Quantitation of Extent, Depth, and Severity of Planar Thallium Defects in Patients Undergoing Exercise Thallium-201 Scintigraphy

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Previous quantitation of exercise-redistribution planar ^{201}Tl scintigraphy has shown high sensitivity and specificity in the detection of coronary artery disease and improved detection of individual coronary stenoses over visual analysis. By using similar methodology based on the circumferential profile method, we studied 133 patients to quantitatively assess the extent, depth, and severity of thallium defects compared with consensus visual analysis. These quantitative measurements are objective, requiring only three operator interactions. In comparing quantitative and visual results, a close correlation was found for measurement of extent of thallium defect (r = 0.73) and severity of defect (r = 0.79). In detecting patients with the high-risk scintigraphic pattern of a severe stress thallium defect, a quantitative depth score of ≥36 had an 81% sensitivity and an 82% specificity. Thus, this nearly automatic, computerized quantitative method allows objective determination of extent, severity, and depth of planar ^{201}Tl defects.

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To date, exercise planar thallium-201 (^{201}Tl) scintigraphy has been used primarily for the detection of hemodynamically significant coronary artery disease (CAD). Recently, certain visual parameters have been found useful in assessing the prognosis of patients with coronary disease and for the identification of patients with a critical underlying stenosis. In patients without prior myocardial infarction (MI), Brown et al. (*1*) have shown that the number of segments that have a reversible thallium defect correlates with future coronary events. We have previously demonstrated (*2,3*) that a region with a severe reduction in thallium uptake during stress indicates an underlying critical stenosis of the vessel supplying that region. The severe stress ^{201}Tl defect has also been shown to identify a subset of patients at a very high risk for subsequent events (*4*). In an attempt to incorporate the magnitude of reduction in thallium uptake with the extent of perfusion abnormality, we have developed a visual scoring system that combines the number of abnormal segments and the degree of reduction in ^{201}Tl uptake in each segment to yield a visual exercise severity score (*5*). Although useful for assessment of disease extent and severity, and therefore prognostic categorization, the visual method is subject to observer variability (*6,7*) and is thus highly dependent on the expertise of the reader.

Our previously described quantitative ^{201}Tl analysis technique offers a reproducible objective analysis of stress ^{201}Tl scintigrams (*8,9*). In its present form, this technique is used for determining the presence or absence of a perfusion defect as well as identifying a region with abnormal washout of ^{201}Tl. The goals of this study are: (a) to develop an objective, quantitative method of determining the extent, depth, and severity of ^{201}Tl perfusion abnormality from planar ^{201}Tl scintigrams, (b) to determine the relationship of these quantitative

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measurements to similar measurements by expert consensus visual analysis, and (c) to determine whether this quantitative technique can be used in the detection of patients with the high risk scintigraphic pattern of a severe stress thallium defect.

PATIENTS AND METHODS

Patient Population

We studied 133 patients who underwent exercise ^{201}Tl scintigraphy for the assessment of known or suspected CAD. The patient population consisted of 107 males and 26 females with a mean age of 57 ± 11 yr, of whom 30 had electrocardiographic evidence of prior MI.

Exercise Myocardial Perfusion Imaging

All patients underwent graded treadmill exercise testing according to the standard Bruce protocol. Patients were tested in the fasting state after having been instructed to discontinue beta-blocking medications 48 hr prior to testing and long-acting nitrates on the day of the test. Exercise was continued until the development of exhaustion, severe angina, serious arrhythmia, or hypotension. A dose of 2 mCi of ^{201}Tl was administered intravenously at peak exercise and exercise was continued for 45–60 sec after injection.

After termination of exercise, multiple-view myocardial scintigrams were obtained at ~6 min and again at 3–5 hr. In the present study, only the immediate postexercise (and not the redistribution) scintigrams were quantitated for defect extent, depth, and severity. At each interval, imaging was performed in the anterior, 45°, and steep left anterior oblique (LAO) views for 10 min per view. Patients were instructed to have only a small meal between imaging periods. For imaging, a standard field-of-view camera was used, equipped with 37 photomultiplier tubes, a ¼-in.-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 disk in a 128 × 128 × 8 bit matrix.

Visual Scintigraphic Interpretation

The exercise scans were interpreted from analog images displayed on Polaroid film. A Polaroid camera with three lenses of varying F stops was used to record the images at three intensities. No background subtraction, contrast enhancement, or smoothing was performed.

