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# Myocardial Perfusion Imaging with Technetium-99m-Tc NOET: Comparison with Thallium-201 and Coronary Angiography

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We compared TcN-NOET [bis(N-ethoxy, N-ethyl dithiocarbamato)nitrido  $^{99m}\text{Tc}$ ] and  $^{201}\text{Tl}$  images to estimate the utility of this compound in the detection of coronary artery disease (CAD). **Methods:** Twenty-five patients undergoing cardiac catheterization had stress-redistribution-reinjection  $^{201}\text{Tl}$  SPECT imaging, stress-delayed (2, 4 and 6 hr postinjection) and rest-delayed (4 hr postinjection) TcN-NOET SPECT imaging. **Results:** Nineteen patients had coronary stenosis  $\geq 50\%$  and six were normal. Stress TcN-NOET and  $^{201}\text{Tl}$  imaging were concordant for the presence of CAD in 22/25 patients (88%,  $\kappa = 0.76 \pm 0.20$ ). The overall sensitivity of TcN-NOET SPECT imaging was 74% (14/19 patients) and 68% (13/19 patients) for  $^{201}\text{Tl}$  SPECT imaging. The specificity was 100% (6/6 patients) for both techniques. The overall agreement of TcN-NOET and  $^{201}\text{Tl}$  for the presence of disease in individual coronary arteries was 96% (72/75 arteries,  $\kappa = 0.92 \pm 0.16$ ). Segmental analysis of stress images showed a concordance in 211/225 segments (94%,  $\kappa = 0.82 \pm 0.09$ ). Comparison of the 4-hr images showed a concordance between  $^{201}\text{Tl}$  and TcN-NOET in 21/23 patients. Following TcN-NOET injection at rest, seven patients had a defect on the initial images, which had normalized 4 hr postinjection in four patients (57%). **Conclusion:** Perfusion imaging with TcN-NOET and  $^{201}\text{Tl}$  gives comparable diagnostic information in patients undergoing exercise testing for assessment of CAD. Because of the normalization of myocardial activity 4 hr after injection in some patients, we conclude that TcN-NOET is a potential technetium compound equivalent to  $^{201}\text{Tl}$ .

**Key Words:** myocardial perfusion imaging; technetium-99m compounds; TcN-NOET; thallium-201

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**T**he study of myocardial perfusion with  $^{201}\text{Tl}$  has become indispensable during coronary artery disease (CAD) evaluation, whether as a diagnostic tool or in the prognosis of such disease (1-3). Some of the disadvantages of  $^{201}\text{Tl}$ , such as cyclotron production, low photon energy and long half-life, which limits the allowable dose (4), have favored the development of technetium agents for perfusion imaging. To date, three technetium compounds have demonstrated their clinical utility: sestamibi (5), teboroxime (6) and tetrofosmin (7), but none has totally supplanted  $^{201}\text{Tl}$ , which remains the most commonly used tracer. This is partly due to the fact that  $^{201}\text{Tl}$  is used both as a tracer of regional blood coronary flow distribution and as a marker of myocardial cellular viability, while technetium complexes are pure blood flow tracers. This characteristic of  $^{201}\text{Tl}$  is related to its redistribution. An image obtained immediately after  $^{201}\text{Tl}$  injection, during exercise or at rest, enables the assessment of regional myocardial blood flow during exercise or at rest. Subsequent images allow an evaluation of the viability of a hypoperfused territory. Bis (N-ethoxy, N ethyl dithiocarbamato) nitrido  $^{99m}\text{Tc}$ (V) (TcN-NOET), a neutral lipophilic  $^{99m}\text{Tc}$  compound, exhibits high cardiac uptake in various animal species and in humans (8). Studies performed in dogs have shown that TcN-NOET, when injected after partial left anterior descending artery occlusion, redistributed following reflow (9). The myocardial kinetics of TcN-NOET may therefore be similar to that of  $^{201}\text{Tl}$ . To evaluate the kinetics of TcN-NOET in humans and the utility of this compound for the detection of CAD, we have compared TcN-NOET and  $^{201}\text{Tl}$  myocardial perfusion images of patients being evaluated for CAD.

## MATERIALS AND METHODS

### Patients

A prospective multicenter study was carried out in France and Italy involving 25 patients undergoing cardiac catheterization or thallium scintigraphy. Examination was most frequently moti-

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vated by the need to evaluate patients who presented with ST segment depression  $>1$  mm ( $n = 15$ ). Less often, the examination was prompted by the existence of chest pain ( $n = 7$ ) or dyspnea ( $n = 3$ ) during exercise. The interval between the stress test and cardiac catheterization did not exceed 2 mo. There were 19 men and 6 women (mean age  $57 \pm 11$  yr, range 38–71). Nineteen patients had significant CAD by qualitative coronary angiography ( $\geq 50\%$  luminal stenosis), of whom 14 had stenosis  $\geq 70\%$ .

Twelve patients had single-vessel disease, four had double-vessel disease and three had triple-vessel CAD. The six remaining patients had normal coronary arteries. Nine patients had prior myocardial infarction.

