Quantitative Myocardial SPECT for Infarct Sizing: Feasibility of a Multicenter Trial Evaluated Using a Cardiac Phantom

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This study determined the feasibility of performing a multicenter trial using quantitative SPECT myocardial perfusion imaging in patients with acute myocardial infarction. The feasibility was assessed by a cardiac phantom. **Methods:** Twenty-two gamma camera systems in 19 laboratories were evaluated. Each laboratory performed nine studies on the cardiac phantom and performed quality control tests of system uniformity, collimator quality and gantry alignment on their gamma camera system. Defects simulating "hypoperfused" myocardium of differing amounts were placed in the myocardium for eight of the nine studies. Measured defect size was compared to true defect size. **Results:** A total of 198 studies from 22 systems were analyzed. Three studies were technically inadequate. For all 22 systems, the average correlation coefficient between true and measured defect size was 0.992 ± 0.009, with a range from 1.00 to 0.97. Three systems were rejected due to slopes of the regression line outside the limits 1.00 ± 0.10 and mean errors >5% in estimating defect size. The remaining systems had a correlation coefficient of 0.995 + 0.008 with an average slope of 1.00 ± 0.04 and an intercept of 0.11% ± 1.57%. The mean error in estimating defect size was 2.08% ± 0.69%. **Conclusion:** The small interlaboratory variation and the close correlation with true defect size observed in a cardiac phantom indicate the feasibility of quantitative myocardial SPECT as a useful tool in multicenter trials evaluating therapy in acute myocardial infarction. Preliminary objective testing is required, however, to identify systems with technical deficiencies.

Key Words: technetium-99m-sestamibi; cardiac phantom; infarct sizing, single-photon emission computed tomography

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Over the past 6 yr, the Nuclear Cardiology Laboratory at Mayo Clinic has pioneered the use of tomographic imaging with ^{99m}Tc-sestamibi for measuring the assessment of myocardium at risk, infarct size and treatment efficacy in acute myocardial infarction (*1–3*). We have employed this radiopharmaceutical in multiple clinical studies examining the pathophysiology of the response to reperfusion therapy in acute myocardial infarction (*4–6*). Myocardial salvage assessed by this agent was the primary endpoint in a randomized trial comparing immediate angioplasty and thrombolysis in acute myocardial infarction (*7*). In order to fully utilize the information available from ^{99m}Tc-sestamibi tomographic images, a simple threshold technique for quantitation of infarct size from the short-axis tomographic slices of the heart was validated in a phantom model (*1,8*). Comparable results to those obtained in the phantom model have been obtained in animal models using a similar threshold technique (*9,10*).

One of the disadvantages of tomography is that it is considered to be technically difficult and, by inference, poorly suited for the use in multicenter trials or studies involving centers with different types of gamma cameras. It is possible that variables including the number of detector heads, type of collimation, type of computer system, acquisition protocol and processing technique could all lead to differences in the final image quality and thereby could adversely influence the results of a quantitative technique, such as that used in our laboratory for measurement of infarct size (*11,12*).

The purpose of this study was to evaluate the feasibility of a multicenter trial employing quantitative SPECT imaging of the heart. In particular, this study evaluated the ability of multiple different gamma camera and computer systems in different centers to replicate the previously published phantom studies from this institution. In these phantom studies, infarct size was determined as a percentage of total myocardial mass.

METHODS

Study Group

A total of 22 gamma camera systems from 19 laboratories were studied. Seven different computer systems were employed. Table 1 presents a breakdown of the different gamma cameras and computers used by the participating laboratories. All data were submitted to the core laboratory on floppy diskettes (8″, 5.25″ or

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TABLE 1
Equipment Used by Participating Laboratories

No. of systems	Gamma camera system/computer system
2	Elscint SP-4/Elscint SP-1
6	G.E. 2000–6000 series/G.E. Starcam
1	G.E. 400 AT/G.E. Starcam
1	Phillips Arc 3000/ADAC 3300 computer
2	Picker SX300/ADAC 3300 computer
1	Picker Prism/Picker Odyssey
2	Siemens Orbiter/Siemens Microdelta
1	Siemens Orbiter/Siemens ICON
1	Siemens Diacam/Siemens ICON
2	Sopha DS-7/Sopha computer
3	Toshiba GCA 901A/Toshiba computer

