Quantitative Planar Imaging with Technetium-99m Methoxyisobutyl Isonitrile: Comparison of Uptake Patterns with Thallium-201

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To compare the myocardial uptake pattern of ^{99m}Tc-labeled methoxyisobutyl isonitrile ([^{99m}Tc] MIBI) and ^{201}Tl, planar scintigraphy were performed in both patients with documented coronary artery disease and subjects with a low likelihood of disease. Quantitative analysis was employed using a standard interpolative background subtraction algorithm and a new algorithm modified to better accommodate for the differences in extracardiac activity seen with [^{99m}Tc]MIBI rest images. Among patients with coronary artery disease, the standard algorithm yielded no significant difference in relative defect magnitude between [^{99m}Tc]MIBI and ^{201}Tl on stress scintigrams ($p = 0.48$), although the magnitude of [^{99m}Tc]MIBI defects was greater on resting images ($p = 0.02$). When the modified algorithm was employed, defect magnitude was similar for both stress ($p = 0.91$) and rest ($p = 0.20$) images. Normal segmental uptake ratios derived from a comparison of contralateral segments (e.g., septal:posterolateral) in the low likelihood patients were similar for both [^{99m}Tc]MIBI and ^{201}Tl. Thus, modification of the standard interpolative background subtraction algorithm is necessary for quantitative planar [^{99m}Tc]MIBI perfusion imaging. When appropriate background subtraction is employed, myocardial uptake and quantitative defect magnitude of [^{99m}Tc]MIBI and ^{201}Tl planar images are similar.

J Nucl Med 30:1456–1463, 1989

The clinical value of quantitative thallium-201 (^{201}Tl) myocardial perfusion imaging for the detection of ischemia is well established (*1–4*). However, the low energy and long halflife of ^{201}Tl make it less than ideal for myocardial imaging. A new technetium-99m-(^{99m}Tc)labeled myocardial perfusion agent, methoxyisobutyl isonitrile ([^{99m}Tc]MIBI), has been proposed as a potentially more optimal agent for the assessment of myocardial perfusion at rest and under conditions of stress (*5–8*).

The initial myocardial distribution of [^{99m}Tc]MIBI is proportional to blood flow as is ^{201}Tl (*9*). Technetium-99m MIBI, unlike ^{201}Tl, does not redistribute (*10*) after transient ischemia and requires separate injections of the radionuclide during stress and at rest to distinguish between reversible and irreversible myocardial injury. Prior to widespread clinical testing and application of this promising new agent, a careful investigation of the optimum imaging methodology to be employed for maximizing the accuracy of quantitative scan analysis has been initiated.

In preliminary communications, differences have been reported in the observed magnitude of perfusion defects with [^{99m}Tc]MIBI and ^{201}Tl (*11,12*). These differences may be artifactual because of improper background subtraction, particularly in rest [^{99m}Tc]MIBI images where extracardiac background is more prominent (*13*). Crucial to the success of quantitative perfusion imaging is a valid background subtraction method that does not oversubtract or undersubtract which could result in misinterpretation of defects. Accordingly, the aim of the present pilot study was to compare exercise and rest [^{99m}Tc]MIBI scintigrams with exercise and redistribution ^{201}Tl scintigrams in patients with a low pretest likelihood of coronary artery disease (CAD) and

Received Sept. 29, 1988; revision accepted May 12, 1989.

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patients with angiographic documented CAD. For this comparison, images were analyzed by quantitative computer-assisted methods utilizing the standard interpolative background subtraction algorithm (*14*) as well as a newly modified interpolative background subtraction algorithm derived to better account for the intense extracardiac activity seen with rest [^{99m}Tc]MIBI images (*15*). The hypothesis tested was that quantitative [^{99m}Tc] MIBI perfusion imaging could be accurately accomplished if the background problems on rest images caused by the high visceral uptake of the radionuclide could be alleviated.

MATERIALS AND METHODS

Patients

Ten patients with known or suspected CAD who were referred for exercise ^{201}Tl scintigraphy and had coronary angiography within 1 mo of scintigraphic evaluation underwent stress and rest imaging with [^{99m}Tc]MIBI. An additional eight patients with a low likelihood of coronary artery disease referred for exercise ^{201}Tl scintigraphy for evaluation of atypical chest pain, and who did not undergo catheterization also underwent stress and rest [^{99m}Tc]MIBI imaging. This low likelihood population was selected by the following criteria: (a) age less than 50 yr, (b) absence of hypertension, (c) normal physical examination, (d) normal resting electrocardiogram, (e) normal two-dimensional echocardiogram, and (f) normal graded-exercise treadmill test. These 18 patients comprise the study population. All patients included in the study gave informed consent to the protocols approved by the Human Investigation Committee at the University of Virginia, School of Medicine. Stress imaging with [^{99m}Tc]MIBI was performed within 14 days of the stress ^{201}Tl imaging (mean of 7 ± 6 days) at an identical heart rate without intervention or change in medical therapy.

