Influence of the assessment of defect severity and intravenous nitrate administration during tracer injection on the detection of

Influence of the assessment of defect severity and intravenous nitrate administration during tracer injection on the detection of viable hibernating myocardium with data-based quantitative technetium 99m–labeled sestamibi single-photon emission computed tomography

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Background. **This study aimed to verify whether the assessment of defect severity and the infusion of nitrates during tracer injection improve the capability of data-based ^{99m}Tc-labeled sestamibi single-photon emission computed tomography (SPECT) to recognize hibernating myocardium.**

Methods and Results. **Of 66 asynergic coronary territories in 40 patients with left ventricular dysfunction, 28 had postrevascularization functional recovery (hibernating) and 38 had unchanged dysfunction (fibrotic). Defect severity was lower in the hibernating than in the fibrotic territories on both baseline ($p < 0.01$) and nitrate SPECT ($p < 0.002$). Nitrate was superior to baseline SPECT to differentiate the hibernating from the fibrotic territories (sensitivity 96% vs 75%, $p < 0.05$; receiver-operating characteristic curve area 0.75 vs 0.63, $p < 0.001$) and to identify the patients with improved left ventricular ejection fraction (receiver-operating characteristic curve area 0.68 vs 0.58; $p < 0.05$).**

Conclusions. **The analysis of defect severity in combination with nitrate infusion clearly improves the value of ^{99m}Tc-labeled sestamibi SPECT for the recognition of hibernating myocardium and the prediction of postrevascularization recovery. (J Nucl Cardiol 1996;3:221-30.)**

Key Words: myocardial viability • nitrates • sestamibi

^{99m}Tc-labeled sestamibi is at present the sole ^{99m}Tc-labeled myocardial perfusion tracer to have gained widespread clinical acceptance. It offers various advantages over ^{201}Tl: in particular it has optimal features for single-photon emission computed tomography (SPECT).[1] ^{99m}Tc-labeled sestamibi SPECT has been demonstrated to be accurate in the detection of coronary artery disease,[1] and its reliability has been increased by the availability of validated methods for the quantitative analysis of SPECT according to the comparison with databases of normal control subjects.[2] However, previous data obtained with planar imaging suggested that rest ^{99m}Tc-labeled sestamibi uptake defects could be found in regions with preserved wall motion.[3] More recently, specific concern has been expressed about the capability of rest ^{99m}Tc-labeled sestamibi to detect viable hibernating myocardium in asynergic regions.[4-9] On the other hand, other reports suggested that the quantification of the abnormal uptake (defect severity) might be helpful to differentiate between viable and nonviable myocardium.[3,8,10]

Another major point in dealing with the problem of myocardial viability is the choice of a suitable imaging protocol, as shown by previous experiences with ^{201}Tl.[11-13] Most studies[3-7,9,10] that used ^{99m}Tc-labeled sestamibi as a viability tracer examined the results of only standard rest imaging. On the other hand, the collection of redistribution images[8] may be promising to improve the detection of myocardial viability with ^{99m}Tc-labeled sestamibi. This indicates that modifications of the usual imaging protocol for rest ^{99m}Tc-labeled sesta-

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mibi SPECT could be helpful for the detection of hibernating myocardium. Data obtained with ^{201}Tl and ^{99m}Tc-labeled teboroxime suggest that the combination of tracer injection with the acute administration of nitrates could be useful.[14,15]

The aim of this study was to evaluate the relationship between myocardial viability and the severity of significant uptake defects at rest in data-based quantitative ^{99m}Tc-labeled sestamibi SPECT. Moreover, we investigated the possibility of increasing the recognition of myocardial viability with ^{99m}Tc-labeled sestamibi by performing the tracer injection in combination with the infusion of nitrates.

METHODS

Patient Population. Among all patients who were referred for myocardial perfusion imaging, 48 consecutive patients with a history of prior myocardial infarction, low-threshold effort angina, and left ventricular dysfunction (left ventricular ejection fraction [LVEF] <50%) and who were scheduled for a revascularization procedure were prospectively enrolled. Part of the data of 19 of these patients was included in a previous report.[16] Patients whose myocardial infarction dated back to less than 3 months, with a history of unstable angina of less than 3 months, with cardiac conditions other than coronary artery disease or who had already undergone a revascularization procedure were excluded. After enrollment, six patients refused the proposed intervention, one had a perioperative infarction, and in one patient the preoperative studies were incomplete. Therefore the final study cohort included 40 patients.

Study Protocol. The study protocol had been approved previously by the ethics committee of our institution. Informed consent was obtained from all patients. Before revascularization, all patients underwent cardiac catheterization with coronary angiography, baseline two-dimensional echocardiography for the assessment of regional wall motion, first-pass radionuclide angiocardiography for the calculation of LVEF, and baseline rest and nitrate myocardial perfusion SPECT with ^{99m}Tc-labeled sestamibi. In patients who used nitrates, the drug was discontinued 48 hours before the scintigraphic studies. All other medications remained unchanged. None of the patients were taking β-blockers. All studies were completed within 1 week, with the exception of cardiac catheterization, which was performed within 15 days. During the entire study period, the clinical conditions of all patients remained stable. After revascularization, regional wall motion was assessed by two-dimensional echocardiography and LVEF was measured by first-pass radionuclide angiocardiography. The postoperative evaluation was obtained after a minimum of 3 months in the case of coronary bypass grafting or after a minimum of 1 month and no later than 2 months in the case of coronary angioplasty. Restenosis was ruled out by exercise stress testing.