3.5"). Because of the variety of vendor-specific file formats, a number of different techniques were used to convert data to a file format compatible with the computer system used in the core laboratory (Pinnacle system, Medasys Inc, Ann Arbor, MI). With many of the more recent computer systems, file exchange was accomplished via Interfile as an intermediate file format (*14*). Currently, most of the current generation of nuclear medicine computer systems provide the capability of exporting data in this format. Older file formats were accommodated either by means of an intermediate file conversion system (Sudbury Systems, Sudbury, MA) or by direct conversion programs written on the Pinnacle systems.

Cardiac Phantom

The methodology for these phantom studies has been previously described (*1,8*). All participating laboratories were supplied with a cardiac phantom (Model RH-2, Capintec, Ramsey, NJ) containing a heart, lungs and a spine (Fig. 1). The heart consisted of right and left ventricles with separate compartments for the blood pool and the myocardium. Eight latex insets (defects), ranging in size from 5% to 70% of myocardial volume were used to simulate hypoperfused or infarcted myocardium (Fig. 1). Each laboratory performed a total of nine SPECT acquisitions with the phantom, one for each of the eight defects and one with no defect. The myocardium and defects were marked to facilitate consistent positioning of the defects within the myocardial chamber. The small defects (<40% of myocardial volume) were placed in the inferior or infero-lateral region, and were designed to simulate infarcts resulting from occlusion of the right coronary artery. The larger defects were placed in the antero-septal region, simulating infarcts resulting from occlusion of the left anterior descending artery. A previous phantom study from this laboratory has found that for a given defect, its location within the myocardium (e.g., anterior versus inferior) will result in a small (3%–4%) variation in measurement of defect size (*8*).

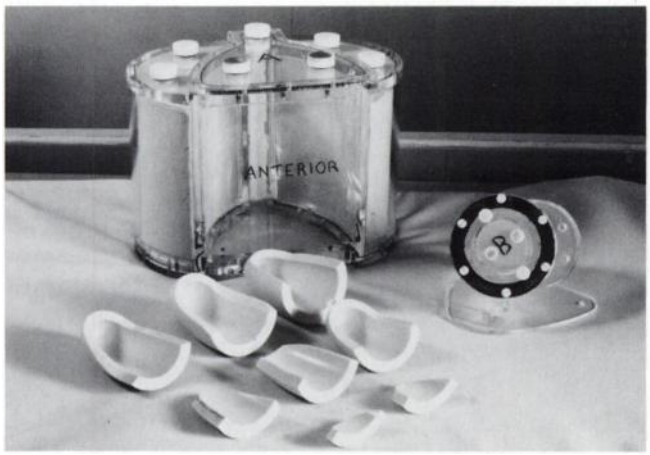

FIGURE 1. Cardiac phantom (Model RH-2, Capintec) comprising a central chamber for the heart, lungs (wood powder) and a spine (Teflon rod). The heart contains right and left ventricles with separate compartments for myocardium and blood pool. Eight latex insets are shown ranging in size from 5% to 70% of myocardial volume.

All phantom studies were performed with ^{99m}Tc to simulate clinical studies employing ^{99m}Tc-sestamibi. For the study with no myocardial defect, 2 mCi of ^{99m}Tc was placed in the background chamber and 1.5 mCi of ^{99m}Tc was placed in the myocardium. These activities were found to give a myocardial-to-background ratio comparable to that seen in clinical studies (*8*). With the introduction of the various defects, myocardial activity was reduced in proportion to defect size.

One laboratory employed a triple-headed gamma camera system equipped with high-resolution collimators. Acquisitions were performed over 360° and data were acquired into 60 views using a 64 × 64 matrix. In all other laboratories, studies were performed on conventional single-headed gamma camera systems equipped with either low-energy, all-purpose or low-energy, high-resolution collimators. Acquisitions were performed over 180°, beginning at 45° RAO and ending at 45° LPO. Data was acquired into either 30 or 32 views using 64 × 64 matrix size. The raw data from each of the nine acquisitions, together with a center of rotation study and a 30 million count flood image, were submitted on floppy diskette to the core laboratory. All raw data were converted to the Pinnacle format, the appropriate flood and COR corrections were applied and the data were reconstructed using a conventional back-projection algorithm with a Ramp-Hann filter (cut-off at 0.5 × Nyquist frequency). Five of the participating laboratories also submitted data (short-axis, horizontal and vertical long-axis slices of the heart) reconstructed on their own computer system for comparative analysis.

