Quantitative Thallium-201 Exercise Scintigraphy for Detection of Coronary Artery Disease

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In 140 patients with chest pain quantitation of regional myocardial Tl-201 activity was performed by serial scintigraphic images after treadmill exercise. Criteria for an abnormal thallium scintigram included: (a) ≥25% persistent reduction in Tl-201 uptake in anterolateral, anteroseptal, posterolateral, and inferoapical segments, or ≥35% reduction in the inferior segment; (b) an initial defect with delayed redistribution; and (c) abnormal Tl-201 washout. Of 110 patients with significant coronary artery disease (CAD), 100 had abnormal Tl-201 scintigrams, while 27 of 30 patients with angiographically normal coronary arteries had normal scintigrams; 91% sensitivity, 90% specificity, and 97% predictive accuracy. Sensitivity and specificity were not significantly different when the 95 patients with diagnostic (≥85% maximum heart rate) and 45 with inconclusive (≤85% maximum HR) Ex tests were compared. Comparison of qualitative and quantitative image analyses in a subset of these patients showed that both specificity and multivessel disease prediction were greater when the quantitative approach was used (90 against 73% and 78 against 39%, respectively). Sensitivity for CAD detection was reduced by 10% with visual interpretation alone. Thus, quantitative exercise Tl-201 scintigraphy appears highly sensitive and specific for CAD detection in patients with chest pain.

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The clinical utility of conventional graded exercise stress electrocardiography for the detection of coronary artery disease (CAD) remains controversial (*1–7*). This controversy, as well as limitations of exercise-stress testing, has prompted the development of noninvasive radionuclide methods for CAD detection. In recent years, myocardial perfusion imaging with thallium-201 has been used in conjunction with exercise testing for CAD detection in patients presenting with chest pain. When compared with electrocardiography alone (*8–15*), Tl-201 perfusion imaging, performed in combination with exercise electrocardiography, has enhanced our ability to noninvasively detect underlying significant coronary artery stenoses. To date, the results using this approach have been variable, probably because of the reliance on visual assessment for myocardial image interpretation.

We have developed a quantitative computer-assisted method for myocardial Tl-201 scintigraphy (*16*), based upon our prior clinical and experimental studies of thallium kinetics in normal and ischemic myocardium (*17–21*). The goal of the present study was to determine the sensitivity, specificity, and predictive value of quantitative perfusion imaging with Tl-201, as compared with qualitative image analysis and with stress electrocardiography, for CAD detection in patients referred for the angiographic evaluation of chest pain.

METHODS

Patient selection. The study group comprised 140 patients referred to the Medical Center for evaluation of chest pain by coronary angiography. There were 127 men and 13 women. The mean age was 51 yr (range

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33-69). Thirty-seven had electrocardiographic evidence of prior myocardial infarction. No patient had concomitant congenital, valvular, or cardiomyopathic heart disease.

Rest and exercise electrocardiography. The resting and stress electrocardiograms (ECGs) were interpreted by two of the investigators without knowledge of scintigraphic or angiographic results. Q waves of duration ≥0.04 sec on the resting ECG were considered to represent prior transmural myocardial infarction. Their location was matched with the appropriate myocardial segment on Tl-201 scintigrams for correlation purposes. Patients were exercised using the Bruce protocol (*22*) after having fasted for at least 8 hr, but medications were intentionally not omitted. Exercise was stopped at 100% of age-predicted maximum heart rate, or because of chest pain, dyspnea, fatigue, or lower extremity discomfort. A 12-lead ECG was recorded at rest and at 1-min intervals during exercise and recovery. The exercise test was considered positive if there was ≥1 mm of ST-segment depression or elevation when compared with the resting tracing, if it lasted for 0.08 sec in three consecutive beats. The test was considered negative in patients who achieved ≥85% maximum predicted heart rate without a clear positive response. In patients who achieved >85% maximum heart rate but who had an uninterpretable ECG, the exercise level was considered adequate. If the patient achieved less than 85% maximum heart rate without a positive response, the test was considered inconclusive.

Exercise imaging protocol. Most of the studies were performed within 1 wk of coronary angiography, and all within 1 mo. Patients were injected intravenously with 1.5 mCi of Tl-201 at peak exercise, followed by a 10-cc flush with 0.9% NaCl. The patient was encouraged to continue walking for an additional 30-60 sec. At 10 min after injection, imaging commenced in the anterior projection, followed sequentially by 45° left anterior oblique and 70° left anterior oblique. The anterior and one of the two oblique images (usually the 45°) were repeated at the end of the initial image sequence and again 2-3 hr after Tl-201 administration. All images were recorded for a preset time of 10 min, typically with collection of at least 300,000 counts, on a portable gamma camera using an all-purpose, medium-resolution collimator and a 25% window centered on the 80-keV x-ray peak. In addition to the conventional scintiphoto imaging on transparency film, all thallium images were stored in a computer for standardized image formation and quantitation of relative myocardial thallium uptake.

