Quantitative rotational thallium-201 tomography for identifying and localizing coronary artery disease

EUGENE E. DEPASQUALE, M.D.,* AGATHA C. NODY, M.D.,* E. GORDON DEPUEY, M.D.,
ERNEST V. GARCIA, PH.D., GEORGE PILCHER, M.D.,** CLAYTON BREDLAU, M.D.,***
GARY ROUBIN, M.D., ANITA GOBER, C.N.M.T., ANDREAS GRUENTZIG, M.D.,†
PAUL D’AMATO, M.D., and HARVEY J. BERGER, M.D.****

ABSTRACT The purpose of this study was to develop and validate a method for quantifying the uptake, redistribution, and washout of thallium-201 (201Tl) obtained with rotational tomography. This method generates maximum count circumferential profiles of the short-axis slices of the left ventricle, translates them into polar coordinate profiles, and displays them as a bullseye plot, which consists of a series of concentric circles with the apex at the center and the base at the periphery. Normal limits were established for the distribution of 201Tl in 36 patients with a low (<5%) probability of coronary artery disease (CAD). Forty-five patients who had undergone coronary angiography were used as a pilot group to define criteria for the identification and localization of perfusion defects. The best agreement with the results of angiography was found when abnormal regions of the bullseye were defined as contiguous defects over 2.5 SDs below normal. These criteria were applied prospectively to 210 points (179 points with >50% diameter stenosis and 31 with <50%). Visual, quantitative, and combined visual and quantitative analysis were compared for overall detection of disease and for detection of individual vessel involvement. The overall sensitivity for detection of disease by these methods was 97%, 95%, and 95%, respectively. The specificities were 68%, 74%, and 71% respectively. The sensitivity for detection of individual vessel involvement with the bullseye alone was 78% for the left anterior descending artery (LAD), 89% for the right coronary artery (RCA), and 65% for the left circumflex (LCx). For visual analysis, the results were 70%, 88%, and 50%, respectively, while the use of visual and quantitative analysis combined identified 75% of LAD, 87% of RCA, and 55% of LCx lesions. We conclude that quantitative analysis of rotational 201Tl tomographic images is a highly accurate technique for determining the presence and location of CAD.


EXERCISE thallium-201 (201Tl) myocardial perfusion imaging has gained wide acceptance as a useful noninvasive technique for the identification and evaluation of patients with known or suspected coronary artery disease (CAD).1–7 However, because of the limitations of planar 201Tl imaging it has been less successful at identifying the specific coronary arteries involved or the extent of disease than at detecting the presence of CAD.8–11 These limitations include the low energy of 201Tl, its low target-to-background activity ratio and the superimposition of regions of the myocardium on each other in the planar image. In addition, when visual analysis of 201Tl images is used there is observer variability.12, 13 A major advance in the attempt to overcome these limitations has been the quantification of the uptake and washout of 201Tl and the use of normal limits for comparison.14–21 More recently, rotational 201Tl tomography has been used but there has been limited experience in quantification of tomographic studies.22–27 The aim of this study is to develop and validate a new quantitative technique, using polar coordinate maps, for evaluation of the
uptake and redistribution of $^{201}$Tl obtained with rotational tomography. To accomplish this we first defined the normal spatial distribution of $^{201}$Tl in patients with a low ($<5\%$) probability of CAD. Next, the optimal criteria for defining the presence and location of a defect at stress and redistribution were determined in a pilot group. Finally, in a prospective group the sensitivity, specificity, and predictive accuracy of this technique for identifying and localizing CAD were assessed.

**Methods**

This study of 291 patients consisted of three parts. In part I, the normal spatial distribution of $^{201}$Tl was determined in 36 clinically normal subjects. Part II consisted of a pilot study in which the optimal criteria for defining the presence and location of a significant coronary stenosis using rotational $^{201}$Tl tomography were determined. In part III these criteria were evaluated prospectively in 210 patients who underwent cardiac catheterization.

**Patients.** Part I involved 36 subjects who were referred for diagnostic $^{201}$Tl imaging and who were believed to be clinically normal. They ranged in age from 27 to 69 years. There were 20 men (mean age 41 years) and 16 women (mean age 39 years) in this group. Normality was defined as a less than 5% likelihood of having CAD as estimated by Bayesian analysis of age, sex, symptom classification, coronary risk factors and the results of an electrocardiographic stress test. All subjects had a normal resting ECG, achieved more than 85% of their age-predicted maximum heart rate, and did not have chest pain or electrocardiographic changes during exercise.

Part II involved 45 patients (38 men and seven women) with a mean age of 57 years who underwent both $^{201}$Tl imaging and cardiac catheterization. Patients who had previously undergone coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) were excluded. The $^{201}$Tl images were reviewed in conjunction with the angiographic data.