The defect size was quantitated using a previously published technique (*1,8*). Briefly, short-axis slices of the heart were generated every 6 mm and normalized to peak counts in the heart. From representative apical, mid-ventricular and basal slices and two intermediate slices (midway between the apex and the mid ventricle and midway between the mid ventricle and the base), circumferential count profiles were generated by identifying the peak counts every 6° around the left ventricle. Measurement of myocardial mass was calculated by measuring the average radii of the five selected slices. The slices were assumed to represent a series of hollow cylinders, with the exception of the apex, which was assumed to be a hollow cone. Measurement of defect size was determined from the fraction of radians (60 per slice) that fell below a threshold of 60% of peak counts in each slice. Previous studies have shown that this threshold value gave the highest correlation between true and measured defect size (*1,8*). These fractions were weighted by the slice radii and summed to yield the fraction of the myocardium that was not perfused.

The above analysis was performed on all nine studies from each laboratory and the measured defect size correlated with true defect size by regression analysis. The slope and intercept of the regression line, and the mean error in the estimation of defect size were determined for each laboratory. Based on the performance

of the laboratories participating in this study, minimum acceptable values were defined as a slope of the regression line between 0.90 and 1.10 and an average error in estimation of defect size of <5%. For the five laboratories that submitted both raw and reconstructed data, results were compared using a paired t-test analysis.

Quality Control

In addition to the flood and center of rotation corrections, each laboratory was required to perform the following quality control procedures on their gamma camera system.

Rotational Uniformity. This procedure assessed the stability of uniformity with rotation. The laboratory was requested to affix a lightweight ^{57}Co sheet source to the collimator face with adhesive tape. An overnight SPECT acquisition was performed, with 8–12 frames acquired over a 360° orbit. Each frame contained approximately 20–40 million counts. For each image, the total counts and the integral and differential uniformity were measured. From these, changes in uniformity with rotation were determined. SPECT systems were required to exhibit variations of <1%–2% in integral uniformity with rotation.

Collimator Hole Alignment. A 40-cm plastic rod with four small filling ports spaced 10 cm apart, was supplied to each laboratory. Each filling port was filled with ^{99m}Tc and the rod was taped to the end of the SPECT tabletop along the system's axis of rotation. A SPECT acquisition was performed with the following parameters: 20-cm radius of rotation; 128 × 128 matrix; 60–64 views; 5–10 sec/view. Center of rotation (COR) analysis of the four point sources along the axis of the collimator was performed, and the maximum variation in COR along the length of the collimator used as a measure of collimator hole alignment (*15*). For high quality SPECT, the maximum variation should not exceed 2–3 mm, at a 20-cm radius of rotation, over the length of the collimator (*16*).

System Sensitivity. A small 25-cc tissue culture flask was supplied to each laboratory. The flask was filled with a known amount of ^{99m}Tc (50–100 μCi) in 10–15 ml of water, placed directly on the collimator face and counted for 2 min. From ROI analysis of counts in the image, system sensitivity was determined for the collimator. Acceptable values were >150 cts/min/μCi. This limit encompasses most all-purpose and high-resolution collimators. Ultrahigh-resolution collimators were acceptable on multidetector systems if the combined sensitivities from the detectors exceeded the above limit.

Gantry Alignment. Laboratories were requested to level the detector head with the gantry at 0°. The gantry was then rotated through 180° and the detector head was again checked to ensure that it was level.

Data analysis of rotational uniformity and collimator hole alignment was performed in the core laboratory, while analysis of system sensitivity and gantry alignment was performed by the participating laboratory.

