Improved Noninvasive Assessment of Coronary Artery Disease by Quantitative Analysis of Regional Stress Myocardial Distribution and Washout of Thallium-201

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SUMMARY Visual interpretation of stress-redistribution thallium-201 (201TI) scintigrams is subject to observer variability and is suboptimal for evaluation of extent of coronary artery disease (CAD). An objective, computerized technique has been developed that quantitatively expresses the relative space-time myocardial distribution of 201TI. Multiple-view, maximum-count circumferential profiles for stress myocardial distribution of 201TI and segmental percent washout were analyzed in a pilot group of 31 normal subjects and 20 patients with CAD to develop quantitative criteria for abnormality. Subsequently, quantitative analysis was applied prospectively to a group of 22 normal subjects and 45 CAD patients and compared with visual interpretation of scintigrams for detection and evaluation of CAD. The sensitivity and specificity of the quantitative technique (93% and 91%, respectively) were not significantly different from those of the visual method (91% and 86%). The quantitative analysis significantly (p < 0.05) increased the sensitivity of 201TI imaging over the visual method in the left anterior descending artery (from 56% to 80%), left circumflex artery (from 34% to 63%) and right coronary artery (from 65% to 94%) without significant loss of specificity. Using quantitative analysis, sensitivity for detection of diseased vessels did not diminish as the number of vessels involved increased, as it did with visual interpretation. In patients with one-vessel disease, 86% of the lesions were detected by both techniques; however, in patients with three-vessel disease, quantitative analysis detected 83% of the lesions, while the sensitivity was only 53% for the visual method. Seventy percent of the coronary arteries with moderate (50–75%) stenosis were detected quantitatively, compared with 35% by the visual method.

We conclude that this quantitative technique for analysis of stress-redistribution 201TI scintigrams is objective and more sensitive than the visual method, especially in patients with multiple-vessel disease and those with moderate coronary artery stenosis.

EXERCISE THALLIUM-201 (201TI) myocardial perfusion scintigraphy is a useful noninvasive method for detecting and evaluating patients with significant coronary artery disease (CAD). However, interpretation of 201TI images is usually visual, and even when analyzed by experienced readers, there is substantial observer variability. Furthermore, although the method is highly specific for localization of CAD, it has major limitations in sensitivity for detection of individual coronary stenoses. The visual method is particularly limited in detection of individual coronary lesions in patients with multiple-vessel CAD and when the degree of stenosis is not severe. Finally, although the regional washout characteristics of the myocardium for 201TI contain important diagnostic information, washout abnormalities are difficult to detect by visual inspection.

We have developed a computerized technique that objectively expresses the relative distribution of 201TI in the myocardium as a function of space and time. The method is a synthesis of the best components of previously described techniques with unique features relating to washout analysis and the computerized identification of regional abnormalities. This study was undertaken to compare the sensitivity and specificity of our quantitative technique to standard visual analysis for diagnosis of CAD as well as for the identification of disease in specific coronary vessels, and to compare the regional sensitivity of the two techniques with respect to number of diseased vessels and the severity of coronary stenosis.

Methods

Patient Population and Study Design

The study population consisted of 118 patients who were referred to our cardiac stress laboratories between June 1979 and March 1980 for detection and evaluation of CAD. All patients underwent multiple noninvasive stress testing, including stress and redistribution 201TI myocardial scintigraphy, exercise electrocardiography and cardiokymography, cardiac fluoroscopy for coronary calcification, and often, exercise multiple-gated equilibrium scintigraphy.

The study consisted of two phases: development of interpretive criteria and prospective application. In the first phase, we studied 31 consecutive “normal” patients (group A) and 20 consecutive CAD patients (group B) who were undergoing clinical evaluation in our laboratory. Patients were considered normal if they had less than 1% likelihood of CAD based on subsequent Bayesian analysis of age, sex, symptom classification, coronary risk factors, and at least three negative noninvasive tests other than 201TI scintigraphy. Previous studies from this laboratory have established that these predictions based on noninvasive tests correspond closely to the prevalence of...
disease at coronary angiography.\textsuperscript{14} In the CAD patients, the presence of CAD was established by coronary angiography.

Patients in groups A and B were used to establish criteria for quantitative analysis of regional myocardial \textsuperscript{201}TI uptake and washout. These criteria were applied prospectively to analyze the stress and redistribution scintigrams of the subsequent 67 patients, who were separated into a normal group (group C) and a CAD group (group D).