Immediate postexercise 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 diminished uptake in each of the 15 segments (five segments per view) was rated by consensus, using a four-point scoring system: 0 = normal, 1 = slightly (equivocally) reduced uptake, 2 = moderately (definitely) reduced uptake, and 3 = severely reduced uptake such that activity in that segment approximated background activity (Fig. 1). A "visual extent score" was defined as the number of abnormal myocardial segments (scores of 2 or 3) in all three views. A "visual depth score" categorized patients into one of four groups according to the most severe reduction in thallium uptake in any of the 15 segments. A "visual severity score" was derived by adding the visual scores of all 15 segments.

Computer Processing and Analysis

The circumferential profile technique used in this study has been previously described by our group (*8,11*). Briefly, the operator first draws a rectangular boundary around the heart after which background subtraction is automatically performed using modified interpolative background subtraction. To decrease the statistical noise associated with counting, the images are smoothed using a standard nine-point weighted-average algorithm. The center of the ventricle is then designated by the operator. From these images, circumferential maximum count profiles corresponding to the myocardial distribution of ^{201}Tl are then obtained. Each point in these profiles represents the maximum counts per pixel along radii, spaced 6° apart, which originate from the center of the left ventricular chamber and traverse the myocardium and represent the relative ^{201}Tl segmental concentration as an angular function. These profiles are extracted for each view and they are normalized so that the maximum pixel value in the curve is set to 100%. In order to correct the profiles to a standard frame of reference, they are aligned by the operator so that 90° in each view corresponds to the scintigraphic left ventricular apex. Thus, our quantita-

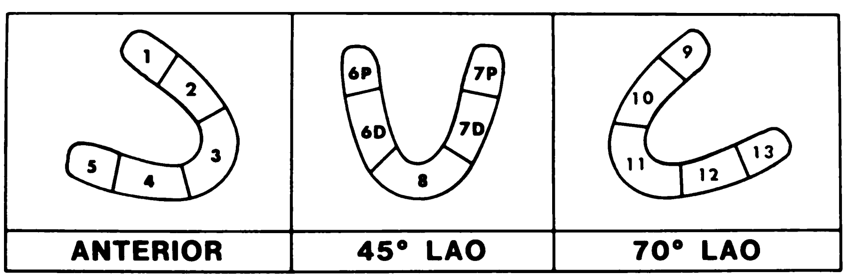


FIGURE 1
Visual analysis of ^{201}Tl scintigrams. Magnitude of reduction in thallium uptake was scored in each of 15 segments. Score code for regional uptake: 0 = Normal; 3 = Severely decreased

tive technique requires only three operator interactions: (a) drawing a box around the ventricle, (b) designation of the center of the ventricle, and (c) alignment of the apex.

In each patient three quantitative measurements of thallium abnormality are automatically generated (Fig. 2). Each measurement is obtained by comparing the patient's profile to the normal mean profile derived from 49 "normal" patients having <1% likelihood of coronary artery disease based on sequential Bayesian analysis of age, sex, symptoms, and results of exercise electrocardiography. The profile in each view which corresponds to the arc from 210–330° is considered to represent the outflow tract and is not included in any of the three quantitative scores. The "quantitative extent score" is the number of profile angles falling below the mean normal profile in all three views. The "quantitative depth score" is determined as the largest deviation from the mean normal value for any angle in any of the three views. The depth score is measured in units of percent counts. The "quantitative severity score" is defined by the integrated area of the patient's profile below the mean normal value in all three views.