RESULTS

Phantom Experiment

Raw data was acquired on a total of 198 studies from 22 gamma camera systems. Of these, two were lost and one was technically inadequate due to poor mixing of radioactivity within the myocardium, leaving 195 studies. Technical problems were observed in some of the phantom studies. These were incorrect placement of the 5% and 10% defects within the myocardium (defects placed near the apex rather than the base in 8/22 cases), and incorrect ratio of activity in the myocardium and background chambers of the phantom (2/22 cases), making it difficult to distinguish the myocardium from the surrounding background. Positioning problems led to a slight increase in the measured defect size for the defects positioned apically (4.9% ± 2.0% and 10.5% ± 1.7%) compared to those correctly positioned in the base (4.5% ± 0.9% and 8.7% ± 1.8%), these differences were significant only for the 10% defect ($p = 0.038$). No significant effects were observed for the two cases where incorrect activities were placed in the chambers of the phantom.

TABLE 2
Relationship Between True and Measured Defect Size for the 22 Systems

System no.	Line of regression: Slope	Line of regression: Intercept	Correlation coefficient
1	1.04	0.27	0.994
2	1.06	−0.83	0.986
3	1.05	−2.59	0.988
4*	1.17	−1.15	0.983
5	0.96	1.51	0.996
6	1.02	0.70	0.998
7*	0.80	2.55	0.969
8*	0.87	0.53	0.970
9	0.93	1.92	0.992
10	0.99	0.17	0.995
11	1.00	−0.16	0.994
12	1.04	−1.22	0.997
13	0.98	−0.89	0.994
14	1.05	−3.55	0.998
15	1.01	−0.05	0.997
16	0.98	1.44	0.993
17	1.05	−0.91	0.999
18	1.06	0.35	0.998
19	0.94	1.63	0.995
20	0.96	0.04	0.998
21	0.97	1.34	0.997
22	0.99	2.87	0.984
Mean ± s.d.	1.00 ± 0.07	0.18 ± 1.57	0.992 ± 0.009

*Systems that were considered to have unacceptable results.

For each gamma camera system, the nine cardiac phantom studies were used to obtain a correlation of true versus measured defect size by linear regression analysis. Table 2 presents the slopes, intercepts and correlation coefficients for all 22 systems. Figure 2 shows the regression lines for these systems compared to the line of identity. Three systems (#4, #7 and #9) had slopes of 1.17, 0.80 and 0.87, which were outside the acceptable range 0.90–1.10. The remaining 19 systems had a slope of 1.00 ± 0.04 (mean ± s.d.), and an intercept of 0.11% ± 1.57% (mean ± s.d.); all had correlation coefficients >0.98. Figure 3 plots the mean error in the estimation of defect size for each gamma camera system. The three systems with unacceptable slopes had mean errors of 5.4, 5.1 and 5.0, which were at or above the acceptable limit of 5%. For all 22 systems, this parameter had a value of 2.50% ± 1.25% (mean ± s.d.), which

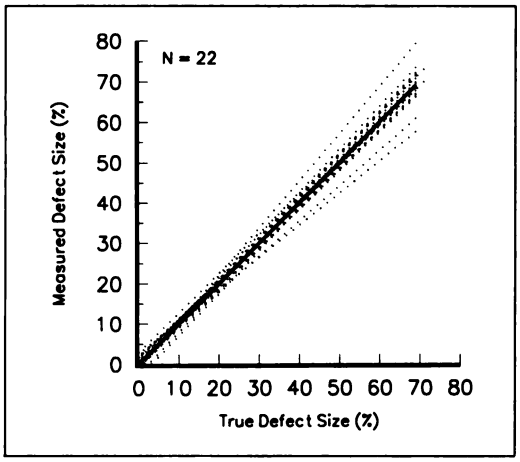

FIGURE 2. Linear regression analysis comparing true versus measured myocardial defect size for the 22 systems. The solid line represents the line of identity.