Group C consisted of 11 consecutive patients with less than 1% calculated likelihood of CAD and 11 consecutive patients with normal coronary arteriograms. Group D consisted of 45 consecutive patients with angiographically documented CAD. Patients who underwent testing after coronary bypass surgery were excluded from the study population, as were four patients who failed to perform adequate exercise. Exercise was considered adequate if the patient achieved at least 85% of the predicted maximum heart rate or developed angina or at least 1 mm ST-segment depression at a lower heart rate. Table 1 is a summary of the characteristics of the population.

Coronary Arteriography

Selective coronary arteriography was performed using the Judkins or Sones technique within an average of 31 days of the time of \textsuperscript{201}TI testing. Coronary cineangiograms were obtained in multiple views and were recorded on 35-mm film using a cineangiographic system equipped with a camera with an 80-mm or 100-mm lens and an image intensifier. Arteriograms were interpreted by two independent observers unaware of the scintigraphic findings. Coronary artery stenosis was graded according to the most severe narrowing of the lumen. For purposes of this study, coronary arteries with less than 50% diameter narrowing were considered normal. Those with 50% or more stenosis were considered to have significant CAD. Moderate coronary artery stenosis was defined as 50–75% and severe stenosis as greater than 75% luminal narrowing.

Coronary arteriography in group B revealed significant disease involving one vessel in four, two vessels in six, and three vessels in 10. In group D seven patients had one-vessel, 11 had two-vessel and 27 had three-vessel disease.

Exercise and Imaging Procedures

Patients were exercised using a multistage treadmill test according to the Bruce protocol. Exercise was terminated only with exhaustion, development of severe angina, serious arrhythmia or hypotension. A dose of 2 mCi of \textsuperscript{201}TI was injected at peak exercise, and exercise was continued for 45–90 seconds after injection. After termination of exercise, multiple-view myocardial scintigrams were obtained at approximately 6 minutes, 40 minutes and 3–5 hours after injection of \textsuperscript{201}TI. At each interval imaging was performed in the anterior, 45° and 70° left anterior oblique (LAO) views for 10 minutes per view. During the acquisition of the anterior view, the shape of the myocardium was evaluated. If significant heart rotation was noted, the view was repeated by changing the angulation of the camera. Subsequent images were compensated accordingly for heart rotation by the technician. Patients referred to our laboratory for exercise testing are routinely instructed to discontinue propranolol for 24–48 hours and to avoid nitrates, food and drink for 3 hours before exercise testing, and to limit their activity and have only a small meal between imaging periods. For imaging, a standard field-of-view camera was used, equipped with 37 photomultiplier tubes, \textfrac{1}{4}-inch-thick sodium iodide crystal and a high-resolution, parallel-hole collimator. A 25% energy window centered on the 80-keV photopeak and a 15% window centered on the 167-keV photopeak were used. All images were stored by the computer on magnetic disc in a 128 × 128 × 8-bit matrix.

Computer Processing and Analysis

Each image was compensated for tissue crosstalk using modified interpolative background subtraction.\textsuperscript{3,9} With this approach, the bilinear interpolative background subtraction technique described by Goris et al.\textsuperscript{8} was modified by using a proximity weighting

<table>
<thead>
<tr>
<th>Table 1. Description of Patient Population by Group</th>
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<tr>
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</tr>
<tr>
<td>Pilot study population</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
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<tr>
<td>Prospective study population</td>
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<tr>
<td>C</td>
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<td></td>
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<tr>
<td>D</td>
</tr>
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Abbreviations: CAD = coronary artery disease; MI = myocardial infarction.
function described by Watson et al. To improve statistical accuracy, images were then smoothed using a standard nine-point weighted-average algorithm. From these images, circumferential maximum count profiles corresponding to the myocardial distribution of $^{201}$TI were obtained in a manner similar to that proposed by Meade et al. and Vogel et al. The operator assigned the maximum radius to which the computer will search. This is done to prevent the algorithm from searching outside the left ventricular myocardium into other structures. The operator then examined the flagged maximum count pixels to ensure that the points sampled were within the myocardium. Each point in the distribution profiles represented the maximum counts per pixel along a radius traversing the myocardium. The profile was constructed by the computer from the result of 60 radii spaced at $6^\circ$ intervals plotted clockwise, quantitating the segmental activity as an angular function referenced from the visually located center of the left ventricular cavity. These profiles were then aligned by the operator such that the $90^\circ$ point in each view corresponded to the scintigraphic apex, and were plotted for each view at each time interval. The number of counts in each pixel was normalized to the maximum count in the profile of each view, and all values were then plotted as percent of maximum count vs angle.

In addition to the distribution profiles, an important feature of our quantitative method was the calculation of washout rate circumferential profiles that were used to evaluate segmental myocardial washout characteristics for $^{201}$TI. These washout rate profiles were calculated as percent washout from stress for the 40-minute and 4-hour intervals. Quantitative analysis was performed by computer operator unaware of the patient's clinical or angiographic findings.

