Tomographic Thallium-201 Myocardial Perfusion Scintigrams After Maximal Coronary Artery Vasodilation with Intravenous Dipyridamole

Comparison of Qualitative and Quantitative Approaches

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SUMMARY Eighty-six patients had thallium-201 (201Tl) myocardial perfusion scintigrams after intense coronary artery dilation with i.v. dipyridamole. The dipyridamole was infused at 0.15 mg/kg/min for 4 minutes. Significant side effects were infrequent. Coronary angiography showed that 24 of our 86 patients had normal coronary vessels or ≤ 30% luminal obstruction in one coronary artery; 11 patients had a moderate coronary obstruction (30–55% diameter narrowing or systolic compression) in one major vessel; and 51 patients had significant coronary artery disease (CAD) (≥ 70% luminal obstruction in one or more major vessels). Tomographic and planar 201Tl scintigrams were obtained in each patient. Tomographic scintigrams were interpreted using quantitative or visual criteria; planar scintigrams were assessed using visual criteria only. From the tomographic images, “lower limit of normal” curves were derived from the normal group by computing a “mean minus N standard deviations” curve and by computing a range curve. Using the mean minus standard deviations curve, we could not obtain a test with high (> 80%) sensitivity and specificity. The range approach produced better results. Inclusion of patients with moderate obstructions in the normal group significantly distorted the resulting lower limit of normal curve. When visual criteria were used, interobserver variability was 40% for tomographic scintigrams and 44% for planar scintigrams. In the 24 patients with normal or nonsignificant CAD, quantitative analysis of the tomograms (range approach) indicated that one of 24 (4%) had a positive image (specificity 96%); in contrast, when visual criteria were used to interpret the tomographic or planar 201Tl scintigrams, eight of 24 (33%) had positive scintigrams (specificity 67%). In the 51 abnormal patients, the sensitivity of detecting CAD was 46 of 51 (90%) for tomographic scintigrams interpreted quantitatively, 39 of 51 (76%) for tomographic scintigrams interpreted visually and 41 of 51 (80%) for planar scintigrams assessed visually. The tomographic imaging procedure (quantitative interpretation) also demonstrated a high sensitivity (89%) and specificity (100%) in 28 patients (10 normal and 18 CAD), with a clinical diagnosis of unstable angina pectoris. Overall, the predictive accuracy of an abnormal scintigram with quantitative tomographic imaging (98%) was significantly better (p < 0.05) than either qualitative planar or pinhole imaging.

THALLIUM-201 (201Tl) perfusion scintigraphy is widely used in the diagnosis of coronary artery disease (CAD).1-8 Although it enhances our ability to detect CAD, three major problems are associated with conventional 201Tl perfusion images: interpretation of the scintigrams has usually involved qualitative visual criteria; exercise is required to induce coronary vasodilation;1-8 and sensitivity (usually 65–90%) is not optimal.1-8

When 201Tl myocardial perfusion scintigrams are interpreted using qualitative criteria, many problems arise, including considerable interobserver variability,9 observer experience,10 dependence on display format and quality,11 and difficulty in dealing with the normal variations in 201Tl distribution.12 These problems can be partially resolved by using quantitative techniques.13-18 However, quantitative analysis of 201Tl perfusion scintigrams requires a precise definition of the normal scintigram. Therefore, one purpose of this study was to test several quantitative approaches to determining the lower limit of the normal 201Tl distribution and to determine whether moderate coronary obstructions are associated with 201Tl perfusion defects.

We have addressed two other problems associated with conventional 201Tl perfusion scintigrams in this study. In place of exercise, coronary artery vasodilation was induced pharmacologically with i.v. dipyridamole before injections of 201Tl, as suggested by Gould.20 To improve sensitivity, a tomographic imaging technique with a seven-pinhole collimator was used.11,18 Another purpose of this investigation was to determine the combined effects of three approaches (quantitative image analysis, coronary dilation with dipyridamole, and tomographic scintigrams) on the sensitivity and specificity of detecting significant CAD with 201Tl scintigraphy.

