Significance of Rest Technetium-99m Sestamibi Imaging for the Prediction of Improvement of Left Ventricular Dysfunction After Q Wave Myocardial Infarction: Importance of Infarct Location Adjusted Thresholds

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Objective. The value of rest technetium-99m (Tc-99m) sestamibi scintigraphy under oral nitrate medication to predict myocardial viability was examined in patients with chronic infarcts.

Background. The value of rest Tc-99m sestamibi to predict viability in infarct regions has not been fully established because significant underestimation of viability, especially in the inferior myocardial wall, has been reported.

Methods. Forty patients with Q wave myocardial infarction underwent Tc-99m sestamibi single-photon emission computed tomography under nitrate medication before revascularization of the infarct-related artery. Wall motion was quantified from paired angiograms before and 4 months after revascularization. Tracer uptake was quantified in the central infarct region identified on the angiogram.

Results. The average Tc-99m sestamibi uptake in the central infarct region of patients with anterior infarcts and improvement of left ventricular function was significantly higher (68 ± 12%, mean ± SD) than in patients without improvement of function (40 ± 14%, p < 0.02). The average Tc-99m sestamibi uptake in the central infarct region of patients with improvement of function and inferior infarcts was significantly lower (43 ± 7%) than in patients with anterior infarcts (68 ± 12%, p < 0.003), but was significantly higher than in patients with inferior infarction and no improvement of function (31 ± 7%, p < 0.02). Using an infarct location adjusted optimal threshold (50% for anterior infarcts, 35% for inferior infarcts), Tc-99m sestamibi had a positive predictive value of 90% and a negative predictive value of 91% for improvement of left ventricular function.

Conclusion. Quantitative rest Tc-99m sestamibi scintigraphy after oral nitrates reliably predicts improvement of left ventricular function after revascularization if infarct location adjusted thresholds are used.

(J Am Coll Cardiol 1998;32:648–54) ©1998 by the American College of Cardiology

Scintigraphic techniques are widely used for the reliable detection of residual viability in infarct regions. Among the tracers used, 18F-fluorodeoxyglucose (FDG) (1) and thallium-201 (Tl-201) (2) are the most common. In addition, technetium-99m (Tc-99m) sestamibi has been used to detect residual viability in the infarct regions (3). However, the ability of Tc-99m sestamibi single-photon emission computed tomography (SPECT) to detect viable myocardium in the infarct region and to predict functional improvement after myocardial infarction has been controversially discussed because in some studies Tc-99m sestamibi SPECT underestimated myocardial viability identified by FDG positron emission tomography (PET) or Tl-201 SPECT (4–6). These findings contrast to recent reports showing good agreement of Tl-201 and Tc-99m sestamibi in the detection of residual viability (7,8) and the prediction of functional improvement (7,9,10). These discrepancies may be explained in part by differences of the imaging protocol and the analysis of the data: late imaging (11), imaging after nitrate administration (12,13) or the quantitative analysis of Tc-99m sestamibi uptake (7,8,11) can improve the diagnostic accuracy of Tc-99m sestamibi SPECT to detect residual viability.

On the basis of these findings we hypothesized that Tc-99m sestamibi SPECT after oral nitrate with quantitative analysis would have similar accuracy as FDG PET in detecting viable myocardium in the infarct region and predicting improvement of left ventricular function. We further hypothesized that the average Tc-99m sestamibi uptake would depend on the infarct location and would be significantly lower in inferior infarct regions than in anterior infarct regions due to attenuation effects. Accordingly, we analyzed the predictive value of Tc-
Also in subgroups according to infarct location (inferior vs. with myocardial infarction and successful revascularization but 99m sestamibi SPECT not only in the total group of patients but also in subgroups according to infarct location (inferior vs. anterior infarcts).

Methods

Study patients. Forty patients with Q wave myocardial infarction and angiographically documented coronary artery disease (at least one infarct-related major coronary vessel with >75% diameter stenosis) and regional severe hypokinesia, akinesia or dyskinesia by visual analysis of left ventricular angiograms were prospectively studied. Infarct had occurred in all patients >3 months before the first scintigraphic study. Independently of the findings of the scintigraphic studies, all patients underwent revascularization of the infarct-related coronary artery between November 1994 and December 1996. Four months after revascularization all patients underwent repeat angiography and ventriculography.