Scintigraphic analysis. Quantitative assessment of serial myocardial images obtained from each patient was performed according to methods described in detail in this issue (*16*). Briefly, a nonuniform background reference plane was generated from a region of interest circumscribing the heart. This background is generated and subtracted from each image separately. The sequential images of myocardial counts above background were repositioned by the computer to achieve image overlap between the initial and delayed images of the same obliquity. Multiple profile slices were generated from identically positioned profiles in the image sequence. Myocardial activity was determined from the peak profile counts from regions in the anterolateral, apical, and inferior segments on the anterior image, and septal, inferoapical, and posterolateral segments in the left anterior oblique image. Time-activity curves were constructed by plotting peak profile counts from the same myocardial target region in the initial and sequential delayed images.

Unprocessed scintiphotos, along with quantitative data from each patient, were examined jointly by three of the investigators without knowledge of the catheterization results. Each myocardial segment was analyzed separately. The anterolateral and/or anteroseptal walls were assumed to represent the distribution of the left anterior descending coronary artery (LAD); the high posterolateral wall, the left circumflex artery (LCx) distribution; and the inferior and inferoapical segments, the distribution of the right coronary artery (RCA). The quantitative criteria used for judging each myocardial segment were developed in a separate study using a different independent population of normal subjects (*16*). Briefly, a myocardial segment was designated as abnormal if one or more of the following were demonstrated: (a) a persistent reduction in regional thallium uptake of ≥25% compared with the maximum count in any region in the anterolateral, anteroseptal, posterolateral, or inferoapical segment, and of ≥35% in the inferior segment; (b) an initial defect with delayed redistribution; or (c) abnormal segmental thallium washout as indicated for a myocardial segment if the net thallium activity in that segment remained constant or increased in the delayed images. Partial redistribution was designated when incomplete filling of an initial defect was quantitated. A normal exercise thallium study was defined as having uniform thallium uptake on the initial postexercise image, with subsequent decreasing thallium activity over the 2-3 hr imaging period, as indicated by the quantitative evaluation. Abnormal thallium kinetics by quantitative criteria in more than one vascular segment was considered to reflect multivessel disease.

Several months after completion of the study, coded unprocessed scintiphotos from 70 randomly chosen CAD patients and from all 30 patients with normal coronary arteries were interpreted by visual inspection alone, without patient identification or knowledge of the quantitative scintigraphic or angiographic results. These scans were read by three of the investigators independently and designated as normal or as indicating coronary artery disease. When one observer's reading dif-

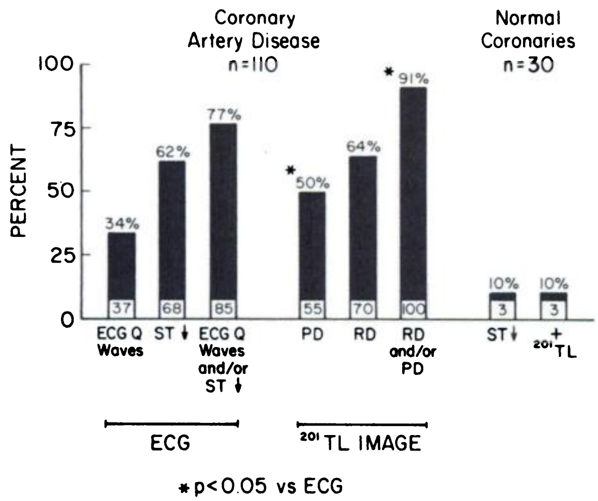

FIG. 1. Summary of electrocardiographic (ECG) and Tl-201 imaging data. Percent prevalence (77%) of abnormal ECG Q waves, ischemic ST-segment depression (ST↓) are compared with prevalence of persistent or partial redistribution Tl-201 defects (PD) and redistribution defects (RD). Prevalence of false-positive ST-segment responses and false-positive Tl-201 defects in patients with normal coronary arteries is shown on right. Sensitivity of Tl-201 imaging (91%) was significantly greater than the combination of ECG Q waves and/or ST depression. Specificity (90%) of exercise ECG and Tl-201 imaging was similar.

fered from those of the other two, the designation of the two similar interpretations was accepted. Multivessel disease was designated when two or more vascular segments showed abnormal thallium uptake as assessed by visual analysis. Quantitative and qualitative scan interpretations were then compared with respect to sensitivity and specificity values as well as for accuracy of multivessel disease recognition.