Methods and Materials

Patient Population

Eighty-six patients scheduled to have a diagnostic cardiac catheterization and coronary angiography were
studied. Patients were excluded if they had an acute myocardial infarction in the previous 6 weeks or life-threatening cardiac dysrhythmias, such as recurrent ventricular tachycardia or ventricular fibrillation.

The precatheterization diagnosis in the 51 patients shown to have significant CAD (≥ 70% diameter narrowing) was stable angina in 18, unstable angina in 18, valvular heart disease in 14, and atypical chest pain in one patient. Patients classified as having unstable angina had either one or more prolonged episodes (> 30 minutes) of substernal chest pain unresponsive to nitroglycerin or a 50% increase in the frequency of their angina within 2 months before admission. None of the patients with unstable angina was having frequent episodes of rest pain or required narcotic drugs for pain relief within 3–7 days of the imaging procedure.

The 35 patients with insignificant CAD were divided into a group that had no or minor CAD (≤ 30% diameter narrowing of a coronary artery (24 patients) or moderate CAD (30–55% diameter narrowing or systolic compression of one coronary artery). Twenty of the 24 patients with insignificant CAD had no coronary obstructions and four had one-vessel obstruction (25–30% diameter narrowing in the left anterior descending coronary artery). The clinical diagnosis in those patients was atypical chest pain in 12, unstable angina in eight, and valvular heart disease in four. The clinical diagnosis in 11 patients shown to have moderate CAD were atypical chest pain in three, unstable angina in two and valvular heart disease in six.

At the time of scintigraphy, 22 patients were taking propranolol, nine digitalis glycosides and 31 nitrates.

Studies were performed with the approval of the Human Subjects Review Committee at the University of Iowa. All participants gave informed consent.

Cardiac Catheterization

Multiple views of the right and left coronary arteries were obtained in all patients using the Judkins technique. Each patient also had a left ventriculogram using either an angiographic or radionuclide approach. Analysis of the coronary arteriograms and ventriculograms were performed by two of the investigators, who did not know the results of the 201TI studies. The location, percent diameter narrowing and the length of each coronary lesion was measured from cine frames projected on the screen of a Tage-Arno projector. Differences between observed measurements were resolved by consensus. Significant CAD was defined as ≥ 70% diameter narrowing in one or more major vessels in one angiographic projection. Global and segmental wall motion abnormalities on the ventriculograms were noted. Abnormal left ventricular function was defined as a left ventricular ejection fraction < 45% or the presence of dyskinesis, akinesis or hypokinesis in one or more ventricular segments.

Dipyridamole Infusion

With the patient in the supine position, dipyridamole was infused through a 21-gauge butterfly needle placed in a forearm vein. A calibrated infusion pump delivered the drug at 0.15 mg/kg/min for 4 minutes. During the procedure, arterial pressure was recorded with a sphygmomanometer, and a 12-lead ECG recording was obtained each minute. Cardiac rhythm was monitored continuously. After the dipyridamole infusion was completed, the patient sat up, stood, and then walked in place at a rate of 10–30 steps/min. At this point (30–60 seconds after cessation of the dipyridamole), 1.5 mCi of 201TI was injected i.v. and the cannula was flushed with 5 ml of saline. The patients continued to walk in place for 4–5 minutes longer. Patients were standing before the 201TI injection because left atrial pressure was lower in the upright than the supine position. At lower left atrial pressures, the heart/lung ratio of 201TI activity is increased, and consequently image quality improves. At the end of the procedure, the venous cannula was removed and the patient was taken to the nuclear medicine laboratory. The imaging procedure was usually begun within 10–15 minutes from the time of 201TI injection. Aminophylline (250 mg), which promptly reverses the effects of dipyridamole, was available during each procedure.

Cardiac Imaging

Each patient had both a planar (conventional) and tomographic 201TI myocardial perfusion scintigram. The order of performing these studies was alternated. We used a Searle large-field-of-view gamma camera (model 6413) and a seven-pinhole collimator (Cardiac Medical Systems). The design of these pinholes is such that photons project through all seven pinholes simultaneously onto nonoverlapping sections of the scintillation crystal. The camera was placed in the 40° left anterior oblique position and adjusted so that the views covered as much of the crystal face as possible and the central pinhole image was more annular than the other views. Each seven-pinhole study consisted of two data acquisition images of 350,000 counts each. The energy discriminator was set at 80 keV with a 30% window. These two images were collected over 10–15 minutes.