An infarct was defined as anterior if the electrocardiogram (ECG) showed pathological Q waves >30 ms in at least three of the anterior infarct leads (I, aVL, V_{1-3}) and a severe wall motion abnormality in at least one of the anterior segments of the right anterior oblique (RAO) angiogram (anterobasal, anterolateral or apical); an infarct was defined as inferior if the ECG showed pathological Q waves in at least two inferior leads (II, III, aVF, V_{6}) and a wall motion abnormality in at least one of the inferior segments of the RAO angiogram (posterobasal or diaphragmatic).

For detection of myocardial viability all patients underwent FDG PET and Tc-99m sestamibi SPECT on 2 separate days. The revascularization procedure was performed within 5 days after completion of the scintigraphic studies. No cardiac event (myocardial infarction, unstable angina) occurred in any patient between the scintigraphic studies and angiography nor between baseline and control angiography 4 months later. The study was approved by the Hospital Human Rights Committee (Institutional Review Board) and informed consent was obtained from every patient.

Of the 40 patients initially included in the study, 9 were excluded from analysis of the relation between Tc-99m sestamibi uptake and improvement of function because of significant restenosis (≥75% diameter reduction) of the dilated artery (n = 6) or severe stenosis or occlusion of the bypass graft (n = 3) as persisting ischemia could have precluded an improvement of function, and inclusion of patients with restenosis would have led to false calculation of the positive and negative predictive values of Tc-99m sestamibi SPECT. Thus, the Tc-99m sestamibi data are analyzed in two ways: 1) the relation of viability as defined by FDG PET and average Tc-99m sestamibi uptake was analyzed (40 patients); 2) the relation of viability as defined by improvement of left ventricular function after successful revascularization and Tc-99m sestamibi uptake was evaluated (31 patients).

Angiography and ventriculography. Selective coronary angiography was performed by the Judkins technique and arteries were viewed in multiple projections. Coronary artery narrowing was measured in the projection showing the most severe stenosis using electronic calipers. A diameter reduction of ≥50% was considered significant.

Biplane left ventriculography was performed in the right (RAO) and left anterior oblique position. Regional left ventricular wall motion of the infarct region was quantified and expressed as standard deviation (SD) of a normal population per chord using the centerline method (14). Wall motion analysis was performed using the RAO projection because hypokinesia is more accurately detected in this projection for anterior and inferior infarction (14). In addition, the analysis in the RAO projection avoids inclusion of septal segments with wall motion abnormalities caused by coronary artery bypass graft surgery. Two patients had a hypoplastic right coronary artery and a dominant circumflex coronary artery as the infarct artery leading to akinesia of the inferior wall. The ventriculograms of these patients were also analyzed in the right anterior oblique projection. Wall motion in the central infarct region was analyzed by averaging the motion of chords lying in the most abnormally contracting 50% of the infarct territory and is expressed as mean SD/chord. An increase in SD of the central infarct region at control angiography by ≥0.8 SD in patients with anterior infarcts and ≥0.6 SD in patients with inferior infarcts was defined as significant improvement of left ventricular wall motion indicative of recovery of viable myocardium (14). Global left ventricular ejection fraction was calculated from end-diastolic and end-systolic contours using the area length method (15).

Scintigraphic studies. Tc-99m sestamibi SPECT. All patients received their individually tolerated maximal oral doses of long-acting nitrates (mean doses 85 ± 35 mg of nitrates) at 8:00 AM on the day of SPECT examination. Two hours later, 740 MBq (20 mCi) of Tc-99m sestamibi (Cardiolite, DuPont, Bad Homburg, Germany) were injected. One hour after this injection all patients received a standard meal to improve Tc-99m sestamibi clearance from the hepato-biliary tract. SPECT was finally started 2 h after Tc-99m sestamibi injection. Tc-99m sestamibi imaging was performed with a triple-head gamma camera (Prism 3000; Picker International GmbH, Cleveland, OH and Munich, Germany) equipped with high resolution collimators, as previously described (16). In a step-and-shoot-mode, 120 planar images (128 × 128-pixel matrix), each with an acquisition time of 30 s, were acquired over a 360° arc. Transaxial tomograms of 2 mm thick sections (1 pixel)
were reconstructed by means of filtered backprojection (Butterworth filter, order 6, cut off frequency 0.35 cycles/pixel). The images were then transferred to a SUN workstation for further analysis.