Stress ^{201}Tl Imaging Protocol

Patients were injected intravenously with a mean of 2 mCi of ^{201}Tl (range 1.9 to 2.1 mCi) at peak exercise followed by a 10-cc flush with 0.9% NaCl. The patients were encouraged to walk for an additional 60 sec. At 10 min after injection, stress imaging commenced in the anterior projection followed sequentially by 45° LAO and 70° LAO projections. The same imaging sequence was repeated 2–3 hr after the initial ^{201}Tl injection, providing three redistribution images. All images were recorded using a 64 × 64 matrix size for a preset time of 8 min, typically with collection of at least 300,000 counts on a Technicare gamma camera using an all-purpose low-to-medium energy collimator and a 25% window centered on the 80 keV x-ray peak.

Stress and Rest [^{99m}Tc]MIBI Imaging Protocol

Stress and rest [^{99m}Tc]MIBI images were obtained for each patient following separate injections of the radionuclide at a mean interval of 24 hr. For stress images, patients were injected intravenously with a mean of 18 mCi of [^{99m}Tc]MIBI (Du Pont Cardiolite; dose range 7.1 to 30.3 mCi) at peak exercise followed by a 10-cc flush with 0.9% NaCl. The patients were encouraged to walk for an additional 60 sec following injection. At a mean of 107 min (range 60 to 210) after injection, imaging commenced in the anterior projection, followed sequentially by 45° and 70° LAO projections. Rest imaging commenced at a mean of 107 min (range 60 to 150) after a separate rest injection of [^{99m}Tc]MIBI with a mean dose of 18.5 mCi (range 7.6 to 30.7) using the same imaging sequence. There was a delay between the time of MIBI injection and imaging so as to permit washout from surrounding extracardiac tissues. All [^{99m}Tc]MIBI were recorded for a preset time of 10 min, using a 64 × 64 matrix size. Collection of at least 1 million counts were obtained, using the same imaging equipment as used for ^{201}Tl imaging but having a 20% window centered on the 140-keV gamma ray peak of ^{99m}Tc.

Background Subtraction

A new method of generating the background reference plane was developed which is a modification of our standard interpolative background subtraction algorithm (*14*) as adapted from the Goris Method (*16*). This modified method of generating the background reference plane is illustrated in Figure 1. First, a boundary region is chosen which encloses the heart. The edges of the background reference box were placed so as to just touch the cardiac borders, including the left and right ventricle. Then the background in the interior region or reference plane is calculated for each pixel within the boundary using the formulas outlined (Fig. 1 and Appendix). The actual boundary values A, B, C, and D used in the formula were derived from a box which was expanded in all dimensions by a factor which is linearly related to the size of the heart (Fig. 2A). This method provides a more rapid fall-off of the background reference plane as it moves beneath the heart away from a region of intense extracardiac activity (Fig. 2B), and a better approximation of the shape of the actual edge of the extracardiac organ.

Quantitative Correlation of Scintigrams

Stress and rest myocardial ^{201}Tl and [^{99m}Tc]MIBI images were processed using background subtraction and then the

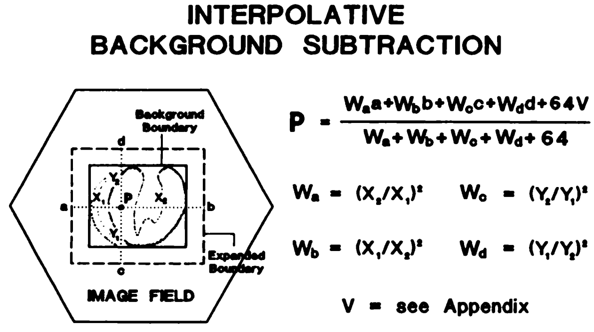

FIGURE 1
Myocardial image field with computer-defined, background boundary circumscribing heart (left). Background value P for each pixel enclosed within the boundary is computed according to formula (right). The terms Wa, Wb, Wc, and Wd represent weighting factors. See Appendix for proposed modification of the term, V.