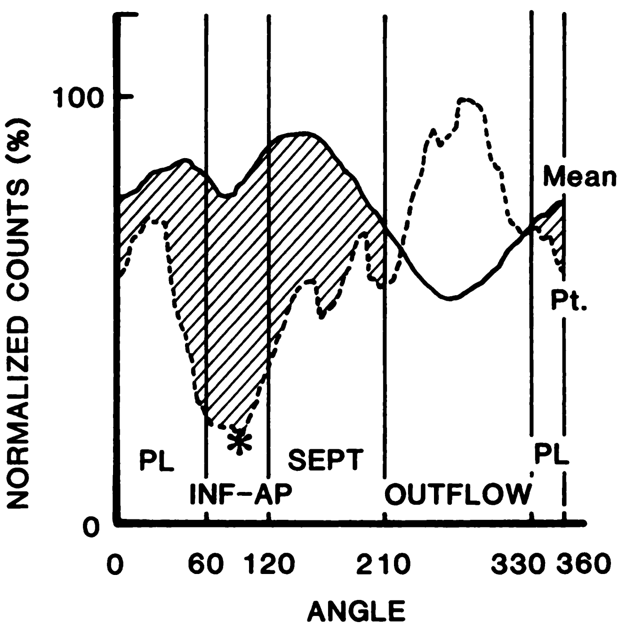


FIGURE 2
Stress LAO-45. Case illustration of method for determining three quantitative scores from postexercise LAO 45° view. Solid line is mean profile of our normal patient group and dotted line represents patient's profile. Quantitative severity score is total integrated area of patient's profile below mean (hatched area). Quantitative extent score is number of 60° angles of patient's profile falling below mean. Maximum of 40 points (240°) is possible in each view. Severity and extent scores of all three views are added to derive total severity and extent scores. Quantitative depth score (star) reflects maximum deviation in any of three views of patient's profile from mean normal profile. All scores exclude area of outflow tract (210°–330°). PL = posterolateral wall; Inf-Ap = inferoapex; Sept = septum

Statistical Analysis

Comparisons between quantitative and visual techniques for assessment of extent and severity were assessed by performing linear regression analysis. Comparisons of the three quantitative measurements to the visual depth score were performed by one-way analysis of variance, with multigroup comparison using Scheffe's Test (*10*). The relationship between different quantitative measurements was examined using Pearson correlation coefficients. A value of <0.05 was considered significant for all statistical analyses.

RESULTS

Comparison of Quantitative and Visual Extent Scores

The quantitative extent score was compared with our visual extent score (represented by the total number of visually abnormal myocardial segments) (Fig. 3). A good correlation was found between these two measures: r = 0.73, 95% confidence interval of 0.64 – 0.82.

Comparison of Visual and Quantitative Depth Scores

Patients were also grouped according to the visual depth score. Thirty-six patients had at least one segment with a severe reduction of thallium uptake (score of 3), 61 patients had at least a moderate reduction of thallium uptake (score of 2), 22 patients had a mild to equivocal reduction in thallium uptake (score of 1), and

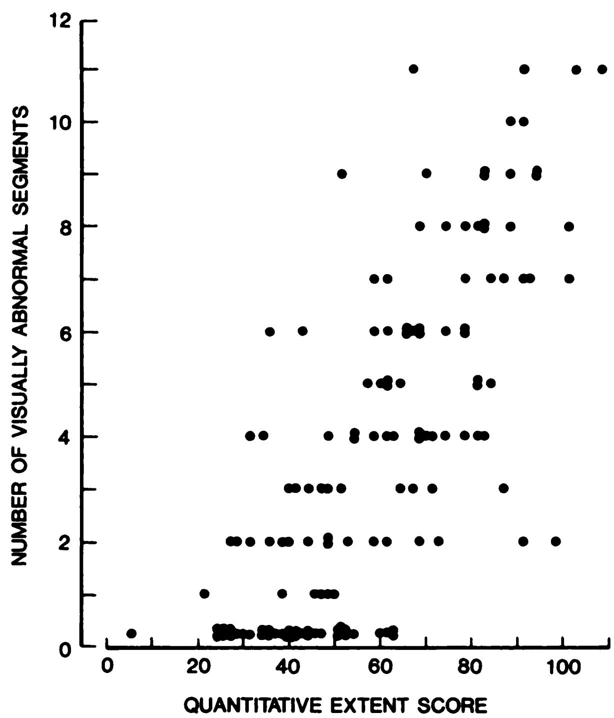
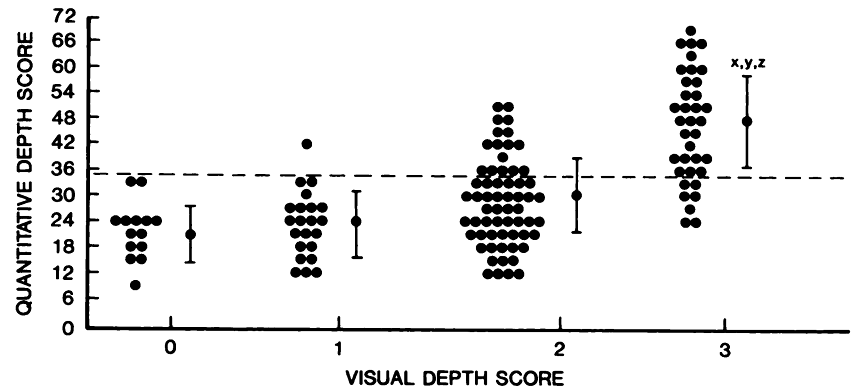