FDG PET. 18F-fluorodeoxyglucose PET was performed using a whole body scanner (Siemens CTI ECAT Exact 921, Erlangen, Germany). To improve myocardial glucose uptake, each patient received a solution of 50 g of glucose 1 h before the administration of FDG. Images were corrected for attenuation by using coefficients measured by a transmission scan of 30-min duration. Emission scans (6×5 min) were started 30 min after injection of 370 MBq of FDG, as previously described (17).

Image analysis. Positron emission tomography and SPECT images were analyzed using computer generated polar maps on a SUN SPARC 20 workstation by a single observer unaware of the functional outcome of the patient after revascularization. The FDG images were normalized to the region with maximal Tc-99m sestamibi uptake (normalized, maximum FDG uptake). The average FDG and Tc-99m sestamibi uptake in the central infarct region were then quantified in the midventricular, sagittal long axis slice, showing the largest cavity, using a continuous color scale and matching the scintigraphic images and the right anterior oblique angiogram as its centerline analysis side by side (Fig. 1). Slice thickness of the sagittal image was 2.5 cm for both the Tc-99m sestamibi and FDG PET images.

We have previously shown that a threshold of 50% of maximal FDG uptake discriminates myocardium with larger amounts of viable myocardium sufficient to improve left ventricular function after revascularization (viable) with high sensitivity and specificity from myocardium with only minimal residual viability insufficient to improve left ventricular function (nonviable) (17). Accordingly, the central infarct region with an average FDG uptake of <50% of maximal, normalized FDG uptake was defined as nonviable; the central infarct region with an average uptake of ≥50% of maximal, normalized FDG uptake was defined as viable.

Statistics. All data are presented as mean ± SD. Differences between the mean values were compared using the Wilcoxon signed rank test or the Mann-Whitney U-test, where appropriate. The null hypothesis was rejected at the 95% confidence level considering a p value <0.05 as significant.
Positive and negative predictive values and the diagnostic accuracy of scintigraphic values were calculated using standard formulas.

**Results**

**Patient characteristics.** A total of 40 patients underwent PET, Tc-99m sestamibi SPECT and revascularization of the infarct-related vessel (Table 1). Indication for revascularization included typical angina pectoris or a pathologic stress test in 36 patients and severe dyspnoe judged as of cardiac origin in 4 patients.

The mean ejection fraction at baseline was $54 \pm 12\%$; 16 patients had single vessel disease, 6 patients had two vessel disease and 18 patients had three vessel disease. The infarct-related vessel was totally occluded in 11 patients, whereas a subtotal occluded infarct-related vessel was found in 20 patients. The remaining nine patients had $>75\%$ diameter stenosis of the infarct-related vessel. Figure 1 shows a representative example of a patient with an inferior infarct and improvement of wall motion abnormality 4 months after successful revascularization.

**Average Tc-99m sestamibi uptake in regions defined as viable and nonviable by PET.** The average Tc-99m sestamibi uptake in the central infarct region of patients defined as viable by FDG PET was $51 \pm 14\%$ (n = 23) in the total group and was significantly higher than in patients with an FDG uptake $<50\%$ ($33 \pm 7\%; n = 17; p < 0.007$).

The average Tc-99m sestamibi uptake in the central infarct region of patients with anterior infarcts scored as viable by FDG PET was significantly higher ($65 \pm 14\%; n = 8$) than in patients with anterior infarcts scored as nonviable by FDG PET ($33 \pm 9\%, n = 10; p < 0.0003$; Fig. 2).