The study was approved by the study's ethical committee and all patients gave written informed consent.

### TcN-NOET Preparation

TcN-NOET was prepared from a liquid kit, the formulation of which has been previously reported (8). Briefly, the tracer was obtained through a two-step reaction. In the first step, [ $^{99m}\text{Tc}$ ]-pertechnetate (50 mCi or 1850 MBq) was added to a vial containing 3.0 mg of tris(*m*-sulfophenyl)phosphine,  $[\text{P}(\text{m-C}_6\text{H}_4\text{SO}_3)_3]\text{Na}_3$  (TPPS) and 1.0 mg of *N*-methyl, *S*-methyl dithiocarbamate [ $\text{H}_2\text{N}(\text{CH}_3)\text{-C}(=\text{S})\text{SCH}_3$ ], (DTCZ) dissolved in 1 ml of 0.1 *M* HCl. The resulting solution was treated at  $100^\circ\text{C}$  for 15 min, then cooled to room temperature. The pH of the solution was raised to 8.0 by adding 1 ml of sodium phosphate buffer and 1 ml of an aqueous solution containing 10 mg of the sodium salt of *N*-ethoxy, *N*-ethyl dithiocarbamate (NOET). The final compound is formed almost instantaneously at room temperature. Due to the lack of charge and high lipophilicity, the final complex will be absorbed into the vial walls or into the walls of the syringe to a great extent. To avoid this adsorption, 20 mg of gamma-cyclodextrin were added to the final solution.

Radiochemical purity was routinely checked by thin-layer chromatography. The method consisted of a Scheicher and Schull Silicagel strip ( $2.5 \times 15$  cm) eluted using ascending chromatography with dichloromethane. In this system, free pertechnetate and unreacted TcN species remain at the origin, whereas the TcN-NOET complex migrates in the middle of the strip. The mean radiochemical purity of the product was  $96\% \pm 2\%$  immediately after the preparation; this value remained stable for at least 6 hr.

### Exercise Protocol

Exercise myocardial perfusion scintigraphy with  $^{201}\text{Tl}$  and TcN-NOET was performed using an ergometer bicycle protocol in the upright position with permanent monitoring of a 12-lead EKG. Each exercise was symptom-limited stress. All patients were asked to discontinue anti-ischemic drugs (beta-blocking agents, calcium antagonists) at least 48 hr before the procedure. The test started at 25 or 50 W, and work was increased by 25-W increments every 3 min. Arterial blood pressure was measured prior to each increment. Termination of exercise and abnormality criteria were conventional.

### Thallium-201 SPECT Imaging

A standard procedure was used to obtain images of thallium-SPECT during exercise as well as at redistribution and after reinjection. At peak exercise, 2.5 to 3 mCi (92.5 to 111 MBq) of  $^{201}\text{Tl}$  was injected intravenously. The initial images (stress) were obtained 10 min after the injection of the tracer using a rotating gamma camera equipped with a low energy, high resolution collimator, the spectrophotometer of which was centered on the 68 keV photopeak with a 20% window, and on the 167 keV

photopeak with a 15% window. The head of the camera turned through a  $180^\circ$  arc in a circular orbit around the patient's thorax at 6-degree increments for 30 sec each (32 projections).

Redistribution images were obtained at rest 4 hr after the injection of  $^{201}\text{Tl}$  using an identical technique. During the period separating the initial imaging and the redistribution, the patient remained in a sedentary position and had only a light meal. Immediately after redistribution imaging, a 1 mCi additional thallium dose was administered at rest and reinjection images were acquired 15 min thereafter.

Initial imaging, redistribution and reinjection data were processed to obtain transaxial sections by filtered back-projection (ramp or Hamming-Hann filter) without attenuation correction. These transaxial sections were reoriented into the three standard cardiac planes (short, horizontal-long and vertical-long axes) to allow visual interpretation.

### TcN-NOET SPECT Imaging

The same procedure was used following the intravenous injection of TcN-NOET; at peak exercise, 15 mCi (555 MBq) were injected intravenously. The initial images were obtained 30 min after the injection of the tracer using a rotating gamma camera equipped with the same collimator used for the thallium images with the exception of the spectrophotometer, which was centered on the 140 keV photo-peak with a 15% window. The head of the camera turned through a  $180^\circ$  arc at 6-degree increments for 30 sec each. Redistribution images were obtained at rest, 2, 4 and 6 hr after injection of TcN-NOET in 13 patients, at 2 and 4 hr in 16 patients, and 4 hr after injection in all patients using an identical technique.

Furthermore, with a 24-hr interval prior to or after the injection during exercise, the patients received 15 mCi (555 MBq) of [ $^{99m}\text{Tc}$ ] TcN-NOET injected at rest. A series of images were obtained 30 min and 4 hr after injection in 24 patients.

The images obtained were processed to obtain transaxial sections by filtered back-projection (Ramp or Hamming-Hann filter) without attenuation correction and reoriented into the three standard cardiac planes to allow visual interpretation.