Nitrate Imaging. The nitrate infusion was performed with the patient lying supine, under electrocardiographic and blood pressure monitoring. Isosorbide dinitrate (10 mg diluted in 100 ml isotonic saline solution) was infused at the rate of 0.5 mg/min. As soon as the systolic blood pressure dropped 20 mm Hg or greater or a systolic blood pressure value less than 90 mm Hg was measured, ^{99m}Tc-labeled sestamibi was injected. If neither of these two criteria was fulfilled, the tracer was injected 15 minutes after the beginning of the infusion. The nitrate infusion was always maintained for at least 2 minutes after tracer injection. None of the patients had adverse reactions to the nitrate infusion.

Cardiac Catheterization. Coronary angiography was performed by the percutaneous femoral (Judkins) technique, acquiring multiple projections of each of the main coronary arteries. Two experienced observers, who had no knowledge of the clinical and scintigraphic data, evaluated each major epicardial vessel with callipers. Significant stenosis was considered if the lesion restricted the lumen 50% or greater.

Regional Wall Motion Assessment. Both the preoperative and postoperative assessments of the regional wall motion and thickening were performed by two-dimensional echocardiography. An Aloka SSD-870 echocardiograph with 2.5 to 3.5 MHz transducers (Aloka Co., Ltd., Tokyo, Japan) was used. Patients were studied at rest in the left lateral decubitus position. Parasternal long-axis, parasternal short-axis at basal and midventricular levels, and apical two- and four-chamber views were obtained and recorded on videotape. The two studies were analyzed in random sequence by two experienced observers, blinded to the clinical, angiographic, and scintigraphic data. The left ventricle was divided into 13 segments[17]: a single apical segment plus six sections (anteroseptal, anterior, anterolateral, posterolateral, posteromedial, and posteroseptal), each subdivided into a basal and midventricular segment. The basal and midventricular anteroseptal, anterior, and anterolateral segments and the apex were attributed to the left anterior descending artery. The basal and midventricular posterolateral segments were assigned to the circumflex artery. The basal and midventricular posteromedial and posteroseptal segments were assigned to the right coronary artery. The wall motion and thickening of each segment were analyzed according to a semiquantitative score: 1 = normal, 2 = hypokinesis, 3 = akinesis, and 4 = dyskinesis.[17,18] For each coronary territory a wall motion index (WMI) was calculated by dividing the total score of the related segments by the number of segments assigned to that territory.[18] Discrepancies between the two observers were resolved by consensus. According to their WMI, the vascular territories were classified as follows: 1 = normokinetic; greater than 1 and less than 1.5 = minimal asynergy; 1.5 or greater and less than 2 = moderate asynergy; and 2 or greater = severe asynergy.[18] Myocardial viability was considered to be questionable in the coronary territories with WMI of 1.5 or greater. Among these territories, those that showed a WMI reduction after revascularization were considered to be hibernating; those that exhibited no changes or a worsening in wall motion were defined as fibrotic. A decrease in wall motion score of one grade or greater in at least one segment in the cases of the right coronary or left circumflex territory or in at least two contiguous segments in the case of the left anterior descending territory was required to define significant improvement in postrevascularization WMI.[6,10,17,18]

Measurement of LVEF. LVEF was calculated with a first-pass study acquired during the injection of ^{99m}Tc-labeled sestamibi for baseline rest perfusion SPECT. First-pass radionuclide angiocardiography was acquired in the 30-degree right anterior oblique projection, with the patient supine, with an Elscint Apex SP4 gamma camera (Elscint Inc., Boston, Mass.) equipped with a low-energy all-purpose collimator, and a 20% window centered at the 140 keV photopeak of ^{99m}Tc. Twenty-five millicuries (925 MBq) ^{99m}Tc-labeled sestamibi was injected as a compact bolus according to our already-described procedure.[19] The quality of bolus was always found acceptable (full width at half maximum <1 second). The study was acquired in frame mode, with a ×2 magnification factor. The LVEF was calculated from the background-subtracted time-activity curve of the representative cycle and the mean value of the two calculations used for the data analysis.[19] The follow-up first-pass study was acquired either in the context of a ^{99m}Tc-labeled sestamibi perfusion scintigraphy or as an isolated study with ^{99m}Tc-labeled pertechnetate.