FDG PET was significantly lower ($43 \pm 6\%; n = 15$) than in patients with anterior infarcts ($65 \pm 14\%, p < 0.002$), but was significantly higher than in patients with inferior infarction scored as nonviable by FDG PET ($32 \pm 5\%; n = 7; p < 0.002$, Fig. 2).

**Prediction of viability by Tc-99m sestamibi data.** As anterior and inferior infarcts had significantly different mean Tc-99m sestamibi uptake in regions with an average FDG uptake $\geq 50\%$, positive and negative predictive values were calculated separately according to infarct location.

A threshold of $50\%$ in patients with anterior infarcts yielded the best positive ($100\%$ [7 of 7 patients]) and negative predictive value ($91\%$ [10 of 11 patients]) for an average FDG uptake of $\geq 50\%$. The diagnostic accuracy was $94\%$ (17 of 18 patients). In contrast, in patients with inferior infarcts a threshold of $35\%$ yielded the best positive ($93\%$ [14 of 15 patients]) and negative predictive values ($86\%$ [6 of 7 patients]) for an average FDG uptake of $\geq 50\%$. The diagnostic accuracy was $91\%$ (20 of 22 patients).

Using infarct location adjusted, optimal Tc-99m sestamibi thresholds ($50\%$ of maximal uptake for anterior infarcts and $35\%$ of maximal uptake for inferior infarcts), the positive predictive value was $95\%$ (21 of 22 patients) and the negative predictive value was $89\%$ (16 of 18 patients) for an average FDG uptake of $\geq 50\%$ in the central infarct region in the total group. The diagnostic accuracy was $93\%$ (37 of 40 patients).

**Tc-99m sestamibi uptake in the central infarct region of patients with and without improvement of left ventricular function.** Parameters of wall motion abnormality. Wall motion abnormality in the central infarct region improved in 19 patients significantly by $1.1 \pm 0.78$ SD (from $-3.1 \pm 0.6$ to $-2.0 \pm 0.8$, $p < 0.0001$), while in 12 patients wall motion abnormality remained almost unchanged ($-2.9 \pm 0.45$ SD to $-2.8 \pm 0.8$ SD, $p = $ NS). Similarly, left ventricular ejection fraction increased only in patients with significant improvement of wall motion abnormality of the central infarct region (from $50 \pm 13\%$ to $58 \pm 13\%, p < 0.01$), while in patients without significant improvement of wall motion abnormality of the central infarct region, left ventricular ejection fraction remained almost unchanged (from $57 \pm 8\%$ to $54 \pm 7\%, p = $ NS).
Average Tc-99m sestamibi uptake. The average Tc-99m sestamibi uptake assessed before revascularization in the central infarct region of patients with improved left ventricular function (n = 19) was 50 ± 13% and was significantly higher than in patients without improvement of function (37 ± 12%; n = 12; p < 0.006). The average Tc-99m sestamibi uptake in the central infarct region of patients with anterior infarcts and improvement of left ventricular function (n = 5) was significantly higher (68 ± 12%) than in patients without improvement of function (40 ± 14%; n = 8; p < 0.02, Fig. 3). The average Tc-99m sestamibi uptake in the central infarct region of patients with inferior infarcts and improvement of left ventricular function (n = 14) was significantly lower (43 ± 7%) than in patients with anterior infarcts and improvement of function (68 ± 12%, p < 0.003), but was significantly higher than in patients with inferior infarction and no improvement of function (31 ± 6%; n = 4; p < 0.02; Fig. 3).

Prediction of improvement of wall motion abnormality assessed by angiography from Tc-99m sestamibi data. For patients with anterior infarcts an average Tc-99m sestamibi uptake of ≥50% had the best positive (83% [5 of 6 patients]) and negative predictive value (100% [7 of 7 patients]) and a diagnostic accuracy of 92% (12 of 13 patients) for improvement of wall motion. For patients with inferior infarcts an average Tc-99m sestamibi uptake of ≥35% had the best positive (93% [13 of 14 patients]) and negative predictive value (75% [3 of 4 patients]) and a diagnostic accuracy of 89% (16 of 18 patients) for improvement of wall motion abnormalities. Using an infarct location adjusted optimal Tc-99m sestamibi threshold (≥50% for anterior infarcts, ≥35% for inferior infarcts) for the total successfully revascularized group, the positive predictive value was 90% (18 of 20 patients), the negative predictive value was 91% (10 of 11 patients) and the diagnostic accuracy was 90% (28 of 31 patients) for improvement of left ventricular function.

