9. Gould KL, Goldstein RA, Mullani NA, et al. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. VIII. Clinical feasibility of positron cardiac imaging without a cyclotron using generator-produced rubidium-82. *J Am Coll Cardiol* 1986;7:775–789.
10. Demer LL, Gould KL, Goldstein RA, et al. Assessment of coronary artery disease severity by positron emission tomography. Comparison with quantitative arteriography in 193 patients. *Circulation* 1989;79:825–835.
11. Goldstein RA, Kirkeeide RL, Smalling RW, et al. Changes in myocardial perfusion reserve after PTCA: noninvasive assessment with positron tomography. *J Nucl Med* 1987;28:1262–1267.
12. Go RT, Marwick TH, MacIntyre WJ, et al. A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in the diagnosis of coronary artery disease. *J Nucl Med* 1990;31: 1899–1905.
13. Stewart RE, Schwaiger M, Molina E, et al. Comparison of rubidium-82 positron emission tomography and thallium-201 SPECT imaging for detection of coronary artery disease. *Am J Cardiol* 1991;67:1303–1310.
14. Herrero P, Markham J, Shelton ME, Bergmann SR. Implementation and evaluation of a two-compartment model for quantification of myocardial perfusion with rubidium-82 and positron emission tomography. *Circ Res* 1992;70:496–507.
15. Green MA, Mathias CJ, Welch MJ, et al. Copper-62-labeled pyruvaldehyde bis(N^4-methylthiosemicarbazonato) copper(II): Synthesis and evaluation as a positron emission tomography tracer for cerebral and myocardial perfusion. *J Nucl Med* 1990;31: 1989–1996.
16. Mathias CJ, Margenau WH, Brodack JW, et al. A remote system for the synthesis of copper-62-labeled Cu(PTSM). *Appl Rad Isotopes* 1991;42:317–320.
17. Pastakia B, Lieberman LM, Gatley SS, et al. Tissue distribution of copper-labeled 3-ethyoxy-2-oxobutyraldehyde bis (thiosemicarbazone) (Cu-64 KTS) in mice and rats: concise communication. *J Nucl Med* 1980;21:67–70.
18. Minkel DT, Saryan LA, Petering DH. Structure-function correlations in the reaction of bis (thiosemicarbazone) copper(II) complexes with ehrlich ascites tumor cells. *Cancer Res* 1978;38:124–129.
19. Green MA. A potential copper radiopharmaceutical for imaging the heart and brain: copper-labeled pyruvaldehyde bis(N^4-methylthiosemicarbazone). *Nucl Med Biol* 1987; 14:59–61.
20. Green MA, Klippenstein DL, Tennison JR. Copper(II) bis(thiosemicarbazone) complexes as potential tracers for evaluation of cerebral and myocardial blood flow with PET. *J Nucl Med* 1988;29:1549–1557.
21. Shelton ME, Green MA, Mathias CJ, et al. Kinetics of copper-PTSM in isolated hearts: a novel tracer for measuring blood flow with positron emission tomography. *J Nucl Med* 1989;30:1843–1847.
22. Shelton ME, Green MA, Mathias CJ, et al. Assessment of regional myocardial and renal blood flow with copper-PTSM and positron emission tomography. *Circulation* 1990;82:990–997.
23. Herrero P, Markham J, Weinheimer CJ, et al. Quantification of regional myocardial perfusion with generator-produced ^{62}Cu-PTSM and positron emission tomography. *Circulation* 1993;87:173–183.
24. Mathias CJ, Welch MJ, Raichle ME, et al. Evaluation of a potential generator-produced PET tracer for cerebral perfusion imaging: single-pass cerebral extraction measurements and imaging with radiolabeled Cu-PTSM. *J Nucl Med* 1990;31:351–359.
25. Mathias CJ, Bergmann SR, Green MA. Development and validation of a solvent extraction technique for determination of Cu-PTSM in blood. *Nucl Med Biol* 1993;20:343–349.
26. Bergmann SR, Herrero P, Anderson CJ, et al. Measurement of regional myocardial perfusion in human subjects using copper-62-PTSM [Abstract]. *J Nucl Med* 1992;33: 837.
27. Bergmann SR, Herrero P, Hartman JJ, et al. Use and limitations of copper-62 pyruvaldehyde bis methylthiosemicarbazone and positron emission tomography for measuring regional myocardial perfusion in human subjects [Abstract]. *Circulation* 1993;88:1-171.
28. Beanlands RSB, Muzik O, Mintun M, et al. The kinetics of copper-62-PTSM in the normal human heart. *J Nucl Med* 1992;33:684–690.
29. Beanlands RSB, Muzik O, Hutchins GD, et al. Heterogeneity of regional nitrogen-13-labeled ammonia tracer distribution in the normal human heart: Comparison with rubidium-82 and copper-62-labeled PTSM. *J Nucl Cardiol* 1994;1:225–235.
30. Melon PG, Brihaye C, Degueldre C, et al. Myocardial kinetics of potassium-38 in humans and comparison with copper-62-PTSM. *J Nucl Med* 1994;35:1116–1122.
31. Ter-Pogossian MM, Ficke DC, Yamamoto M, Hood JT Sr. Super PETT I: a positron emission tomograph utilizing photon time-of-flight information. *IEEE Trans Med Imaging* 1982;MI-1:179–187.
32. Ter-Pogossian MM, Ficke DC, Beecher DE, et al. The Super PET 3000-E: a PET scanner designed for high count rate cardiac applications. *J Comput Assist Tomogr* 1994;18:661–669.
33. Herrero P, Hartman JJ, Senneff MJ, Bergmann SR. Effects of time discrepancies between input and myocardial time-activity curves on estimates of regional myocardial perfusion with PET. *J Nucl Med* 1994;35:558–566.
34. Mathias CJ, Bergmann SR, Green MA. Species-dependent binding of copper(II) bis(thiosemicarbazone) radiopharmaceuticals to serum albumin. *J Nucl Med* 1995;36: 1451–1455.
35. Feldman RL, Nichols WW, Pepine CJ, Conti CR. Acute effect of intravenous dipyridamole on regional coronary hemodynamics and metabolism. *Circulation* 1981;64:333–344.
36. Brown BG, Josephson MA, Petersen RB, et al. Intravenous dipyridamole combined with isometric handgrip for near maximal acute increase in coronary flow in patients with coronary artery disease. *Am J Cardiol* 1981;48:1077–1085.