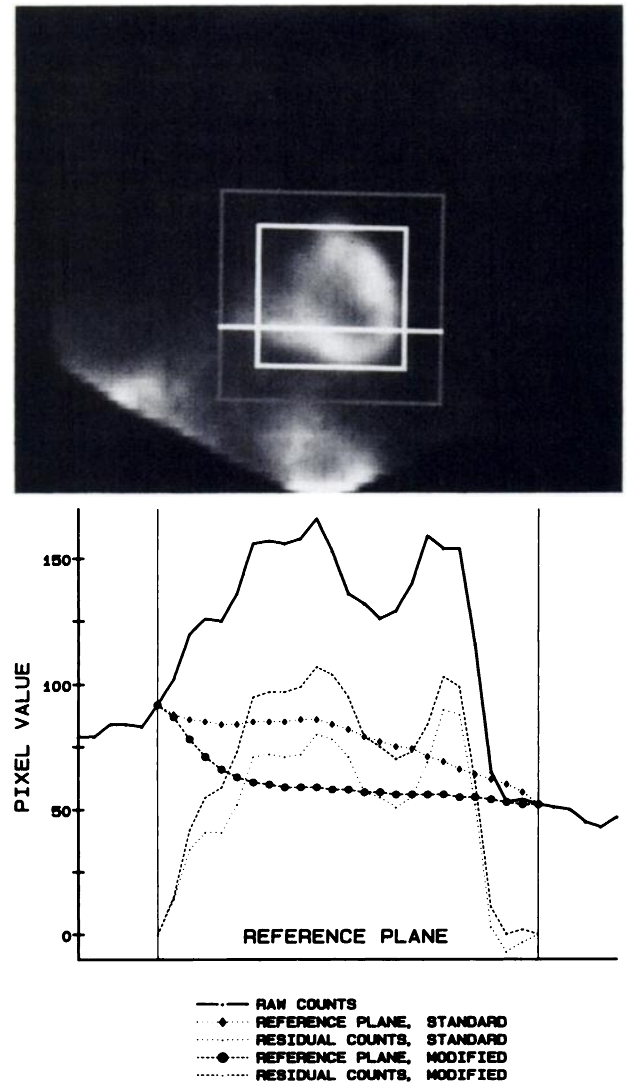

FIGURE 2
Analog [^{99m}Tc]MIBI image (anterior view) of a "low risk" patient (Fig. 2a) is shown with placement of the initial reference boundary, the expanded boundary and the placement of a representative horizontal profile. The raw uncorrected MIBI activity profile, calculated background reference planes and background corrected profiles using the standard algorithm and our newly modified algorithm are illustrated (Fig. 2B), for the selected profile drawn in Figure 2a.

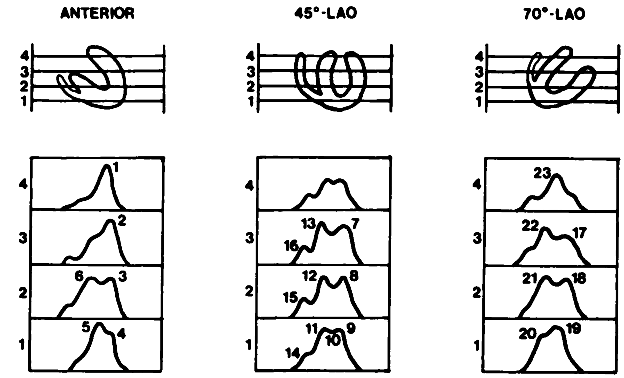

FIGURE 3
Illustrates placement of four activity profile slices on myocardial images for three views analyzed. Number (1 to 23) define preselected myocardial segments utilized for quantitative correlation of [^{99m}Tc]MIBI and ^{201}Tl images.

initial and delayed image pairs were brought into precise image registration by a computer process previously described (*14*). Four count profile slices across each myocardial image were generated (*14*). The slices actually represent a 9-pixel neighborhood average. Regional peak activity was derived from the four profile slices for pre-selected myocardial segments (Fig. 3). Segments which corresponded to valve planes were excluded from the analysis. As shown in Figure 3, this yielded a total of 23 myocardial segments (20 left ventricular, three right ventricular) among the three views available for quantitative analysis. Activity in each myocardial segment was expressed as a fraction of the mean activity of the selected left ventricular segments for each view.

Our standard interpolative background subtraction and the newly modified interpolative background subtraction algorithm described above were applied to all images. Both the analog ^{201}Tl and [^{99m}Tc]MIBI images and corresponding background subtracted images were displayed on the same standardized gray scales. No form of threshold suppression or contrast enhancement was used.

Stress and rest [^{99m}Tc]MIBI and stress and redistribution ^{201}Tl images were compared on a segment-by-segment basis using both the "standard" and the "modified" background subtraction algorithms.