Discussion

The data of this study indicate that rest Tc-99m sestamibi SPECT can reliably predict myocardial viability as defined by FDG PET or improvement of left ventricular function provided that Tc-99m sestamibi SPECT is carried out under nitrate medication and that infarct location adjusted thresholds are applied.

Tc-99m sestamibi and myocardial viability. Tc-99m sestamibi scintigraphy has been used to assess residual viability after myocardial infarction over several years, but the results have been controversial. Initially, Tc-99m sestamibi uptake has been shown to underestimate the extent of viable myocardium in comparison to FDG PET or rest Tl-201 scintigraphy (4–6). Soufer et al. (4) also showed that Tc-99m sestamibi scintigraphy significantly underestimated the extent of viable myocardium defined by FDG PET and improvement of left ventricular function. Interestingly, most of the Tc-99m sestamibi nonviable/FGD viable segments (the mismatch segments) were found in inferior infarct regions (22 regions) while in anterior infarct regions only four regions showed a mismatch pattern. This suggests that in some patients with inferior infarcts, attenuation problems might account for the underestimation of viability. Similarly, Sawada et al. (5) examined 20 patients with Tc-99m sestamibi SPECT and FDG PET and showed that in about 50% of segments with severely depressed Tc-99m sestamibi uptake, a considerable FDG uptake could be found. This is indicative of persistent viability.

Improved techniques to detect viability by Tc-99m sestamibi. In contrast to these data, recent data indicate that rest Tc-99m sestamibi scintigraphy can reliably detect residual viability if late scintigraphy (11), scintigraphy under nitrate medication (12,13) or quantitative analysis of Tc-99m sestamibi uptake (7,8,11) were used.

Although it was initially believed that Tc-99m sestamibi does not redistribute, recent data show that a considerable redistribution in defects with initially severely reduced Tc-99m sestamibi uptake may occur. Dilsizan et al. (11) examined this effect in 18 patients with chronic myocardial infarction who underwent TI-201 SPECT and rest/stress Tc-99m sestamibi SPECT and a delayed (4 h) Tc-99m sestamibi scan. The delayed scan improved the concordance between rest TI-201 and rest Tc-99m sestamibi scintigraphy from 71% to 82% with regard to the detection of viability.

A further improvement of the detection of residual viability after myocardial infarction by Tc-99m sestamibi SPECT has been shown by the administration of nitrates before the injection of Tc-99m sestamibi (13,18). Maurea et al. (13) examined 31 patients after myocardial infarction with Tc-99m sestamibi scintigraphy under baseline conditions and after oral nitrates and with Tl-201 rest-redistribution scintigraphy. Eight patients were also examined after revascularization. The administration of nitrates improved the Tc-99m sestamibi uptake in 54 segments with initially severely depressed Tc-99m sestamibi uptake (from 42% to 60%, p < 0.001); all of these segments were viable on rest-redistribution, Tl-201 scintigraphy. In the eight patients studied after revascularization, 87% of the segments with reversible Tc-99m sestamibi defects showed recovery, while 89% of the segments with irreversible defects did not. Thus, nitrate administration seems to increase blood flow and Tc-99m sestamibi uptake to severely ischemic...
but viable regions and improves detection of viable myocardium.