Technetium-99m-Sestamibi SPECT to Detect Restenosis after Successful Percutaneous Coronary Angioplasty

Elisa Milan, Orazio Zoccarato, Arturo Terzi, Federica Ettori, Ornella Leonzi, Luigi Niccoli and Raffaele Giubbini

Nuclear Medicine and Cardiology Departments, Civic Hospital and University of Brescia, Brescia; and Nuclear Medicine Department, Fondazione Clinica del Lavoro-Veruno, Lavoro-Veruno, Italy

This study evaluated the accuracy of ^{99m}Tc SPECT in predicting restenosis after primary successful PTCA. **Methods:** Thirty-seven patients with equivocal symptom-limited exercise stress testing were evaluated. All patients underwent separate day exercise-rest ^{99m}Tc-sestamibi SPECT. The perfusion studies were evaluated using three different methods of analysis: visual inspection, semiquantitative and quantitative polar map analysis. The perfusion studies were interpreted in absence of a pre-PTCA scan. All patients underwent a control coronary angiography within 1 mo. **Results:** Sensitivity and specificity of ^{99m}Tc-sestamibi SPECT in predicting restenosis were 87.5–78%, 50–65% and 75–74% for visual inspection, semiquantitative and quantitative polar map analysis, respectively. Sensitivity and specificity related to the vascular territories were: LAD territory 93–73% (qualitative analysis), 53–60% (semiquantitative analysis), 80–67% (quantitative analysis); LCX territory 83–100% (qualitative analysis); and 33–100% (semiquantitative analysis), 67–100% (quantitative analysis); and RCA territory 67–80% (qualitative analysis), 67–60% (semiquantitative analysis), 67–80% (quantitative analysis). **Conclusion:** These data suggest that ^{99m}Tc-sestamibi SPECT is a useful noninvasive tool in the follow-up evaluation of patients who have undergone angiographically successful coronary angioplasty even in the absence of a pre-PTCA perfusion study.

Key Words: angioplasty; restenosis; technetium-99m-sestamibi

J Nucl Med 1996; 37:1300–1305

Despite the immediate efficacy of percutaneous transluminal coronary angioplasty (PTCA), its long-term efficacy is limited by the presence of restenosis reported in approximately 30% to

Received July 10, 1995; revision accepted Oct. 8, 1995.

For correspondence or reprints contact: Elisa Milan, MD, Nuclear Medicine Department, Civic Hospital, Piazza Spedali Civili, 1, 25100 Brescia, Italy.

45% of patients who have undergone the procedure (*1–3*). The increase in balloon angioplasty with application to more complex situations has led to a justified increase in the likelihood of restenosis.

Restenosis is reported to be a time-related phenomenon, having a peak incidence between 2 and 3 mo after the procedure (*4,5*). However, in several cases restenosis can be observed later and, moreover, the progression of CAD in previously normal vessels is unpredictable.

The capability to predict this phenomenon on the basis of clinical and procedural parameters remains limited. In the era of multivessel PTCA and partial revascularization, the ability to localize ischemia noninvasively is crucial to patient care. These findings have generated an increasing interest in the use of myocardial perfusion studies to detect myocardial ischemia in the myocardial territory supplied by the restenosed vessel in both symptomatic and asymptomatic patients (*6–11*). Scintigraphic studies performed before and after PTCA (*10,11*) have been demonstrated to be effective in predicting restenosis.

However, a crucial point is that pre-PTCA scintigraphic studies are rarely available and studies must be read without knowledge of the pre-PTCA myocardial perfusion pattern. The aim of the present study was the evaluation of the diagnostic accuracy of myocardial SPECT with ^{99m}Tc-sestamibi to predict restenosis in a group of patients, with no pre-PTCA perfusion study, referred to our laboratory for equivocal exercise stress test (asymptomatic patients with positive exercise ECG, patients with atypical angina or without angina and positive or nondiagnostic exercise ECG, patients with typical angina and negative exercise ECG) after successful PTCA.

METHODS

Patients

Thirty-seven consecutive patients (33 men, 4 women; aged 55 ± 11 yr) with equivocal exercise stress test after successful PTCA for chronic stable angina pectoris due to single or multiple coronary artery disease (CAD) were studied.

Seventeen patients had a history of previous (>6 mo) myocardial infarction (12 Q-wave and 5 non-Q-wave myocardial infarction) in the region of the diseased coronary artery, none were treated by aortocoronary bypass graft surgery (CABG) and all of them had a positive exercise test for myocardial ischemia before PTCA. The PTCA procedure was considered successful when the residual stenosis was less than 50% in diameter with a good runoff and filling of the distal vessel on angiography.

All the patients had equivocal exercise stress test after PTCA and therefore received a follow-up ^{99m}Tc-sestamibi SPECT followed by a coronary angiography within 1 mo. Coronary angiography was interpreted visually without knowledge of the noninvasive test results.