Part III involved 210 patients (170 men and 40 women) with a mean age of 54 years who underwent exercise $^{201}$Tl imaging and cardiac catheterization. Patients who had undergone either CABG or PTCA were excluded. At least one coronary stenosis of over 50% was present in 179 of these patients while 31 had normal coronary arteries or only subcritical lesions. Of the 179 patients with CAD, 93 had one-vessel, 73 two-vessel, and 13 three-vessel disease. Forty-seven had a myocardial infarction by electrocardiographic evidence (defined as a Q wave of 40 msec or greater). One hundred of these patients were randomly selected for assessment of observer variability.

**Coronary arteriography.** Coronary arteriography was performed in all patients in parts II and III within an average of 14 days, and in all cases within 3 months, of the time of $^{201}$Tl imaging. Significant CAD was defined as a 50% or greater luminal narrowing of one or more coronary artery or its major branches, including the diagonal branch of the left anterior descending artery (LAD), the obtuse marginal branches of the left circumflex artery (LCx), and the posterior descending branch of the right coronary artery (RCA) in a right-dominant system or the LCX in a left-dominant system. An isolated left main coronary artery lesion was considered to produce significant disease in the LAD and LCX. A ramus intermedium artery was considered equivalent to the diagonal branch of the LAD. Digital electronic calipers were used for measurement. The final diameter stenosis was expressed as the mean of measurements in multiple projections by experienced observers without knowledge of the scintigraphic findings using the method of Meier et al.29 Vessels with stenoses of 45% or greater or with sequential subcritical lesions of greater than 30% but less than 50% were also identified for separate analysis.

**Exercise protocol and tomographic acquisition.** All patients were exercised in a fasting state according to the Bruce treadmill protocol. The ECG, heart rate, and blood pressure were recorded at rest and during each minute of exercise. Exercise was to a symptom-limited maximum end point with termination by fatigue, dyspnea, angina, ventricular arrhythmias, or hypotension. At peak exercise 3.5 mCi of $^{201}$Tl was injected (resulting in an estimated total body absorbed dose of 0.74 rads), and exercise was terminated approximately 60 sec later. With a rotating large-field-of-view gamma camera (GE 400AC), initial (after 5 min) and delayed (after 3 to 5 hr) data were acquired over 180 degrees from the 45 degree right anterior oblique position to the 45 degree left posterior oblique position. Thirty-two projections were obtained, in a $64 \times 64$ matrix of a $40$ cm field of view, for 40 sec per image. A 20% energy window was centered on the low energy x-ray peak (approximately 70 to 80 keV) of $^{201}$Tl. Each projection was corrected for nonuniformity with a 30 million count flood with use of a cobalt-57 source. Filtered back projection was performed with a Ramp-Hanning filter with a cutoff value of 0.5 cycles/pixel. Axial filtration (1-2-1) was performed in the direction perpendicular to the slice. No attenuation or scatter correction was used. After the acquisition of the stress projections, the arms were imaged for 30 sec to determine whether significant local infiltration of $^{201}$Tl had occurred, which was defined empirically as a tracer concentration at the site of injection that was greater than 1.5 times the concentration in the same area of the other arm. Patients who failed this test were not used for the study. Orthogonal images were generated by oblique angle reconstruction producing short-axis, vertical long-axis, and horizontal long-axis slices each 6 mm thick. These images were analyzed visually by the consensus interpretation of three experienced observers who were unaware of the clinical diagnosis or the angiographic findings. The vertical long-axis slices were divided into anterior, apical, and inferior territories. The short-axis slices were divided into anterior, septal, inferior, and lateral territories. The horizontal long-axis slices were divided into septal, apical, and lateral territories. A four-point scoring system was used for each wall: 0 = normal, 1 = mildly reduced tracer concentration, 2 = moderately reduced tracer concentration, and 3 = markedly reduced tracer concentration.

**Quantification of $^{201}$Tl images by generation of bullseye polar coordinate maps.** This method is used to display and quantify the data from an entire study in a single functional image. Using the stress vertical long-axis slice with the greatest cavity length as a guide, the operator selects the short-axis slices for quantification to extend from the first slice with apical activity to the last one with significant activity at the base. The same procedure is repeated for the delay study and an equal number of slices are chosen. Next, the operator defines the center of the left ventricular cavity and the radius of search on a summed image of the short-axis slices. In figure 1, A, alternating short-axis slices of the left ventricle are displayed from base to apex. Approximately 12 slices are obtained from a normal-sized heart. In this example there is a defect in the septum, highlighted in the middle slice. In figure 1, B, this slice has been divided into 40 sectors of 9 degrees each. The septum is represented by the sectors from 90 to 180 degrees. The maximum counts per pixel within each sector is determined.