The planar 201TI images were obtained with a Searle LEM small-field-of-view gamma camera using a low-energy, parallel-hole, all-purpose collimator. The images were obtained in the anterior, 40° and 60° left anterior oblique and left lateral projections. The energy discriminators were set at 164 keV with a 25% window and 74 keV with a 35% window. The total imaging time for the conventional images was 25–40 minutes. No redistribution images were obtained.

Analysis of 201TI Scintigrams

The planar and tomographic 201TI scintigrams were analyzed visually by three experienced observers who did not know the names of the patients, results of the cardiac catheterizations or clinical history. An abnormality was defined as a discrete region of absent or decreased 201TI activity. The scintigrams were graded
as normal or abnormal. Disagreements in interpretation were resolved by consensus. During the initial reading, if the interpretation of the various observers differed (abnormal vs normal), this was recorded as an instance of interobserver variability.

**Tomographic Analysis**

From each seven-pinhole scintigram and previously acquired calibration images, we constructed 12 cross-sectional cardiac images (tomograms) using a computer system (Medical Data Systems) and a previously reported simultaneous multiple-angle reconstruction technique.27,28 These images are formed at approximately 1-cm intervals. We used the three most central scintigrams of the left ventricle (apical, central and basal) for quantitative analysis. We have developed a computer program (fig. 1). The program asks the operator to indicate the center of the ventricular cavity in the apical plane. The computer then divides the cardiac image into 60 6° "pie segments." The "hottest," or maximal, pixel in each segment is located and displayed to the operator as a contour superimposed on the myocardial image. This program does not use a ray-sampling technique, and thus does not ignore any pixels in the image.29 If the contour of the hot pixels falls wholly within the myocardium, the operator instructs the computer to plot the magnitude of the hot pixels around the circumference of the heart. If the contour falls partially outside of the myocardium, the radius within which the program searches for the maximal pixel is shortened until the contour falls wholly within the myocardium. The curve is normalized by expressing each point as a percentage of the hottest pixel in the image. The above procedure is repeated for the central and basal planes. Our program is similar in function to that described by Vogel et al.18 and Burow et al.29

Starting at the 3 o'clock position and proceeding counterclockwise, the left anterior descending coronary artery distribution corresponds to 0–270° in the apical plane and 100–270° in the central and basal planes of the tomogram. The left circumflex artery distribution was taken to correspond to 270–360° in all three planes, while the right coronary artery corresponded to 0–100° in the central and basal planes.

In each patient, three curves (apical, central and basal) derived as described above were used for quantitative analysis of the tomograms.

**Lower Limit of Normal Curves**

The "lower limit of normal" curve defines the normalized 201Tl activity below which a patient's perfusion distribution curve must fall in order to be considered abnormal. Figure 2 is a typical curve and a lower limit of normal curve from the apical plane for a normal patient. The upper curve is the patient's perfusion curve. If the patient's perfusion curve crosses below the lower limit or normal curve in any one of the three planes, the patient is considered to have a perfusion defect and the tomogram is positive.

Mean curves in each of three planes were derived from the patients with normal coronary arteries by averaging their individual curves point by point. One patient's data were excluded from our normal distribution because she was an obvious false positive. In determining the specificity of our imaging procedure, however, this patient was included. A set of lower limit of normal curves was derived by subtracting a variable number (1.0–4.0) of standard deviations (also calculated on a point-by-point basis) from the mean curve.

An alternative approach for defining the lower limit of normal is to use the range. Such a range curve was calculated by finding the minimum value (point by

![Figure 1](http://circ.ahajournals.org/DownloadedFrom/...)

**Figure 1.** Quantitative analysis techniques. After operator selection of the center of the ventricular cavity, the computer divides the cardiac image into 60 6° "pie segments." The maximal pixel in each segment is located and displayed as a contour superimposed on the myocardial image. If the contour of maximal pixels falls wholly within the myocardium, the computer plots the magnitude of the maximal pixels around the circumference of the heart. The curve is expressed as a percentage of the maximal pixel in the image.