FIGURE 3
Comparison of quantitative extent score to visual extent score (number of visually abnormal segments). Significant correlation ($p < 0.001$) was noted between quantitative and visual determination of extent of thallium defect. N = 133; r = 0.73

FIGURE 4
Quantitative depth score in patients divided into four groups according to visual depth score. Quantitative depth score of ≥36 (represented by dashed line) was optimal for identifying patients with severe stress thallium defect (those with visual depth score of 3). p Value ($p < 0.001$) reflects significant intergroup difference by analysis of variance. x = Significantly greater than Group 2; y = Significantly greater than Group 1; z = Significantly greater than Group 0



14 patients had normal thallium scintigrams (score of 0).

The quantitative depth score was compared among all four groups (Fig. 4). A significant intergroup difference was observed. The scores (mean ± s.d.) for the groups with a visual score of 3, 2, 1, and 0, respectively, were (46.6 ± 12.8 vs. 28.6 ± 10.4, 22.9 ± 7.8, 21.9 ± 6.6). Patients with a visual depth score of 3 had a significantly higher quantitative depth score than those with a 2, 1, or 0.

The identification of patients with a visual depth score of 3 (severe stress thallium defect) was also examined using the quantitative depth score (Fig. 4). A quantitative depth score of ≥36 had an 81% (29/36) sensitivity and an 82% (80/97) specificity for detection of patients with this visual scintigraphic pattern. This quantitative measurement had a positive predictive value of 63% (29/46). Of the 17 patients with a quantitative depth score of 36 or greater who did not have a severe thallium defect, 16 had a visual depth score of 2 and the remaining one patient had a visual depth score of 1. A quantitative depth score of <36 had negative predictive value of 92% (80/87) for excluding patients without a severe stress defect.

Comparison of Quantitative Severity and Extent Scores to Visual Depth Score

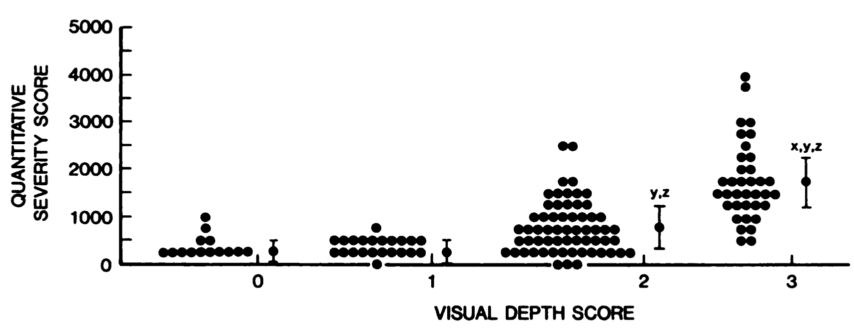
The quantitative severity score was also compared among the four groups and a significant intergroup difference was observed (Fig. 5). The scores (mean ± s.d.) for the groups with a score of 3, 2, 1, and 0, respectively, were (1,752.0 ± 830.3, 791.2 ± 544.9, 339.1 ± 176.4, 371.4 ± 2). Those with a score of 3 had a significantly higher quantitative severity score than those with a score of either 2, 1, or 0. Those with a score of 2 also had a significantly higher quantitative severity score than those with scores of 1 or 0. No significant difference was observed when comparing those with a score of 0 to 1 by this quantitative measurement.

A significant intergroup difference was also noted when comparing the four patient groups by the quantitative extent score (Fig. 6). The scores (mean ± s.d.) for the four groups with a visual score of 3, 2, 1, and 0, respectively, were: 78.6 ± 15.7, 58.7 ± 18.4, 39.2 ± 12.9, 42.4 ± 13.1. Those with a visual score of 3 had a significantly higher quantitative extent score than those with a visual score of 2, 1, or 0. Those with a visual score of 2 also had a significantly higher quantitative extent score than those with a visual score of 1 or 0. No significant difference was noted when comparing those with a score of 0 to 1 by quantitative measurement.

Comparison of Quantitative and Visual Severity Scores

The quantitative severity score was compared with the visual severity score (Fig. 7). An excellent correlation by linear regression between those two analyses of severity of thallium abnormality was found: $r = 0.79$, 95% confidence interval of 0.73 − 0.85.