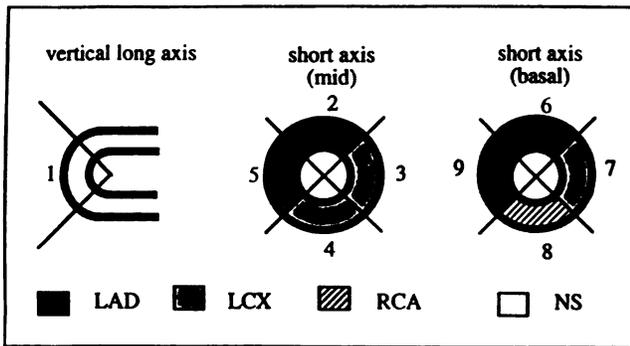
### Image Analysis

The quality of scintigraphic images was appraised visually by consensus using a scoring system where a score of 2 = a good quality image; 1 = a medium quality image; and 0 = a poor quality image that nevertheless allowed diagnosis. Nondiagnostic images were declared impossible to interpret.

The left ventricle was divided into nine segments (Fig. 1). Qualitative analysis was performed and a general consensus was obtained from all the investigators, all of whom had no knowledge of clinical and follow-up data. Each segment, on each set of images, was classified visually as normal or abnormal. On stress images, tracer uptake was scored by consensus of two experienced observers using a four-point grading system (0 = normal; 1 = mildly reduced; 2 = moderately reduced; and 3 = defect). At a second stage, each abnormal segment during exercise was classified as a transient abnormality if the segment showed improved activity on the images obtained 2, 4 or 6 hr after TcN-NOET injection, and 4 hr after  $^{201}\text{Tl}$  injection, or as a permanent abnormality if the relative hypoactivity present during exercise persisted on the images obtained later.

### Statistical Analysis

Results were expressed as the mean  $\pm 1$  s.d. Sensitivity was defined as true positive  $\times 100$  divided by the sum of true-positive



**FIGURE 1.** Diagrammatic representation of SPECT images illustrating assignment of anatomic left ventricular segments and vascular territories. LAD = left anterior descending coronary artery; RCA = right coronary artery; LCX = left circumflex coronary artery; NS = nonspecific territory.

plus false-negative tests. Specificity was defined as the number of true-negative  $\times$  100 divided by the sum of the true-negative and the false-positive tests. The accuracy was defined as [sensitivity  $\times$  coronary artery disease prevalence] + [specificity  $\times$  (1 - prevalence)]. Sensitivity and specificity of TcN-NOET and  $^{201}\text{Tl}$  were compared using the McNemar test. Comparisons of exercise variables were made with a paired Student's *t*-test; comparisons of the quality scores of the images and of the severity of the defect were performed using the Wilcoxon test for paired data. Concordance of  $^{201}\text{Tl}$  and TcN-NOET results was assessed using the kappa ( $\kappa$ ) statistic. A  $\kappa$  value  $>0.75$  indicates excellent concordance.

## RESULTS

### Adherence to Protocol

The interval between stress TcN-NOET SPECT imaging and stress thallium-imaging was on average  $2.0 \pm 1.6$  days for 23 patients, and 12 and 20 days for the remaining 2 patients. The interval between stress TcN-NOET SPECT imaging and rest TcN-NOET SPECT imaging was on average  $1.3 \pm 0.6$  days. The mean interval between stress TcN-NOET SPECT imaging and coronary angiography was  $12.0 \pm 17.0$  days (range: 1-60), and that between  $^{201}\text{Tl}$ -SPECT imaging and coronary angiography was  $13.5 \pm 21.0$  days (range: 1-66).

### Exercise Parameters

The comparison of hemodynamic data for stress  $^{201}\text{Tl}$ -SPECT imaging and stress TcN-NOET SPECT imaging (Table 1) showed that the heart rate-blood pressure product and percentage of maximum predicted heart rate were identical. The number of patients with chest pain or ST segment depression greater than 1 mm was comparable in both groups.

### TcN-NOET Imaging Quality Compared with Thallium-201

Following exercise, the score of the image quality obtained with TcN-NOET was inferior to that of  $^{201}\text{Tl}$  ( $1.76 \pm 0.44$  versus  $1.94 \pm 0.22$ ,  $p < 0.05$ ). The good quality images on 19/25 patients for TcN-NOET and 24/25 for  $^{201}\text{Tl}$ ; the proportion of those with medium quality images was 6/25

**TABLE 1**  
Hemodynamic Data during Exercise

|  | $^{201}\text{Tl}$ | $^{99\text{mTc}}\text{TcN-NOET}$ |
|--|-------------------|----------------------------------|
| Peak heart rate (bpm)                        | $136 \pm 23$      | $135 \pm 20$                     |
| Maximum predicted heart rate (%)             | $84 \pm 13$       | $83 \pm 10$                      |
| Peak systolic blood pressure (mmHg)          | $182 \pm 30$      | $185 \pm 29$                     |
| Double product (mmHg $\times$ bpm)           | $25,053 \pm 6861$ | $25,188 \pm 6390$                |
| Angina during exercise (patients)            | 7/25 (28%)        | 6/25 (24%)                       |
| ST-segment depression (mm)                   | $0.98 \pm 0.9$    | $1.06 \pm 0.98$                  |
| ST-segment depression $\geq 1$ mm (patients) | 15/25 (60%)       | 15/25 (60%)                      |