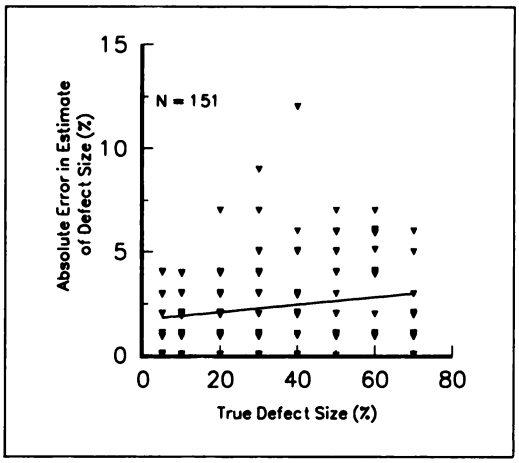

FIGURE 4. Variation in the absolute error in estimating myocardial defect size as a function of defect size for 151 studies in 19 systems.

was reduced to 2.08% ± 0.69% when the three systems that failed to pass the acceptable limits for slope and mean error were eliminated from the analysis. These three systems were excluded from further analysis. For the remaining 19 systems, the studies with no defect present were correctly measured as having a 0% defect in all cases. Figure 4 plots the error in estimating defect size as a function of true defect size for the 151 studies with defects in the 19 systems. Regression analysis failed to show any significant correlation ($r < 0.2$) between the measurement error and true defect size.

Comparison of the results obtained from the five systems in whom both the raw data and the reconstructed short-axis data were analyzed indicated that results obtained with the submitted short-axis data were inferior to those obtained with the raw data. While the average slope of the regression line did not show much difference (0.96 ± 0.11 versus 0.94 ± 0.15: raw versus submitted, p = ns), the mean error in estimating defect size was larger for the submitted data (4.12% ± 1.73%) than for the raw data (2.74% ± 1.59%), with $p < 0.001$.

Figure 5 shows circumferential count profiles from apical and midventricular short-axis slices, for the "normal myocardium" study (no defect). Examples are presented from four different gamma camera systems in order to illustrate the variability in profile shape that can be anticipated between systems. While significant intersystem variations were observed, these variations ranged from 100%–75% of peak counts and did not drop below the 60% threshold. Based on the results in Table 2 and Figure 2, they do not appear to have significantly influenced estimation of defect size.

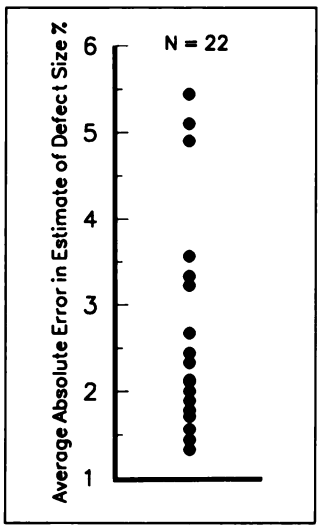

FIGURE 3. Mean error (average of nine studies) in estimating myocardial defect size for the 22 systems. Maximum acceptable error was <5%.

Quality Control Data

The 30-million count flood images and COR studies were submitted in all cases. All systems had COR values within 1 pixel of the true value (32.5). Table 3 presents the integral uniformity (extrinsic), the maximum variations in integral uniformity with rotation, the maximum variations in COR over the collimator face and system sensitivity results for all systems. Integral uniformity over the useful field of view, averaged 5.4% + 2.3% and ranged from 3.0%–11.2%. Two of the three systems that failed to give acceptable results with the cardiac phantoms, had integral uniformity values >10% (systems 7 and 8, Table 3). Four laboratories were unable to measure rotational uniformity for technical reasons. In the remaining 18 systems, the average variation in uniformity with rotation was 0.75% ± 0.37%, with a range from 0.2%–1.5%. The largest variation was seen in system 8 (Table 3). All systems employed standard all-purpose (16 systems) or high-resolution (6 systems) collimators and system sensitivity averaged 295 ± 74 cts/min/μCi with a range from 168–420 cts/min/μCi. Collimator hole alignment data were only obtained in 17 systems, due to technical problems in reading large studies spanning multiple floppy diskettes. The average COR variation along the collimator was 1.4 ± 0.9 mm with a range