Definition of Normal Segmental Uptake Ratios

The clinical interpretation of myocardial perfusion images is dependent on the discrimination of segmental differences in uptake. Segmental uptake ratios were derived from analysis of stress and rest [^{99m}Tc]MIBI images and stress and redistribution ^{201}Tl images from eight low-risk patients. Five ratios were derived from the three views for each patient. From the anterior view, the inferior to anterolateral ratio was calculated by dividing the average of the peak uptake in segments 5 and 6 by the average of the peak uptake in segments 1, 2, and 3 (Fig. 3). From the 45° LAO view, ratios were calculated as follows: (a) septal to lateral walls by dividing the average peak uptake of segments 12 and 13 by the average peak uptake of segments 7 and 8; (b) inferoapical to lateral by dividing the average peak uptake of segments 9, 10, and 11 by the average peak lateral uptake; and (c) right ventricular to septal by dividing the average peak uptake of the three right ventricular segments (14, 15, and 16) by the septal peak uptake. From the 70° LAO view, the inferior to anterior ratio was calculated by dividing the average peak uptake of segments 18 and 19 by the average peak uptake of segments 21, 22, and 23 (see Fig. 3).

Statistical Analysis

Differences in relative segmental perfusion defect magnitude were assessed by the paired Student's t-test. Normality of the distributions was verified with the Kolmogorov-Smirnov test. Population characteristics and exercise parameters are expressed as a mean plus or minus the standard deviation.

RESULTS

Patient Population

The study population consisted of ten patients (eight male, two female) with CAD confirmed by cardiac catheterization, and eight patients (three male, five female) with less than a 5% likelihood of coronary artery disease based on age, sex, history, physical examination and results of treadmill exercise testing.

The patients with CAD had a mean age of 56 yr (range 42 to 80 yr). All ten patients had a previous history of myocardial infarction (anterior in three, inferior in seven, lateral in one, non-Q in one). Cardiac catheterization demonstrated single vessel disease in two patients, two-vessel disease in four patients and three-vessel disease in four patients.

The mean age of the low pretest likelihood control patients was 40 yr (range 29 to 49 yr). None had evidence of exercise-induced ischemia by electrocardiographic or quantitative ^{201}Tl scintigraphic criteria.

Exercise Performance

In both the low-risk and CAD groups, there was no significant difference in the results of the ^{201}Tl and [^{99m}Tc]MIBI stress tests with respect to peak heart rate, peak systolic pressure, METs achieved, or treadmill time (Table 1).

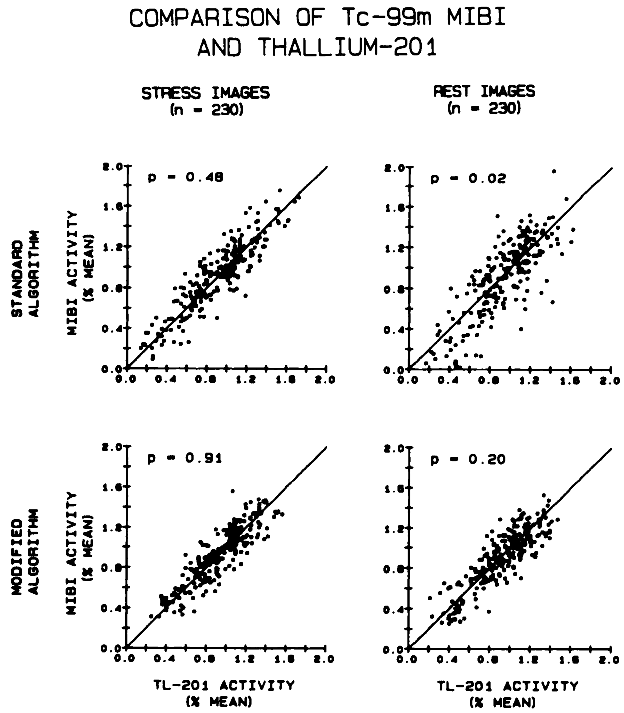

FIGURE 4
Comparison of [^{99m}Tc]MIBI and ^{201}Tl uptake using the "standard" background subtraction algorithm for stress images (A) and rest images (B) and the "modified" algorithm for stress image (C) and rest image (D). The line (—) in each graph represents the line of identity, not a line of regression.

Comparison of Methoxyisobutyl Isonitrile and ^{201}Tl Myocardial Scintigrams

Comparison of the regional [^{99m}Tc]MIBI and ^{201}Tl activity after background subtraction in the ten patients with coronary artery disease is shown in Figure 4. Residual peak activity for the 23 previously defined segments (Fig. 3) was normalized to the mean left ventricular activity on that view. Regional activity was quantitated after applying both the standard (Fig. 4A,B) and the modified (Fig. 4C,D) background subtraction algorithms. Among the 230 segments analyzed, there was no significant difference ($p = 0.48$) in segmental defect magnitude between the [^{99m}Tc]MIBI and ^{201}Tl when the standard algorithm was applied to the stress images (Fig. 4A). However, as illustrated in Figure 4B when the standard algorithm was applied to the rest images, there was a significant difference ($p = 0.02$) in defect magnitude between the two radionuclides. This difference is reflected by the points of Figure 4B near the origin which lie to the right of the identity line. In these regions, uptake was underestimated by [^{99m}Tc] MIBI relative to ^{201}Tl. The apparent oversubtraction of the [^{99m}Tc]MIBI rest images produced by the standard background subtraction algorithm occurred predominantly in segments which were situated adjacent to areas of increased extracardiac activity.