Twenty-eight left anterior descending (LAD), 10 left circumflex (LCX) and 12 right coronary (RCA) were analyzed. The time interval between PTCA and ^{99m}Tc-sestamibi SPECT ranged from 1 to 30 mo (10.2 ± 7.7). The clinical definition of restenosis was indicated by an increase in the stenosis diameter of the dilated lesion above 50% of the initial value.

Exercise Stress Testing

Bicycle exercise testing was performed during the drug washout period. All patients underwent multistage-symptom limited-exercise testing after an overnight fast. A 12-lead electrocardiogram and blood pressure were recorded every 3 min. The exercise work load was increased by 30 watts every 3 min and each patient exercised until 85% of the maximal predicted heart rate was reached. Exercise end-points were excessive fatigue, shortness of breath or severe angina, 2 mm or more downsloping or horizontal ST depression, hypotension or complex ventricular arrhythmias. At peak exercise ^{99m}Tc-sestamibi was injected and the patient was asked to continue exercising for an additional 2 min.

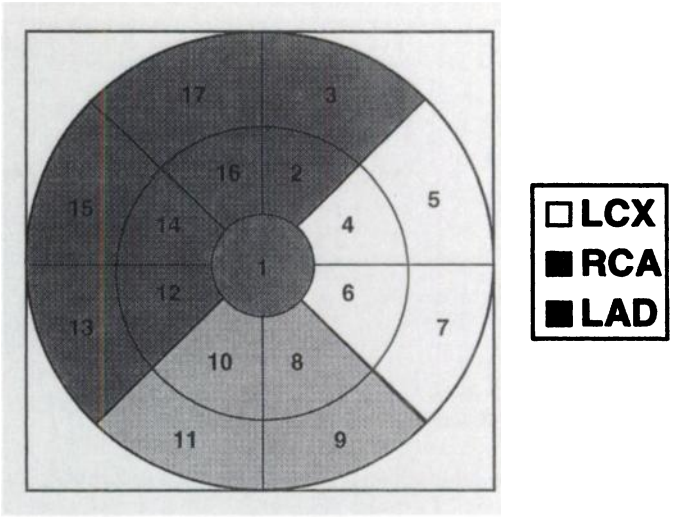

FIGURE 1. Seventeen-segment SPECT model used for ^{99m}Tc bull's eye SPECT analysis. Segments 1, 2, 3, 12, 13, 14, 15, 16 and 17 were attributed to the LAD territory; segments 4, 5, 6 and 7 to the LCX territory; and segments 8, 9, 10 and 11 to the CDX.

Technetium-99m-Sestamibi SPECT Acquisition and Processing

The stress and rest studies were performed on two different days using 1100 MBq of ^{99m}Tc-sestamibi each. Image acquisition started 60–90 min after the injection and followed a light meal. SPECT imaging was performed on a LFOV gamma-camera computer system fitted with a high-resolution collimator (FWHM = 7 mm). Beginning from the right anterior oblique to the left posterior oblique, 60 projections over a 180° circular orbit, in a step-and-shoot mode, were obtained using a 20% energy window centered on the 140-keV photopeak. Images were stored on a 64 × 64 matrix, with a 1.3 zoom factor. One-pixel thick transaxial sections were reconstructed after correction for flood dishomogeneity, by filtered backprojection (10 mm Wiener filter). From transaxial slices, 16-mm thick slices of short, vertical and horizontal long axes were reconstructed. From 3-mm thick short-axis slices, polar maps were obtained.

Analysis of Technetium-99m-Sestamibi SPECT

Qualitative Analysis. For purposes of visual interpretation, stress and rest tomograms were evaluated by consensus of two observers (RG, EM) aware of the patient history.

Severe reversible perfusion defects were considered a marker of restenosis. Finally the scans were read as normal or abnormal in the territory supposed to be perfused by the vessel treated by PTCA.

Semiquantitative Analysis. Stress and rest polar maps were evaluated in a different reading session by two observers (RG, EM) using a 17-segment model. Both readers were unaware of patient history and qualitative analysis results. Each segment was assessed using a four-point scoring system (0 = normal, 1 = slightly reduced uptake, 2 = severely reduced uptake, 3 = absence of uptake).

Disagreement regarding the classification of segments into normal, abnormal, reversible perfusion defect or fixed defect was observed in <2% of the segments; final agreement was reached by consensus. We considered as positive for ischemia a scan showing a reversible defect in at least two adjacent segments in the territory referring to the vessel treated by PTCA.

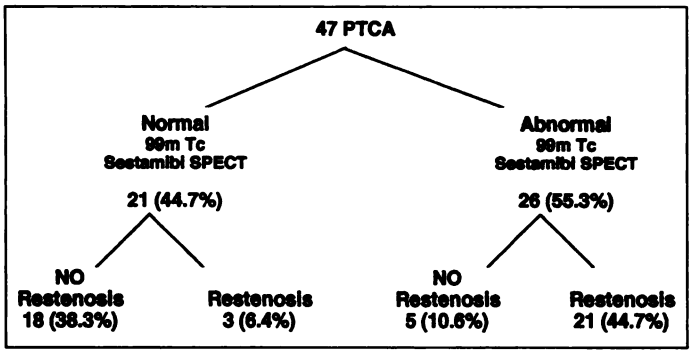

FIGURE 2. Relation between ^{99m}Tc-sestamibi SPECT study and angiographic findings at follow up. Numbers in brackets represent percent of the total number of vessels subjected to PTCA.

The 17 sectors were grouped and matched to the distribution of the three major coronary arteries (Fig. 1).