Coronary angiography. All patients underwent coronary arteriography and left ventriculography using the Judkins or Sones techniques. Ventriculography was performed in the 30° right anterior oblique projection and 60° left anterior oblique projection. Cineangiograms were interpreted independently by two of the investigators, and differences in interpretation were resolved by consensus with a third angiographer present. Coronary stenoses were considered significant if there was greater than 50% narrowing of the luminal diameter.

Statistical analysis. Chi-square test, with or without Yates correction or Ficher's exact test, were used to determine the significance of difference in observed rates of occurrence. McNemar's test was also used to compare relative group difference when appropriate. The following definitions were used: Sensitivity (%) = (true positives)/(true positives + false negatives) × 100; Specificity (%) = (true negatives)/(true negatives + false positives) × 100; Predictive accuracy of a positive test (%) = (true positives)/(true positives + false positives) × 100.

RESULTS

Figure 1 compares the electrocardiographic and scintigraphic data for the entire group of 140 patients. There were 110 patients with angiographically demonstrable CAD and 30 patients with normal coronary arteries and normal ventriculograms. The exercise ECG was positive in 68 of the 110 patients (62%) with CAD. An additional 17 patients had abnormal Q waves on the resting ECG but did not develop ST-segment depression with exercise, yielding an overall ECG sensitivity of 77% for CAD detection. Thallium-201 imaging, using the quantitative scintigraphic method, demonstrated initial defects with redistribution in 70 patients (64%) and persistent defects or partial redistribution in an additional 30 patients with an overall sensitivity of 91% for CAD detection ($p < 0.01$). Of the 30 patients with normal coronary arteries, 27 had normal scintigrams, yielding a specificity of 90%. Of the three patients with false-positive scans, one had a persistent inferior and two had persistent posterolateral defects. There were no instances of false-positive "redistribution defects." The combination of a positive scintigram or ECG yielded an overall sensitivity of 95% (104 of 110) for CAD detection, but specificity fell to 80% (24 of 30). Abnormal scintigraphic studies were found in 90% (26 of 29) of patients with one-vessel disease, 94% (29 of 31) of patients with two-vessel disease, and 90% (45 of 50) of patients with three-vessel disease. For the overall group, predictive accuracy was 97% (100 of 103) for a positive thallium scintigram and 96% (68 of 71) for a positive exercise test. The predictive accuracy of a negative thallium scintigram was 73%.

Table 1 shows a comparison of qualitative and quantitative image analyses in the subgroup of 100 patients

TABLE 1. COMPARISON OF QUALITATIVE AND QUANTITATIVE THALLIUM-201 SCINTIGRAPHY FOR CAD DETECTION AND RECOGNITION OF MULTIVESSEL DISEASE

	Sensitivity	Specificity	MVD* recognition
Qualitative	85% (60 of 70)	73% (22 of 30)	39% (20 of 51)
Quantitative	94% (66 of 70)	90% (27 of 30)	78% (40 of 51)
p value	<0.08	<0.08	<0.002

* Multivessel coronary artery disease.

TABLE 2. CLINICAL DATA IN 110 PATIENTS WITH CAD

	Diagnostic GXT* (Group 1) (n = 95)	Inconclusive EXT* (Group 2) (n = 45)
Age (mean, range)	52.1 (33–69)	57.6 (29–63)
Sex	88M, 7F	40M, 5F
Propranolol	54 (57%)	32 (71%)
Digoxin	10 (11%)	5 (11%)
CAD	82 (87%)†	28 (61%)
Mean no. vessels/ patient	2.2	2.0
Q waves	25 (27%)	12 (26%)

* GXT = Graded exercise test; F = female, M = male.
† $p < 0.001$.

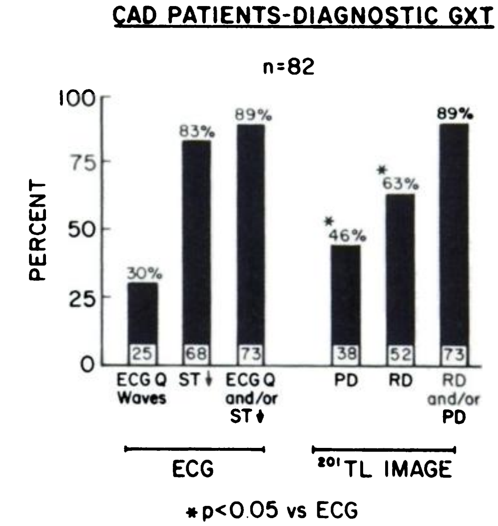

FIG. 2. Comparison of ECG and Tl-201 imaging results in 82 patients with coronary artery disease (Group 1) with diagnostic or adequate (achieved ≥85% of maximum predicted heart rate) graded exercise tests (GXT). Overall sensitivity for rest and exercise ECG was comparable to that of Tl-201 imaging. (Abbreviations are as in Fig. 1).