The close correlation of [^{99m}Tc]MIBI and ^{201}Tl segmental activity using the modified background subtraction algorithm is shown in Figures 4C and D. There was no significant difference in defect magnitude for

TABLE 1
Comparison of exercise performance for low risk population and patients with coronary artery disease during ^{201}T1 and ^{99m}Tc-MIBI stress testing

	Exercise performance			
	Low risk population (n = 8)		Coronary artery disease (n = 10)	
	^{201}T1	MIBI	^{201}T1	MIBI
Peak heart rate (bpm)	167 ± 15	167 ± 16	129 ± 20	130 ± 19
Peak systolic BP (mm Hg)	166 ± 19	166 ± 21	138 ± 14	138 ± 18
METs achieved	8 ± 2	9 ± 2	5 ± 3	5 ± 3
Treadmill time (min)	6.7 ± 3	7.3 ± 3	6.1 ± 2	6.6 ± 3

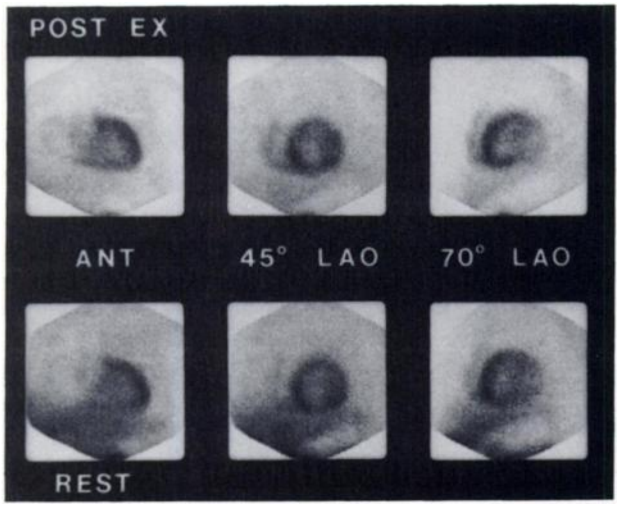

FIGURE 5
Analog [^{99m}Tc]MIBI images post-exercise (top) in the anterior (ANT), 45° LAO, and 70° LAO projection from a patient with a documented inferior myocardial infarction. Analog [^{99m}Tc]MIBI rest images (bottom) in the same three projections demonstrate significant extracardiac activity adjacent to the inferior myocardial segments.

either stress ($p = 0.91$) or rest ($p = 0.20$) images, and no evidence of oversubtraction.

The difference in the degree of extracardiac activity seen between stress and rest states with [^{99m}Tc]MIBI are illustrated in Figure 5. Figure 6 demonstrates oversubtraction of [^{99m}Tc]MIBI activity using the standard background subtraction algorithm in inferior myocardial segments adjacent to areas of high visceral uptake. Using the modified background subtraction algorithm (Fig. 7), this problem is alleviated, permitting more accurate quantitative analysis of regional tracer activity.

Criteria for Interpretation of [^{99m}Tc]MIBI Images: Definition of Normal Segmental Uptake Ratios

The five segmental stress and rest uptake ratios for [^{99m}Tc]MIBI and ^{201}Tl derived from the normal subjects is illustrated in Figure 8. There was no statistical difference between the ratios for stress and rest [^{99m}Tc]MIBI images when applying the standard background subtraction algorithm. The ratios for [^{99m}Tc]MIBI were not significantly different from the ^{201}Tl ratios with the inferior:anterolateral, septal:lateral, inferoapical:lateral, and inferior (70° LAO view):anterior (70° LAO view) ratios all approximating unity.

DISCUSSION

Quantitative myocardial imaging with ^{201}Tl has been shown to be clinically useful in the evaluation of myocardial ischemia and is now considered the standard for the noninvasive evaluation of myocardial perfusion using single photon emission radionuclides. Thallium-201 is not an ideal myocardial imaging agent because of its long half life (73 hr), low-energy photopeak (69–83 keV), and high cost. In recent years, there has been a great impetus to develop a ^{99m}Tc-labeled perfusion agent which would have improved physical characteristics and could be produced in kit form. Recent efforts have been directed at a new class of cationic technetium compounds; the hexakis alkylisonitrile technetium (I) complexes (*17–21*).