$p =$  not significant for all parameters.

for TcN-NOET and 1/25 for  $^{201}\text{Tl}$ . No patient had poor quality images. Four hours after the injection, image quality was inferior to that of stress images for both tracers, but the score did not differ significantly between TcN-NOET and  $^{201}\text{Tl}$  ( $1.58 \pm 0.63$  versus  $1.65 \pm 0.48$ ,  $p = \text{ns}$ ). The numbers of patients imaged with TcN-NOET and  $^{201}\text{Tl}$  with good quality images were 16/25 and 17/25, respectively; 7/25 and 7/25 patients had medium quality images; and 0/25 and 1/25 patients had poor quality images; however, in two patients, TcN-NOET images obtained 4 hr after the injection were considered impossible to interpret. Six hours after stress injection, the image quality score was  $1 \pm 0.82$  and in one patient, images were considered impossible to interpret. Following TcN-NOET injection at rest, the images were of medium quality regardless of whether they were obtained 30 min ( $1.37 \pm 0.71$ ) or 4 hr after injection ( $1.42 \pm 0.67$ ). In one patient, TcN-NOET images were considered impossible to interpret (normal images are shown in Fig. 2).

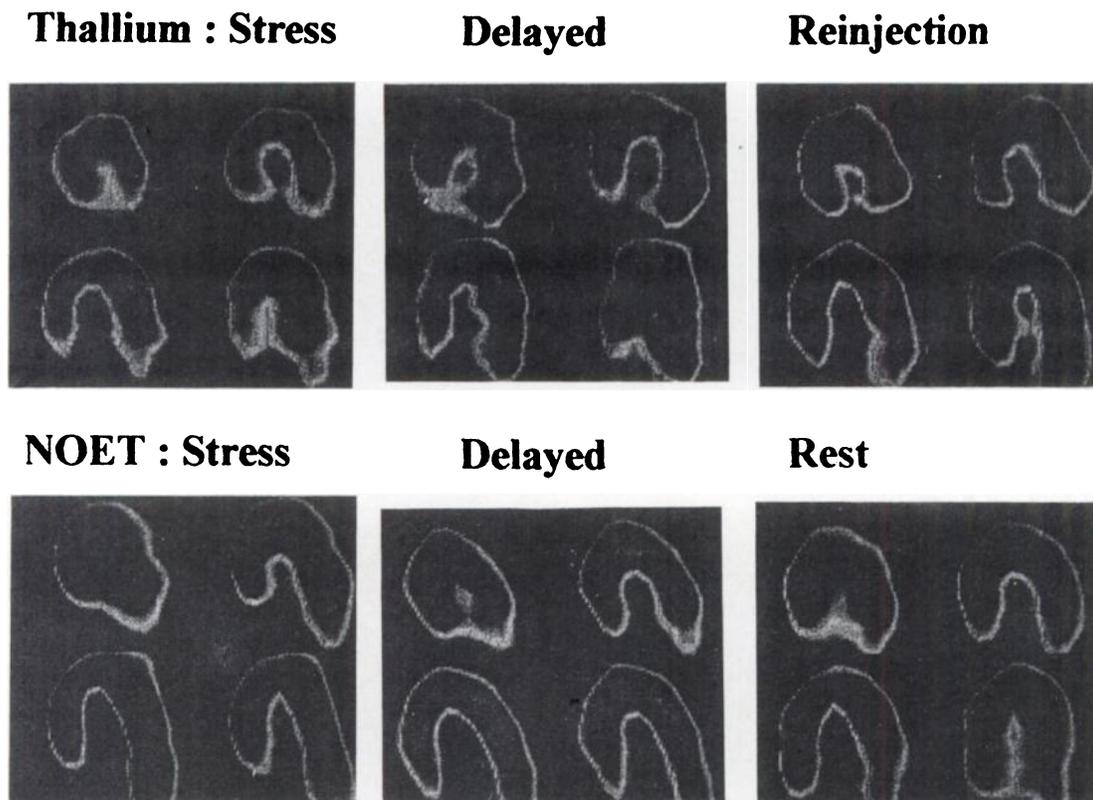
### Detection of CAD

Stress TcN-NOET and  $^{201}\text{Tl}$  imaging were concordant for the presence of coronary artery disease in 22/25 patients (88%,  $\kappa = 0.76 \pm 0.20$ ). In patients with prior myocardial infarction, the concordance was 89% (8/9). The overall sensitivity for the detection of coronary artery disease was 74% (14/19) with TcN-NOET SPECT imaging and 68% (13/19) with  $^{201}\text{Tl}$  SPECT imaging ( $p = \text{ns}$ ). The specificity was 100% (6/6) with both markers. The accuracy was 0.80 for TcN-NOET and 0.76 for  $^{201}\text{Tl}$ .

