and should be easily assimilated. Additionally, all quantitative information is stored or reproduced on a single image, allowing easy storage and reproduction at a modest cost.

General limitations to our approach can be related (1) to this particular method of analysis or (2) to SPECT per se. Our analysis requires the definition of the apex of the heart, a region often involved in perfusion abnormalities. When totally nonperfused, the location of the apex must be estimated. For defects in areas of the myocardium other than the apex, the boundary is chosen either on the basis of the location of the boundary on the previous slice or by assuming radial symmetry about the long axis of the left ventricle. These approaches were also satisfactory for some of the apical slices. For others, however, it was necessary for the technician to estimate the location of the apex from a visual impression of overall myocardial shape. Both our results and the reproducibility studies suggest that this approach was satisfactory in our study animals, eight of which had perfusion defects involving the apex. An alternative approach might be one in which a tomographic gated blood pool image is used to define the apex. Another limitation for patient studies is the lack of an optimal perfusion imaging agent. However, the results with $^{201}$TI in this study support the feasibility of its clinical use. For this study, the base arbitrarily chosen on the tomographic images was that which corresponded to the anatomically defined base (see Methods). For clinical studies, the base could be identified by the 45% threshold method used for identifying the apex and the epicardial boundaries or by the operator.

When the size of the defect was expressed as the volume in cubic centimeters of myocardium involved, our tomographic estimate was systematically high. This overestimation occurred, to a large extent, because the tomographic analysis included the blood pool in the regions of interest applied to the short-axis slices, whereas the ventricular cavity was excluded in the analysis of the anatomic slices. The blood pool was included in the tomographic images because (1) it was difficult to determine the precise location of the blood pool-endocardial boundary on the tomographic slices, and (2) the contribution of activity from the blood pool to any of the 32 sectors in each slice is nil compared with the contribution from the myocardial activity. Since this analysis is based on the maximum counts per pixel per sector, the pixel with the maximum number of counts will not be located in the blood pool. When our analytical approach is applied clinically, the count distribution for an individual patient is compared with that in a series of normal subjects without ventricular hypertrophy or any recognizable heart disease. However, variations in ventricular length may be greater in patients than normal individuals. Because of this, count heterogeneity may be greater in patients than in our normal subjects and sizing of the defect volume may be less accurate than in animals. However, expression of defect size as a percentage of the left ventricle involved minimizes this problem and makes interpatient comparisons easier.
A general limitation of SPECT in the thorax is the absence of a satisfactory method for attenuation correction. Without this, measurement of blood flow in milliliters per gram of myocardium cannot be accomplished. The scaling of the images and subsequent slice-by-slice comparison with a normal mean determined by the same technique partially corrects for attenuation losses. That is, attenuation losses in the normal control subjects should be similar to those in patients.

Resolution of the current imaging devices available for SPECT is limited and small perfusion abnormalities remain beneath the resolution of the gamma camera. Perfusion defects smaller than 5 to 10 cm$^3$ will probably not be detected by this approach. We have previously shown that, even when imaged in vitro by SPECT, counts in myocardial perfusion defects are overestimated.$^{13}$ Keyes et al.$^{8,9}$ have also observed in hearts imaged in vitro that defects of less than 5 g could not be detected reliably by a SPECT imaging system. In patient studies, because of the larger size of most defects, this may be less of a problem, although small areas of malperfusion will presumably be undetectable.

There are no universally accepted methods for defining perfusion defects in vitro. Because of the short-term nature of this study, staining techniques dependent on the absence of lactate dehydrogenase or depletion of other enzymes were not appropriate. Microposphere techniques, which were used in this study, are widely accepted as the gold standard for the measurement of coronary blood flow distribution.$^{17,18}$ Based on the work of Marcus et al.$^{18}$ we believe that the use of 2 SDs below the mean counts per gram per minute in the samples centered about the normally perfused artery in each slice is an acceptable approach for determining abnormally perfused myocardial samples.

In summary, we have described an approach to the quantitation of SPECT myocardial perfusion images in an idealized animal preparation and then applied it under conditions similar to those in a clinical imaging situation. The results show that accurate quantitation of relative perfusion defects is possible. We have also developed a single-summary, two-dimensional image displaying all of the quantitative three-dimensional data. This method holds the promise of improved non-invasive quantitation of relative myocardial perfusion defects in the diagnosis and treatment of coronary artery disease.

We thank Ms. Ann Coleman, Ms. Kaye Gaines, and Mr. John Harris for their assistance in data acquisition and Mrs. Patricia Jenkins and Mrs. Maxine Cormier for preparation of the manuscript.

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Circulation 53: 879, 1981
Quantitation of size of relative myocardial perfusion defect by single-photon emission computed tomography.

J H Caldwell, D L Williams, G D Harp, J R Stratton and J L Ritchie

Circulation. 1984;70:1048-1056
doi: 10.1161/01.CIR.70.6.1048

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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