^{99m}Tc-labeled Sestamibi Scintigraphy. SPECT was collected 60 minutes after Tc^{99m}-labeled sestamibi injection.[9,10] An Elscint Apex SP4 gamma camera equipped with an ultra-high-resolution collimator and a 20% window centered at the 140 keV photopeak of ^{99m}Tc was used. Sixty projections of 20 seconds each were acquired in step-and-shoot mode over a 180-degree arc, with a zooming factor 1.4 and 64 × 64 matrixes. The image reconstruction was performed with back-projection without a preprocessing filter and with a Wiener reconstruction filter. No attenuation or scatter correction was used. The transaxial slices were realigned along the heart axis obtaining short-axis, vertical, and horizontal long-axis slices. For the quantitative evaluation of the SPECT images, the short-axis slices from the first slice with apical activity to the last one with activity at the base were used. Their count profiles were generated by computer software and plotted onto a two-dimensional volume-weighted polar map, which was subsequently divided into three territories corresponding to the distribution of the three main coronary arteries.[20] The count profile of each patient was compared with a sex-specific database of rest ^{99m}Tc-labeled sestamibi studies performed on normal control subjects (subjects with either normal coronary angiograms or a <2.5% pretest probability of coronary artery disease on the basis of the Bayesan analysis of age, sex, symptoms, rest, and exercise electrocardiography). The lower limit of the normal range was set at 2.5 SDs below the mean of the sex-specific control group.[20] The extent of the abnormality was expressed as a percent of the entire left ventricular wall and a percent of each single coronary territory involved. In the latter case, to be considered significant, a defect had to be greater than 12% of the left anterior descending and the circumflex territories and greater than 8% of the right coronary artery territory.[21] For the assessment of defect severity, the number of standard deviations (with 0.5 SD steps) by which the counts in each pixel within the defect area were below the mean of the normal control subjects was iteratively estimated. In each pixel the resulting value could range from 0 (minimal severity, first iteration, counts = −2.5 SDs of the mean of normal) to 1 (maximal severity, last iteration, counts ≤−20 SDs of the mean of normal). The total defect severity was calculated by multiplying the number of pixels within the defect by the severity value of each of them.[20] The total severity of all present defects was obtained and expressed as a percent of the entire left ventricular wall. The severity of each single defect was expressed as a percent of the maximal value possible within the involved coronary territory.

Statistical Analysis. Data are expressed as appropriate as the mean ± SD. The within-group comparisons were made with the Wilcoxon signed rank test for paired data and the between-group comparisons with the Mann-Whitney *U* test for unpaired data, with corrections for multiple comparisons as appropriate. The comparisons of proportions were made with the Fisher exact test. Receiver-operating characteristic (ROC) curves were calculated by variation of the cutoff values to compare the accuracy of the different imaging modalities, and Wilcoxon statistics were used to assess significance.[22] A value of $p < 0.05$ was considered significant.

RESULTS

Clinical, Angiographic, and Echocardiographic Data. The mean age of the patients was 59 ± 10 years (range 39 to 77 years). There were six women and 34 men. The site of the prior myocardial infarction was anterior in 26 and inferior in 22 cases (eight patients had two infarct sites each). The LVEF was 34.9% ± 9.3% (range 16% to 49%) and was less than 40% in 29 patients. All patients were found to be affected by significant coronary artery disease (12 patients had one-vessel, 12 two-vessel, and 16 three-vessel disease). A total of 84 vessels had significant coronary artery obstruction. In the echocardiographic evaluation performed before revascularization, there were 66 coronary artery territories (all subtended by stenotic vessels) with a WMI of 1.5 or greater and hence questionable viability.

Follow-Up Evaluation. Complete revascularization of all stenosed major epicardial vessels was obtained with multiple bypass grafting in 24 cases and coronary angioplasty in 16 cases. Perioperative infarction had been excluded in all patients on the basis of the usual clinical, electrocardiographic, and enzymatic criteria. After revascularization, all patients reported an improvement in their anginal symptoms. The postrevascularization LVEF increased greater than 5% in 20 patients (from 35.4% ± 8.7% to 42.9% ± 7.1%) and remained unchanged or decreased in the remaining 20 patients (from 34.6% ± 10.1% to 31.1% ± 8.9%). Of the 66 coronary territories with a WMI of 1.5 or greater, 28 showed a significant improvement in the wall motion pattern and were classified as hibernating and the remaining 38 were classified as fibrotic. Twenty-six of the hibernating territories were detected in the 20 patients who showed a postrevascularization increase in LVEF.

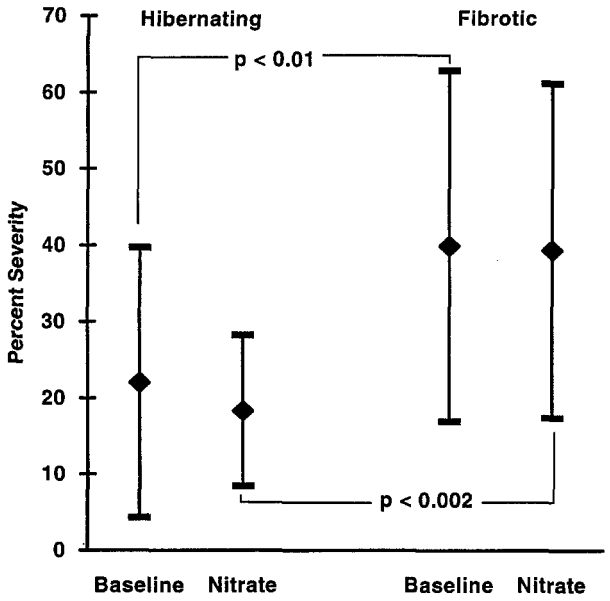

Figure 1. Diagram shows mean ± SD percent severity of significant uptake defects detected by baseline or nitrate SPECT in territories with prerevascularization WMI of 1.5 or greater but with postrevascularization recovery (hibernating) and in those with unchanged regional dysfunction (fibrotic). Significantly higher severity of latter defects can be appreciated.