![Figure 2](http://circ.ahajournals.org/DownloadedFrom/...)

**Figure 2.** Thallium-201 (201Tl) distribution in a normal patient (apical plane), indicating the relative distribution of 201Tl around the cardiac circumference. If the patient's 201Tl distribution crosses below the lower limit of normal, the tomogram is considered abnormal.
point) of the curves from patients with normal coronary arteries.

**Moderate CAD**

To assess the effect of including patients with moderate CAD on the definition of the normal curve, we calculated a range curve from all patients without significant CAD, i.e., normal subjects and patients with moderate CAD.

A scintigram was considered abnormal if the patient’s values dropped below the normal range at one or more points. The location of a coronary lesion was said to be concordant with the perfusion defect on the tomogram if the patient’s perfusion curve fell below the lower limit of normal at one or more points in the distribution of the obstructed coronary artery.

**Statistical Analysis**

Sensitivity was defined as (true positives)/(true positives + false negatives). Specificity was (true negatives)/(true negatives + false positives). Predictive accuracy of an abnormal test was (true positives)/(true positives + false positives). The false-positive rate was 1 minus the specificity. The data were analyzed by chi-square and Cochran’s tests where appropriate.

**Results**

**Adverse Effects of Dipyridamole**

Dipyridamole was well tolerated by most of the patients in our study. There were no significant arrhythmias or episodes of severe angina pectoris. In most patients, systolic blood pressure decreased by 5–10 mm Hg and heart rate increased by 5–15 beats/min during the infusion. About one-third of the patients complained of mild symptoms, such as dizziness, mild chest discomfort or nausea, which did not require any treatment or alteration in the protocol. Two patients were given i.v. aminophylline for severe nausea or vomiting that occurred 5–10 minutes after the 201Tl had been injected. The nausea and vomiting quickly abated after injection of the aminophylline (250 mg, i.v.). Both of these patients had positive planar and tomographic images. In one patient, the dipyridamole infusion was discontinued and aminophylline was administered because of a 40-mm Hg decrease in systolic blood pressure. Normotension was promptly restored. This patient had severe left ventricular dysfunction (left ventricular ejection fraction of 18%). Three patients who were asymptomatic had 2–4 mm of flat or downsloping ST-segment depression during the dipyridamole infusion. The ST-segment depression disappeared spontaneously within 10 minutes after the dipyridamole infusion. None of the patients with unstable angina developed significant symptoms during the dipyridamole infusion.

**Lower Limit of Normal Curves**

Figure 3 shows the mean curve (apical plane) derived from 23 normal patients. Two lower limit of normal curves are shown. One is the range curve and the second is the “mean minus 2 standard deviations.”

As expected, the range curve is somewhat lower than the mean minus 2 standard deviations curve at almost every point. The false-positive rate obtained using the mean minus 2 standard deviations lower limit of normal curve is 50% (12 of 24). The diagnostic performance of each of the lower limit of normal curves (i.e., −1 SD, −2 SD, etc.) was assessed by measuring its sensitivity and specificity in detecting significant CAD. These data were then used to plot a “receiver operating characteristic” curve. This curve is a simultaneous plot of the sensitivity and specificity of a test as a function of some variable. We show the performance of the mean minus standard deviations approach with the number of standard deviations as the variable. Figure 4 shows the sensitivity and specificity that would have been realized for various definitions of normal. For example, using the mean minus 2 standard deviations results in a sensitivity of 86% and a specificity of 50%. The receiver operating characteristic curve does not cross into the shaded region, which implies that with this approach it is not possible to simultaneously achieve a sensitivity and a specificity greater than 80%. In contrast, using the range approach to the definition of the lower limit of normal results in a sensitivity of 90% and a specificity of 96% (fig. 4).