In figure 2, A, these 40 values have been plotted as a circumferential profile of the maximal counts per pixel vs angular location. A similar profile is constructed for each slice, except
the first two containing the apex, which are represented by a single value representing the maximal counts per pixel within the entire slice. To take into account variations in the number of slices per study, these curves are linearly interpolated to produce a total of 15 profiles. Each of these rectangular coordinate profiles is translated into a polar coordinate profile, which displays the curve as a circle composed of 40 pixels (figure 2 b). In figure 2, c, these data are displayed as a polar map called a bullseye plot, which consists of a series of 15 concentric circles with the apex at the center and the base at the periphery. Individual bullseye plots are constructed for the stress and delay images as well as for percent washout, which is calculated on a pixel-by-pixel basis by subtracting the delay value from the stress value and multiplying by 100/stress value. The bullseye plots from a patient with disease of the LAD are displayed in figure 3. In this display format, the stress and delay bullseye plots are adjusted by multiplying each pixel in the delay bullseye by the ratio of the maximal counts per pixel in the stress bullseye to the maximal counts per pixel in the delay bullseye. Note the large anteroseptal defect at stress, which demonstrates marked redistribution in the delay bullseye.

In part I, gender-matched normal files were developed from the group with low probability of disease in which the mean values and standard deviations were established from the pooled data for each of the angular locations in each of the 15 profiles of each bullseye plot. The mean counts in the apex and anterior, septal, lateral, and inferior walls of men and women were determined and compared. Normalization of the bullseye plots occurs only when the profiles are compared with the gender-matched normal files. This is accomplished by dividing each bullseye into four regions of 90 degrees each (anterior, septal, inferior, and lateral) from profiles 4 through 12 and determining the ratio of the average counts per pixel in each region of the patient's bullseye to the same region in the appropriate normal file. The region with the highest ratio is assumed to be normal, and each pixel in the patient's bullseye is multiplied by the reciprocal of this ratio. Before comparing the washout profiles to the corresponding normal profiles, the normal profiles are adjusted to correspond to the same acquisition interval as the patient's study in the same manner as Garcia et al. have demonstrated but with a 360 instead of a 732 min effective half-time based on data derived from the work of Gober et al. The comparison of each patient's bullseye with a gender-matched normal file results in the conversion of the bullseye into a standard deviation map displaying pixels that are 1, 2, 2.5, and 3 SDs below normal. The pixels that fall below these limits are submitted to a clustering criteria that prevents pixels without two adjacent abnormal neighbors from being displayed. In part II these quantitative images, as well as the consensus visual interpretations of the oblique images, were compared with the angiographic data to determine the best criteria for identifying the presence and location of a significant coronary stenosis. After completion of part II, the oblique images and bullseye plots of the 210 patients in part III were read separately by three expe-
Results

Part I: normal subjects (n = 36). The mean relative normal stress $^{201}$TI distributions for men and women, determined from gender-matched pooled normals, are displayed as bullseye plots in figure 4. In both sexes, the lateral wall demonstrates the highest $^{201}$TI activity. The most significant difference was found in the inferior wall, in which the relative uptake of $^{201}$TI is significantly reduced (p < .01) in men as compared with women. The relative uptake in the septum of men was also significantly decreased (p < .05).

Part II: pilot group (n = 45). When the bullseye plots of the patients in this group were compared with the angiographic data, the best agreement was found to exist when abnormal regions of the bullseye were defined as contiguous defects greater than 2.5 SDs below normal. In men these defects had to contain at least 1.5% of the pixels in the bullseye to be significant.
while 3% were required in women. Two types of washout abnormality were noted: diffuse slow washout, in which the entire bullseye was abnormal, and localized slow washout, in which the abnormality was confined to one or two vascular territories. Thereafter a series of guidelines was developed for assigning a defect to a specific coronary lesion. The territory of the LAD was found to extend from 0 degrees counterclockwise to 160 degrees (figure 5), that of the RCA extends from 160 to 270 degrees, and that of the LCx extends from 270 to 0 degrees. There was, however, significant overlap at the boundaries of these lesions, and defects found primarily in one territory that did not extended significantly over the border of another territory were considered to represent one lesion. Objective criteria were

established from the pilot study, which defined the amount of significant overlap that would have to exist to identify multiple-vessel disease from one contiguous defect. This criterion consisted of defining a second set of boundaries, which from the reference frame in figure 5 would lie at exactly 45, 135, 225, and 315 degrees (12, 9, 6, and 3 o’clock, respectively). Thus a perfusion defect whose angular range exceeded 45 degrees in the RCA territory would have to cross the exact 315 degree boundary at the medial or basal levels to include the LCx artery as a diseased vessel. The same rule was applied to all combinations of multiple vessels and second set boundaries. The stress and delay bullseye plots from a patient with double-vessel disease involving the LAD and RCA are displayed in figure 6. The pixels more than 2.5 SDs below normal are displayed in black. Note the discrete antero septal and inferior defects at stress.