FIGURE 5
Quantitative severity score in patients grouped into four groups according to visual depth score. p Value ($p < 0.001$) reflects significant intergroup difference by analysis of variance. x = Significantly greater than Group 2; y = Significantly greater than Group 1; z = Significantly greater than Group 0



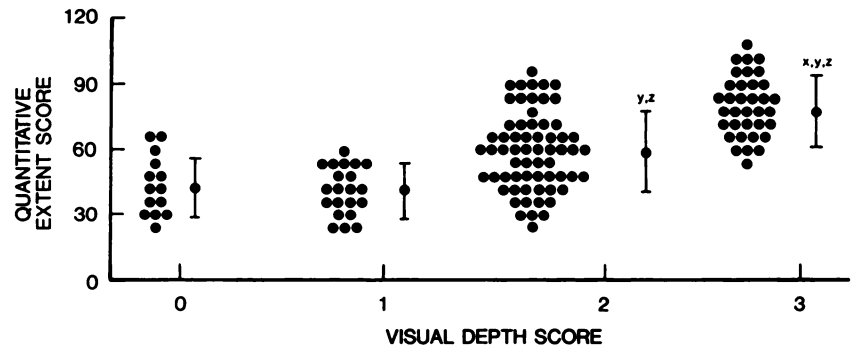


FIGURE 6
Quantitative extent score in patients grouped into four groups according to visual depth score. p Value ($p < 0.001$) reflects the significant intergroup difference by analysis of variance. x = Significantly greater than Group 2; y = Significantly greater than Group 1; z = Significantly greater than Group 0

Relationship of Quantitative Measures

Although each of our quantitative scores reflects a different aspect of thallium defect, they are interrelated. In fact, a high degree of correlation was found among all three quantitative measurements. The quantitative severity score was highly correlated with the quantitative extent score ($r = 0.92$, $p < 0.001$). The quantitative severity score was also highly correlated to the quantitative depth score ($r = 0.85$, $p < 0.001$). The quantitative extent score was also found to correlate with the quantitative depth score ($r = 0.74$, $p < 0.001$).

Case Illustration

Figure 8 illustrates an example of our quantitative approach. The visual thallium scintigram reveals a large anterior, septal, and apical myocardial infarction with a severe reduction (visual score of 3) in thallium uptake. This large thallium defect postexercise involved eight of 15 segments with a visual exercise severity score of 24. The quantitative extent score in this patient was 93, the quantitative severity score was 2,791 and the quantitative depth score was 65.

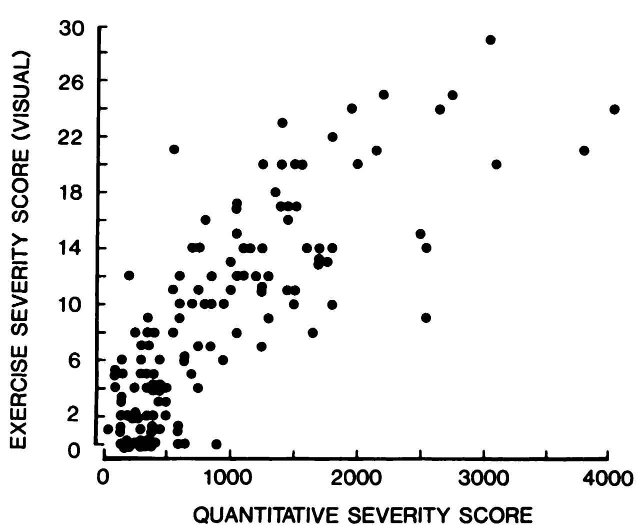


FIGURE 7
Comparison of quantitative severity score to the visual exercise severity score. A significant correlation ($r = 0.79$, $p < 0.001$, $N = 133$) was noted between quantitative and visual determination of severity of thallium defect

DISCUSSION

Our initial work on quantitative analysis of ^{201}Tl scintigraphy focused primarily on determining whether abnormal thallium perfusion or washout was present in a myocardial region when compared with normal profiles (*8*). This method was then applied prospectively (*9*) and revealed excellent sensitivity and specificity (93 and 91%, respectively) for the detection of CAD as well as improved accuracy for the detection of individual coronary stenoses compared with the standard visual technique. In the present study we have further developed the circumferential profile method to determine the extent, depth, and severity of thallium perfusion abnormality and to assess the relationship of these quantitative parameters to visually determined parameters that have been shown to be of clinical significance.