In 1984, Holman et al. presented the first human ^{99m}Tc-perfusion imaging studies after the intravenous administration of an isonitrile cationic complex, ^{99m}Tc t-butyl isonitrile (*18*). There were problems with this agent related to persistently high hepatic activity. The higher background activity resulted in failure to identify a significant number of hypoperfused areas demonstrated on ^{201}Tl scintigrams in the same patients, thereby diminishing sensitivity (*19*).

Other studies with [^{99m}Tc]carbomethoxyisopropyl isonitrile yielded images of good quality with less lung and hepatic uptake than seen with t-butyl isonitrile (*21*). However, ^{99m}Tc-labeled methoxyisobutyl isonitrile utilized in the present study shows the most favorable imaging characteristics of any of the isonitriles (*5,9,22–24*). The initial myocardial uptake is proportional to blood flow similar to ^{201}Tl (*8*). The first-pass extraction fraction is somewhat lower than that of thallium (*25,26*). Technetium-99m methoxyisobutyl isonitrile, unlike ^{201}Tl, is cleared very slowly from the myocardium and there is so little recirculated through the blood that redistribution is negligible (*10*). Because [^{99m}Tc]MIBI does not redistribute, separate stress and rest injections are required to distinguish reversible stress-induced ischemia from irreversible perfusion defects. Injection of [^{99m}Tc]MIBI under stress and rest conditions produces differences in the distribution of [^{99m}Tc]MIBI among body tissues (*13*). The splanchnic activity is much higher on rest [^{99m}Tc]MIBI images than either stress [^{99m}Tc]MIBI images or ^{201}Tl images.

Pilot clinical investigations comparing qualitative analysis of segmental perfusion on stress and rest ^{201}Tl images with stress and rest [^{99m}Tc]MIBI images have demonstrated a high concordance of perfusion abnormalities (*5,9,27*), with comparable specificity and sensitivity for the detection of coronary disease on angiography.

Maddahi et al., using quantitative segmental analysis of planar ^{99m}Tc-MIBI and ^{201}Tl images in five patients, have suggested that the magnitude of a perfusion defect, when expressed as a percentage of normal, is significantly less for [^{99m}Tc]MIBI than for ^{201}Tl (*11*). Karcher et al. compared a defect score derived from quantitative analysis of short axis slices of single photon emission computed tomography (SPECT) [^{99m}Tc]MIBI and ^{201}Tl images in 30 patients (*12*), and demonstrated a good correlation for both stress and rest images. The defect sizes were reportedly smaller for [^{99m}Tc]MIBI, particu-

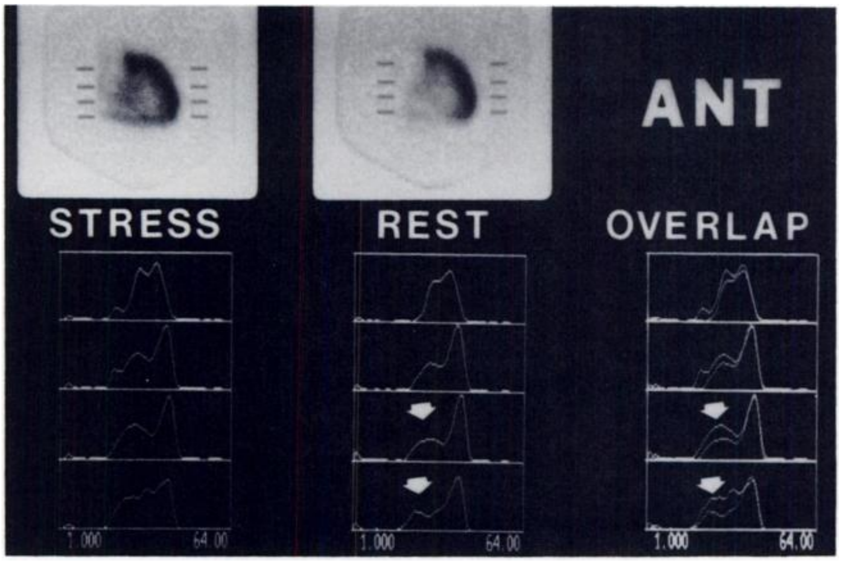

FIGURE 6
Interpolative background subtracted [^{99m}Tc]MIBI images (top) in the anterior (ANT) projection from the same patient shown in Figure 4, using the old background subtraction algorithm. Corresponding quantitative profiles are shown below each image. In the lower right, the stress and rest profiles are superimposed. The arrows indicate the inferior regions in which oversubtraction has occurred.

larly in the inferior segments. The smaller defect magnitude observed in the inferior segments with SPECT [^{99m}Tc]MIBI imaging may be the result of tissue cross-talk from adjacent extracardiac tissues, or could represent differences in scatter and attenuation between [^{99m}Tc]MIBI and ^{201}Tl.