**Moderate CAD**

Using the lower limit of normal as the range derived from 23 patients with no or minor CAD, five of 11 patients (45%) with moderate CAD had perfusion defects. The percent diameter narrowing in four of these patients was 40%, 40%, 40% and 55%. One of the five patients had systolic compression. The mean number of points at which these five patients’ perfusion curves crossed below the lower limit of normal curve was 36 ± 25 points. In all five, the location of the perfusion defect was concordant with the angiographically documented location of the coronary lesion.
The overall effect on the range curve of including patients with moderate CAD is shown in figure 5. The relative depression of $^{201}$TI distribution in the 180–270° segment is due to inclusion of 11 patients with moderate coronary obstructions. Eight of 11 of these patients had lesions in the left anterior descending coronary artery, which perfuses the region of depressed $^{201}$TI distribution shown in figure 5.

Sensitivity, Specificity and Predictive Accuracy of $^{201}$TI: Comparison of Approaches

The sensitivity and specificity of the approaches to $^{201}$TI scintigraphy are shown in figure 6. In the absence of quantitative analysis, tomographic imaging did not improve specificity or sensitivity significantly. The predictive accuracy of an abnormal tomographic $^{201}$TI scintigram interpreted with quantitative criteria was significantly greater ($p < 0.05$) than the predictive accuracy of a positive image obtained with the other two imaging approaches (fig. 6).

Interobserver Variability

When planar or tomographic $^{201}$TI images were interpreted using visual criteria, interobserver variability was 40% for tomographic images and 44% for planar images. Quantitative analysis of tomographic images eliminated interobserver variability.

Effects of Extent of CAD on Sensitivity

With planar scintigrams, sensitivity tended to increase with the extent of CAD, but the differences were not statistically significant (table 1). When tomographic images were interpreted with quantitative criteria, sensitivity was not related to the severity of CAD. Only three of the 52 CAD patients in our series did not have either one coronary vessel with a 90% or greater obstruction or abnormal left ventricular function. Thus, our data concerning the sensitivity of detecting CAD with $^{201}$TI scintigraphy are only applicable to patients with severe coronary obstructions.

Effects of Left Ventricular Function on Sensitivity

In patients with CAD who had abnormal ventricular function, the percentage of patients with positive $^{201}$TI scintigrams was significantly increased ($p < 0.05$) regardless of the imaging approach that was used. In CAD patients with normal left ventricular function, quantitative tomograms tended to be more sensitive in detecting CAD than visual interpretation of either planar or tomographic $^{201}$TI scintigrams (table 2).

Sensitivity and Specificity of $^{201}$TI Scintigrams in Patients with the Clinical Syndrome of Unstable Angina

In patients with the clinical syndrome of unstable angina, the sensitivity and specificity of diagnosing CAD was best with tomographic $^{201}$TI images if the interpretation was based on quantitative criteria (table 3).

Discordant Results

In 11 patients with CAD, the tomograms interpreted with quantitative criteria and planar images yielded discordant results. Eight patients had a positive tomogram and a negative planar image and three had a

Figure 4. ‘Receiver operating characteristics’ curve showing the diagnostic performance of the ‘mean minus N standard deviations’ approach to defining the lower limit of normal. This curve plots the sensitivity and specificity in detecting significant coronary artery disease as a function of the number of standard deviations used. With this approach it is not possible to achieve a high (> 80%) sensitivity and specificity (shaded region). The ‘lower limit of normal’ curves were derived from 23 patients with no or minor coronary disease. ×

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Table 1. Effects of the Extent of Coronary Artery Disease on the Sensitivity of Thallium-201 Perfusion Scintigrams

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>Planar scintigrams (visual analysis)</th>
<th>Tomographic scintigrams (visual analysis)</th>
<th>Tomographic scintigrams (quantitative analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vessel</td>
<td>6/9 (67%)</td>
<td>8/9 (89%)</td>
<td>9/9 (100%)</td>
</tr>
<tr>
<td>2 vessels</td>
<td>15/20 (75%)</td>
<td>14/20 (70%)</td>
<td>17/20 (85%)</td>
</tr>
<tr>
<td>3 vessels</td>
<td>20/22 (90%)</td>
<td>17/22 (77%)</td>
<td>21/22 (96%)</td>
</tr>
</tbody>
</table>

Values represent the number of patients in the subgroup with positive tests, the total number of patients in the subgroup and the percentage with a positive test.