If the significance threshold is defined as greater than or equal to 70% stenosis, both markers showed identical sensitivity (79%; 11/14) and their specificity was very similar (73%, 8/11 for TcN-NOET and 82%, 9/11 for  $^{201}\text{Tl}$ ;  $p = \text{ns}$ ).

### Detection of Disease in Individual Coronary Vessels

Regional perfusion abnormalities seen on the scans were assigned to one of nine wall segments corresponding to the vascular distribution illustrated in Figure 1. The overall concordance between TcN-NOET and  $^{201}\text{Tl}$  (Table 2) for the presence of disease in individual coronary arteries was 96% (72/75,  $\kappa = 0.92 \pm 0.16$ ). This concordance was the same in all the coronary territories.



**FIGURE 2.** Stress redistribution and reinjection  $^{201}\text{Tl}$  (horizontal long-axis) tomographic images in a patient with normal coronary arteries. Corresponding TcN-NOET images: stress images, 4-hr delayed images and initial rest images.

The overall sensitivity and specificity of TcN-NOET and  $^{201}\text{Tl}$  imaging for the detection of disease in individual vessels were identical, with a sensitivity of 59% (17/29) and a specificity of 93% (43/46) (Table 3).

#### Segmental Analysis

In the 225 segments, there was good agreement for normal versus abnormal perfusion between  $^{201}\text{Tl}$  and TcN-NOET, with concordance in 211/225 segments (94%,  $\kappa = 0.82 \pm 0.09$ ) (Fig. 3).

#### Defect Severity

Of the 51 abnormal segments detected during stress with  $^{201}\text{Tl}$ , 42 were abnormal during stress with TcN-NOET

(82%). Of these 51 segments, 29 had identical scores (57%), 19 had lower scores with TcN-NOET (37%) and 3 had higher scores with TcN-NOET (6%). The mean score assessing the severity of the defect was  $2.47 \pm 0.70$  with  $^{201}\text{Tl}$  and  $2 \pm 1.23$  ( $p < 0.01$ ) with TcN-NOET, indicating lower defect contrast with TcN-NOET.

#### Comparison Between Thallium-201 and TcN-NOET Delayed Images

In the 16 patients for whom an image obtained 2 hr after the injection of TcN-NOET during exercise was available, concordance between delayed thallium and TcN-NOET images was demonstrated in 13 patients (13/16). The images were normal in seven of these patients, showed an initial defect with normalization two hours after the injection in three patients, and showed a permanent defect in the remaining three patients. Two of the patients for whom concordance was not obtained had a transient defect with  $^{201}\text{Tl}$ , which appeared permanent with TcN-NOET. The other patient for which concordance was not obtained was normal during exercise with  $^{201}\text{Tl}$  while TcN-NOET identified a transient posterior defect.

The images obtained 4 hr after the injection of TcN-NOET during exercise could be interpreted in 23 patients. Concordance between  $^{201}\text{Tl}$  and TcN-NOET was achieved in 21 patients, with 8 normal images, 9 patients with normalization 4 hr after injection (Fig. 4) and 4 with a perma-

**TABLE 2**  
Agreement Between TcN-NOET and Thallium-201 for Disease in Individual Vessels

| Vessel  | Agreement | %   |
|---------|-----------|-----|
| LAD     | 24/25     | 96  |
| RCA     | 24/25     | 96  |
| LCx     | 24/25     | 96  |
| Overall | 72/75     | 96* |

\* $\kappa = 0.92 \pm 0.16$ .

LAD = left anterior descending; RCA = right coronary artery; LCx = left circumflex.

**TABLE 3**  
Sensitivity and Specificity of TcN-NOET and Thallium-201 for Angiographic Coronary Artery Disease by Vessel

| Vessel  | Sensitivity (%) |                   | Specificity (%) |                   |
|---------|-----------------|-------------------|-----------------|-------------------|
|         | TcN-NOET        | <sup>201</sup> Tl | TcN-NOET        | <sup>201</sup> Tl |
| LAD     | 44 (7/16)       | 50 (8/16)         | 100 (9/9)       | 100 (9/9)         |
| RCA     | 88 (7/8)        | 75 (6/8)          | 82 (14/17)      | 88 (15/17)        |
| LCx     | 60 (3/5)        | 60 (3/5)          | 95 (19/20)      | 95 (19/20)        |
| Overall | 59 (17/29)      | 59 (17/29)        | 91 (42/46)      | 93 (43/46)        |

LAD = left anterior descending; RCA = right coronary artery; LCx = left circumflex.

ment defect. In the two remaining patients, one had a normal image with <sup>201</sup>Tl, which was identified as a transient posterior defect with TcN-NOET. The other had a normal <sup>201</sup>Tl during exercise with reverse redistribution in the inferior and posterior territories, whereas TcN-NOET showed a transient defect in these same regions. This latter patient had an inferior infarct and complete obstruction of the right coronary artery on coronary angiography.

In segmental analysis, when the pattern of uptake (normal, transient, permanent) of TcN-NOET and <sup>201</sup>Tl was compared (Fig. 5), there was concordance in 206/225 segments (92%,  $\kappa = 0.84 \pm 0.09$ ). Concordance was 68% (25/37) in segments showing a transient defect with <sup>201</sup>Tl, 100% (14/14) in segments with permanent defect, and 97% (167/172) in normal segments.