When the visual analysis of tomographic data in this group was compared with the angiographic data, the territory of the LAD was found to include the anterior wall and septum, whereas that of the RCA included the inferior wall and that of the LCx included the lateral wall. Isolated apical defects were not assigned to a specific artery. Our previous experience with the visual interpretation of tomographic studies had led us empirically to require scores of one or greater in two segments to identify disease in a specific artery. These criteria were applied in the pilot study and were found to identify significant stenoses with a high degree of accuracy.

![Diagram illustrating the means by which regions of the bullseye plot are assigned to specific coronary arteries.](image)

**FIGURE 5.** Diagram illustrating the means by which regions of the bullseye plot are assigned to specific coronary arteries.

![Bullseye plots from a patient with an 85% diameter stenosis of the LAD and a 55% diameter stenosis of the RCA. Pixels greater than 2.5 SDs below normal are displayed in black. The anteroseptal and inferior defects present at stress (left) undergo complete redistribution on the delay (right) plot.](image)

**FIGURE 6.** Bullseye plots from a patient with an 85% diameter stenosis of the LAD and a 55% diameter stenosis of the RCA. Pixels greater than 2.5 SDs below normal are displayed in black. The anteroseptal and inferior defects present at stress (left) undergo complete redistribution on the delay (right) plot.
Detection of CAD with Thallium-201 Tomography

![Graph showing detection of CAD with Thallium-201 Tomography](Graph.png)

**FIGURE 7.** Comparison of the sensitivity, specificity, and accuracy of visual, quantitative (bullseye), and visual plus quantitative analysis combined for detection of CAD by $^{201}$Tl rotational tomography. TP = true positives; TN = true negatives.

**Part III: prospective study (n = 210).** The overall sensitivity, specificity, and accuracy for detecting CAD by visual analysis, interpretation of the bullseye plots alone, and the use of the two combined are displayed in figure 7. In the combined analysis, a disagreement between the results of visual and quantitative analysis was resolved empirically by a consensus of the observers. Of the 179 patients with significant CAD, visual analysis identified 173 (97%) whereas analysis of the bullseye alone identified 170 (95%) as did the combination of visual and quantitative analysis. Of the 31 patients without significant CAD, 21 (68%) had negative findings by visual analysis alone, 23 (74%) had negative findings by analysis of the bullseye, and 22 (71%) had negative findings when visual and quantitative analysis were combined. The overall accuracy of visual analysis alone and of the Bullseye alone was 92%, and the accuracy of the two combined was 91%.

The ability of $^{201}$Tl rotational tomography to identify individual coronary stenoses is displayed in table 1 for each major coronary artery and for the LCx and RCA combined. When the 87 patients who achieved 85% or greater of the age-predicted maximum heart rate on exercise were separately analyzed the overall sensitivity was 93% for the bullseye alone, whereas 76% of LAD lesions, 94% of those in the RCA, 63% in the LCx, and 89% of those in the RCA and LCx combined were identified. These results were not significantly different than those for the prospective group as a whole.

Further data from the analysis of the bullseye alone are presented in table 2. No significant difference in either the overall sensitivity and specificity or the sensitivity and specificity for individual vessels was found when patients without myocardial infarction, men, and women were considered separately. When vessels with either stenoses of 45% or greater or sequential sub-critical lesions (>30%) were considered significant, in an attempt to maximize specificity while maintaining sensitivity, the sensitivities and specificities for individual vessels were unchanged as was the overall sensitivity. The overall specificity with these criteria was 91% as compared with 74% at 50% diameter stenosis. This difference approached statistical significance (p = .08). Six of the eight overall apparent false positives with 50% diameter stenosis as a criterion were associated with lesions that were significant with 45% diameter stenosis plus sequential lesions as the criteria, including three that had gradients of 60, 63, and 69 mm Hg at the time of PTCA. Overall, 21 of the 25 lesions considered significant only by the 45% diameter stenosis plus sequential lesions criteria were correctly identified.