The computer processing was performed using a standard nuclear medicine computer with 32K core memory, and could be implemented on 16K core memory systems. The time required for entire computer processing averaged 30 minutes per patient. Recently, with the aid of hardware floating point and multiply-divide options, we have reduced the processing time to 10 minutes per patient.

To investigate the interobserver variability, sequential $^{201}$TI scintigrams were analyzed by two independent observers in 14 patients, including five normal subjects and nine CAD patients.

### Assignment of Coronary Territories to Myocardial Images

Three regions in each view were individually assessed visually and quantitatively (fig. 1). In quantitative analysis, the profile in each view which corresponded to the arc from $210-330^\circ$ was considered to represent the outflow tract. The arc from $60-120^\circ$ was designated as representing the apex in the anterior and $70^\circ$ LAO views and to represent the inferoapical area in the $45^\circ$ LAO view.

For localization of anatomic disease, the anterior wall (anterior and $70^\circ$ LAO views) and interventricular septum (45° LAO view) were considered to represent the distribution of left anterior descending (LAD) coronary artery, the inferior wall (anterior and $70^\circ$ LAO views) the distribution of the right coronary artery (RCA) and the posterolateral wall (45° LAO view) the left circumflex (LCX) distribution. An apical or inferoapical abnormality alone was interpreted as indicating CAD but was not used to localize disease to

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**Figure 1.** Myocardial regions assessed visually (A) and quantitatively (B) in each view. In quantitative analysis, the arc from 210-330° in each view was considered to represent the outflow tract and was not evaluated. See text for assignment of the different myocardial regions to specific coronary arteries. **ANT** = anterior; **INF** = inferior; **SEPT** = septum; **INF-AP** = inferoapical; **PL** = posterolateral.
a specific coronary artery. This adopted system for assignment of myocardial regions to individual coronary arteries has been used as an approach to localization of anatomic disease.1, 6

Visual Scintigraphic Interpretation

For visual scintigraphic interpretation, analog images were displayed on Polaroid film. A Polaroid camera with three lenses of varying F stops was used to record the image at three intensities.18 This approach was chosen because it represents the most frequently used method for visual 201Tl analysis; no background subtraction, contrast enhancement or smoothing was performed.

Stress and redistribution thallium scintigrams were inspected for regions of decreased uptake by three experienced observers who had no knowledge of the clinical data, stress test results or angiographic findings. The magnitude of uptake in each segment was graded by consensus, using a four-point scoring system: 0 = normal uptake, 1 = slightly (equivocally) reduced uptake, 2 = moderately (definitely) reduced uptake and 3 = severely reduced uptake. Regions rated 2 or 3 were designated positive and those rated 0 or 1 were considered negative. We were concerned only with the presence of disease in given regions rather than with viability; thus, regional myocardial reversibility was not assessed. The redistribution scintigrams, however, were used to increase certainty regarding the presence or absence of abnormality.

Quantitative Scintigraphic Interpretation

Definition of Normal Limits

The mean ± SD were established from the pooled data of 31 normal subjects (group A) for each of the 60 angular locations of the anterior, 45° LAO and 70° LAO images for each time interval. The time between the stress and redistribution imaging, if other than 4 hours, was used to extrapolate the washout rate profile to exactly 4 hours. This was done for each normal subject by assuming a normal monoexponential washout1a between stress and redistribution during the actual imaging delay of 3–5 hours and correcting to 4 hours using a standard decay formula.

The lower limit of normal for the stress profile was established as the profile that was 2 standard deviations below the mean observed initial distribution profile. The normal limits for washout rate at both 40 minutes and 4 hours were determined in an identical manner. Use of 2 standard deviations with a one-tailed analysis establishes statistical criteria that include 97.5% of the normal population.

Development of Criteria for Abnormality

Stress and washout rate circumferential profiles for the 51 patients in groups A and B were interpreted by a computer program which compared each curve, aligned at the apex, to the normal limits described above. The computer was programmed to identify any arc of the profile that was outside the normal limits. The portions of the profile between 210° and 330° (corresponding to the base of the left ventricle) were evaluated during the normalization process but were excluded from interpretation.

Different quantitative criteria for type and magnitude of abnormality were assessed in all 51 patients in groups A and B for their ability to best discriminate normal subjects (group A) from patients with CAD (group B).

Based on features of regional myocardial 201Tl kinetics, three types of abnormality were studied: (1) diminished initial distribution (stress defect) evidenced by the patient’s stress profile falling below the normal limit; (2) delayed peaking of myocardial 201Tl concentration as seen by the early (40-minute) distribution profile lying above the normal limit and/or the early washout-rate profile falling below the normal limit; and (3) slow washout of 201Tl after initial distribution shown by the 4-hour distribution profile lying above the normal limit and/or the 4-hour washout-rate profile falling below the normal limit. The magnitude of abnormality was also quantified in six multiples of the 6° arc as 6°, 12°, 18°, 24°, 30°, 36°, and greater than 36°.