Data-Based Quantitative ^{99m}Tc-Labeled Sestamibi SPECT. The baseline perfusion images showed abnormal ^{99m}Tc-labeled sestamibi uptake of a significant extent as defined by the comparison with the normal database (47.4% ± 26.9%) in 81 vascular territories, all with 50% or greater stenosis. Of these 81 territories, 17 had a WMI less than 1.5 and 64 1.5 or greater by prerevascularization echocardiography. Two territories with a WMI of 1.5 or greater had normal ^{99m}Tc-labeled sestamibi uptake. All 28 hibernating territories were abnormal by baseline SPECT. The nitrate perfusion images showed abnormal ^{99m}Tc-labeled sestamibi uptake of a significant extent (51.4% ± 23.2%; difference not significant vs baseline) in 64 vascular territories (difference not significant vs baseline), including six with a WMI less than 1.5 and 58 with a WMI of 1.5 or greater in prerevascularization echocardiography. Only 22 of the 28 hibernating territories showed a significant uptake defect in nitrate SPECT ($p < 0.05$ vs baseline).

Analysis of Defect Severity and Recognition of Hibernating Myocardium. In baseline SPECT, a significantly lower percent severity of the uptake defects was demonstrated in the 28 hibernating territories compared with those without postrevascularization functional recovery: 22% ± 17.7% (95% confidence interval [CI] = 15% to 29%) versus 39.9% ± 23% (CI = 32.2% to 47.5%; $p < 0.01$) (Figure 1). Also, in nitrate SPECT the significant uptake defects found in the 22 hibernating territories had a significantly lower severity compared with those detected in the 36 fibrotic territories: 18.3% ± 9.9% (CI = 13.8% to 22.8%) versus 39.3% ± 21.9% (CI = 32% to 46.6%; $p < 0.002$) (Figure 1). Figure 2 shows the ROC curves calculated for both baseline and nitrate SPECT with different cutoff values of the percent severity to differentiate between the uptake defects, which included mainly hibernating from those that included mainly fibrotic myocardium. The defects with a lower percent severity were considered hibernating together with those without a significant uptake defect. The area under the ROC curve was significantly larger with nitrate than with baseline SPECT (0.75 vs 0.63; $p < 0.001$). An arbitrary cutoff value of 30% of the maximal severity appeared to give the best possible differentiation between the two groups in both baseline and nitrate SPECT. When this cutoff value was applied, the sensitivity of baseline rest ^{99m}Tc-labeled sestamibi imaging for the recognition of hibernating myocardium was 75%, and its specificity was 66%. The overall accuracy was 70%. In nitrate SPECT sensitivity was 96% ($p < 0.05$ vs baseline), specificity 66%, and overall accuracy 79%. Table 1 shows the positive and negative predictive values of percent severity in baseline and nitrate SPECT according to the 30% cutoff.

Table 1. Value of the analysis of defect severity to predict the postrevascularization outcome of the territories with WMI greater than 1.5

	Baseline SPECT (%)	Nitrate SPECT (%)	*p* Value
PPV	62	68	NS
NPV	78	96	0.05
PA	70	79	NS

PPV, Positive predictive value; *NS*, not significant; *NPV*, negative predictive value; *PA*, predictive accuracy.

Figure 3 shows the example of a patient in whom the presence of viable myocardium within a hibernating territory was demonstrated by the analysis of defect severity in both baseline and nitrate SPECT. Figure 4 shows consonance of baseline and nitrate SPECT in excluding the presence of viable hibernating myocardium in another patient. Finally, Figure 5 shows an example of disagreement between baseline and nitrate SPECT in recognizing a hibernating territory on the basis of the defect severity.

Quantitative ^{99m}Tc-Sestamibi SPECT and Prediction of Improvement in Global Left Ventricular Function. The possible relationship between the total percent severity of the uptake defects and the changes in LVEF observed after revascularization was also investi-

gated. In baseline SPECT the mean total percent severity in the 20 patients with a greater than 5% postoperative increase in LVEF was not significantly different from the value observed in the 20 patients with unchanged or worsened LVEF: 15.7% ± 7.8% (CI = 12% to 19.4%) versus 18% ± 10.9% (CI = 12.9% to 23%). Conversely, a significantly lower value was found in the first group with nitrate SPECT: 11.1% ± 6.4% (CI = 8.1% to 14.1%) versus 18.5% ± 10.1% (CI = 13.8% to 23.2%) ($p < 0.05$). Furthermore, the baseline and nitrate total percent severity of the unimproved patients was not significantly different, whereas the nitrate total percent severity of the improved patients was significantly lower than the baseline value in the same patients ($p < 0.002$) (Figure 6). Figure 7 shows the ROC curves calculated for both baseline and nitrate SPECT according to different cutoff values of total percent severity to differentiate between patients with improved LVEF and patients with unchanged LVEF. Nitrate SPECT gave better results than baseline SPECT, as demonstrated by the significantly larger area under the ROC curves: 0.68 versus 0.58 ($p < 0.05$). Table 2 compares the predictive values of baseline and nitrate SPECT when the optimal cutoff value of percent severity was adopted for each imaging modality.