in this study. Visual interpretation alone of unprocessed scintiphotos without background subtraction yielded an 85% sensitivity for CAD detection, compared with 94% when quantitative criteria were applied to the same scintigrams. Specificity was 73% for qualitative interpretation, lower than the 90% value for the quantitative approach. These differences were of borderline significance ($p = 0.08$). Qualitative image analysis predicted presence of multivessel disease in only 39% of patients with two- or three-vessel disease, whereas quantitative analysis identified 78% of patients in this group ($p < 0.002$).

CAD patients without prior infarction. The sensitivity for CAD detection using quantitative Tl-201 scintigraphy was further examined in the group of patients without clinical or electrocardiographic evidence of prior myocardial infarction. There were 73 patients with CAD by angiography but no prior infarction. Sixty-four of these 73 had abnormal scintigrams, yielding a sensitivity of 88%. Of these 73, only 48 developed ischemic ST-segment depression during the exercise test, yielding a sensitivity of 66% for stress electrocardiography in this group. Thus these data indicate that the sensitivity and specificity of exercise thallium scintigraphy are both high in the detection of stress-induced hypoperfusion and/or ischemia in patients with chest pain and normal resting electrocardiograms and are not significantly different from those of the entire group.

Table 2 summarizes the clinical, angiographic, and electrocardiographic characteristics of the study group. There were no significant differences with respect to age, sex, drug therapy, extent of coronary artery disease, or prevalence of prior myocardial infarction in patients with diagnostic and inconclusive exercise tests. However, there were significantly more patients with normal coronary arteries in the group with inconclusive exercise tests. The difference in propranolol therapy was not quite statistically significant ($p = 0.053$).

Patients with diagnostic (or adequate) exercise tests (Group 1). There were 82 patients with CAD and 13 with normal coronary arteries who had either positive exercise ECGs at any workload or achieved 85% or more of their maximum predicted heart rate during the stress test. Thus these patients had "adequate" or "diagnostic" stress tests. One patient with normal coronary arteries had left bundle branch block, and one with CAD had an intraventricular conduction delay at this level of stress. Figure 2 summarizes the electrocardiographic and scintigraphic findings in this subgroup (Group 1). Sixty-eight patients with CAD had a positive exercise ECG result (83%) and an additional five patients had Q waves, yielding an 89% ECG sensitivity for CAD detection. Two patients had false-positive stress ECGs.

Thallium-201 scintigrams were abnormal in 73 patients with CAD (89%), with no false-positive scintigrams in this group. Specificities (83% against 100%) and predictive accuracy (97% against 100%) for the ECG and thallium imaging were comparable. Thus, when patients achieved a high level of exercise, stress electrocardiography and thallium imaging yielded comparable results.

Patients with inconclusive exercise tests (Group 2). There were 28 patients with CAD and 17 with normal coronary arteries who achieved less than 85% of maximum predicted heart rate but did not develop ischemic ECG changes. The scintigraphic and ECG results for this group of patients are summarized in Fig. 3. One patient with normal coronary arteries had an intraventricular conduction defect. Twelve patients with CAD had Q waves (43%). None achieved the specification for ST-segment depression during exercise. Thallium scin-

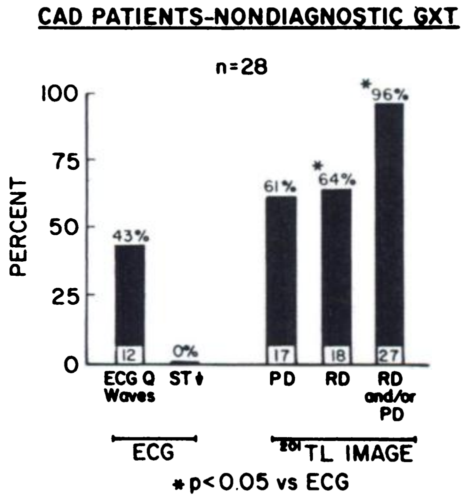

FIG. 3. Comparison of ECG and Tl-201 imaging data in 28 CAD patients (Group 2) with inconclusive (achieved <85% of maximum predicted heart rate with no ST↓) graded exercise tests (GXT). Tl-201 images were abnormal in all but one of these patients; 43% had abnormal Q waves, and none had ST↓.

tigrams were abnormal in 27 of these 28 patients and normal in 15 of 18 patients with normal coronary arteries, yielding sensitivity and specificity of 96% and 83%, respectively. The predictive accuracy for positive thallium scintigrams was 90% in this group. These values were not significantly different from those resulting from thallium scintigraphy in Group 1 patients with diagnostic or adequate exercise tests. The three false-positive thallium scintigrams all demonstrated persistent defects, two involving the posterolateral wall and one the inferior segment. Thus, the only false-positive scintigrams observed in this study occurred in patients who could not achieve 85% or more of maximum predicted heart rate.