Discussion

Value of Dipyridamole

Dipyridamole has four advantages over exercise in achieving coronary dilation before injection of Thallium-201. First, the intensity of coronary dilation produced by dipyridamole is at least as great as that associated with exercise. Most studies indicate that moderate-to-maximal treadmill exercise is usually associated with a threefold increase in coronary blood flow. Third, dipyridamole increases coronary blood flow three- to five-fold, and this increase may be potentiated if the drug infusion is coupled with isometric exercise. In addition, the increase in coronary blood flow that occurs with exertion quickly disappears after cessation of exercise; the coronary dilation secondary to dipyridamole infusion declines at a rate of 50% per 45 minutes.

Second, infusion of dipyridamole requires less time and equipment than a treadmill exercise tolerance test. This may decrease the overall cost of a Thallium scintigraphic procedure.

Third, the side effects of i.v. dipyridamole are probably not greater than those associated with treadmill exercise tolerance tests in patients with CAD. The majority of patients with CAD experience chest pain, dyspnea or ECG evidence of myocardial ischemia during a treadmill exercise tolerance test. In contrast, i.v. infusion of dipyridamole is infrequently associated with electrocardiographic evidence of myocardial ischemia and, in our experience, no patient developed cardiac arrhythmias or dyspnea. Only 15% developed

Table 2. Effects of Left Ventricular Function on the Sensitivity of Thallium Scintigraphy Using Three Approaches

<table>
<thead>
<tr>
<th></th>
<th>Planar scintigrams (visual interpretation)</th>
<th>Tomographic scintigrams (visual interpretation)</th>
<th>Tomographic scintigrams (quantitative interpretation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal left ventricular function</td>
<td>24/25 (96%)*</td>
<td>23/25 (92%)*</td>
<td>25/25 (100%)*</td>
</tr>
<tr>
<td>Normal left ventricular function</td>
<td>17/26 (65%)</td>
<td>16/26 (62%)</td>
<td>21/26 (81%)</td>
</tr>
</tbody>
</table>

*p < 0.05 vs normal left ventricular function.

Values represent the number of patients in the subgroup with positive tests, the total number of patients in the subgroup and the percentage with a positive test.
fleeting chest pain. In contrast, Albro et al.25 reported that fleeting angina occurred during infusion of dipyramidole in 12 of 43 patients (28%) with CAD. In this same series, two of 43 patients with CAD had significant angina that required treatment with amiphylline. Thus, the symptoms or other adverse effects associated with infusion of dipyramidole in patients with CAD are probably no greater than those associated with exercise tests.

The fourth and principal advantage of dipyramidole is that it can increase coronary blood flow in patients who cannot achieve intense levels of exercise. This includes patients with symptomatic claudication, unstable angina pectoris, chronic obstructive pulmonary disease, skeletal abnormalities, psychiatric illnesses or patients taking drugs that produce β blockade.

Dipyramidole has disadvantages: The diagnostic information associated with exercise (ST depression, symptoms, and assessment of exercise capacity, etc.) is not obtained; it decreases the ability of myocardial cells to extract 201TI37 and i.v. dipyramidole is not commercially available.

Quantitation of Perfusion Scintigrams

Perfusion scintigrams are usually interpreted subjectively by visually analyzing the uniformity of 201TI distribution in the heart.1-8 However, subjective interpretation of 201TI images is markedly influenced by observer experience, image quality, myocardium-to-background contrast, display format, and the underlying variability in the normal pattern of 201TI distribution. As a result, visual interpretation of 201TI scintigrams is associated with considerable interobserver variability.9 Some investigators have used computer-based quantitative techniques for the analysis of perfusion scintigrams. These techniques either enhance visual analysis or provide partial or complete quantitative analysis. Techniques primarily intended to aid visual interpretation include sophisticated background-subtraction algorithms,18, 19 imaging smoothing and enhancement40 and color display.40-43 Quantitative approaches to image interpretation include histogram analysis,43, 44 segmental analysis of five to eight regions of interest by calculation of perfusion ratios,45-47 computerized planimetry of percent defect area48 and circumferential profiles of 201TI distribution.29, 49-51 This last technique is similar to the region-of-interest approach except that many more regions are considered.