The effect of stenosis severity on detection of lesions is displayed in table 3. Overall 86% of lesions greater than or equal to 75% diameter stenosis were identified vs 67% of those under 75% diameter stenosis (p < .001). The positive and negative predictive values for

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tbody>
<tr>
<td></td>
<td>LAD (n = 96)</td>
<td>RCA (n = 104)</td>
</tr>
<tr>
<td>SENS</td>
<td>SPEC</td>
<td>SENS</td>
</tr>
<tr>
<td>Visual</td>
<td>70</td>
<td>82</td>
</tr>
<tr>
<td>Bullseye</td>
<td>78</td>
<td>83</td>
</tr>
<tr>
<td>Visual + bullsey</td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td>Bullseye + isolated washout abnormality</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>Bullseye + isolated and diffuse washout abnormality</td>
<td>81</td>
<td>74</td>
</tr>
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</table>

SENS = sensitivity; SPEC = specificity.
detection of individual coronary stenoses are displayed in table 4.

The sensitivity and specificity of quantitative analysis of the bullseye for identifying patients with CAD is displayed in figure 8. In patients with single-vessel disease, 91% were identified at the 50% diameter stenosis level and 90% at the 45% diameter stenosis plus sequential lesions level. In patients with two-vessel disease, 99% were identified by either criterion for a significant lesion. All patients with triple-vessel disease were identified.

The ability to detect individual coronary stenoses in relation to the number of diseased vessels is displayed in table 5. In patients with one-vessel disease, 87% of the individual lesions were correctly identified with 50% diameter stenosis as the criterion and 86% if 45% diameter stenosis plus sequential lesions was used. In patients with two-vessel disease, 75% and 78% of the individual lesions were correctly identified. In patients with three-vessel disease these numbers were 72% and 73%. Overall 79% of diseased vessels were correctly identified with either criteria.

The effect on the sensitivity and specificity for identifying individual stenoses of adding analysis of washout to the interpretation of the bullseye is displayed in table 1. Localized slow washout, if considered significant, would have added two true positives and nine false positives at the 50% diameter stenosis level and four true positives and seven false positives at the 45% diameter stenosis plus sequentials level. Diffuse slow washout occurred in five patients with adequate exercise. Four of these patients had one-vessel disease and one had two-vessel disease. All five patients were identified as abnormal without washout. In the analysis of individual vessels, the use of diffuse slow washout would have added one true positive and eight false positives.

The results of the interobserver and intraobserver analyses of the bullseye were excellent for experienced observers, as seen in table 6. When the interpretations of an inexperienced observer were compared with the consensus interpretation of these experienced observers, the agreement ranged from 87% for the RCA to 96% for the LCx.

**Discussion**

The method of rotational tomography described provides a comprehensive means of acquiring planar projections, reconstructing transaxial and orthogonal tomograms, creating maximum-count circumferential profiles for each short-axis slice for stress, redistribution, and washout, comparing these profiles to previously established normal limits, and displaying these profiles in comprehensive functional images for stress, redistribution, and washout that express the extent and depth of perfusion defects. The results of the prospec-

**TABLE 2**

Sensitivity and specificity (%) for detection of individual coronary artery stenosis with quantitative 201TI tomography

<table>
<thead>
<tr>
<th>Diameter stenosis</th>
<th>LAD SENS SPEC</th>
<th>RCA SENS SPEC</th>
<th>LCx SENS SPEC</th>
<th>RCA/LCx SENS SPEC</th>
<th>Overall SENS SPEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%--all patients (n = 210)</td>
<td>78 (75/96) 83 (95/114)</td>
<td>89 (93/104) 88 (92/106)</td>
<td>65 (51/78) 95 (126/132)</td>
<td>90 (122/136) 86 (64/74)</td>
<td>95 (170/179) 74 (21/31)</td>
</tr>
<tr>
<td>Patients without myocardial infarction (n = 165)</td>
<td>84 (83/103) 77 (48/62)</td>
<td>90 (89/99) 88 (58/66)</td>
<td>63 (37/58) 95 (102/107)</td>
<td>87 (82/94) 87 (62/71)</td>
<td>92 (123/134) 74 (23/31)</td>
</tr>
<tr>
<td>Men (n = 170)</td>
<td>78 (63/87) 83 (74/89)</td>
<td>90 (83/92) 87 (68/78)</td>
<td>65 (45/69) 95 (96/101)</td>
<td>92 (110/119) 88 (45/51)</td>
<td>96 (148/154) 75 (12/16)</td>
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<tr>
<td>Women (n = 40)</td>
<td>86 (12/14) 85 (22/26)</td>
<td>77 (10/13) 89 (24/27)</td>
<td>67 (6/9) 97 (30/31)</td>
<td>71 (12/17) 83 (19/23)</td>
<td>88 (22/25) 73 (11/15)</td>
</tr>
<tr>
<td>45% + sequentials--all patients (n = 210)</td>
<td>79 (90/114) 96 (92/96)</td>
<td>89 (98/109) 88 (92/101)</td>
<td>65 (52/80) 96 (125/130)</td>
<td>89 (126/141) 91 (63/69)</td>
<td>94 (176/187) 91 (21/23)</td>
</tr>
</tbody>
</table>