Figure 4 shows representative serial postexercise images in a patient with normal coronary arteries and no scintigraphic abnormalities in this study. The initial postexercise image (at 10 min) shows uniform thallium uptake throughout the left-ventricular myocardium on both the anterior and 45° LAO projections. Delayed images show normal washout of thallium during the postexercise period. The time-activity curves shown below each series of images show no significant difference in thallium activity in the various segments analyzed.

Figures 5 and 6 are representative examples of abnormal scintigrams obtained in patients with underlying coronary artery disease. In each instance, abnormalities in thallium uptake and washout are confirmed by quantitative criteria applied to the time-activity curves.

Effect of propranolol. Forty-nine of the 68 CAD patients with positive exercise tests were taking propranolol ($p < 0.01$). However, 17 of the 28 CAD patients with inconclusive exercise tests were taking propranolol ($p < 0.02$). With omission of propranolol, the exercise heart rates in this subgroup may have been higher and ischemic ST-segment depression may have appeared. Thus, propranolol may increase the number of nondiagnostic exercise tests in patients with coronary artery disease. Eighteen of the 30 patients with normal coronary arteries were receiving propranolol. Only two were able to achieve 85% of predicted maximum heart rate, whereas 16 were not ($p < 0.001$). Ten of the 12 patients with normal coronary arteries not receiving propranolol were able to achieve ≥85% of maximum predicted heart rate.

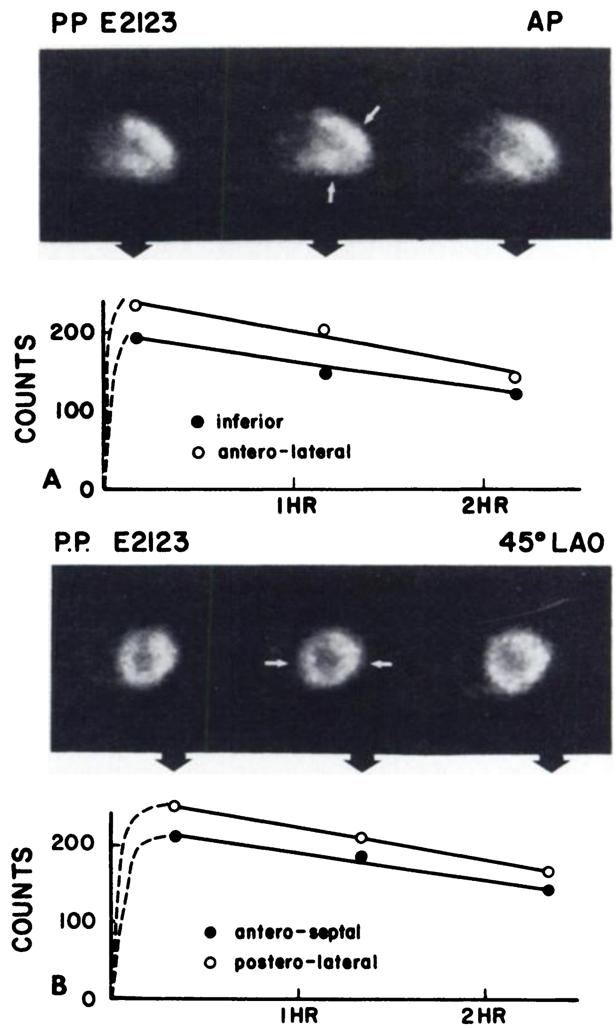

FIG. 4. Serial anterior (AP) and 45° left anterior oblique (LAO) images in patient with chest pain and angiographically normal coronary arteries. Arrows indicate regions from which time-activity curves were constructed. (A) Anterior projection image 10 min after exercise (left panel) showing uniform myocardial uptake of Tl-201 images obtained at 70 min (middle panel) and 135 min (right panel) after exercise demonstrate normal myocardial clearance of Tl-201. Quantitative time-activity curves from anterolateral and inferior segments indicate that regional Tl-201 activity in the two regions are not significantly different (<35%) and confirm normal washout. (B) Serial 45° LAO images show uniform Tl-201 uptake in septal and posterolateral myocardial segments. Time-activity curves shown below images confirm normal myocardial uptake and washout of thallium.