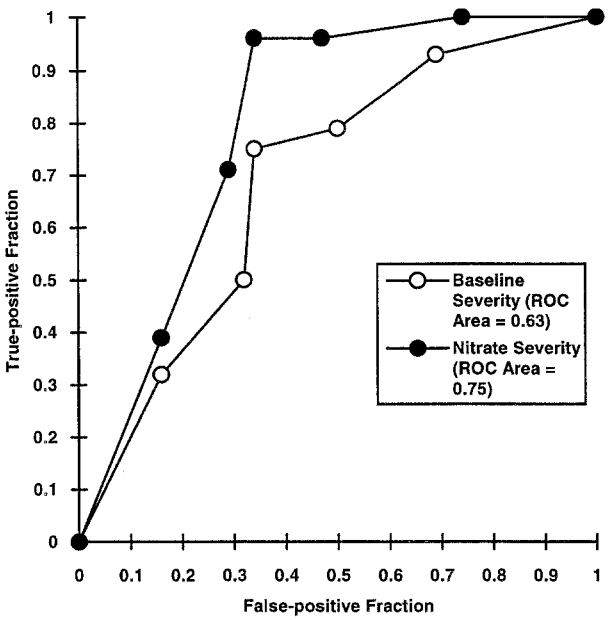

Figure 2. ROC curves for baseline and nitrate SPECT of diagnostic accuracy of percent severity in detection of hibernating myocardium within territories with moderate or severe regional dysfunction.

DISCUSSION

Positron emission tomography (PET) is considered the best available method for the recognition of viable hibernating myocardium,[23,24] but high costs and limited availability preclude its widespread use. ^{201}Tl perfusion imaging according to appropriate acquisition protocols is a reliable alternative to PET for the issue of myocardial viability, but its lower accuracy has been demonstrated.[24] Experimental studies[25,26] have shown that ^{99m}Tc-labeled sestamibi uptake and retention require cell viability, but the comparisons with ^{201}Tl or PET in humans[4,5,7,8] suggest that ^{99m}Tc-labeled sestamibi might underestimate viable myocardium. However, it is only by comparing results of ^{99m}Tc-labeled sestamibi with the most accurate index of the presence of hibernating myocardium, which is the detection of reversible dysfunction after adequate revascularization, that it is possible to define its value as a viability tracer. Conflicting conclusions have been reported. With quantitative planar ^{99m}Tc-labeled sestamibi imaging, Marzullo et al.[6] showed that some segments with a decreased tracer uptake had a postrevascularization recovery and concluded that ^{99m}Tc-labeled sestamibi should be not used as a viability tracer. Conversely, Udelson et al.[10] demonstrated that the analysis of the severity of uptake defect in ^{99m}Tc-labeled sestamibi and ^{201}Tl SPECT achieved comparably good results so as to define the functional outcome of asynergic segments. Maublant et al.,[9] performing qualitative evaluation of ^{99m}Tc-labeled sestamibi SPECT, found a rough relationship between tracer uptake score and presence of hibernating myocardium.

As shown by our study, many viable territories (with normal or near-normal baseline wall motion or postrevascularization recovery) had a significant uptake defect in baseline ^{99m}Tc-labeled sestamibi SPECT. However, the capability of rest ^{99m}Tc-labeled sestamibi to detect viable hibernating myocardium improved when the severity of the uptake defects was considered. There was a significant difference in percent severity between the defects in territories with postrevascularization functional recovery and those in territories with unchanged dysfunction. It was also possible to identify a cutoff point that differentiated most hibernating territories from the others and allowed a reasonable prediction of which territories would or would not benefit from a revascularization procedure. Our data support the results of Udelson et al.[10] on the value of ^{99m}Tc-labeled sestamibi for the detection of hibernating myocardium when the degree of tracer uptake is assessed. Furthermore, the achieved predictive values are similar to those reported by Ragosta et al.,[13] who obtained a 57% positive and 77% negative predictive value with quantitative planar rest-distribution ^{201}Tl imaging. The advantage of our approach to quantitative assessment of severity is that the parameter is obtained by the comparison with a normal database and is related directly to the involved coronary vascular territory.