The images obtained 6 hr after stress injection were available in 13 patients. On the 12 interpretable images, 11 were in concordance with 4-hr delayed imaging. In one patient, 6-hr delayed images showed normalization of an initial defect that was confirmed by a normal rest TcN-NOET image.

#### TcN-NOET Images at Rest

Images of medium quality could be interpreted in 23 of the 24 patients in whom images were obtained after the injection of TcN-NOET at rest. Initial and delayed images were normal in 16 patients. An initial defect was identified in 7 patients, out of which 4 (4/7, 57%) showed normaliza-

|          |      | Thallium 201 |      |   |
|----------|------|--------------|------|---|
|          |      | NI           | Abnl |   |
| TcN-NOET | NI   | 167          | 9    | Agreement : 211 / 225 (94%)<br>Kappa $\pm$ SD = 0.82 $\pm$ 0.09 |
|          | Abnl | 5            | 44   |   |

**FIGURE 3.** Segmental agreement between TcN-NOET and <sup>201</sup>Tl for the presence of stress defects. NI = normal segment; Abnl = abnormal segment with stress defects.

tion of cardiac activity 4 hr after injection. Six of those patients had a prior myocardial infarct. In the remaining three patients who had an infarct, the TcN-NOET images at rest were normal; however, the images obtained during exercise showed a transient defect identical to that seen with <sup>201</sup>Tl in two of these patients, and a normal uptake of both TcN-NOET and <sup>201</sup>Tl in the third.

Comparison of the initial images obtained after the injection of TcN-NOET at rest with images acquired during exercise 4 hr after the injection using the same tracer demonstrated concordance in 16 of the 21 patients where an evaluation was possible (76%,  $\kappa = 0.40 \pm 0.27$ ). In six patients, the stress-delayed TcN-NOET images indicated a transient defect and the rest TcN-NOET images were normal. In three patients, there was a permanent defect after stress-delayed TcN-NOET SPECT imaging and the rest TcN-NOET images were abnormal. Finally, in seven patients, the stress and rest TcN-NOET SPECT images were normal. According to the segmental analysis, out of the 47 segments with initial TcN-NOET stress defect, 30 normalized 4 hr after the injection and 17 remained hypoactive. The initial rest TcN-NOET images were normal in 23 out of 30 segments and abnormal in 14 out of 17 segments. Concordance was achieved for 37/47 segments (79%,  $\kappa = 0.56 \pm 0.15$ ).

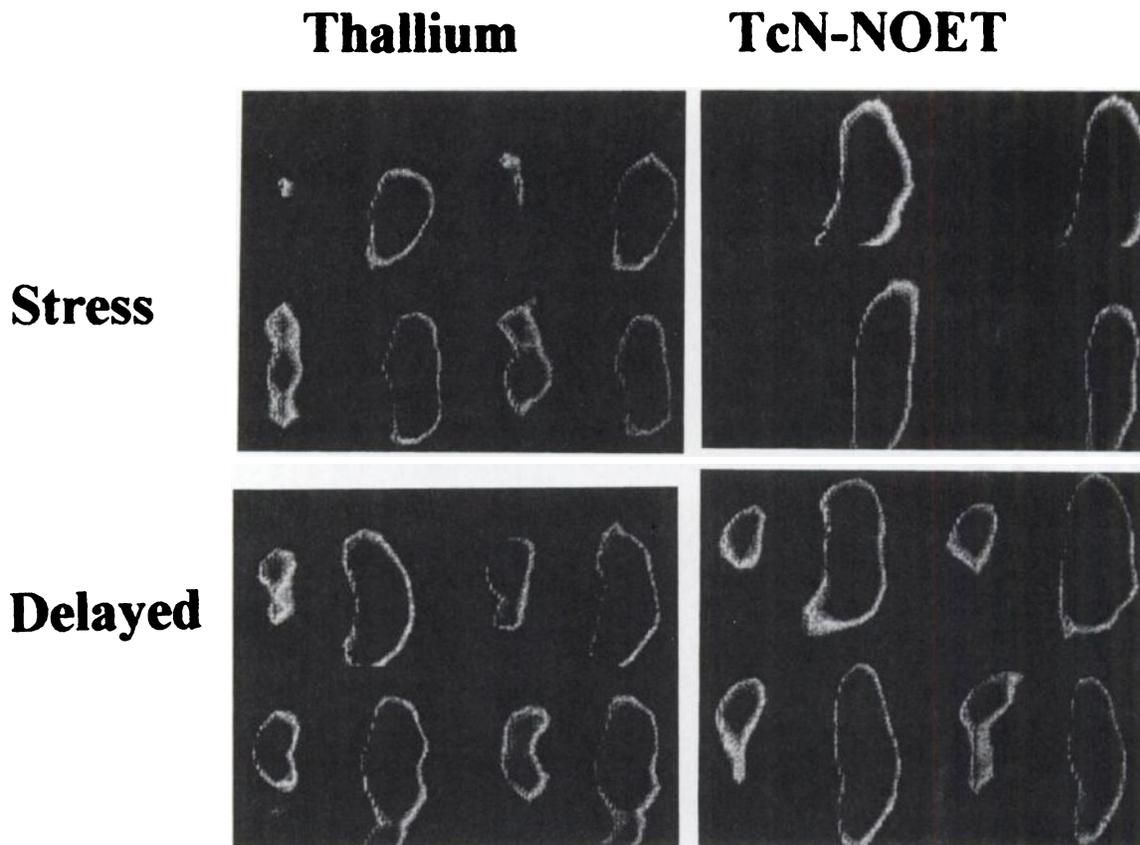
The comparison of the rest-delayed TcN-NOET images with those obtained after <sup>201</sup>Tl reinjection demonstrated a concordance in 19 out of the 22 patients where an evaluation was possible (86%,  $\kappa = 0.49 \pm 0.35$ ). In the 18 patients with normal <sup>201</sup>Tl reinjection images, 17 had normal initial images after injection of TcN-NOET at rest or an initial defect which normalized 4 hr later. In the four patients with a defect after reinjection of <sup>201</sup>Tl, two had a permanent defect and two had a transient defect on the rest-delayed TcN-NOET imaging.