In order to correctly quantitate regional myocardial activity of a perfusion agent, background must be subtracted. The magnitude of a perfusion defect will be underestimated if insufficient background is subtracted, while the defect magnitude will be overestimated if too much background is subtracted. In the present study, the quantitative comparison of [^{99m}Tc]MIBI and ^{201}Tl images using the standard interpolative background subtraction algorithm demonstrated perfusion defects of greater relative magnitude on resting images with [^{99m}Tc]MIBI than ^{201}Tl. Comparison of the stress images using the standard algorithm did not demonstrate this difference in defect magnitude. The differences in the magnitude of perfusion defects between [^{99m}Tc] MIBI and ^{201}Tl observed in our analysis of rest images using the standard algorithm and reported by others, may represent an artifact of improper background subtraction. Our data indicates that when proper account is taken for extracardiac background, the distribution of [^{99m}Tc]MIBI is similar to that of ^{201}Tl. Quantitative defect magnitude yielded by the two different tracers is equal, within the limitations of statistical accuracy of this study. This result is supported by the observation that myocardial distribution of both [^{99m}Tc]MIBI and ^{201}Tl are similarly proportional to flow (*8*). In canine models of ischemia, the myocardial uptake of both radionuclides have also been shown to be comparable (*28–30*).

The shape of the background reference plane was found to be more critical for [^{99m}Tc]MIBI studies when making precise comparisons of local myocardial uptake between rest and stress images, since the extracardiac

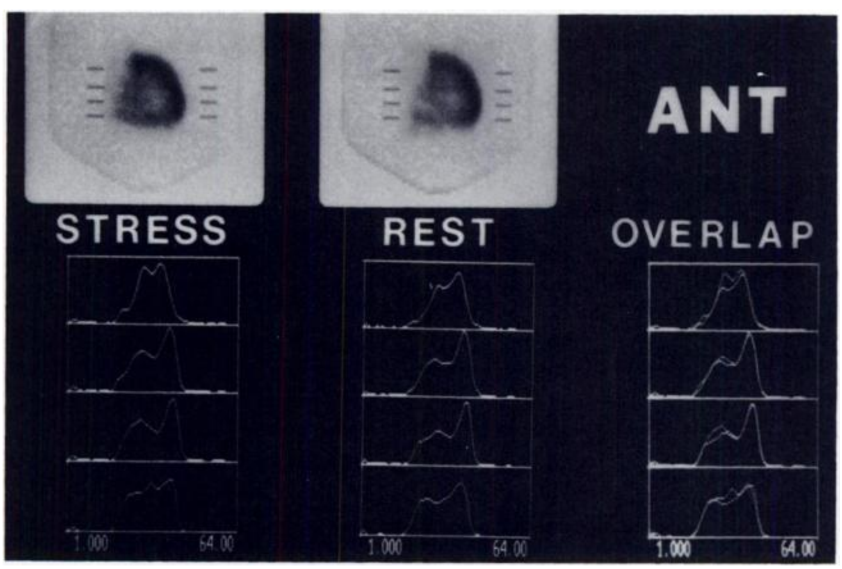

FIGURE 7
Interpolative background subtracted [^{99m}Tc]MIBI images (top) in the anterior (ANT) projection from the same patient shown in Figures 4 and 5, using the new algorithm. Corresponding quantitative profiles are shown below each image. In the lower right, the superimposed profiles show the similarity of the background corrected stress and rest images. This similarity in myocardial uptake is also present in the analog images.