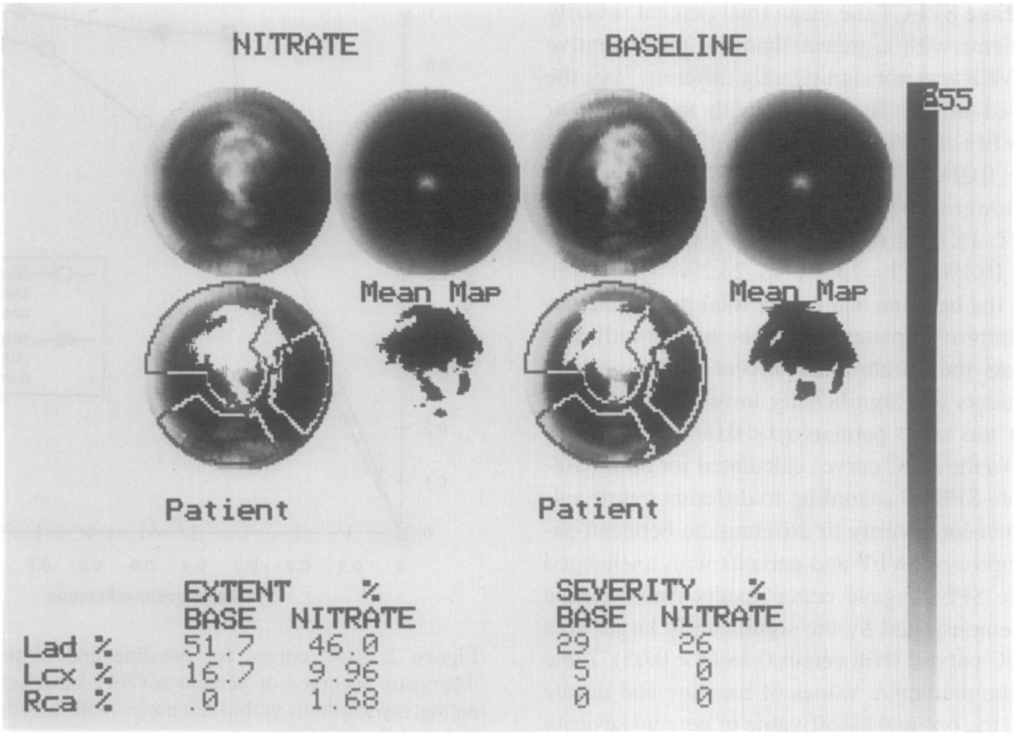

Figure 3. Polar map displays of patient with left anterior descending *(Lad)* obstruction and anteroapical akinesis. On *left,* nitrate study: *upper left map* depicts patient's count distribution; *lower left map* shows in *white* uptake defect (activity <2.5 SDs below normal limit); *upper right map* is database count distribution (mean map); uptake defect is shown in *lower right panel.* On *right,* baseline study is shown with same image disposition. Analysis of defect severity indicates that left anterior descending and left circumflex *(Lcx)* territories should be classified as viable in both baseline and nitrate SPECT. Left circumflex territory was normokinetic in prerevascularization echocardiogram; left anterior descending territory showed significant recovery after coronary angioplasty. (*Rca,* Right coronary artery.)

We also evaluated the possibility of improving the capability of ^{99m}Tc-labeled sestamibi to detect viable hibernating myocardium by modifying the imaging protocol for rest scintigraphy. Collecting a 4-hour ^{99m}Tc-labeled sestamibi redistribution study, Dilsizian et al.[8] had already demonstrated an increased consonance with ^{201}Tl reinjection SPECT and PET. However, the clinical importance of ^{99m}Tc-labeled sestamibi redistribution remains questionable.[25] Furthermore, no correlation with the postrevascularization evolution of regional wall motion was reported in that study. Alternatively, the administration of nitrates at the time of ^{99m}Tc-labeled sestamibi injection could be considered, under the assumption that the increase in coronary blood flow[27] might improve tracer uptake in severely hypoperfused viable areas, as shown for ^{201}Tl[14] and ^{99m}Tc-labeled teboroxime.[15]

In a prior report we had demonstrated that the nitrate-induced changes in extent of ^{99m}Tc-labeled sestamibi defects were significantly correlated with the presence of viable hibernating myocardium.[16] In this study all 17 territories with an abnormal defect extent in the baseline images that became normal in nitrate SPECT included viable myocardium: 11 had a WMI less than 1.5 in the prerevascularization echocardiogram and six were hibernating. In spite of that, a ^{99m}Tc-labeled sestamibi uptake defect of significant extent was still observed in 22 of 28 hibernating territories. Thus when the nitrate images were examined separately and the nitrate-induced changes left out of consideration, the finding of a defect of significant extent did not imply the absence of myocardial viability and very limited advantage over baseline SPECT was registered. Conversely, the quantification of defect severity in nitrate SPECT achieved better results than in baseline imaging, as demonstrated by the significantly larger ROC curve area. With the same optimal cutoff point applied to the baseline images, the sensitivity of nitrate SPECT in identifying the hibernating territories was significantly higher (96% vs 75%; $p < 0.05$). The ROC analysis of the accuracy of the total percent severity in the recognition of patients who had an improvement in the global left ventricular function showed significant superiority of