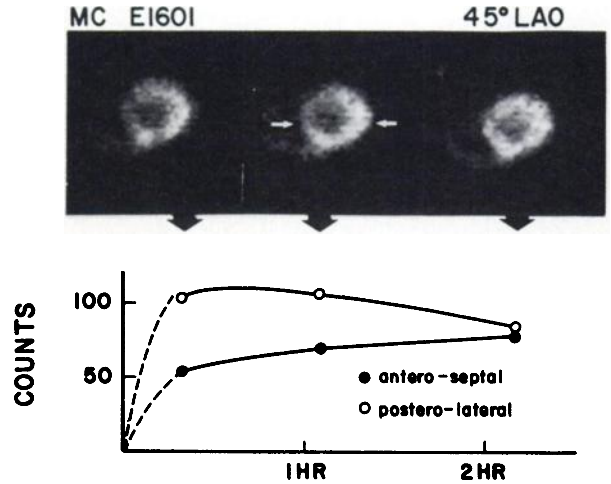

FIG. 5. Serial 45° LAO images obtained after exercise in a 43-year-old patient who achieved 73% of maximum predicted heart rate without ischemic ST-segment depression. Resting ECG was normal. Angiography demonstrated high-grade stenosis in left anterior descending coronary artery. Note defect in anteroseptal segment on initial postexercise image (left panel). Delayed images (middle and right panels) show redistribution of thallium, with filling in of defect. Quantitative time-activity curves show >25% reduction in thallium counts in anteroseptal segment compared with posterolateral. By 2 hr, counts between the two regions have equalized.

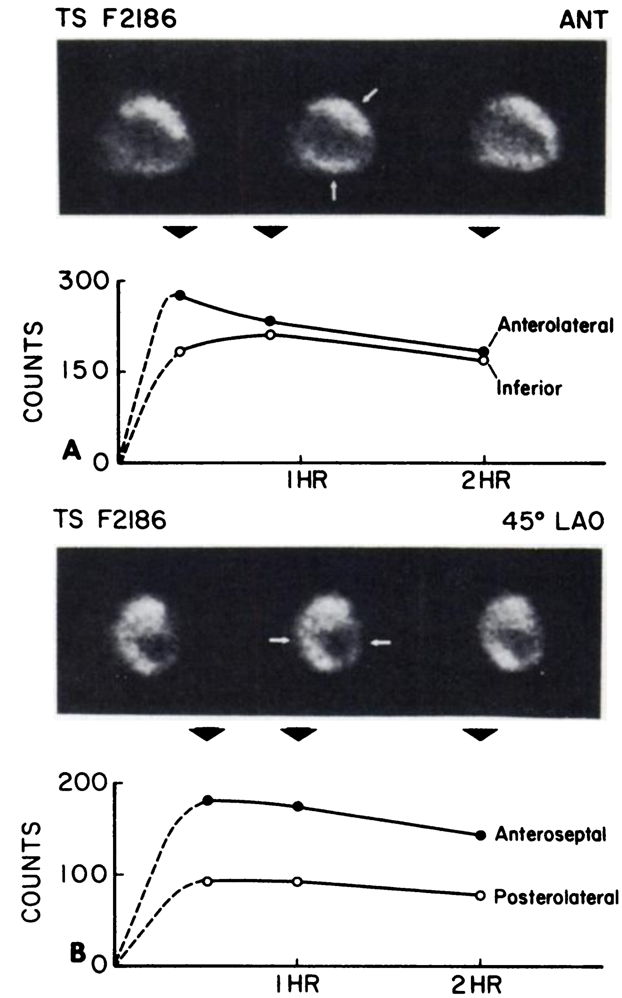

FIG. 6. Serial anterior (ANT) and 45° left anterior oblique (LAO) images in 55-year-old patient receiving 160 mg of propranolol daily, who achieved 80% of his predicted maximum heart rate without ischemic ST-segment depression. Resting ECG was normal. Angiography revealed three-vessel disease. Arrows indicate segments from which time-activity curves were constructed. Quantitative scintigraphic analysis predicted presence of multivessel disease (right and circumflex involvement). (A) Anterior projection image 10 min after exercise (left panel) showed an inferior defect. Delayed images show redistribution, with disappearance of defect. Time-activity curves show a significant initial decrease in Tl-201 counts in inferior segment, with subsequent equalization of activity on delayed images (middle and right panels). (B) Serial 45° LAO images in same patient show persistent defect in posterolateral wall. Time-activity curves demonstrate persistent diminution in Tl-201 counts in posterolateral segment.