When circumferential profiles are obtained, typically 40-100 radial29, 49, 51 or hemiangular50 lines from the center of the cardiac image are formed. The average myocardial perfusion along these lines is calculated and expressed as a percentage of the maximum myocardial perfusion. Vogel et al.18 applied this quantitative circumferential profile technique to the analysis of 201TI tomograms. They calculated the maximum percent perfusion along each of 60 radial lines, spaced at 6° increments. We have used a very similar approach except that we divided the cardiac image into 60 6° pie segments. This has the theoretical advantage of not ignoring any pixels within the image.

In evaluating 201TI perfusion, one must consider the normal regional variation in 201TI distribution, both in planar and tomographic imaging.29, 52 Our results (fig. 3) support this concept. For quantitative interpretation of 201TI scintigrams, a precise definition of the lower limit of normal is needed. Usually, a fixed threshold of 60-80% of the maximum is used as the lower limit of normal.30, 46, 47, 49, 53 If the regional 201TI distribution falls below the lower limit of normal, the scintigram is interpreted as abnormal. A fixed threshold is probably inappropriate because the normal regional 201TI distribution is variable and one would expect the regional lower limit of normal to be quite variable. Of course, a fixed threshold may be used if the threshold is lowered enough to account for the regional variability.52 When this is done, the specificity is high but the sensitivity is low.

Another approach to defining the lower limit of normal is to use the mean minus 2 standard deviations.19, 29, 53 When this technique is applied to circumferential profile analysis, the lower limit of normal varies with anatomic location. Using this approach with “minor editing,” Vogel et al.18 found that seven-pinhole 201TI tomography was 94% sensitive and 96% specific in detecting CAD. Using 2 standard deviations for the lower limit of normal, we found a sensitivity of 86% and a specificity of 50%. These results are very similar to those reported by Ritchie et al.,19 who found a sensitivity of 86% and a specificity of 57% using the mean minus 2 standard deviations approach for detecting prior myocardial infarction. We could not improve the diagnostic performance using any number of standard deviations (fig. 4), and suggest that the range may be a better lower limit of normal.

One of the difficulties in computing the lower limit of normal on a regional basis is consistent patient positioning. This problem is particularly acute when the heart is divided into many regions. Thus, it is impossible to determine whether the normal curve in figure 3 accurately reflects regional variation in 201TI distribution or whether it is distorted by variable patient or heart position. In planar imaging, Burow et al.29 has used the apex as an internal landmark by which to align circumferential profiles. In obtaining 201TI tomograms, we have given careful attention to patient positioning.

Other workers54 have noted that the characteristics of tomographic perfusion scintigrams depend upon the scintillation camera, the computer system and the reconstruction software. These factors have an important

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**TABLE 3. Sensitivity and Specificity of Thallium-201 Scintigrams in Patients with the Clinical Syndrome of Unstable Angina**

<table>
<thead>
<tr>
<th></th>
<th>Planar scintigrams (visual interpretation)</th>
<th>Tomographic scintigrams (visual interpretation)</th>
<th>Tomographic scintigrams (quantitative interpretation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>14/18 (78%)</td>
<td>13/18 (72%)</td>
<td>16/18 (89%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>3/10 (70%)</td>
<td>3/10 (75%)</td>
<td>0/10 (100%)</td>
</tr>
</tbody>
</table>

Values represent the number of patients in the subgroup with positive tests, the total number of patients in the subgroup and the percentage with a positive test.
effect on quantitative analysis of $^{201}$TI tomograms. Because these factors and patient positioning procedures vary among institutions, each institution must define its own normal curve. This concept is supported by figure 7, which is a comparison of our normal curves with those from another institution.*

Inherent in the definition of a lower limit of normal curve is the definition of the normal population. Various investigators have used normal volunteers29 or patients with coronary stenosis of less than 50% diameter narrowing14-18 to define the normal distribution of $^{201}$TI. We used only patients with less than 30% obstruction to define our normal curve. Our results (fig. 5) suggest that moderate coronary obstructions (30-55% diameter narrowing or systolic compression) may be associated with perfusion defects. Thus, including such patients in the normal population is inappropriate.