Quantitative Analysis. Our method for quantitative analysis of ^{99m}Tc-sestamibi SPECT has been previously described (*12*). Briefly each polar map was normalized for peak myocardial activity and compared with the normal limits evaluated in 50 gender-matched subjects with less than 5% likelihood of coronary artery disease. Pixels in which tracer uptake deviated >2.5 s.d. below normal mean values were considered abnormal. In order to obtain the total extent of the myocardial defect the abnormal area on each short-axis slice was multiplied by a correction factor (*13*) which took into consideration differences in myocardial slice mass from apex to base and was corrected for spatial distortion due to the display of a volume two dimensionally.

Abnormalities in the antero-septal, anterior, antero-lateral and apical areas were considered to represent disease in the LAD territory, those involving the inferior area suggest involvement of RCA and the postero-lateral areas were attributed to LCX.

Statistical Analysis

Clinical and angiographic data are expressed as mean ± s.d. For the comparison of clinical and angiographic characteristics and the extent of the SPECT perfusion defects of patients with and without restenosis, the Student's t-test for unpaired data was used. Test for paired proportions was performed with χ^2 analysis or with Fischer exact test when appropriate. A probability value of <0.05 was used to reject the null hypothesis.

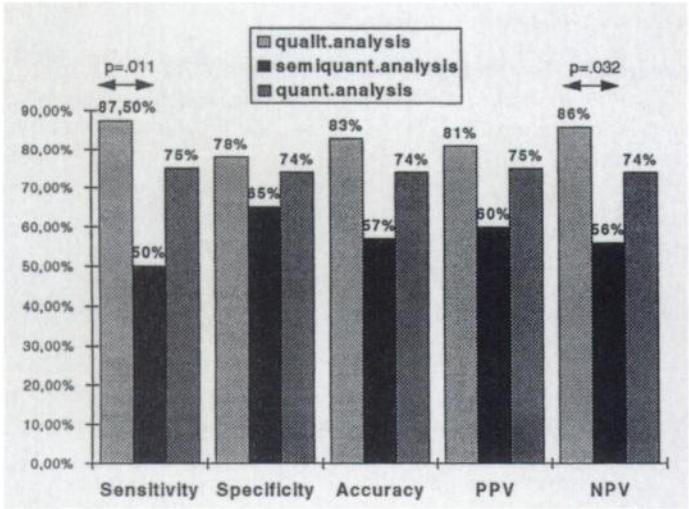

FIGURE 3. Bar graph showing diagnostic accuracy in significant detection of angiographic restenosis after PTCA for qualitative, semiquantitative and quantitative analysis of ^{99m}Tc-sestamibi SPECT. Significant differences in sensitivity and in negative predictive value were found between qualitative and semiquantitative analysis.

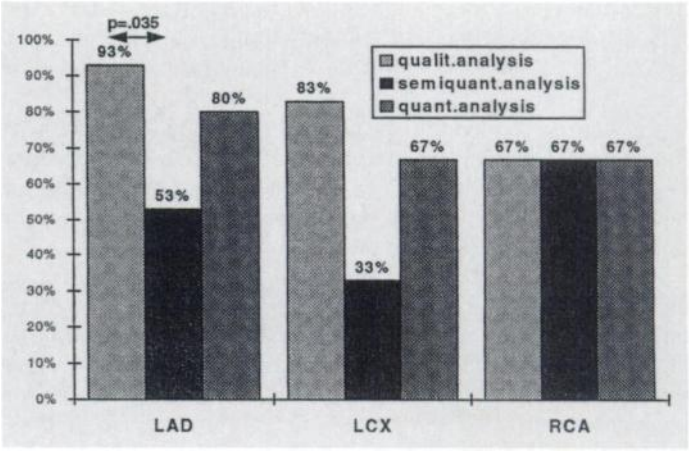

FIGURE 4. Bar graph showing values of sensitivity of qualitative, semiquantitative and quantitative analysis methods in different vascular territories. Significant difference was found between qualitative and semiquantitative analysis in LAD territories.

RESULTS

Angioplasty Data

Angiographically successful coronary angioplasty was obtained in 37 patients: 25 patients (68%) with single-vessel disease (LAD in 20 patients, RCA in 4 and LCX in 1) and 12 patients (32%) with multivessel disease. A total of 47 PTCA were performed (30 on LAD, 9 on LCX and 8 on RCA): single dilation in 28 patients, dilation of two lesions in 8 patients and dilation of three lesions in 1 patient.

Late coronary angiography was obtained in all patients. Restenosis occurred in 23 of 37 (62%) patients and in 25 of 47 (53%) lesions. Restenosis occurred more frequently in patients who had undergone dilation of multiple (7 of 9 [78%]) rather than single (16 of 28 [57%]) coronary stenosis (p = ns) and occurred in 9 of 19 (47%) lesions in the multidilated group.

The severity of vessel occlusion before angioplasty was similar in patients with (84 ± 11%) and patients without (79 ± 11%) late angiographic restenosis (p = ns). No difference was found between patients with and patients without angiographic restenosis with regard to age, gender and history of previous myocardial infarction. Development of significant disease in vessels without narrowing at the time of the angioplasty was noted in four patients, all of whom had no associated restenosis of the dilated vessel.