Propranolol also appears to increase the number of inconclusive exercise tests in patients with normal coronary arteries.

DISCUSSION

The results of this study demonstrate that quantitative exercise Tl-201 scintigraphy is sensitive and specific for detection of coronary artery disease in a patient population referred for the evaluation of chest pain. The approach uses a sequential imaging technique after a single intravenous dose of Tl-201 administered at peak exercise (*23*). The rationale for this method is based upon knowledge of Tl-201 distribution and redistribution kinetics in normal and ischemic myocardium (*20,21*). The method is based upon the observation that there is redistribution of Tl-201 over time into areas of transient relative underperfusion or ischemia, whereas areas of scar of infarction or severe ischemia show persistent defects in Tl-201 uptake. The explanation for this phenomenon is that initially at peak exercise normally perfused myocardial segments acquire an increased fraction of the intravenously injected thallium, which is attributed to the exercise-induced increase in coronary blood flow. Myocardial segments supplied by stenotic coronary arteries may receive adequate resting flow but not an adequate increase in flow during exercise. Thus, in the initial distribution phase, focal defects in Tl-201 uptake are observed in these relatively underperfused segments. During the 2–3 hr postexercise resting phase, underperfused segments with an initial diminution in Tl-201 uptake may continue to accumulate thallium or may decrease their thallium concentration at a slower rate (abnormal washout) than normal myocardial segments. In the equilibrium phase, normally perfused and underperfused myocardial segments will then approach equal Tl-201 concentration, and images obtained 2–3 hr after exercise will show relatively uniform thallium concentration in the myocardium.

In the present study, quantitative criteria were applied to sequential images using a computer-assisted method.

This quantitative approach involved the determination of regional myocardial thallium activity and myocardial time-activity curves for multiple scan segments in the distribution of left anterior descending, left circumflex, and right coronary arteries. The quantitative criteria for an abnormal Tl-201 scintigraphic pattern applied to these time-activity curves were derived previously in a study on a population of normal subjects (*16*). Each myocardial segment was considered to be abnormal based on one or more of the three following criteria: (a) a focal defect was indicated if any myocardial segment initially showed an uptake <75% of that in the segment of highest uptake, with exception of an isolated nonredistributing inferior defect, which was graded as significant if uptake was <65%; (b) redistribution was indicated if a segment with an abnormal ratio on the initial image tended to normalize on the delayed image; or (c) abnormal washout from a segment was indicated by the absence of net washout or by the further accumulation of thallium in the 2–3 hr image, above the initial content. The methods by which these measurements were made and the derivation of the interpretative criteria are described in detail in a separate publication (*16*).

In the present study group of 140 patients presenting with chest pain, the overall sensitivity for CAD detection by the described quantitative scintigraphic analysis was 91%, compared with 77% sensitivity for rest and/or stress electrocardiographic abnormalities. When patients with prior myocardial infarctions (as judged by abnormal Q waves or a typical history) were excluded, the sensitivity and specificity values were comparable to values obtained for the entire group. The sensitivities for detection of CAD in patients with one-, two-, and three-vessel disease were also comparable. With this method the specificity was 90%. The specificity for stress electrocardiography in this series was also high, perhaps related to the relatively few female patients in the group with normal coronary arteries and the fact that for most of the patients these were the first stress tests performed. In prior studies of exercise electrocardiography, the highest percentage of false-positive exercise tests were in asymptomatic patients. In the present study, all patients had chest pain, and the study group was not biased toward a large number of patients referred because of a previous positive exercise test suspected of being false positive.

Both qualitative and quantitative approaches to image interpretation were compared by re-reading 100 unprocessed scintigrams 2 mo after completion of the study, without knowledge of patient identification, quantitative image data, or angiographic results. Sensitivity for CAD detection fell by only 10% when visual interpretation alone was used. Specificity, however, fell from 90 to 73%, indicating a greater number of false-positive scan interpretations than is observed with the quantitative technique. The greatest difference between the two approaches was in the accuracy of predicting the existence of multivessel disease (MVD), defined scintigraphically as abnormal thallium uptake and/or washout in more than one vascular segment of the scan. Only 39% of patients with angiographically documented MVD were predicted to have MVD by visual image interpretations, compared with 78% predicted by inspection of thallium time-activity curves derived from peak profile counts in multiple myocardial segments on serial postexercise images. The explanation for this marked difference is that with only visual inspection of serial images, certain segments demonstrating abnormal thallium washout or increasing uptake over time are not readily identified. On the other hand, persistent defects or redistribution defects of significant magnitude appear to be detected with comparable frequency by the two approaches to scan analysis. In the majority of patients with MVD, a dominant defect was present, usually in the distribution of the coronary artery with the highest grade of stenosis and/or in an area of prior infarction. This dominant defect could usually be observed in both unprocessed and background-subtracted scintigrams. In these patients, other vascular segments perfused through stenoses usually showed increasing uptake of thallium on delayed images, or failure of washout, with constancy of thallium activity on the delayed image. As expected, these abnormal scan segments were more readily detected by the quantitative technique. Occasionally, uniform thallium uptake was observed on the initial postexercise scintigrams in patients with three-vessel CAD. In these instances, redistribution in all segments was confirmed by upsloping time-activity curves. This global increase in myocardial thallium activity was not detected by qualitative image analysis.