Assessment of Extent of Defect

Recent work has demonstrated an important relationship between the extent of visual thallium perfusion defects postexercise, i.e., number of myocardial segments, showing redistribution and the occurrence of future cardiac events (*1*). Others (*12–14*) have used quantitative techniques for studying the relationship between the extent of myocardium with a thallium perfusion defect and the extent of myocardium subserved by the underlying stenosed coronary vessel supplying that region. This latter methodology required manual outlining of the borders of the defect by two independent observers and resolving disagreements by arbitration between the two observers. In the present study, our technique, which utilizes automatic detection of defect extent, revealed a close correlation ($r = 0.73$) between the quantitative extent score and the visual extent score (number of abnormal segments). This automatic approach may accurately and reproducibly identify the extent of hypoperfused myocardium without the subjective variability inherent in the visual approach as well as in manual quantitative methodologies.

Assessment of Depth of Defect

Since the myocardial distribution of thallium activity during exercise is linearly related to regional myocardial

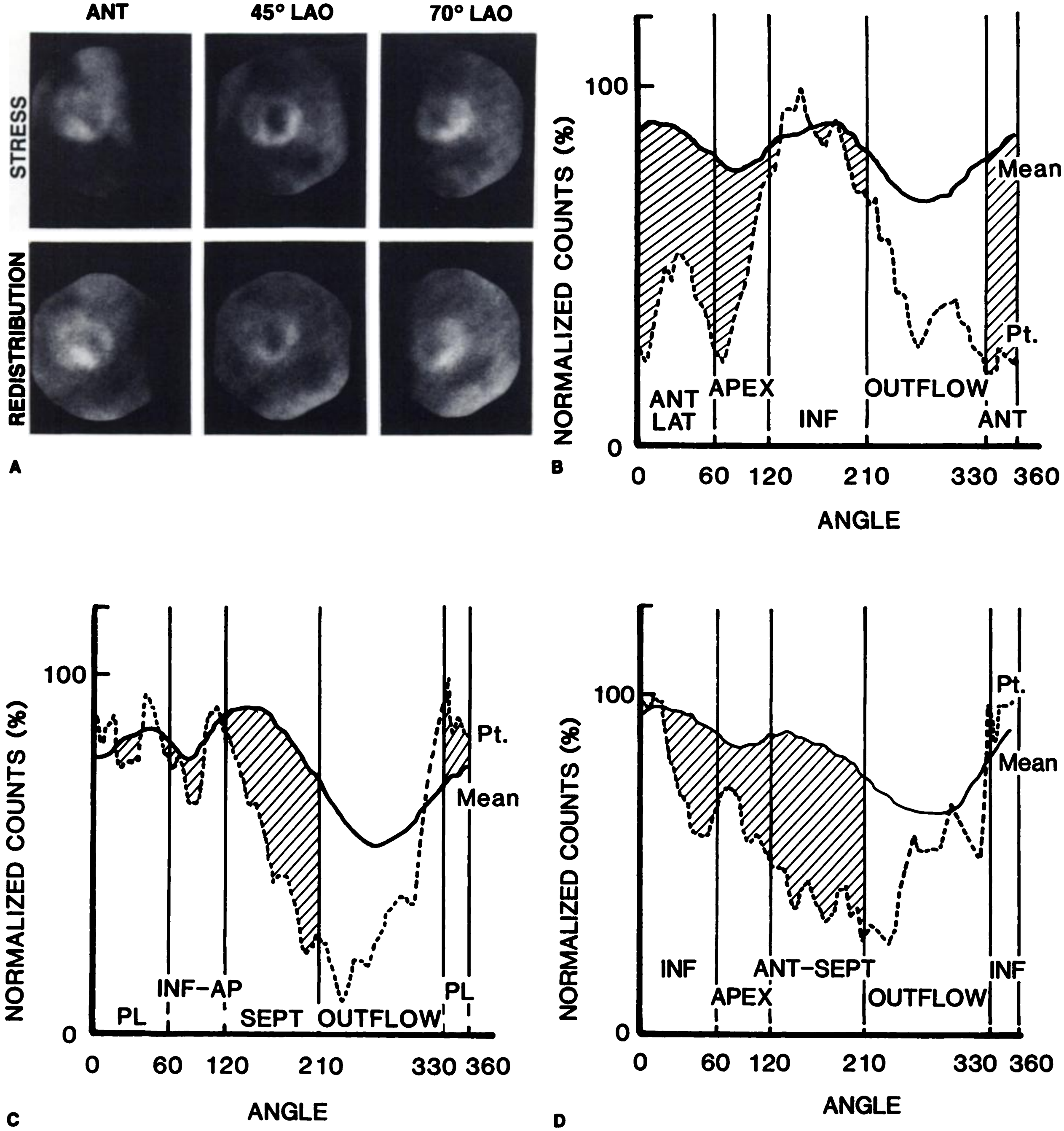


FIGURE 8

A: Example of thallium scintigram from patient with anterior, septal, and apical myocardial infarction. Visual exercise severity score in this patient was 24 and number of visually abnormal segments (visual extent score) during stress imaging was 8. Visual depth score placed this patient in group with severe reduction in thallium uptake (Group 3).B–D: Illustration of exercise curves of patient shown in Fig. 8A compared to mean normal values in all three views. B: Stress Ant.; C: Stress LAO-45; D: Stress LAO-70. Quantitative extent score in this patient was 93, quantitative severity score was 2,791, and quantitative depth score was 65. Ant Lat = anterolateral wall; Inf = inferior wall; Ant = anterior; PL = posterolateral wall; Inf-Ap = inferoapex; Sept = septum; Ant-Sept = anteroseptal wall

blood flow (*15*), the degree of reduction in thallium uptake during exercise bears a direct relationship to the degree of reduction in flow of the involved coronary artery. Thus, the ability to quantitatively measure the depth of reduction in thallium uptake should have important clinical implications. We have previously shown that myocardial regions with a severe reduction in thallium uptake by our visual four-point scoring system (score of 3) more frequently were associated with a critical (≥90%) stenosis (88% of regions) than regions with a score of 2 (62%) or those with a score of 1 (45%) (*3*). When patients are divided into four groups according to the most severe visual reduction in thallium uptake by our four-point scoring system (visual depth score), important prognostic information is also noted. We have demonstrated that patients with at least one