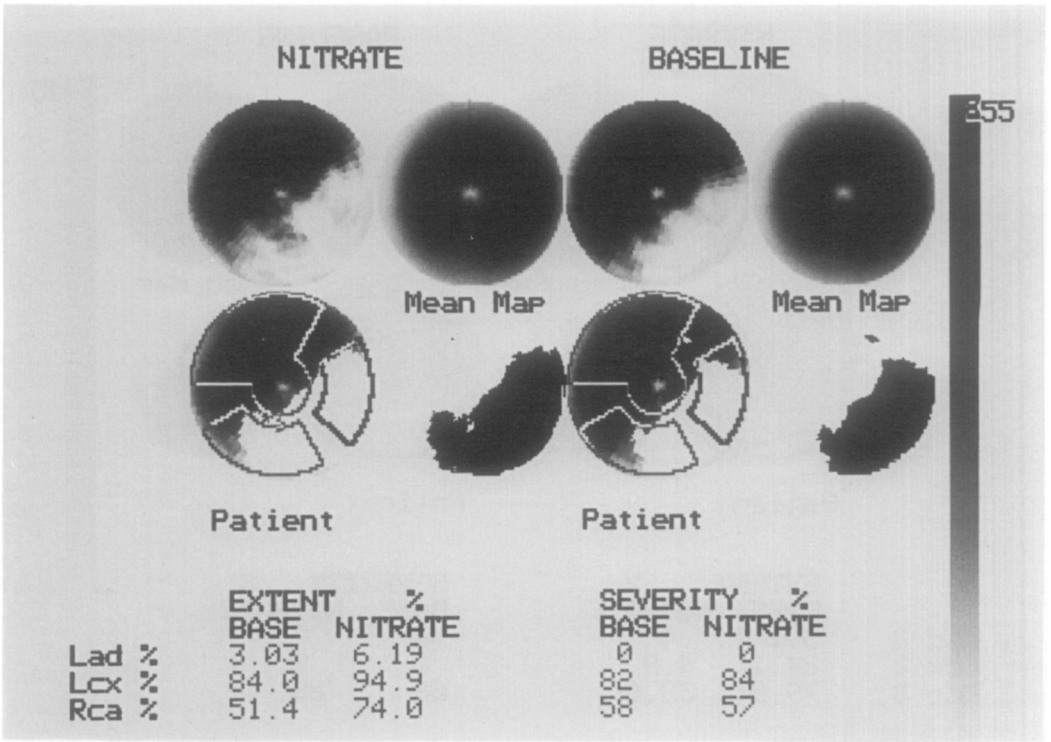

Figure 4. Polar map displays of patient with three-vessel disease who had inferior and inferolateral akinesis in preoperative echocardiogram. Image disposition and abbreviations are same as in Figure 3. Analysis of defect severity in both baseline and nitrate SPECT indicated that left circumflex and right coronary artery territories were not viable. After triple bypass grafting, patient showed improvement in anginal symptoms but no functional recovery in either territory.

nitrate compared with baseline SPECT, with predictive values near those reported with ^{201}Tl planar rest-redistribution.[13] Moreover, for recovery of regional dysfunction, the infusion of nitrates in combination with the analysis of defect severity in ^{99m}Tc-labeled sestamibi SPECT allowed accuracy and predictive values that are higher than those reported with ^{201}Tl planar rest-redistribution scintigraphy.[13] Particularly remarkable compared with previous studies of ^{99m}Tc-labeled sestamibi was the very high negative predictive value (96%). In addition, these results have been obtained leaving the nitrate-induced changes out of consideration, which is an advance over our previous data.[16] Hence there is no need to perform a baseline reference study.

As for most reports[5,6,9,10,13] about myocardial viability, the small patient population is a limitation of our study. Another pitfall is the comparison of echocardiographic and SPECT data, which could explain some discrepancies between predicted and observed functional changes. We did not use a normal database conceived for the evaluation of viability; thus all the selected control subjects had a ventricle of normal size and the database did not take into account the changes in regional ^{99m}Tc-labeled sestamibi activity caused by a dilated ventricle,[28] which is a common finding in patients with severe asynergy. However, this problem should have similarly affected both baseline and nitrate SPECT. In contrast, the data-based quantitative analysis of nitrate images could have been influenced specifically by the direct favorable effects of nitrates on left ventricular wall motion in asynergic regions,[29] with possible apparent increase of tracer activity through the partial volume effect.[28] This interference cannot be excluded,

Table 2. Value of ^{99m}Tc-labeled sestamibi SPECT to predict the postrevascularization evolution of the global left ventricular function

	Baseline SPECT (%)	Nitrate SPECT (%)	*p* Value
PPV	62	68	NS
NPV	63	72	NS
PA	63	70	NS

The following cutoff values were used to differentiate the patients with improved LVEF from the others: for baseline SPECT, defect severity less than 20%; for nitrate SPECT, defect severity less than 15%.
See Table 1 for abbreviations.