With respect to the type of regional abnormality, two criteria best separated group A (normal subjects) from group B (CAD): a stress defect, defined by the stress profile lying below normal limit, and “slow washout,” defined by the 4-hour washout-rate profile lying below the normal limit.

Regarding the magnitude of abnormality, when all views and both initial distribution and washout rate profiles were examined, at least two arcs, each 18° (three contiguous radii), had to extend below the normal limit to be considered abnormal. The other criteria considered did not further distinguish normal subjects from CAD patients.

Segments adjacent to a large apical abnormality were considered abnormal only if the apical abnormality extended at least 18° beyond the borders of the apex (60–120°) into those segments. For example, in a patient with an apical defect in the anterior view, the adjacent anterior wall was considered abnormal only if the region below the normal limit extended to 42°, and the adjacent inferior wall was considered abnormal only if the apical abnormality extended to 138°.

Using the above criteria, quantitative analysis of 201Tl images was normal in all 31 group A patients and in one of 20 group B patients.

Analysis of Findings in the Prospective Population (Groups C and D)

Stress and washout circumferential profiles for the 67 patients in the prospective population were analyzed by comparison to normal limits in the same fashion as described for the pilot group, and the two criteria developed in the pilot group were applied to identify regional abnormalities in each patient.

Statistical Analysis

McNemar’s test17 was used to assess the significance of the difference between both the sensitivity
TABLE 2. Sensitivity and Specificity of Visual and Quantitative Methods for Overall Detection of Coronary Artery Disease

<table>
<thead>
<tr>
<th>CAD patients (group D) (n = 45)</th>
<th>Normals (group C) (n = 22)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Quant.</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Visual</td>
<td>39</td>
</tr>
<tr>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>41/45 (91%)</td>
<td>19/22 (86%)</td>
</tr>
<tr>
<td>Quant.</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Visual</td>
<td>3</td>
</tr>
<tr>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>42/45 (93%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Visual = visual analysis; quant. = quantitative analysis; CAD = coronary artery disease.

and specificity of the quantitative and the visual techniques in regards to overall detection of CAD and detection of disease in individual coronary arteries. A p value of less than 0.05 was considered significant. For these analyses, only the prospective population (groups C and D) was used.

Results

Interobserver Agreement

In 14 patients used for assessment of reproducibility of computer analysis, each of the three views was divided into three segments, for a total of nine segments per patient. Each segment was analyzed by computer as to whether it was normal or abnormal. Concordant results were obtained by the two observers in 115 of 126 segments (93% agreement). No patient was erroneously called normal or abnormal due to this variation. The main cause of discrepancy was variation in aligning the apex at 90° in patients with large apical defects, which explained eight of the nine discordant segments.

Overall Sensitivity and Specificity of Visual and Quantitative Methods (table 2)

Forty-one of 45 patients with CAD in group D were considered abnormal by visual assessment and 42 of 45 by the quantitative technique. Thus, the sensitivity of the visual and quantitative techniques were 91% and 93%. These were not significantly different from one another. Of the 22 normal subjects in group C, 20 had normal circumferential profiles, yielding a 91% specificity for the quantitative method. Three of these 22 normal subjects were considered abnormal by visual assessment, yielding a specificity of 86%, which was not statistically different from that of the quantitative technique. For both methods of analysis, the false-positive studies in group C occurred only in patients with normal coronary arteriograms. None of the patients with less than 1% calculated likelihood of CAD in this group had positive 201Tl studies by either approach.

Comparison Between Visual and Quantitative 201Tl Interpretation for Assessment of Disease in Individual Coronary Arteries

The sensitivity of visual and quantitative 201Tl interpretation in each of the three major coronary arteries is listed in table 3. The sensitivity of the visual method for detection of disease in each of the coronary arteries was low, 56%, 34% and 65% for the LAD, LCX and RCA, respectively. Thus, of 110 diseased vessels, only 57 were detected by the visual method (52% sensitivity). The quantitative technique, however, had significantly higher sensitivity for detection of disease in individual coronary arteries (80% for LAD, 63% for LCX and 94% for RCA). The overall sensitivity for detection of disease in any vessel was 79% (87 of 110). Of the 57 diseased regions by visual interpretation, quantitative analysis demonstrated a

<table>
<thead>
<tr>
<th>Disease in LAD (n = 41)</th>
<th>Disease in LCX (n = 35)</th>
<th>Disease in RCA (n = 34)</th>
<th>Disease in any coronary artery (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>Visual</td>
<td>Visual</td>
<td>Visual</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>22/41 (56%)</td>
<td>12/35 (34%)</td>
<td>22/34 (65%)</td>
<td>57/110 (52%)</td>
</tr>
<tr>
<td>Quant.</td>
<td>Quant.</td>
<td>Quant.</td>
<td>Quant.</td>
</tr>
<tr>
<td>11/41</td>
<td>21/43</td>
<td>35/110</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td>Quant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23/41 (56%)</td>
<td>33/41 (80%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Abbreviations: LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; Quant. = quantitative analysis.