segment with a visual score of 3 have a significantly higher 1-year cardiac event rate—death, MI, or worsening angina—than those with lesser defects. The cardiac event rate per 100 patients was 21.4 for those with a visual score of 3, 11.7 for those with a visual score of 2, and 1.6 events for those with a visual score of 1 (*4*). In the present study, when patients were divided into four groups according to the visual depth score, the quantitative depth score of ≥36 was found to virtually exclude patients with normal or equivocal scans and have an 81% sensitivity and an 82% specificity for detecting the high risk scintigraphic pattern of a severe stress thallium defect. Thus, this quantitative measurement may be useful in assessing the severity of coronary stenosis and in evaluating patient prognosis.

Assessment of Severity of Defect

In an attempt to combine both the extent of thallium defect with the magnitude of reduction in thallium uptake, both our group (*16*) and others (*17,18*) have recently devised the severity score which reflects the total integrated area of abnormality. Using a similar approach, in patients undergoing exercise-redistribution ^{201}Tl scintigraphy with the seven pinhole tomographic technique, Massie and colleagues (*18*) found a significant inverse correlation (r = 0.75) between MI area and decrease in left ventricular ejection fraction. Using a similar approach in quantitation of thallium defect severity by rotational single photon emission computed tomography, we have found this methodology useful in assessing the probability of the presence of coronary disease (*16*). In the present study, using planar thallium scintigraphy, we found a high correlation (r = 0.79) between our automatic quantitative severity score and our visual exercise severity score. Further studies are needed to determine if the quantitative severity score alone, which reflects both the extent and depth of the defect, will be clinically useful as a single, comprehensive measurement of hypoperfused myocardium.

Potential Limitations

A variety of limitations in both the visual and our quantitative approaches to the assessment of ^{201}Tl defects may affect the relationship between the visual and quantitative parameters assessed in this paper.

1. There is well recognized interobserver and intraobserver variability in visual analysis of thallium scintigrams (*6,7*). We have attempted to overcome this problem by consensus visual interpretation of thallium scintigrams. This variability is seen not only in grading the severity of a defect but also in calling a region normal or abnormal. The visual interpretation of the apical area, for example, is subject to high variability due to the common occurrence of normal thinning in this region. The quantitative approach, by virtue of comparing regional ^{201}Tl activity with that of a normal group, objectively (and consistently) accounts for normal regional variation in ^{201}Tl distribution, such as that observed in the apex.