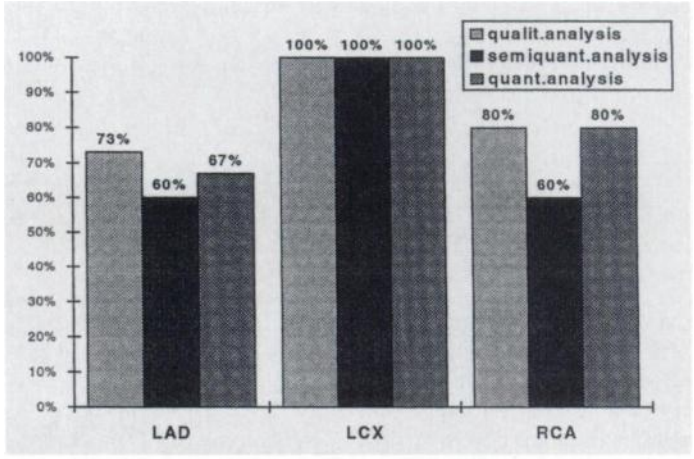

FIGURE 5. Bar graph showing values of specificity of qualitative, semiquantitative and quantitative analysis methods in different vascular territories. No significant differences were found using the three different analysis models.

TABLE 1
Defects Size by Quantitative Analysis of Technetium-99m-Sestamibi SPECT in the Different Vascular Territories

	No. restenosis	Restenosis	p
LAD			
Rest	2.78 ± 6.68	10.28 ± 18.78	ns
Stress	9.07 ± 13.01	30.14 ± 24.36	<0.01
Difference between stress/rest	6.28 ± 8.69	19.85 ± 17.06	<0.05
LCX			
Rest	0 ± 0	7 ± 9.75	ns
Stress	0.33 ± 0.57	30.33 ± 29.62	ns
Difference between stress/rest	0.33 ± 0.57	23.33 ± 22.14	ns
RCA			
Rest	7.6 ± 14.36	18 ± 16.09	ns
Stress	14.8 ± 25.55	23 ± 19.97	ns
Difference between stress/rest	7.2 ± 11.21	5 ± 7.21	ns

Technetium-99m-Sestamibi SPECT Data

Qualitative Analysis. The results of SPECT imaging are summarized in Figure 2 for absolute and relative values, respectively. A normal perfusion pattern was found in 21 territories supplied by the dilated coronary artery and angiographic restenosis was present in only 3 of 21 (14%) territories. In contrast, restenosis was found in 21 of 26 (81%) territories showing a severe reversible perfusion defect at ^{99m}Tc-sestamibi SPECT. Therefore, sensitivity and specificity of qualitative analysis of ^{99m}Tc-sestamibi SPECT in the detection of restenosis were 87.5% and 78%, respectively (Fig. 3). The positive (PPV) and negative (NPV) predictive values were 81% and 86%, respectively. Sensitivity and specificity related to each vascular territory were: 93–73% for the LAD territory; 83–100% for the LCX territory; and 67–80% for the RCA territory (Fig. 4 and 5).

Semiquantitative Analysis. Out of the total 629 segments analyzed, we evaluated 320 segments perfused by a PTCA-treated vessel; of these 89 (28%) showed a reversible perfusion defect. Angiographic restenoses were found in 12 of 20 (60%) polar maps with ischemic patterns, while a normal score was found in 27 polar maps; restenosis was present in 12 (44%) vessels from this group. Therefore, sensitivity and specificity of semiquantitative analysis of exercise ^{99m}Tc-sestamibi SPECT in the detection of restenosis were 50% and 65%, respectively, PPV was 60% and NPV was 56% (Fig. 3). Sensitivity and specificity related to vascular territories were, respectively, LAD territory 53–60%; LCX territory 33–100%; and RCA territory 67–60% (Fig. 4 and 5).

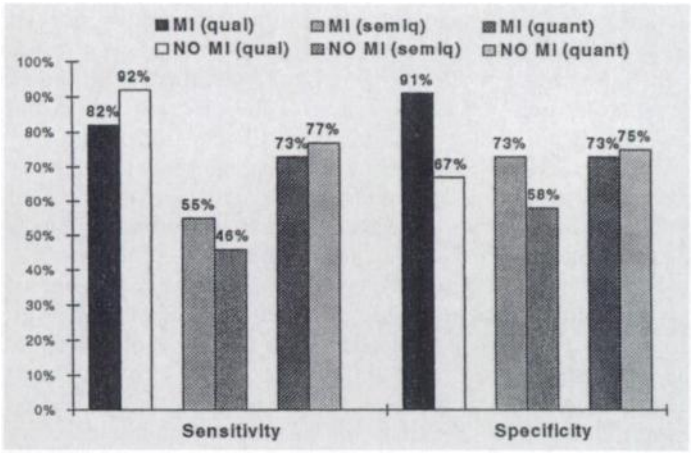

FIGURE 6. Sensitivity and specificity of qualitative, semiquantitative and quantitative analysis of ^{99m}Tc-sestamibi SPECT for detection of restenosis in patients with or without prior myocardial infarction.

Quantitative Analysis. No significant difference between patients showing angiographic restenosis (Group 1) and those without restenosis (Group 2) was observed regarding the severity of perfusion defect size on rest study: group 1 = (6.62 ± 10.22; group 2 = 2.81 ± 5.71; p = ns). The cut off of 7 units (Δ score (stress/rest) ≥7), determined by a receiver operating characteristic (ROC) curve, was found to discriminate best between patients with and without restenosis. Out of 47 territories analyzed, 24 (51%) were found to have a reversible perfusion defect ≥7% ischemic, of these 18 (75%) vessels had an angiographic documented restenosis; 17 of 23 (74%) territories with Δ score <7% were seen to be patent on coronary angiography. The overall sensitivity, specificity, PPV and NPV of quantitative analysis of exercise ^{99m}Tc-sestamibi SPECT to detect angiographic restenosis were 75%, 74%, 75% and 74%, respectively (Fig. 3). Sensitivity and specificity related to a specific vascular territory were LAD territory 80%–67%; LCX territory 67%–100%; and RCA territory 67%–80%, respectively (Fig. 4 and 5).