**TABLE 3**

Sensitivity (%) for detection of individual coronary artery stenosis in relation to diameter stenosis with quantitative 201TI tomography

<table>
<thead>
<tr>
<th>Diameter stenosis</th>
<th>LAD</th>
<th>RCA</th>
<th>LCx</th>
<th>Total</th>
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<tbody>
<tr>
<td>50%--74%</td>
<td>63% (38/60)</td>
<td>80% (37/46)</td>
<td>55% (16/29)</td>
<td>67% (91/135)</td>
</tr>
<tr>
<td>75%--100%</td>
<td>96% (52/54)a</td>
<td>95% (60/63)b</td>
<td>71% (36/51)</td>
<td>88% (148/168)a</td>
</tr>
</tbody>
</table>

aSignificant at p = .001.
bSignificant at p = .05.
TABLE 4
Predictive accuracy (%) for detection of individual coronary artery stenosis with quantitative 201Tl tomography

<table>
<thead>
<tr>
<th>Diameter stenosis</th>
<th>Patients</th>
<th>LAD</th>
<th>RCA</th>
<th>LCx</th>
<th>RCA/LCx</th>
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<tbody>
<tr>
<td>50%</td>
<td>All patients (n = 210)</td>
<td>80</td>
<td>82</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>(75/94)</td>
<td>(95/116)</td>
<td>(93/107)</td>
<td>(92/103)</td>
<td>(51/57)</td>
</tr>
<tr>
<td></td>
<td>Patients without myocardial infarction (n = 165)</td>
<td>86</td>
<td>65</td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>(97/101)</td>
<td>(48/64)</td>
<td>(89/97)</td>
<td>(58/68)</td>
<td>(37/42)</td>
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<tr>
<td></td>
<td>Men (n = 170)</td>
<td>81</td>
<td>80</td>
<td>90</td>
<td>88</td>
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<tr>
<td></td>
<td>(63/77)</td>
<td>(74/93)</td>
<td>(83/93)</td>
<td>(68/77)</td>
<td>(45/50)</td>
</tr>
<tr>
<td></td>
<td>Women (n = 40)</td>
<td>75</td>
<td>92</td>
<td>77</td>
<td>89</td>
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<tr>
<td></td>
<td>(12/16)</td>
<td>(22/24)</td>
<td>(10/13)</td>
<td>(24/27)</td>
<td>(6/7)</td>
</tr>
<tr>
<td>45% + sequentials</td>
<td>All patients (n = 210)</td>
<td>96</td>
<td>79</td>
<td>92</td>
<td>89</td>
</tr>
</tbody>
</table>

tive evaluation of this method demonstrate a high sensitivity and specificity for the detection of CAD in patients and in individual coronary vessels whether visual or quantitative analysis was used. The overall sensitivity for detection of disease is similar to that reported for planar imaging.\(^{17,19,20}\) However, the detection of the specific arteries involved, particularly the LCx, appears to be better. The overall specificity is lower than that reported for planar imaging\(^{17,19,20}\) with the 50% diameter stenosis criterion but is comparable to it when the 45% diameter stenosis plus sequential lesions criterion is used to determine the significance of a lesion. It is important to remember that the specificity depends greatly on the type of patients being tested. As Rosanski et al.\(^{31}\) have demonstrated with exercise radionuclide ventriculography, a fall in specificity is inescapable as a noninvasive test to detect CAD gains acceptance because an abnormal test result becomes an important criterion for recommending coronary arteriography. Indeed, this has already occurred with planar 201Tl imaging. Maddahi et al.\(^{17}\) reported a specificity of 91% for quantitative planar imaging in 1981. Five years later, in a multicenter trial, the specificity for the same technique at the site that developed it had fallen to 43%.\(^{32}\) The relatively low specificity in this report may reflect, in part, a similar pattern. There was no significant difference among men, women, and patients with or without myocardial infarction in the ability of this technique to identify CAD. It was somewhat less sensitive at identifying individual stenoses in patients with multivessel disease or LCx disease. Although not statistically significant (p = .07), there was a trend suggesting improved detection of LCx disease by quantitative as compared with visual analysis. These findings suggest that rotational tomographic 201Tl imaging is capable of assessing stenoses of moderate-to-mild severity accurately. This is supported by the finding that the use of 45% diameter stenosis plus sequential lesions as a criterion for a significant coronary lesion did not decrease the sensitivity or specificity of the technique for identifying individual coronary stenoses while increasing the overall specificity.