Finally, the detection of viable myocardium after myocardial infarction can be further improved by quantitative analysis of Tc-99m sestamibi uptake. Undelson et al. (7) examined 31 patients with coronary artery disease and left ventricular dysfunction using rest-redistribution Tl-201 and rest Tc-99m sestamibi scintigraphy, 18 of whom underwent myocardial revascularization. Quantitative analysis of tracer uptake showed a significant correlation ($r = 0.86$) between regional Tl-201 and Tc-99m sestamibi uptake. The average tracer uptake was similar for both tracers (72% vs. 75%, $p = NS$) in patients with improvement of left ventricular function assessed 20 days after revascularization by echocardiography. Similarly, in regions without improvement of function, no significant difference between both tracers was found (51% vs. 50%, $p = NS$). The authors concluded that rest Tc-99m sestamibi scintigraphy using quantitative analysis was as accurate as Tl-201 scintigraphy to detect viable myocardium and predict improvement of left ventricular function after revascularization.

**Infarct location adjusted threshold for Tc-99m sestamibi uptake.** Based on these findings we combined the three above-mentioned modalities (nitrate medication, delayed scan and quantitative analysis) to optimize the predictive value of Tc-99m sestamibi imaging for detection of residual viability. In addition, we calculated infarct location adjusted thresholds for the detection of residual viability as defined by PET, and improvement of wall motion abnormality as the average Tc-99m sestamibi uptake in viable inferior regions was significantly lower than in anterior regions.

Our data confirm earlier reports in smaller patient populations and extend the knowledge about Tc-99m sestamibi scintigraphy for detection of viability by demonstrating for the first time that infarct location adjusted thresholds will further improve the diagnostic accuracy of Tc-99m sestamibi scintigraphy. Although the attenuation of single photons by surrounding tissue has been early identified as a potential limitation in SPECT (19), this important problem has not yet received much attention in the diagnosis of viability. Moreover, the exact location of myocardial infarcts was not routinely reported in studies analyzing the predictive value of Tl-201 or Tc-99m sestamibi SPECT for assessment of viability, thus making it impossible to draw any conclusions about the average tracer uptake with respect to infarct location. Recently, Maes et al. (9) compared the average Tc-99m sestamibi uptake in patients with left anterior descending stenoses and anterior wall motion abnormalities with the average FDG uptake. They showed a linear relation between the histologically proven extent of necrosis and the regional Tc-99m sestamibi uptake ($r = 0.78$). In addition, a threshold of 50% of maximal Tc-99m sestamibi uptake had the best predictive value for improvement of left ventricular function in these patients with anterior wall motion abnormality. These data are similar to our observation showing that a threshold of ≥50% for anterior infarct had the best positive and negative predictive values. Unfortunately, no histological data exist for patients with inferior infarcts. However, our data indicate that in these patients segments with evidence of viability (FDG uptake ≥50% or improvement of wall motion abnormality) had a significantly lower average Tc-99m sestamibi uptake (43%) than in anterior regions (65%). This finding may explain why in the report by Soufer et al. (4), using a single Tc-99m sestamibi threshold of 50% of maximum Tc-99m sestamibi uptake most of the segments which were nonviable by Tc-99m sestamibi but viable by FDG PET were found in the inferior regions (22 of 39 segments). An infarct location adjusted threshold would probably have improved these results.

**Limitations.** The matching of the RAO angiogram and the scintigraphic images may be less than perfect. However, the scintigraphic studies and the angiogram as its centerline analysis were compared side by side by a single observer, without the knowledge of the functional outcome, thus minimizing any potential bias. A second limitation is that we performed Tc-99m sestamibi scintigraphy 2 h after injection of Tc-99m sestamibi, for logistic reasons. A longer period between injection and scintigraphy may have further improved the predictive value of Tc-99m sestamibi scintigraphy for the detection of viable myocardium. As our study population comprised mainly men with only modestly depressed left ventricular function, the significance of our results for cardiac SPECT in women or patients with severely depressed left ventricular function remains to be determined. In the present study attenuation correction was not used. The routine use of attenuation correction may facilitate the interpretation of cardiac SPECT studies in the future (20).

**Clinical implications.** Rest Tc-99m sestamibi scintigraphy has the potential to assess reliably myocardial viability in patients with Q wave myocardial infarction provided that late scintigraphy after nitrate is performed and that infarct location adjusted thresholds are applied. The broad availability and the convenient logistics in preparing this tracer make Tc-99m sestamibi a cost-effective alternative to the cyclotron-produced FDG for routine assessment of residual viability.

**References**