#### Comparison of Stress-Redistribution-Reinjection Thallium-201 and Stress-Delayed/Rest-Delayed TcN-NOET

When <sup>201</sup>Tl images were normal during exercise (n = 11), the stress TcN-NOET was normal in nine patients and showed a transient defect in the other two. Coronary angiographies obtained in those two patients identified complete occlusion of the right coronary artery in one and a 50% stenosis of the left circumflex artery in the other.

When <sup>201</sup>Tl identified an initial defect with redistribution 4 hr later (n = 10), TcN-NOET also showed an initial defect which normalized 4 hr after the injection in the 9 patients for whom delayed images could be interpreted. In the other patient for whom delayed TcN-NOET images had been considered impossible to interpret, stress images showed a defect in the same territory as <sup>201</sup>Tl, and the TcN-NOET image at rest was normal.

When <sup>201</sup>Tl identified an initial defect without redistribution (n = 4), the stress-delayed TcN-NOET also showed a permanent defect; of those four patients, three had no fill-in following reinjection of thallium, and the rest TcN-NOET



**FIGURE 4.** Stress and 4-hr delayed images (horizontal long-axis) after  $^{201}\text{Tl}$  injection (left panel) show a large apico-septal defect with redistribution in the septal region. Corresponding TcN-NOET images (right panel) show the same defect and improvement activity 4 hr later in the septal region.

was abnormal 30 min after injection. In the remaining patient, the initial defect was normalized at the time of reinjection with  $^{201}\text{Tl}$ , and the TcN-NOET image at rest was normal.

#### DISCUSSION

TcN-NOET is a neutral, lipophilic technetium complex containing a  $(\text{Tc} \equiv \text{N})^{2+}$  ion and two dithiocarbamate ligands that has demonstrated high myocardial uptake in rats and dogs (8). In dogs, myocardial regional distribution

of TcN-NOET correlated well with regional blood flow (measured using radioactive microspheres) over a wide range of coronary flows (9). The images obtained after intravenous injection of TcN-NOET in dogs have shown a high initial uptake of this technetium complex in the lungs (8), but this pulmonary uptake washes out faster than the cardiac uptake, such that the heart/lung ratio increases with time (8). This high pulmonary uptake of TcN-NOET associated with a fast washout of tracer has been confirmed in humans by a biodistribution study performed in three patients with CAD (10). In that study, 24% of the administered dose was recovered in the lungs 30 min after intravenous injection. The half-life of the pulmonary activity was 11 min, whereas cardiac uptake showed little variation between 30 min and 4 hr after the injection (5.2% and 4.8%, respectively, of the injected dose).

These results have led us to wait 30 min after the intravenous injection of TcN-NOET before performing the SPECT-imaging. Despite this 30-min delay following the injection of TcN-NOET during exercise, pulmonary activity remained relatively high in some patients, which is reflected in a visual quality score lower than that of  $^{201}\text{Tl}$ . The pulmonary activity seemed to be more persistent at rest than during exercise. Presently, no clear explanation of this phenomenon can be offered. No correlation could

|          |    | Thallium 201 |    |    |    |   |
|----------|----|--------------|----|----|----|---|
|          |    | NI           | T  | P  | RR |   |
| TcN-NOET | NI | 167          | 9  | 0  | -  | Agreement : 206 / 225 (92%)<br>Kappa $\pm$ SD = 0.84 $\pm$ 0.09 |
|          | T  | 5            | 25 | 0  | 2  |   |
|          | P  | 0            | 3  | 14 | -  |   |

**FIGURE 5.** Segmental agreement between TcN-NOET and  $^{201}\text{Tl}$  uptake patterns. NI = normal segment; T = transient defects; P = permanent defects; RR = reverse redistribution.

be demonstrated between the visual quality score of the TcN-NOET images and the visual quality score of the  $^{201}\text{Tl}$  images, nor between the visual quality score of the TcN-NOET and the severity of coronary lesion. This holds true whether the latter is estimated by the percent of stenosis and the number of stenotic coronaries, or by the extent of ischemia as assessed by the  $^{201}\text{Tl}$  images acquired during stress. An improvement in the quality of TcN-NOET images might be obtained by increasing the injected dose to 30 mCi. This dose is commonly used with sestamibi or other compounds. Improvement could also be achieved following the search for new dispersants, particularly in the cyclodextrin family.