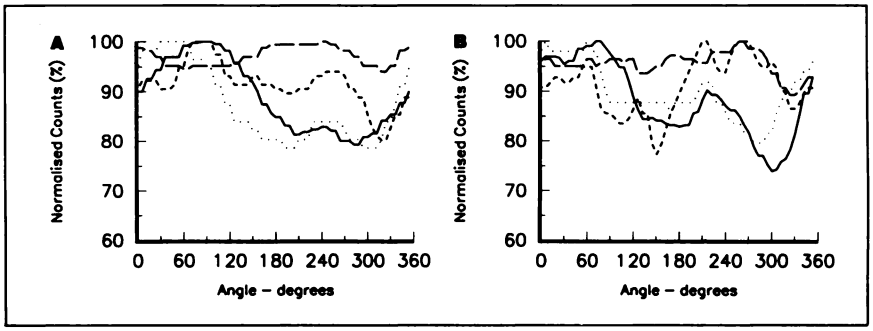

FIGURE 5. Circumferential count profiles for a normal myocardium taken at (A) the apex and (B) midventricle. Results are shown for four different tomographic systems (three single-headed, one triple-headed).

from 0.1–3.3 mm. No problems were observed with gantry alignment in any system.

DISCUSSION

The primary purpose of this study was to evaluate the feasibility of performing quantitative assessment of hypoperfused myocardium using SPECT in multiple centers with a wide spectrum of imaging equipment. Our results demonstrate the feasibility of this approach. Nineteen of 22 systems gave excellent results, with very high correlation coefficients, regression lines close to the line of identity, and with an average error of only 2% in estimating defect size. In clinical studies, this error will be larger, due to variations in patient anthropometric data. This study cannot address this issue, but it confirms the accuracy of objective measurements made under standardized reproducible conditions on different gamma camera and computer systems.

Most SPECT systems were found to have acceptable performance parameters, however, three systems had poor results with the phantom study; two had poor uniformity (>10%) and one showed the largest variation in uniformity with rotation. Only one system had variations in collimator hole alignment of greater than 3 mm (system 11, 3.3 mm). While this fact by itself does not render a system unacceptable, it leads to degradation in image quality and raises a cautionary flag in the evaluation of the other quality control and phantom results for that system. Whether or not the quality control data alone can be used to predict the overall performance of a system is difficult to determine. Of the three systems that failed, two had unacceptable quality control results and the third submitted incomplete quality

TABLE 3
Quality Control Results from the 22 Systems

System no.	Integral uniformity (%)	Rotational uniformity maximum variable (%)	COR maximum variable (mm)	Collimator sensitivity (cts/min/μCi)
1	5.1	0.46	1.6	331
2	4.6	0.90	1.8	339
3	6.5	0.60	0.2	338
4*	3.9	—	—	181
5	5.0	—	1.6	406
6	4.1	1.05	—	365
7*	11.2	0.36	2.0	293
8*	10.0	1.49	1.7	333
9	3.8	0.76	—	290
10	10.5	1.08	0.7	404
11	3.1	0.69	3.3	420
12	4.1	0.20	—	295
13	3.8	—	0.2	315
14	3.3	0.30	0.2	182
15	5.1	1.02	1.8	208
16	5.5	0.55	1.6	298
17	4.7	0.30	1.7	240
18	6.9	—	0.1	168
19	3.3	—	—	—
20	4.1	0.65	0.6	283
21	6.1	1.23	2.2	285
22	3.8	1.09	2.3	221
Mean ± s.d.	5.4 ± 2.3	0.75 ± 0.37	1.4 ± 0.9	295 ± 74

*Systems that had unacceptable results in the phantom studies.

control data (system 4). While the performance of the quality control and phantom studies requires a relatively large time commitment (approximately 8 hr to set up and acquire the nine phantom studies), these data provide essential information on the quality of the clinical studies that can be anticipated and allow problems to be addressed prior to commencement of the clinical trial. The fact that three sites failed to meet the acceptable limits set for the phantom studies emphasizes the value of these studies in eliminating potentially poor quality data from inclusion in clinical studies.

With improved treatment and declining mortality, indirect measurements such as infarct size become more important in clinical trials since increasingly large trials are required to detect differences in endpoints such as mortality (*13*). Therefore, the demonstration that accurate quantitative results can be obtained from SPECT studies, performed on a variety of nuclear medicine imaging systems in different laboratories, is essential to establish the potential use of SPECT perfusion imaging as an endpoint in clinical trials.