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stress defect in 53 (93%) and washout abnormality in 39 (68%).

The specificity of each technique in each of the individual coronary arteries and in all vessels are compared in Table 4. The specificity of the visual and the quantitative techniques was 92% and 85% for the LAD, 97% and 94% for the LCX, 91% and 82% for the RCA, and 93% and 87% for any normal vessel. None of the specificity figures were significantly different between the two methods of analysis.

**Sensitivity of Visual and Quantitative Methods for Detecting Coronary Lesions with Respect to Number of Vessels Involved**

The sensitivities of visual and quantitative techniques were the same (86%) in patients with one-vessel CAD (Table 5). For the visual method, however, the sensitivity decreased to 36% for two-vessel and 53% for three-vessel disease. In contrast, sensitivity of quantitative analysis for detection of coronary lesions did not diminish as the number of vessels involved increased (64% and 83% for two- and three-vessel disease, respectively).

**Sensitivity of Visual and Quantitative Methods with Respect to Severity of Coronary Artery Narrowing**

Table 6 shows the sensitivity of the visual and the quantitative 201Tl analyses in relation to severity of coronary stenosis. Seventy vessels demonstrated greater than 75% luminal diameter narrowing by coronary arteriography. Of these, 43 (61%) were detected visually and 59 (84%) quantitatively. An even greater difference between the two techniques was observed when the sensitivity for detection of 50–75% coronary narrowing was examined. Only 14 of 40 (35%) coronary arteries with 50–75% narrowing were detected visually, compared with 28 of 40 (70%) by the quantitative method.

**Table 4. Identification of Absence of Disease in Individual Coronary Arteries by Visual and Quantitative Assessment of Thallium-201 Scintigrams**

<table>
<thead>
<tr>
<th>Normal LAD (n = 26)</th>
<th>Normal LCX (n = 32)</th>
<th>Normal RCA (n = 33)</th>
<th>Any normal coronary artery (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>Visual</td>
<td>Visual</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Quant. + 5</td>
</tr>
<tr>
<td>Quant. + 2</td>
<td>Quant. + 2</td>
<td>Quant. + 3</td>
<td>Quant. + 7</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>27</td>
<td>78</td>
</tr>
</tbody>
</table>

**Table 5. Relationship Between Extent of Coronary Artery Disease and the Sensitivity of the Two Techniques for Detection of Diseased Vessels**

<table>
<thead>
<tr>
<th>All diseased vessels in 7 pts with one-vessel CAD (n = 7)</th>
<th>All diseased vessels in 11 pts with two-vessel CAD (n = 22)</th>
<th>All diseased vessels in 27 pts with three-vessel CAD (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>Visual</td>
<td>Visual</td>
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<tr>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Quant. + 5</td>
<td>Quant. + 8</td>
<td>Quant. + 39</td>
</tr>
<tr>
<td>-</td>
<td>Quant. + 8</td>
<td>28</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td>Quant. + 8</td>
<td>28</td>
</tr>
<tr>
<td>Quant. + 6/7 (86%)</td>
<td>14/22 (36%)</td>
<td>67/81 (83%)</td>
</tr>
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</table>

**Table 6. Sensitivity of Visual and Quantitative Thallium-201 Analysis with Respect to Severity of Coronary Narrowing**

<table>
<thead>
<tr>
<th>Diseased vessels with 50–75% stenosis (n = 40)</th>
<th>Diseased vessels with &gt;75% stenosis (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual +</td>
<td>Visual +</td>
</tr>
<tr>
<td>Quant. + 12</td>
<td>Quant. + 40</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
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<tr>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>(35%)</td>
<td>(61%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery; Quant. = quantitative analysis.
Quantitative Criteria Responsible for Differences Between the Methods

Of 110 regions supplied by diseased vessels, the quantitative analysis led to correct detection of an additional 35 regions that were missed visually. None of these segments had prior myocardial infarction. Increased sensitivity of the quantitative method was provided by three combinations of quantitative findings: in 19 of 35 (54%) detection of washout abnormalities alone led to detection of additional regions with CAD, in eight of 35 (23%) the quantitative stress defect criterion alone was present and in another eight of 35 (23%) the combination of stress defect and washout abnormality enhanced sensitivity. In 91 regions supplied by nondiseased vessels, quantitative analysis was falsely positive in seven visually normal regions. Two of these regions demonstrated stress defect alone, three had combination of stress defect and slow washout, and two showed isolated slow washout.