The extent of perfusion defects at rest, after stress and the difference between stress/rest related to each vascular territory are summarized in Table 1. A significant difference in the defect size after stress in LAD territory was found between patients with patent vessels and patients with restenosis (9.07 ± 13.01% versus 30.14 ± 24.36%; p < 0.01), while in LCX (0.33 ± 0.57% versus 30.33 ± 29.62%; p = ns) as well as in RCA territories (14.8 ± 25.55% versus 23 ± 19.97%; p = ns) we observed a difference which did not reach threshold significance.

Moreover, a significant difference in reversibility grade was found in the LAD territory distinguishing between patients with no restenosis (6.28 ± 8.69%) and those with restenosis (19.85 ± 17.06%) (p < 0.05) but not in the LCX territory (0.33 ± 0.57% versus 23.33 ± 22.14%; p = ns) or in the RCA territory (7.2 ± 11.21% versus 5 ± 7.21%; p = ns).

Comparison between the Three Methods of Analysis

The comparison between qualitative, semiquantitative and quantitative analysis is reported in Figure 3. A significant difference was observed between sensitivity of qualitative and semiquantitative analysis by the Fischer exact test (p = 0.011); no significant difference was found between semiquantitative and quantitative analysis, nor between qualitative and quantitative analysis (p = 0.461).

No significant differences were found concerning specificity of the three methods of analysis as well as for overall accuracy and PPV. On comparison of the three methods, a significant difference in NPV in qualitative and semiquantitative analysis by the Fischer exact test (p = 0.03) was found but not in semiquantitative and quantitative analysis or in qualitative and quantitative analysis.

Comparison of Patients with or without Prior Myocardial Infarction

Seventeen out of 37 (46%) patients had prior myocardial infarction. In these patients significant CAD was observed: 10 LAD, 5 LCX and 6 RCA.

In this subgroup sensitivity and specificity for detection of restenosis were 82–91%; 55–73% and 73–73% using qualitative, semiquantitative and quantitative analysis, respectively. Sensitivity and specificity of the three methods of analysis for detection of restenosis in patients with or without prior myocardial infarction is reported in Figure 6. No significant statis-

tical difference was found in test sensitivity, specificity, PPV or NPV in patients with or without previous MI.

DISCUSSION

PTCA is considered and accepted as an alternative procedure to CABG for treating coronary lesions suitable for balloon dilatation. Using this procedure, myocardial revascularization is frequently incomplete. Moreover, despite the immediate efficacy of PTCA, restenosis may occur in a high percentage of patients.

The increasing number of patients with recurrent ischemia after successful PTCA may be explained by the increased use of this procedure in multivessel patients and subgroups with higher grades of restenosis (40% to 50% in comparison to 20% to 35% reported in the early era) (*5,14,15*). Multiple studies have documented both clinical and angiographic variables related to procedural outcome after PTCA (*16–19*).

The value of symptoms for detecting restenosis varies widely from study to study. Positive predicting values of symptoms for predicting restenosis range from 44% to 92% (*2,20*); the specificity is commonly very low, owing to many noncardiac causes of chest pain and the presence of incomplete revascularization after PTCA in many patients.

Both stress testing and ^{210}Tl scintigraphy have been used to noninvasively predict and identify restenosis. Although the exercise electrocardiogram may have a good negative predictive value, the predictive value of a positive test is very poor (*21,22*).

Exercise ^{201}Tl SPECT has been described to be accurate in predicting restenosis (*23*) and for this reason it has been recommended in the evaluation of residual ischemia after revascularization.

Noboyoshi et al. (*5*) has stressed the problem that the immediate (24 to 72 hr) post-PTCA evaluation is probably suboptimal because of potential myocardial stunning, remodeling and recoil effects, whereas >4-wk post-PTCA studies might fall within the period of maximal restenosis risk. Moreover, they reported an incidence of 39% of restenosis within 3 mo, with only a slight increase between the third and twelfth months (45% and 48% at 6 and 12 mo, respectively). Based on these results, we have suggested that the detection of restenosis should be performed 3 mo after PTCA.

In a study by Breisblatt et al. (*7*), 26 of 104 (25%) asymptomatic patients studied 4–6 mo after PTCA had a positive ^{201}Tl scan for reversible ischemia. This pattern identified a high-risk group with a restenosis likelihood of 85% within 6 mo and 96% within 1 yr.

Wijns et al. (*6*), using ^{201}Tl planar imaging 1 mo after successful PTCA, studied 89 patients who had undergone angiographic follow up at 6 mo or earlier for recurrent symptoms. The positive predictive value for restenosis of a reversible, exercise-induced defect was 74% and the negative predictive value was 83%.

More recently, Hecht et al. (*21*) evaluated the role of tomographic ^{201}Tl exercise and redistribution imaging in the detection of restenosis after PTCA. They compared exercise electrocardiogram versus SPECT with ^{201}Tl and found that sensitivity increased from 52% to 93% ($p < 0.001$), specificity from 64% to 77% (ns) and accuracy from 57% to 86% ($p < 0.001$).

The use of ^{99m}Tc-labeled tracers, such as sestamibi which improves image contrast and resolution, may offer the opportunity for improvement of the evaluation of patients after PTCA.