Several previous multicenter trials have used quantitative nuclear medicine procedures as part of their protocol. The MILIS Study Group employed radionuclide ventriculograms with the patient data being processed twice in a select group to check the reproducibility of the measurements (*13*). Other studies using radionuclide ventriculography have not reported any validation procedures (*17*). One multicenter trial employed ^{201}Tl SPECT studies acquired in different centers on gamma camera/computer systems of the same make and model (*18*). None of these trials has used an objective standard of the accuracy of the submitted data. With the complexity of SPECT, considerable room for error exists in the application of quantitative techniques to tomographic data. This is the first study to employ an objective standard to verify the accuracy of the submitted data. The failure of three systems to meet the required standards confirms the importance of using an objective assessment of system accuracy. The reason for the failure of these three systems is difficult to determine as a large number of technical factors during acquisition (large collimator to phantom separation during acquisition, detector head not level, etc.), as well as problems with detector performance, can lead to poor results.

The advantages of the quantitative technique employed in this study include (1) flexibility in the acquisition procedure (LEAP versus LEHR collimation, 180° versus 360° orbit); and (2) centralized processing, which removes the confounding effects of vendor-specific filters and reconstruction algorithms. In the five systems where defect size was determined from short-axis slices which were generated both by the participating laboratory and by the core laboratory using the submitted raw data, the inferior results obtained with the submitted processed data suggest that factors such as the reconstruction algorithm, filtration and operator variability in data processing may influence the accuracy of the quantitative technique.

The use of ^{99m}Tc rather than ^{201}Tl and a 60% threshold level adds to the robustness of the technique. A previous multicenter trial utilizing ^{201}Tl (*19*) found that a carefully standardized acquisition and processing protocol was necessary to ensure accurate results, and deviations from the standard imaging times, different rotations (180° versus 360°), different filters, etc., could have unpredictable effects on the accuracy of quantitative polar map techniques. This trial also required a gender-specific normal database for each system, which adds to the complexity of large multicenter trials. Our own experience with ^{201}Tl has indicated that a higher threshold value of 70% is required for accurate estimation of defect size (*20*). At this threshold level, the technique is likely to be far more dependent on the characteristics of the particular imaging system. Figure 5 shows the variations observed with ^{99m}Tc in the circumferential count profiles for the same regions of a "normal" myocardium, for four different tomographic systems. Even larger variations could be anticipated with ^{201}Tl. This variability existed even though the raw data was processed in a consistent manner on a single computer system and may be due to factors such as table attenuation, slight variations in start/end angles and in phantom position on the imaging table, and differences in resolution at depth between systems employing all-purpose and high-resolution collimators. The variations in circumferential count profiles seen in Figure 5 will introduce some bias into the estimation of defect size. Variations in defect location within the myocardium, however, make it difficult to determine the effects of this bias. Clearly, the above factors do not appear to have introduced any substantial error into the accuracy of the quantitative technique as Figure 4 shows that for individual studies, the magnitude of the error in estimating defect size is small and uncorrelated with absolute defect size, with less than 10% of studies having an absolute error of >5%.

There are a number of limitations in this study as it pertains to multicenter trials. The primary one is variability in the imaging characteristics of patients. Differences between centers in the size and shape of patients, in the ethnic population and in sex of the patient (vis-à-vis breast attenuation) will introduce errors in estimation of infarct size. In addition, this study was limited to defects simulating transmural infarcts. Previous work has shown that measurement of infarct size using the threshold technique is relatively inaccurate for subendocardial or subendothelial infarcts (*8*). Furthermore, this trial was designed to evaluate the potential use of ^{99m}Tc-sestamibi in the quantitation of infarct size. Previous work has shown that the threshold technique may not work as well for ^{201}Tl (*20*), as a higher threshold value is required (70%), making the measurement of infarct size susceptible to intersystem variations in the normal profile shape as shown in Figure 5.

CONCLUSION

Results from this study using a cardiac phantom would indicate that myocardial SPECT can be a useful tool in multicenter trials evaluating therapy for acute myocardial

infarction. Even with vastly differing instrumentation, a small interlaboratory variability and close correlation with true defect size can be attained if a central processing laboratory is utilized.

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