Case Illustrations

Figures 2–4 show multiple-view stress-redistribution 201Tl myocardial scintigrams and the quantitative analysis of initial distribution and percent regional washout of 201Tl in a patient with normal coronary arteriograms, a patient with two-vessel CAD, and a patient with three-vessel CAD.

Figure 2 shows the findings in a patient with normal coronary arteries. The analog and background-subtracted images were visually interpreted as normal. The patient's circumferential profiles did not lie below

![Multiple-view stress-redistribution thallium-201 analog scintigrams (A and B), corresponding background-subtracted images (C and D) and circumferential profiles (E and F) in a patient with normal coronary arteriograms. The stress (A and C) and 4-hour redistribution (B and D) images are visually normal. In each view, stress distribution (E) and percent washout profiles (F) of the patient (plotted as +) do not lie below the profile representing the lower limit of normal (plotted as o). ANT = anterior; LAO = left anterior oblique.](http://circ.ahajournals.org/content/64/5/930.f1)
The patient illustrated in figure 3 had 50% proximal left anterior descending, a 75% diagonal and 75% proximal right coronary artery stenosis. Diseased vessels were correctly detected by quantitative analysis, demonstrating a stress perfusion defect in the anterior wall and the apex as well as slow washout rate in a portion of the inferior wall (70° LAO view only). The patient's images were visually interpreted as normal with apical thinning.

The patient shown in figure 4 had 75% proximal LAD, 75% proximal and mid-LCX and 60% mid- and distal RCA stenoses. By quantitative analysis, the washout-rate profiles in this patient demonstrated a slow rate of $^{203}$TI washout from all regions of the myocardium. The analog images were visually interpreted as normal. Therefore, three-vessel CAD was correctly identified only by quantitative analysis of the washout of $^{203}$TI.

**Discussion**

Over the past few years, improved instrumentation and observer experience have led to increased sen-

**Figure 3.** Multiple-view stress-redistribution thallium-201 analog scintigrams (A and B) and the corresponding background-subtracted images (C and D) and circumferential profiles (E and F) in a patient with left anterior descending and right coronary artery stenoses. The stress (A and C) and 4-hour redistribution (B and D) images were visually interpreted as normal, with the variant of apical thinning. In the anterior view (ANT) stress distribution profile (E, left), the patient's profile (plotted as +) falls below the lower limits of normal (plotted as o) from 18° to 108°, thereby defining a quantitative stress defect in the anterior wall. In the 70° left anterior oblique (LAO) view washout rate profile (F, right), the patient's profile falls below the lower limits of normal, from 330° to 30°, defining a washout abnormality in the inferior wall. In this view, although the patient's washout rate profile is also below the lower limit of normal, from 246° to 330°, this region corresponds to a portion of the outflow tract and is not evaluated for abnormality.
sitivity of stress-redistribution $^{201}\text{Tl}$ scintigraphy for detecting CAD.$^{10}$ In our study, using a small field-of-view camera equipped with a $\frac{1}{4}$-inch crystal detector and a high-resolution collimator, visual interpretation of stress-redistribution $^{201}\text{Tl}$ images resulted in a sensitivity of 91% for detecting patients with CAD.

Even with this optimized camera system and consensus reading by experienced observers, however, our visual interpretation of $^{201}\text{Tl}$ scintigrams was associated with a moderately low sensitivity for detection of stenoses in individual coronary arteries, especially in patients with multiple-vessel CAD and those with moderate (50–75%) coronary artery stenoses. These findings for visual analysis of $^{201}\text{Tl}$ images are in agreement with those reported by Rigo et al.$^{16}$ Massie et al.$^2$ Dash et al.$^3$ and McKillop et al.$^5$

The limited sensitivity of conventional visual interpretation of $^{201}\text{Tl}$ images for detection of individual

![Image](http://circ.ahajournals.org/Downloaded from)