We conducted the study in a peculiar, but generally the most common, clinical situation which is the presence of an equivocal stress-test at a variable time interval after PTCA, moreover in the absence of a pre-PTCA reference study comparable with the post-PTCA one. Prior studies have evaluated the diagnostic accuracy of sestamibi SPECT in the detection of CAD by visual analysis (*24,25*) but to our knowledge, this is the first study to test the accuracy of SPECT with sestamibi in the detection of restenosis after successful PTCA. In addition, the population that we analyzed (lack of pre-PTCA perfusion study, variable time interval between PTCA and sestamibi SPECT, equivocal exercise testing) caused major diagnostic problems. Maximum perfusion study efficacy is noted in this group of patients in whom a positive or a negative test result dramatically increases or decreases the post-test likelihood of disease.

Detection of diseased vessel sensitivity of ^{99m}Tc-sestamibi SPECT ranged from 82% to 89% and specificity from 75% to 77% (*23–25*). These results are comparable with the 87.5% sensitivity and 78% specificity in the current study for the detection of restenosis.

Our data seem in general agreement with those of Hecht et al. (*20*) who found exercise ^{201}Tl SPECT to be 93% sensitive, 77% specific and 86% accurate in the detection of restenosis. Moreover, we must emphasize that in our study the evaluation of SPECT was not aided by a pre-PTCA reference study which is definitely helpful especially in patients with previous myocardial infarction.

Our data indicate that the positive and negative predictive values of qualitative analysis are better than both semiquantitative and quantitative methods. Even though quantitative analysis has been reported to improve the interpretation of stress ^{201}Tl scintigraphy by reducing inter- and intraobserver variability and enhancing detection of coronary artery disease over visual analysis (*26,27*), in our study qualitative analysis resulted to be more accurate than both semiquantitative and quantitative methods in the prediction of restenosis. A possible explanation is that both observers were aware of patient angiographical data and clinical history. The knowledge of the results of coronary arteriography at the time of PTCA offers precious information which helps image interpretation: right or left coronary dominant system, variations of coronary anatomy, disease in multiple branches of the same vessel, one or more of which may have been dilated leaving residual areas of ischemia in overlapping territories. We must also consider the fact that qualitative analysis by expert observers might be less sensitive to the impact of image artifacts. Furthermore, our findings are in general agreement with those of Maddahi et al. (*28*) who reported a sensitivity of 80% and specificity of 71% for the detection of coronary artery disease using quantitative analysis of ^{201}Tl SPECT.

It is important to emphasize that the quantitative approach permits not only the identification of the diseased vessel, but also the quantification of the amount of jeopardized myocardium which is difficult to define by visual interpretation. This is a crucial issue because it is widely demonstrated that the risk of future cardiac events is directly related to the extent of jeopardized viable myocardium (*29,30*).

Feiring et al. (*31*) has demonstrated that the amount of myocardium at risk is highly variable even in patients with coronary occlusion in similar locations and therefore it cannot be predicted on an individual basis even when coronary angiograms are available.

Sensitivity and specificity of quantitative and qualitative analysis did not show significant difference when referred to the LAD, LCX or RCA territories. A multicenter trial using quantitative analysis and same-day rest/stress ^{99m}Tc-sestamibi

SPECT has demonstrated sensitivities of 74%, 70% and 71%, with specificities of 82%, 88% and 86% for the LAD, LCX and RCA, respectively (*32*). These data are comparable with ours even though some differences were found in the LAD territory (sensitivity 80%; specificity 67%).

Regardless of the method of analysis, specificity of ^{99m}Tc-sestamibi SPECT tended to be lower for the LAD (73%–60%–67%) and the RCA (80%–60%–80%) compared with the LCX (100%–100%–100%) coronary. However the analysis of the discrepancy between angiography and SPECT revealed the presence of significant disease in previously normal vessels, without restenosis of the dilated vessels, in four patients. Of these, 1 false-positive at qualitative analysis had a 50% stenosis in the left main; the same patient was considered as positive also by semiquantitative analysis which detected similarly to false-positive two more patients with patent LAD but with 80% and 100% stenosis, respectively, of the first diagonal branch. The patient with 100% stenosis of the diagonal branch also resulted positive by quantitative analysis.

One of 1 (100%), 2 of 8 (25%) and 2 of 3 (67%) of the false-negatives by qualitative, semiquantitative and quantitative analysis, respectively, occurred in patients with mild (50%–60%) LAD narrowing in association with more severe stenosis in the RCA.

Sensitivity of the three methods of analysis for the detection of restenosis does not seem to be affected by the presence of prior myocardial infarction while a lower, although insignificant, specificity was found in patients without myocardial infarction using either qualitative or semiquantitative analysis.

CONCLUSION

The present study shows that myocardial ^{99m}Tc-sestamibi SPECT is an accurate and reliable noninvasive tool in the identification of restenosis and in the evaluation of the extension of ischemic myocardium after PTCA. We suggest it be used to define angiographic evaluation in patients with equivocal exercise stress testing. In addition, the qualitative analysis of the tomographic slices compares favorably with both semiquantitative analysis of polar maps and quantitative analysis.