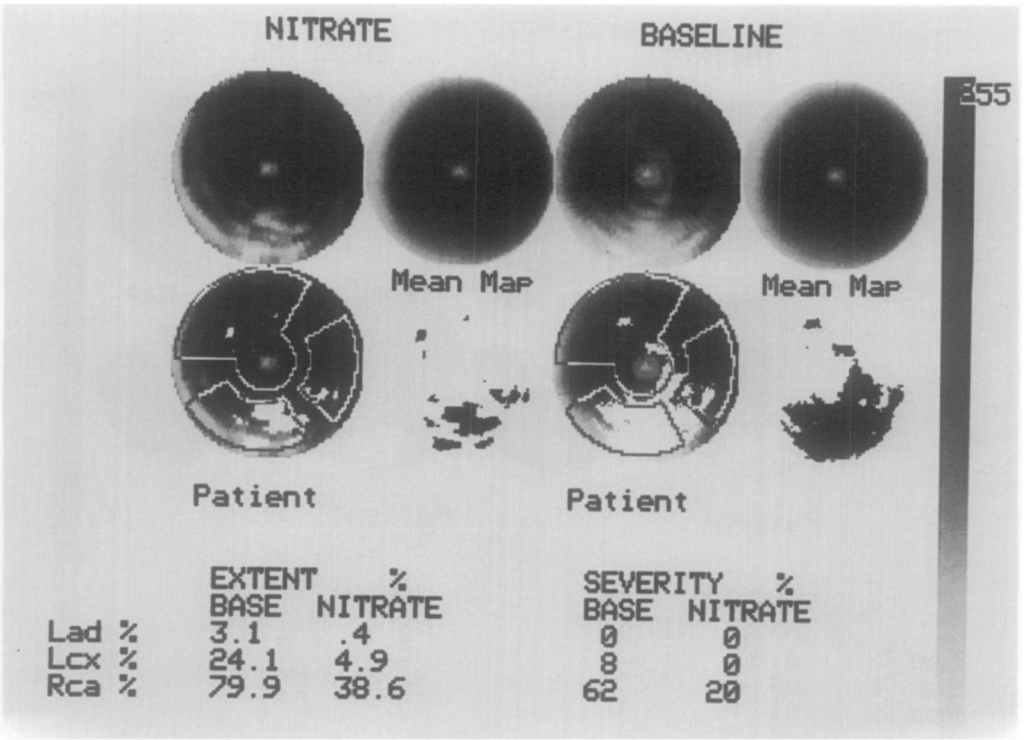

Figure 5. Polar map displays of patient with two-vessel disease, whose prerevascularization echocardiogram showed inferior akinesis and inferolateral minimal hypokinesis. Image disposition and abbreviations are same as in Figure 5. On baseline SPECT two territories (left circumflex and right coronary arteries) had significant uptake defect, but one only (right coronary artery) was nonviable according to severity criteria. On nitrate SPECT, left circumflex territory had nonsignificant uptake defect, whereas right coronary artery territory defect was classified as viable according to severity. After two-vessel angioplasty, patient no longer had effort angina and inferior akinesis improved significantly.

but various points must be considered. First, the blood concentration of isosorbide dinitrate after intravenous infusion returns to the preinfusion levels within 1 hour of infusion, and the concentration of active metabolites is very low by the intravenous route, because of the absent first-pass hepatic metabolism.[30] Second, at the time of SPECT collection all patients had returned to the preinfusion blood pressure and heart rate. Third, the evaluation of the nitrate-induced wall motion changes at the moment of tracer injection with first-pass radionuclide ventriculography showed that in most cases the improvement of regional dysfunction was not accompanied by the finding of an increased tracer uptake in the following SPECT study.[31]

In conclusion, our results indicate that quantitative ^{99m}Tc-labeled sestamibi SPECT may be a reliable technique for the detection of viable hibernating myocardium if the severity of the uptake defects is assessed. Furthermore, when myocardial viability is a major clinical issue the infusion of nitrates during tracer injection increases accuracy. When both the analysis of defect severity and the uptake enhancement with nitrates are performed, ^{99m}Tc-labeled sestamibi gives valuable results for the prediction of the postrevascularization outcome of asynergic areas.

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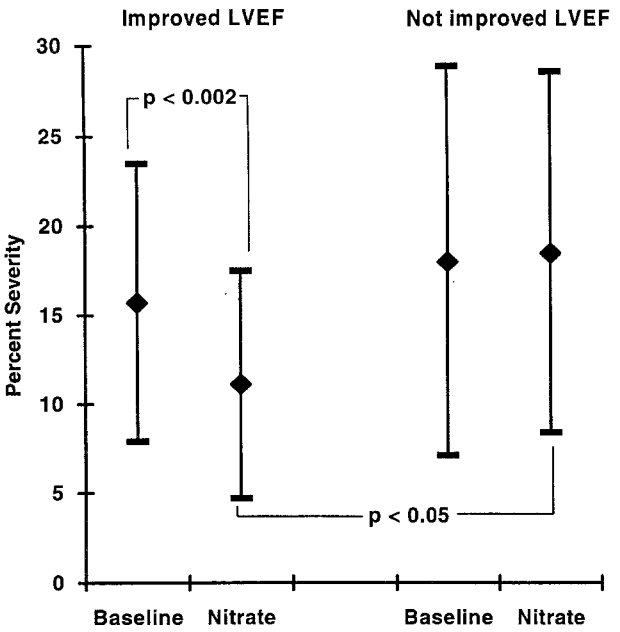

Figure 6. Diagram shows mean ± SD total percent severity detected in baseline or nitrate SPECT in patients with greater than 5% improvement in LVEF after revascularization compared with patients without LVEF changes or with LVEF worsening (not improved).

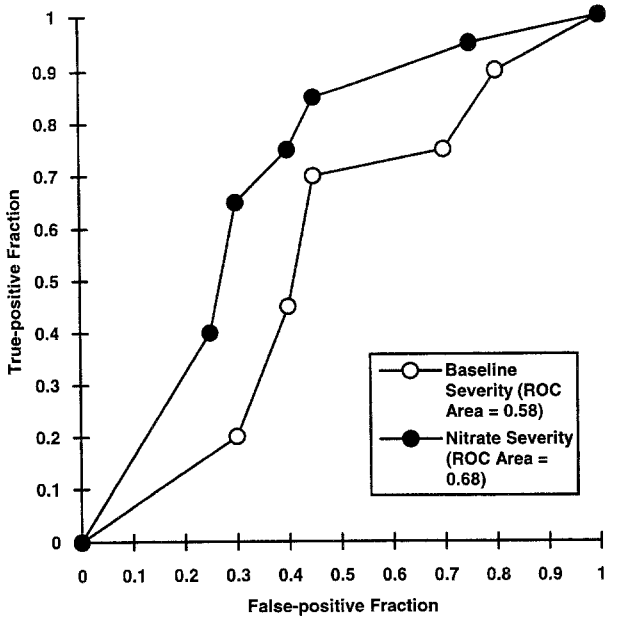

Figure 7. ROC curves for baseline and nitrate SPECT of diagnostic accuracy of total percent severity in detection of hibernating myocardium on patient basis. Postrevascularization LVEF improvement greater than 5% was used as reference for presence of hibernating myocardium.

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