Despite the lower quality of TcN-NOET images when compared with those obtained with  $^{201}\text{Tl}$ , the results of this clinical study indicate that TcN-NOET and  $^{201}\text{Tl}$  give comparative diagnostic information with SPECT exercise perfusion imaging.

#### Detection of CAD

In the presence of CAD, both agents gave concordant results in 22/25 patients (88%). TcN-NOET and  $^{201}\text{Tl}$  showed similar sensitivity (74% versus 68%,  $p = \text{ns}$ ) for the detection of coronary artery disease with a threshold of 50% or more reduction in luminal diameter and the same specificity (100%). When the threshold was defined as greater than or equal to 70% reduction in luminal diameter, the sensitivity was 79% for both tracers and their specificity did not differ significantly (82% for TcN-NOET and 73% for  $^{201}\text{Tl}$ ).

In addition, TcN-NOET and  $^{201}\text{Tl}$  imaging correlated for individual coronary vessels in 96% of the 75 coronary arteries. The sensitivity and specificity of TcN-NOET and  $^{201}\text{Tl}$  for the detection of diseased vessels were identical. Segmental analysis also showed good correlation for the presence of an initial defect (normal versus abnormal) between TcN-NOET and  $^{201}\text{Tl}$ . The severity of defects was lower with TcN-NOET than with  $^{201}\text{Tl}$ . Thus, TcN-NOET behaves as all the other available technetium complexes and seems equivalent to other technetium tracers of coronary blood flow such as sestamibi, teboroxime and tetrofosmin.

#### Detection of Myocardial Viability

Despite its disadvantages,  $^{201}\text{Tl}$  remains the most commonly used tracer because it can be used both as a tracer of coronary blood flow (initial images during exercise or at rest) and as a marker of myocardial cellular viability because of its redistribution several hours after injection. No other flow tracer presents such characteristics. What about TcN-NOET?

In some patients with a defect on the stress TcN-NOET-SPECT images, myocardial activity was normalized on the images acquired 4 hr later. In those patients, there was a defect with redistribution on the stress redistribution  $^{201}\text{Tl}$  SPECT imaging. The concordance between TcN-NOET normalization and  $^{201}\text{Tl}$  redistribution on images obtained 4 hr postinjection was total (13/13 patients with an initial

defect for  $^{201}\text{Tl}$ ), whereas it was incomplete 2 hr after injection. This result highlights the similarity between the apparent myocardial kinetics of both tracers and enables TcN-NOET to be envisaged as a potential marker of myocardial cellular viability.

The single  $^{201}\text{Tl}$ -redistribution image obtained 4 hr after injection is not sufficient to detect all the viable territories in a patient. It has been shown that some cellular viability exists in 50% of the territories where  $^{201}\text{Tl}$  does not redistribute (11).

To compensate for the lack of sensitivity of the single  $^{201}\text{Tl}$ -redistribution image, the method consisting of  $^{201}\text{Tl}$  reinjection has been proposed and validated (12). Furthermore, it has been demonstrated that  $^{201}\text{Tl}$  reinjection gives the same information on myocardial viability as  $^{201}\text{Tl}$  redistribution at rest (13). In our study, comparison between rest-delayed TcN-NOET and  $^{201}\text{Tl}$  reinjection in patients with permanent defect upon redistribution showed a concordance in three of four patients. Of these, two had no myocardial viability, and one exhibited fill-in of  $^{201}\text{Tl}$  and had normal TcN-NOET rest image. As for the fourth patient, the hypoperfused territory showed normalization of TcN-NOET activity on delayed images and no fill-in following  $^{201}\text{Tl}$  reinjection. Because of the small patient population in whom we could address the issue of myocardial viability after 4-hr delayed images had been obtained, it was impossible to draw any conclusion about the value of TcN-NOET as a marker of myocardial viability. These preliminary results, however, enable us to envisage further clinical studies regarding the diagnosis of myocardial cellular viability using TcN-NOET.

#### CONCLUSION

TcN-NOET and  $^{201}\text{Tl}$  perfusion imaging give comparable diagnostic information for patients undergoing exercise testing for assessment of coronary artery disease. Because it is labeled with  $^{99\text{m}}\text{Tc}$ , TcN-NOET does not exhibit the disadvantages of  $^{201}\text{Tl}$ . By contrast, because of its slow myocardial clearance in comparison to teboroxime, it allows the use of classic SPECT. Finally, because of the normalization of myocardial activity 4 hr after injection in some patients, TcN-NOET appears to be a potential technetium compound equivalent for  $^{201}\text{Tl}$ .

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