REFERENCES

1. Leimgruber PP, Roubin GS, Hollman J, et al. Restenosis after successful coronary angioplasty in patients with single-vessel disease. *Circulation* 1986;73:710–717.
2. Mabin TA, Holmes DR, Smith HC, et al. Follow-up clinical results in patients undergoing percutaneous transluminal coronary angioplasty. *Circulation* 1985;71: 754–760.
3. Nobuyoshi M, Kimura T, Ohishi H, et al. Restenosis after percutaneous transluminal coronary angioplasty: pathologic observations in 20 patients. *J Am Coll Cardiol* 1991;17:433–439.
4. Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. *Circulation* 1988;77:361–371.
5. Nobuyoshi M, Kimura T, Nosaka H, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. *J Am Coll Cardiol* 1988;12:616–623.
6. Wijns W, Serruys PW, Reiber JHC, et al. Early detection of restenosis after successful percutaneous transluminal coronary angioplasty by exercise-redistribution thallium scintigraphy. *Am J Cardiol* 1985;55:357–361.
7. Breisblatt WM, Weiland FL, Spaccavento LJ. Stress thallium-201 imaging after coronary angioplasty predict restenosis and recurrent symptoms. *J Am Coll Cardiol* 1988;12:1199–1204.
8. Stuckey TD, Burwell LR, Nygaard TW, et al. Quantitative exercise thallium-201 scintigraphy for predicting angina recurrence after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1989;63:517–521.
9. Breisblatt WM, Barner JV, Weiland FL, Spaccavento LJ. Incomplete revascularization in multivessel percutaneous transluminal coronary angioplasty: the role of stress thallium-201 imaging. *J Am Coll Cardiol* 1988;11:1183–1190.
10. Verani MS, Tadros S, Raizner AE. Quantitative analysis of thallium-201 uptake and washout before and after transluminal coronary angioplasty. *Int J Cardiol* 1986;13: 109–124.
11. Okada RD, Lim YL, Boucher CA, et al. Clinical, angiographic, hemodynamic, perfusional and functional changes after one-vessel left anterior descending coronary angioplasty. *J Am Coll Cardiol* 1985;55:347–356.
12. Galli M, Marcassa C, Bolli R, et al. Spontaneous delayed recovery of perfusion and contraction after the first 5 weeks after anterior infarction. *Circulation* 1994;90:1386–1397.
13. Prigent FM, Maddahi J, Van Train KF, Berman DS. Comparison of thallium-201 SPECT and planar imaging methods for quantification of experimental myocardial infarct size. *Am Heart J* 1991;122:972–979.
14. Holmes DR, Vlietstra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA registry of the National Heart, Lung and Blood Institute. *Am J Cardiol* 1984;53:77c–81c.
15. Leimgruber PP, Roubin GS, Hollman J, et al. Restenosis after successful coronary angioplasty in patients with single-vessel disease. *Circulation* 1986;73:710–717.
16. Baim DS, Diver DJ, Feit F for the TIMI 2 investigators. Coronary angioplasty performed within the thrombolysis in myocardial infarction 2° study. *Circulation* 1992;85:93–105.
17. de Feyter PJ, Suryapranata H, Serruys W, et al. Coronary angioplasty for unstable angina: immediate and late results in 200 consecutive patients with identification of risk factors for unfavorable early and late outcome. *J Am Coll Cardiol* 1988;12:324–333.
18. Mick MJ, Pidmonte MR, Arnold AM, Simpfendorfer C. Risk stratification for long-term outcome after elective coronary angioplasty: a multivariate analysis of 5,000 patients. *J Am Coll Cardiol* 1994;24:74–80.
19. Foley DP, Melkert R, Serruys PW. Influence of coronary vessel size on renarrowing process and late angiographic outcome after successful balloon angioplasty. *Circulation* 1994;90:1239–1251.
20. Califf RM, Ohman EM, Frid DJ. Restenosis: the clinical issues. In: Topol EJ, ed. *Textbook of interventional cardiology*. Philadelphia, PA: WB Saunders; 1990:363–394.
21. Hecht HS, Shaw RE, Bruce TR, et al. Usefulness of tomographic thallium-201 imaging for detection of restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1990;66:1314–1318.
22. Bengston JR, Mark DB, Honan MB, et al. Detection of restenosis after elective percutaneous transluminal coronary angioplasty using the exercise treadmill test. *Am J Cardiol* 1990;65:28–34.
23. Kahn JK, McGhie I, Akers MS, et al. Quantitative rotational tomography with ^{201}Tl and ^{99m}Tc 2-methoxy-isobutyl-isonitrile: a direct comparison in normal individuals and patients with coronary artery disease. *Circulation* 1989;79:1282–1293.
24. Iskandrian AS, Heo J, Kong B, et al. Use of technetium-99m-isonitrile (RP-30A) in assessing left ventricular perfusion and function at rest and during exercise in coronary artery disease, and comparison with coronary arteriography and exercise thallium-201 SPECT imaging. *Am J Cardiol* 1989;64:270–275.
25. Kiat H, Maddahi J, Roy LT, et al. Comparison of technetium-99m-methoxy isobutyl isonitrile and thallium-201 for evaluation of coronary artery disease by planar and tomographic methods. *Am Heart J* 1989;117:1–11.
26. Trobaugh GB, Wackers FJ, Sokole EB, et al. Reproducibility of thallium-201 myocardial imaging: an inter-institutional study of observer variability. *J Nucl Med* 1978;19:359–363.
27. Garcia E, Maddahi J, Berman D, Waxman A. Space/time quantitation of thallium-201 myocardial scintigraphy. *J Nucl Med* 1981;22:309–317.
28. Maddahi J, Van Train K, Pringent F, et al. Quantitative single-photon emission computed thallium-201 tomography for detection and localization of coronary artery disease: optimization and prospective validation of a new technique. *J Am Coll Cardiol* 1989;14:1689–1699.
29. Ladenheim ML, Pollok BH, Rozanski A, et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1986;7:464–471.
30. Iskandrian AS, Chae SC, Heo J, et al. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. *J Am Coll Cardiol* 1993;22:665–670.
31. Feiring AJ, Johnson MR, Kioschos JM, et al. The importance of the determination of the myocardial area at risk in the evaluation of the outcome of acute myocardial infarction in patients. *Circulation* 1987;75:980–987.
32. Van Train K, Areeda J, Garcia E, et al. Quantitation of same-day Tc-99m-sestamibi myocardial SPECT: multicentral trial validation. *J Nucl Med* 1992;33:876.