A variety of factors may be associated with the observed incidence of false positives and false negatives. One is that coronary angiography provides an imperfect standard of reference. The variability in the visual interpretation of coronary arteriograms is so great as to render them of limited value in serving as an objective standard for measuring the severity of a coronary lesion.\(^{33,34}\) Furthermore, angiographic evaluation of the functional significance of a coronary stenosis by measuring the diameter stenosis, even if accurately performed, may not be sufficient since other factors, including the length, shape, eccentricity, and

FIGURE 8. Comparison of the sensitivity and specificity of quantitative analysis for detection of CAD when 50% diameter stenosis and 45% diameter stenosis plus sequential lesions are used as the criteria for abnormality. The sensitivity in one-, two-, and three-vessel disease as well as the overall sensitivity and specificity are compared.
number of lesions in series, may affect coronary flow.35 The use of digital calipers addresses the former consideration, but the problem of adequately assessing the functional significance of a coronary lesion remains. The measurement of coronary flow reserve has been advocated for this purpose, by means of either a hyperemic flow response36 or measurement of x-ray geometry alone.37 However, we elected not to use this approach because good normal standards for the measurement of coronary flow reserve and the meaning of a diminished flow reserve are not well established.38,39 A certain number of false positives and false negatives can therefore be attributed to an underestimation or overestimation of the severity of disease by the coronary arteriogram.

Another cause of false positives and negatives in the identification of individual stenoses is the variability of the coronary anatomy. It was not uncommon, for example, for LCx lesions to produce defects in the territory assigned to the RCA (producing a false positive in the RCA territory and a false negative in the LCx territory) or for an LAD lesion to produce a defect in the region assigned to the LCx. When the RCA and LCx territories were combined into a single zone, the sensitivity and specificity were both quite high. On occasion, in patients with single-vessel disease a large defect in the territory of an abnormal vessel would extend far enough into the territory assigned to another vessel (LAD lesion into inferior territory for example) to cause the erroneous diagnosis of multivessel disease. Although less commonly than in planar imaging, false negatives may occur if the myocardial territory supplied by a vessel with a significant stenosis does not become ischemic. This may be the result of inadequate exercise or, in multivessel disease, because the patient is limited by ischemia in a more severely diseased vessel. Other causes of false positive results include left bundle branch block, attenuation caused by breast tissue resulting in false positive anterior defects, diaphragmatic attenuation resulting in false positive inferior defects, incorrect determination of the center of rotation resulting in artifacts in the reconstructed images, and patient movement during acquisition.

There have been several reports suggesting that rotational tomography enhances the accuracy of $^{201}$Tl myocardial perfusion imaging over that of planar imaging.24,25,40,41 Tamaki et al.26 have reported that the quantification of rotational tomographic images with circumferential profiles improves the sensitivity of $^{201}$Tl imaging. Garcia et al.27 have described a method of quantification of $^{201}$Tl distribution with polar coordinate maps, which they evaluated in a pilot group. This method has now been evaluated prospectively by Maddahi et al.42 in a group of men in whom it was found to be accurate in the overall detection of CAD and in the identification of individual vessel involvement. Ritchie et al. have also used polar coordinate plots to assess infarct size43 and to identify CAD by a method of $^{201}$Tl rotational tomography validated in dogs by Caldwell et al.45 Our method differs from that of Garcia et al. in several respects. We reconstructed three sets of orthogonal images, whereas they constructed only short-axis and vertical long-axis tomograms. We used both visual and quantitative analyses, whereas they used only quantitative analysis. In addition, we quantified all of the short-axis

| TABLE 5 | Sensitivity (%) of individual coronary artery vessel detection with quantitative $^{201}$Tl tomography in relation to number of diseased vessels |
|-------------------|-----------------|-----------------|-----------------|-----------------|
| Diameter stenosis | CAD | LAD | RCA | LCx |
| 50%               | 84 (36/43) | 91 (29/32) | 89 (16/18) | 87 (81/93) |
| 45% + sequential | 84 (38/45) | 90 (26/29) | 83 (10/12) | 86 (74/86) |

| TABLE 6 | Interobserver and intraobserver reproducibility (%) of quantitative $^{201}$Tl tomography (n = 100) |
|-------------------|-----------------|-----------------|-----------------|
|                   | LAD | RCA | LCx | RCA/LCx |
| Experienced readers | Inter | 97 | 91 | 95 | 97 |
| Inexperienced reader | Inter | 94 | 87 | 96 | 89 |
slices in the left ventricle and they excluded the three most basal slices. We divided the short-axis slices into 40 sectors of 9 degrees each and determined the maximal counts per pixel within each sector, while they determined the maximal counts per pixel along 60 radii spaced at 6 degree intervals. We used a clustering criteria for the display of abnormal pixels while they did not. This clustering results in perfusion defects being defined with smoother boundaries in our technique.