2. Another difference between the two techniques is that the visually interpreted thallium scintigrams were based on analog polaroid images, and our quantitatively derived measurements were based on background subtracted images. As is well known, with background subtraction, defects may appear more prominent or more severe than in analog images. However, since our mean normal values are also based on background subtracted scintigrams, we believe that this factor may have only minimally affected the correlation between the visual and quantitative approaches described in this paper.

3. The visual method for determining the extent of myocardial thallium abnormality is based on assessment of five segments per view, with arbitrary "cutoff" between segments. If only part of a segment is abnormal, the whole segment is considered abnormal. On the other hand, by the computerized quantitative extent score in which each view has 40 6° angles (excluding the outflow tract), only that part of the segment below the mean is included in the quantitative extent score. This methodologic difference may account for variability in the comparison between visual and quantitative extent scores, and would also affect the comparison of the visual severity score to the quantitative severity score.

4. Another potential source of variability in comparing the two extent scores is that only segments with a score of 2 or 3 were considered abnormal by the visual technique. Segments that were visually equivocal (mild reduction in uptake) were not considered abnormal. Many of these "equivocal" segments would have ^{201}Tl uptake less than the normal mean and thus would be included in the quantitative extent score. Nonetheless, despite all of these potential methodologic sources of variability between the visual and quantitative techniques, a close correlation between the visual and quantitative parameters of extent, depth, and severity was observed.

Comparison with Lower Limits of Normal Approach

In our previous work we have utilized the lower limits of normal as the criterion for determining if a segment was normal or abnormal. In that study (*8,11*), using receiver operating characteristic curve analysis, it was shown that 2.5 s.d.s below the mean normal profile was the best threshold for optimizing the sensitivity and specificity for the detection of coronary artery disease. A limitation of this approach is that it only allows two possible outcomes, "normal" or "abnormal." Therefore, some regions with a mild or equivocal decrease in thallium uptake could fall within the normal limits and thus could not be differentiated from regions that were definitely normal. Likewise, since this method does not consider the "degree" of abnormality, in regions that were designated as "abnormal" one could not differentiate a region with a mild-to-moderate reduction in thallium uptake from one with a severe reduction in thallium uptake. Since one purpose of the present study was to look at varying degrees of a visual thallium defect, we utilized parameters measuring variation from the mean to express the degree of abnormality. Goris et al. have previously suggested using similar non-threshold dependent methods (*19,20*). Our method allows a region-by-region analysis of the degree of thallium defect extent, depth, and severity. By using this approach one might be able to avoid the simple designation of "normal" compared with "abnormal" and instead determine the probability that a myocardial region is abnormal based on combined criteria. In addition, by combining criteria for optimal detection (lower limits of normal as 2.5 s.d.) with assessment of defect extent, depth, and severity (below mean), one might better be able to determine not only the presence of coronary artery disease but also the extent of myocardium at jeopardy and the severity of reduction in blood flow.

Interrelationship of Quantitative Measurements

Although all three quantitative scores reflect a different aspect of thallium defect evaluation, we observed a correlation between them, suggesting that they are interdependent. There are several explanations for this interrelationship. The quantitative severity score which integrates the total area below the mean reflects both the extent and depth of a defect and therefore bears a direct relationship to both of these parameters. Theoretically, the severity score, a comprehensive index, may be the single best ^{201}Tl measurement to assess a patient's risk from coronary disease. The relationship between extent and depth scores is less obvious but is related to the following: With multiple-view planar imaging a given ^{201}Tl defect which is perceived as severe in a given view is usually seen as a moderate decrease in uptake in at least one view, due to the combined factors of regions being represented in more than one view and overlap of normal and abnormal zones.

Conclusion and Future Directions

We have described a nearly automatic, objective approach for determining the extent, depth, and severity of thallium defects in patients undergoing planar scintigraphy. A close correlation was found between these quantitative measures and similar measurements determined from expert visual analysis. In addition, a quantitative depth score of ≥36 had an 81% sensitivity and an 82% specificity for the identification of patients with our previously described high-risk visual scintigraphic pattern of a severe stress thallium defect. This computer-derived assessment of the extent, depth, and severity of ^{201}Tl defects greatly enhances the clinical utility of quantitation of ^{201}Tl analysis and is likely to prove useful in the detection of patients with critical coronary stenoses, in assessing the hemodynamic significance of questionable angiographic lesions, and in identifying patients with a high probability of future cardiac events.

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