Our explanation for the inability of the mean minus N standard deviations approach to produce a sensitive and specific diagnostic test for CAD is that at each point the variability of $^{201}$TI concentration in groups of patients does not have a gaussian distribution. The percent of maximal perfusion can hardly be gaussian because its range is limited to 0-100%. Since a perfusion curve is considered positive if a single point of 180 (60 points in each of three curves) falls below the corresponding point of the lower limit of normal curve, a patient has 180 "chances" of having a positive tomogram. If the 180 lower limit of normal points (mean minus 2 standard deviations) were gaussian and independent, one would expect a test with a specificity near zero. That such is not the case clearly indicates that the equivalent number of independent points is much less than 180. We have found the range to be a suitable alternative to the mean minus N standard deviations approach.

**Association of Moderate Coronary Obstructions with Perfusion Defects**

The physiologic significance of moderate coronary obstructions, as measured by coronary arteriography, is controversial. This is due to a combination of factors, including intraobserver and interobserver variability,55-57 technical problems58 such as inadequate contrast or vessel overlap, and factors related to lesion geometry such as stenosis length,59 exit angle60 and multiple stenosis.61 Thus, there is no general agreement on the definition of an angiographically significant occlusion. Quantitative analysis of coronary arteriograms62 should be helpful in improving our definition of an angiographically significant coronary lesion.

We recently described a Doppler probe for quantitative measurements of coronary reactive hyperemia in man at the time of cardiac surgery.63 Studies with this probe have shown that equivocal obstructions (25-50%) are often associated with markedly depressed coronary hyperemic responses.64 The abnormal $^{201}$TI scintigrams in about half of our patients with moderate CAD are compatible with the concept that apparently moderate coronary obstructions may significantly alter the functional capacity of the involved vessel.

**Value of Seven-pinhole Tomography**

Our study and others65 suggest that seven-pinhole tomography in and of itself does not contribute in a

*Curves supplied by Medical Data Systems as part of the MSET package of programs. The data were originally obtained at the Denver Veterans Administration Hospital.
major way to the sensitivity and specificity. The advantage of the seven-pinhole scintigrams is that they lend themselves to quantitative interpretation. Recent approaches to the quantitative analysis of planar \textsuperscript{201}TI scintigrams are encouraging. These studies have yielded similar sensitivity and specificity values as those reported for quantitative seven-pinhole tomography.

**Limitations**

Three limitations of our study should be emphasized.

First, our patients were all scheduled for diagnostic coronary arteriography for some complex of symptoms and signs which suggested CAD. Consequently, it would be difficult to extrapolate our results to a nonselected population, especially since we excluded patients with coronary obstructions of intermediate severity.

Second, our patients did not undergo \textsuperscript{201}TI imaging with exercise or have rest or redistribution images. Albro et al. showed that the sensitivity and specificity of \textsuperscript{201}TI planar scintigrams are similar if coronary dilation is achieved with exercise or dipyridamole. Also, the sensitivity and specificity of tomographic \textsuperscript{201}TI scintigrams interpreted with quantitative criteria are similar if either exercise or dipyridamole is used to increase coronary flow. Although rest and redistribution scintigrams have been of help in assessing the probable cause of the \textsuperscript{201}TI abnormalities (infarction vs ischemia), such information would probably not affect the percentage of positive or negative studies. This point is somewhat controversial; some investigators believe that redistribution images may enhance diagnostic accuracy when \textsuperscript{201}TI perfusion scintigrams are interpreted with visual criteria.

Third, our results do not permit us to determine the relative contribution of i.v. dipyridamole, quantitative analysis or seven-pinhole tomograms in affecting the diagnostic accuracy of our approach to assessing the presence or absence of CAD.

This study emphasizes the value of pharmacologically induced coronary artery vasodilation with intravenous dipyridamole using quantitatively interpreted tomography for the detection of significant CAD. Since exercise is not required and the dipyridamole is well tolerated, this imaging technique may well be the preferred procedure for perfusion scintigraphy, especially in patients who cannot exercise vigorously.

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Tomographic thallium-201 myocardial perfusion scintigrams after maximal coronary artery vasodilation with intravenous dipyridamole. Comparison of qualitative and quantitative approaches.

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