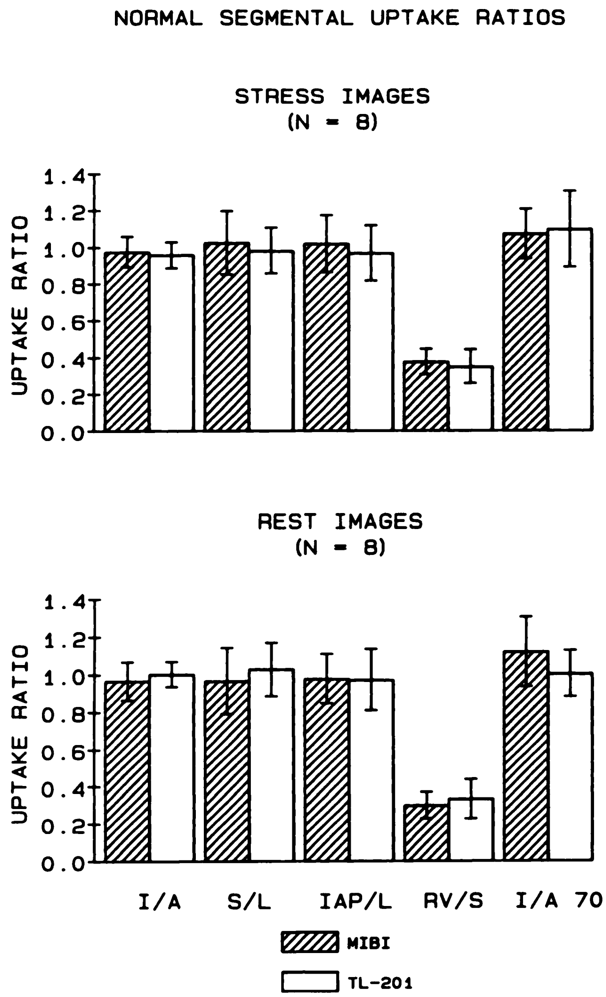

FIGURE 8
Five segmental uptake ratios derived from a low risk patient population are illustrated for stress images (top) and rest images (bottom), from the: anterior projection-inferior:anterolateral (I/A); 45° LAO projection-septal:lateral (S/L); inferoapical:lateral (IAP/L); right ventricular:lateral (RV/L); 70° LAO projection-inferior:anteroseptal (I/A 70).

background following resting injection of [^{99m}Tc]MIBI is quite different in both degree and structure from the background following injection during stress. The shape of the background function is less critical when comparing postexercise ^{201}Tl images with delayed redistribution images because there is less change in the background. The modified background subtraction algorithm should offer improved accuracy for ^{201}Tl studies as well, particularly in instances where there is extremely high lung uptake, and also for dipyridamole studies performed at rest where visceral uptake is more dominant.

While defect magnitude reported in this study was identical comparing ^{201}Tl and [^{99m}Tc]MIBI, there are potential qualifications. A comparison has been reported by Wackers (*31*) using the same background function as described here but quantification in that study was based on a circumferential profile extending throughout the circumference of the heart. It was observed that normal [^{99m}Tc]MIBI uptake in the valve plane regions was less than that of ^{201}Tl. In our quantitative approach we do not make measurements in the valve plane regions. Images with [^{99m}Tc]MIBI are contaminated less by Compton scattered photons and this appears to produce better resolution of valve planes as well as other structures such as the papillary muscle and conjunction of right and left ventricle. Because of these differences, adjustment may be required in the quantitative normal standards depending upon the method and regions which are sampled by the individual quantitative approach.

In conclusion, we report a modification of the standard interpolative background subtraction algorithm which optimized quantitative planar [^{99m}Tc]MIBI perfusion imaging. The modification proposed accommodates for the difference in extracardiac activity of planar [^{99m}Tc]MIBI images and provides a simple quantitative method for the assessment of regional myocardial perfusion. When applying this algorithm, the myocardial uptake pattern of [^{99m}Tc]MIBI and ^{201}Tl appear to be comparable. Before this algorithm can be recommended for routine clinical diagnostic use, further prospective studies in a larger number of patients appear warranted to assess the overall utility of quantitative planar [^{99m}Tc]MIBI imaging in detecting CAD and predicting its extent.

APPENDIX

For this work, V was the average pixel value of the smallest third of pixels on the background boundry. When left lateral views are employed, a portion of the boundary region enclosing the heart may lie outside of the anterior chest wall. This situation could cause a spurious undersubtraction of background activity, since the term V in our algorithm would include values which lie outside of the patient. Subsequent to the work reported in this paper, we have modified the computation of V as follows: all pixels lying on the boundary region are sorted from smallest to largest. The value of V is the average of all pixels included between the 20th and 50th percentile. This modification did not significantly alter the shape of the background subtraction plane or measurably alter the ratios reported in this paper; however, it does slightly raise the magnitude of the reference plane. It avoids a potential problem which could occur if 90° lateral views are performed or with some isolated situations such as if the boundary crosses a pacemaker shadow. We have therefore adopted this modification and recommend that it be used universally.

ACKNOWLEDGMENTS

This work was supported in part by Grant R01 HL-26205 from the National Heart, Lung, and Blood Institute, and E. I. Du Pont de Nemours & Co. (Inc.), Medical Products Department. Albert J. Sinusas, MD, is the recipient of National Research Service Award 1F32HL07745-01 from the National

Heart, Lung, and Blood Institute. The authors thank Jerry Curtis for his expertise in the preparation of the manuscript, and Robert Abbott, PhD, for his recommendations regarding our statistical analysis.

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