**Figure 4.** Multiple-view stress-redistribution thallium-201 analog scintigrams (A and B) and the corresponding background-subtracted images (C and D) and circumferential profiles (E and F) in a patient with three-vessel coronary artery disease. The stress (A) and 4-hour redistribution (B) analog images were visually interpreted as normal. The 45° left anterior oblique (LAO) background-subtracted image (C, middle) shows a distal posterolateral perfusion defect. In the 45° LAO stress distribution profile (E, middle), the patient's profile (plotted as $\bullet$) falls below the lower limits of normal (plotted as $\triangle$) in five contiguous 6° arcs from 30–34° (distal posterolateral wall). Extensive abnormalities were evident in each view in the washout rate profiles (F). In the anterior (ANT) view, washout rate abnormalities were present from 72-180° (apical and inferior walls) and from 330–360° (anterior wall). In the 45° LAO view, washout rate abnormalities were present from 330–156° (posterolateral, inferoapical, and septal regions). In the 70° LAO view, washout rate abnormality was present from 360–12° (inferior wall) and from 180–210° (anterior wall). Again, regions between 210° and 330° in each view are not evaluated because they correspond to the outflow tract. Therefore, in this patient, three-vessel coronary disease was correctly identified only by quantitative analysis of the regional myocardial washout rate of thallium-201.
coronary lesions is generally thought to be due to one or more of the following factors:

1. Prediction of diseased vessels from hypoperfused myocardial segments is not always possible. Coronary distribution to different myocardial segments is variable. Furthermore, there is overlap of blood flow from three major coronary arteries in the apical and inferoapical regions; therefore, abnormalities in these segments cannot be attributed to a specific coronary artery.  

2. Angiographic evaluation of the functional significance of a coronary stenosis may not be accurate. Difficulty in interpretation of the degree of coronary stenosis along with other factors, such as the length of the lesions, the shape of the lesion, the effects of stenoses in series, and the influence of collateral blood flow, may result in discrepancies between angiographic data and scintigraphic perfusion findings.

3. Myocardial segments distal to significant coronary stenoses may not become ischemic during exercise testing. This may occur either because the patient fails to perform adequate exercise or because in multiple-vessel disease, the patient’s performance may be limited by ischemia in the most severely compromised myocardial segment and exercise may be terminated before flow becomes inadequate in vessels with less severe narrowing.

4. Stenosed coronary arteries may cause a perfusion abnormality during stress that is not detected visually. This condition often occurs in patients with multiple-vessel disease. Because the initial $^{201}$TI distribution reflects relative rather than absolute reduction in myocardial blood flow, areas with less hypoperfusion may appear relatively normal compared with the most severely hypoperfused segments. Therefore, patients with three-vessel CAD and balanced reduction of coronary flow might not be detected as abnormal by visual analysis of initial myocardial $^{201}$TI distribution (fig. 4).

While the first three conditions pose perhaps insurmountable limitations on stress-redistribution $^{201}$TI myocardial scintigraphy for detection of individual coronary stenoses, detection of relatively mildly ischemic regions (condition 4) may be possible by several approaches. Application of appropriate background subtraction or image processing and display to planar $^{201}$TI images may enhance the differences between normal and mildly hypoperfused areas, and result in the detection of the latter. Use of tomographic $^{201}$TI imaging may help detect small areas of hypoperfusion that are obscured by superposition of normal regions. Furthermore, an approach that evaluates different myocardial segments in a spatially nonrelative fashion might allow detection of additional ischemic myocardial regions. Recent investigations regarding the myocardial kinetics of $^{201}$TI suggest that ischemic myocardial segments demonstrate altered washout of $^{201}$TI after initial myocardial uptake. Because washout abnormalities cannot be readily assessed by the visual inspection of the myocardial scintigrams, even when images are collected for preset time with preset intensities, accurate analysis of segmental $^{201}$TI washout rate requires a quantitative approach.

We used a comprehensive computer technique for quantitative analysis of both segmental myocardial $^{201}$TI distribution and washout. This technique uses a computer to process the scintigrams, measure and display maximal circumferential profiles corresponding to the myocardial $^{201}$TI distribution at different times, measure and display the washout circumferential profiles and compare each patient’s regional $^{201}$TI distribution and washout to the established normal limits, and print out the extent of regions below these normal limits.

The image processing performed consisted primarily of modified interpolative background subtraction to compensate for tissue crosstalk. This method appears to provide the most satisfactory approximation of the true background in planar $^{201}$TI imaging, because it accounts for nonuniformity in background distribution that is subject to spatial and temporal changes in stress-redistribution imaging. Methods that do not correct for tissue crosstalk or those that use the subtraction of a constant are not considered adequate.

The quantitative method presented showed better interobserver agreement than that reported for visual interpretation by other investigators. This important attribute is expected of a computerized method that minimizes subjective interaction. Although highly automated, the computer method has remaining subjectivity in some of the analytic steps, such as locating the center of the ventricular cavity and the alignment of the apex. Further automation of these steps should reduce the remaining subjectivity.