Turner and coworkers (*24*) concluded that thallium scintigraphy was not sufficiently sensitive for evaluation of patients with chest pain who had normal resting electrocardiograms. In the present study, when we eliminated patients with prior infarction and abnormal Q waves on the resting ECG, sensitivity for CAD detection remained high (88%) and not significantly different from the value for the entire group (91%).

In the present study, there appeared to be no significant difference in sensitivity, specificity, or predictive accuracy of thallium scintigraphy when patients with diagnostic and inconclusive exercise tests were compared. This finding is consistent with a prior study by Blood and coworkers (*10*) in which thallium scintigraphy appeared most useful in patients who were unable to achieve high levels of exercise stress. This may be because in the present study symptom-limited end-points were used in the conduction of exercise stress testing. The majority of CAD patients who were unable to achieve 85% or more of their maximum heart rate experienced symptoms, such as fatigue, chest pain, or dyspnea, that necessitated termination of the test. At this level of exercise stress, ST-segment abnormalities were not evident, although heterogeneity of flow as reflected by the Tl-201 patterns was detected. Also, 43% of the patients in this group had prior myocardial infarction as reflected by Q waves on ECG. It is quite likely that left-ventricular dysfunction, which may have been enhanced by exercise, resulted in diminished exercise tolerance. There was equal sensitivity of the ECG and thallium scintigraphy in detecting myocardial scars in this subgroup. In the remaining patients with CAD and no prior infarctions who had inconclusive exercise tests, a high prevalence of thallium defects was observed in the absence of ST-segment depression.

The results of this study indicated that while propranolol did influence the results of stress electrocardiography, it did not significantly change the percentage of false-positive scintigrams in comparing patients who were and were not receiving propranolol. This finding could simply be the result of a population bias that would occur if patients taking propranolol tended to be those with the more functionally severe stenotic lesions. Patients who achieve suboptimal exercise stress with a normal thallium study and a nondiagnostic ECG do present a problem with interpretation because of the presumed inability of the test to rule out the possibility that perfusion abnormalities could develop at higher stress levels.

In this study, persistent thallium defects or partial redistribution were more frequent than were significant Q waves in the CAD groups. This disparity may result from two factors. Myocardial infarction could not be corroborated by history or enzymatic data in all patients. Consequently, some cross-over between the infarct and noninfarct group, as separated by electrocardiographic data, would be expected. We have also shown in a previous study (*17*) that persistent defects—even those that are observed on serial rest images—may sometimes occur in myocardial segments that are presumably chronically hypoperfused, but may still be viable as indicated by improved thallium uptake (hence perfusion) and improved wall motion following coronary revascularization. Further studies to evaluate the specificity of thallium scintigraphy to differentiate myocardial segments that may be chronically hypoperfused or partially scarred from those segments that are completely scarred appears warranted.

In conclusion, the sensitivity, specificity, and predictive accuracy of the quantitative approach to thallium-201 exercise stress scintigraphy was significantly greater than rest and exercise electrocardiography for the detection of coronary artery disease in patients referred for the evaluation of chest pain. In contrast to stress electrocardiography, sensitivity and specificity for CAD detection remained high in patients who were unable to achieve 85% of maximum heart rate. The use of a computer-assisted quantitative approach to scintigraphic analysis has several important advantages over reliance on visual qualitative interpretation. First, the former provides standardized image formation and objective criteria for image evaluation that appear to enhance somewhat both sensitivity and specificity compared with qualitative image analysis. Second, it significantly enhances the accuracy in detecting presence of multivessel disease. Third, since thallium initially distributes in the myocardium almost in direct proportion to the distribution of myocardial blood flow (*23,25*), it offers the potential to determine the relative degree of maldistribution of coronary blood flow in response to exercise stress. Relative quantitation of thallium activity, performed both spatially and temporally, provides information of a functional nature directly related to the pathophysiology of coronary artery disease.

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