A possible advantage of their method is that the apical portion of the polar coordinate map was derived from quantification of the long-axis slices rather than the short-axis slices in an attempt to circumvent partial-volume effects. However, in our study none of the false-positive results were associated with isolated apical defects. Nevertheless, partial-volume effects at the apex do result in wide normal limits at this location when our method is used, increasing the chance of false negatives to an extent that is not verifiable. The most significant difference in the two techniques is in the method of normalization. In their technique each profile is normalized to the maximum pixel value found in that profile, whereas in our method each pixel is normalized to the most normal region of the bullseye as compared with the normal file. Because of these differences, we used gender-matched normal files while they initially used a single normal file for men and women.\textsuperscript{46} Subsequently Van Train et al.\textsuperscript{47} modified this technique by developing a range rather than SD criteria for identifying abnormal pixels. Maddahi et al.\textsuperscript{48} have developed criteria for identifying areas of abnormal perfusion with this modification and prospectively applied these criteria in a group of men in whom they found to be accurate. The patient population that Maddahi et al.\textsuperscript{42} used to validate their technique or its modification by Van Train et al.\textsuperscript{47} was smaller than ours, was composed exclusively of men, and was compared with a gender-matched normal file. Whether it would be as accurate in a female population is not yet established. Despite these differences, the results of our studies are similar. We both found the use of polar coordinate maps to quantify \textsuperscript{201}TI rotational tomography to be highly accurate for the overall detection and localization of CAD. We both found that the analysis of washout of \textsuperscript{201}TI from the myocardium did not improve the detection of CAD. This is probably the result of improved contrast due to less overlap of diseased and normal myocardium with rotational tomography. However, washout may still be of use in differentiating ischemic from infarcted myocardium.

Our method also has similarities to that used by Ritchie et al.\textsuperscript{43,44} The major differences are in the method of normalization and the type of normals used. They used the single pixel within the bullseye with the maximum counts for normalization to a normal file composed of young volunteers. In their evaluation of this technique in 22 patients with CAD evaluated by digitized angiograms,\textsuperscript{41} they found it to be sensitive for detecting CAD especially in the RCA and LAD.

Tamaki et al.\textsuperscript{26} evaluated visual vs quantitative analysis using circumferential profiles in 104 patients undergoing rotational tomography and cardiac catheterization. Their technique differed from ours in that they reconstructed 12 mm thick slices and quantified only the three middle short-axis slices and the central long-axis slice. They also found the use of rotational tomography to yield excellent results. Similarly to the trend in our data, they found that use of quantification significantly improved the sensitivity for the detection of LCx lesions. In contrast to our data, however, they found that the analysis of \textsuperscript{201}TI washout improved the detection of disease. Perhaps this is due in part to their analysis of only the short-axis and right anterior oblique long-axis tomograms and in part to increased slice thickness resulting in more accurate quantification of washout.

In summary, \textsuperscript{201}TI rotational tomography provides an excellent tool for the detection of patients and individual vessels with CAD. The use of the bullseye plot has several advantages over visual analysis. It synthesizes the tomograms into a single reproducible functional image that can be rapidly, accurately, and objectively reviewed and that serves to point out abnormalities for further review, thus enabling nonexperts to gain experience. It is especially helpful in areas that are difficult to assess by the inexperienced: (1) the LCx territory, where the sensitivity is often low because the images tend to have more counts in the lateral wall than the other walls even if it is abnormal because it is the least attenuated wall, and (2) the inferior wall, where inexperienced observers can have trouble differentiating diaphragmatic attenuation from a true defect. Use of the bullseye plot by experienced observers does not appear to improve on the diagnostic accuracy obtainable with visual analysis. However, that quantitative analysis of the bullseye plots alone can produce results that are not significantly different from those obtained by the visual consensus of three experienced observers and that an inexperienced observer can nearly duplicate these results is remarkable. It appears likely but remains to be tested that an inexperienced observer would benefit from the use of the bullseye plot.
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References
35. Gould KL, Kelley RC, Elston EJ: Comparative accuracy of stress and redistribution thallium-201 cardiac single photon emission trans-
Quantitative rotational thallium-201 tomography for identifying and localizing coronary artery disease.


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