We chose to develop normal limits from a group of patients with a very low (less than 1%) likelihood of CAD rather than from patients with normal coronary arteriograms or normal volunteers. Recent data have demonstrated that patients who undergo coronary angiography due to a high suspicion of CAD and are found to have normal coronary arteriograms are not a homogeneous, normal group and that a significant proportion of these patients have stress-induced regional myocardial hypoperfusion and wall motion abnormalities. Similarly, in this study, three of 11 (27%) patients with normal coronary arteriograms had abnormal $^{201}$TI studies by visual analysis, while no patient with less than 1% likelihood of CAD had visually abnormal $^{201}$TI scintigrams. The alternative approach to defining normal limits using normal volunteers has limitations when age matching is used, because normal volunteers in the CAD age range might have an unacceptably high prevalence of angiographic CAD.

Our quantitative method demonstrated a significant improvement over the visual method in detecting individual coronary artery lesions with minor, but insignificant loss of specificity. None of the 35 segments that were missed visually and detected quantitatively had prior infarction. In 16 of 35 (46%) of these segments, the lesions were detected by the presence on quantitative analysis of an initial defect alone (eight of
35) or in combination with slow washout (eight of 35). Detection of these 16 segments with reduced initial distribution of 201T1 is most likely due to application of background subtraction to the images. The most frequent mechanism of improved detection, however, was detection of isolated washout abnormalities in ischemic myocardial regions that appeared normal by visual analysis. This mechanism alone occurred in 19 of 35 (54%) of the regions detected quantitatively and missed visually.

The finding of isolated stress defects or washout abnormalities in ischemic segments may superficially appear contradictory to animal experiments, which have shown that ischemic regions demonstrate both slow washout and reduced initial uptake of 201T1. However, these experimental findings were obtained in a model with single-region ischemia in which the initial uptake and washout of 201T1 were initial and uniform with those of absolutely normal segments. Analysis of stress-redistribution scintigrams in patients with multiple regions of ischemia may not demonstrate stress defects in an ischemic segment if in a given view all segments are abnormal and the regions in question are the least ischemic. In fact, in our study, in the 35 segments detected only quantitatively, 15 of 19 segments with washout abnormality alone occurred when the remaining myocardial regions in that view were supplied by coronary arteries with equal or greater degree of luminal narrowing than in the arteries supplying the segment with isolated slow washout. With respect to isolated stress defects, this finding in our study appears to be related to the degree of slow washout required for a segment to be considered abnormal. In all eight of the 35 visually assessed ischemic segments with quantitative initial defect alone, a relatively slow washout rate was observed, but the values did not fall more than 2 standard deviations below the mean normal washout rate. Use of these quantitative criteria for interpretation did not impair diagnostic accuracy, because washout abnormality and stress defects were also highly specific for disease; of 85 visually normal regions supplied by nondiseased vessels, only two demonstrated isolated slow washout, three had both stress defect and slow washout, and two showed isolated stress defect.

Patients undergoing submaximal stress testing could falsely demonstrate slow myocardial washout of 201T1. To investigate this possibility, we analyzed the myocardial washout patterns of 18 patients who achieved only submaximal (< 85% predicted maximum) heart rate during stress. Of these 18 patients, nine showed a pattern of generalized slow washout. This result in diagnosis that was appropriate to the coronary anatomy in seven of the nine. Thus, these patients demonstrate that failure to achieve an adequate heart rate does not appear to be associated with generalized abnormality of washout in the absence of CAD.

The quantitative technique was more sensitive in detecting abnormality in regions subtended by coronary vessels with 50–75% stenosis. This finding may be of clinical importance, as 201T1 imaging is frequently used to assess the functional significance of angiographically borderline coronary lesions and low sensitivity of visual analysis limits its value for this application.

In summary, the comprehensive quantitative approach to analysis of the regional stress myocardial distribution and washout of 201T1 was more accurate than visual image interpretation for detection of disease in individual coronary arteries, especially in patients with multiple-vessel CAD and those with moderate coronary artery stenosis. Additionally, this computerized method minimizes many of the problems associated with subjectivity of visual analysis of 201T1 scintigrams. These improvements may expand the use of 201T1 scintigraphy in the noninvasive evaluation of patients with CAD. However, the technique should be assessed in a larger patient population.

Acknowledgment

The authors gratefully acknowledge the research assistance of Nancy Pantaleo, Paciano Tapnio, David Brown and Ken Van Train, and the technical assistance of Fariba Assil and Bonnie Bullard.

References

Improved noninvasive assessment of coronary artery disease by quantitative analysis of regional stress myocardial distribution and washout of thallium-201.
J Maddahi, E V Garcia, D S Berman, A Waxman, H J Swan and J Forrester

Circulation. 1981;64:924-935
doi: 10.1161/01.CIR.64.5.924

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