Dipyridamole Technetium-99m-2-Methoxy Isobutyl Isonitrile Tomoscintigraphic Imaging for Identifying Diseased Coronary Vessels: Comparison with Thallium-201 Stress-Rest Study

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A same-day double injection protocol employing ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) and myocardial single-photon emission computed tomography (SPECT) for detecting coronary artery disease (CAD) was assessed in 30 patients. SPECT was performed 1 hr after a first injection (250 MBq) of ^{99m}Tc-MIBI, given after 0.56 mg/kg dipyridamole (DPD) infusion. Patients were then reinjected at rest (750 MBq) and were reimaged 1 hr later. Within 1 wk, all patients underwent a complete stress-rest SPECT thallium study. Of the 330 myocardial segments evaluated, 25 were judged ischemic by both techniques, while persistent defects were demonstrated in 50 and in 47 with ^{99m}Tc-MIBI and ^{201}Tl, respectively. Six regions were considered for diseased vessels identification. Sensitivity and specificity for CAD were 100% and 75%, respectively, for both ^{201}Tl and ^{99m}Tc-MIBI. Sensitivity for identification of diseased vessels by ^{201}Tl was 68% for LAD, 89% for RCA, and 80% for LCX as opposed to 75%, 89% and 80%, respectively, by ^{99m}Tc-MIBI. Specificity was 93% in both cases for LAD, 73% and 63% for RCA, and 53% and 46% for LCX.

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Thallium-201 (^{201}Tl) is presently the most widely used radiopharmaceutical for coronary artery disease (CAD) detection. Because of its relatively long physical half-life, however, only small doses can be administered, resulting in protracted imaging and an increased potential for overlooking transient ischemia.

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Recently technetium-99m-hexakis analogs have been proposed for cardiac imaging (*1–4*) and one of these, ^{99m}Tc-methoxyisobutyl isonitrile (^{99m}Tc-MIBI), has demonstrated a myocardial uptake proportional to regional coronary blood flow, low lung uptake, and absence of toxicity (*5–7*).

Preliminary clinical studies have demonstrated the utility of this new ^{99m}Tc-labeled compound for CAD diagnosis (*8–11*). However, because of the absence of significant redistribution, two separate injections of ^{99m}Tc-MIBI are needed to differentiate reversible from non-reversible myocardial ischemia.

The aim of our study was to evaluate a "same-day protocol" based upon the injection of a split dose of ^{99m}Tc-MIBI following dipyridamole administration and at rest a few hours later. Short-term feasibility and diagnostic accuracy, compared to coronary angiography and exercise ^{201}Tl tomoscintigraphic data, were evaluated in patients with absent or varying degrees of CAD.

METHODS

Patients

Thirty patients, 26 males and 4 females, mean age 59 ± 8 yr (range 33–72) were studied. All patients underwent diagnostic coronary angiography within 1 mo of nuclear studies. Significant stenosis was defined as ≥75% coronary lumen obstruction. Patients previously submitted for coronary bypass graft (CABG) or angioplasty were not included in the protocol.

Study Protocol (Figure 1)

Patients who fasted overnight were given 0.142 mg/kg/min of DPD intravenously over 4 min. Isometric exercise (handgrip) was then performed by all subjects in a sitting position. After 3–4 min, 250 MBq of ^{99m}Tc-MIBI were injected, fol-

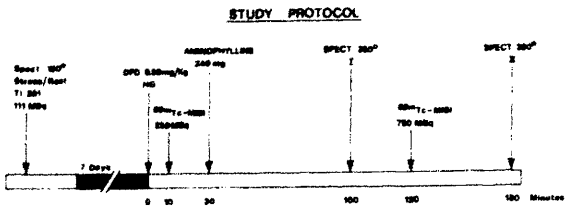

FIGURE 1
Study protocol: A first injection of ^{99m}Tc-MIBI (250 MBq) was performed 10–15 min after commencement of DPD infusion (0.56 mg/kg in 4 min). Aminophylline was then injected to counteract coronary dilation. Cardiac imaging was performed 90 and 180 min after DPD infusion, with the second injection of the radiotracer given at the end of the first examination. A complete stress-rest thallium study was performed in the same patient within seven days.

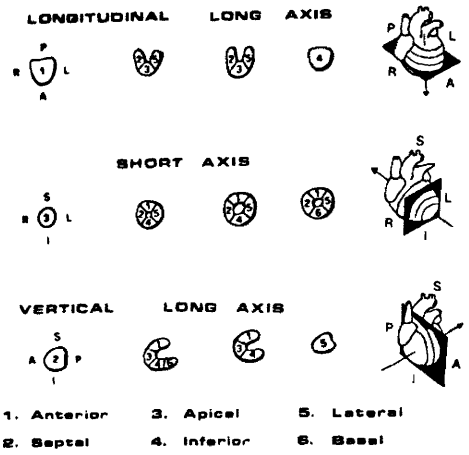

FIGURE 2
Diagrammatic representation of SPECT images. Eleven segments, with reference to middle slices only, were considered (three in the longitudinal, four in the long-vertical and short-axis). They were related to six vascular territories assigned to the three major coronary vessels (for details see text).

lowed 15–20 min later by 240 mg of aminophylline. ECG monitoring was provided throughout the procedure.

Approximately 1 hr after injection, myocardial SPECT was performed. At the end of the first study, a second dose of 750 MBq of ^{99m}Tc-MIBI was injected under rest conditions and patients were reimaged 1 hr later. Between ^{99m}Tc-MIBI administration and imaging procedures, patients were invited to have a light meal to facilitate hepatobiliary excretion. A total time of 3–4 hr was required to complete the whole procedure.

Within 1 wk, the same group of patients underwent immediate postexercise and 3-hr delayed ^{201}Tl tomography after injection of 111 MBq of the tracer at near maximal exercise. Exercise end points were either physical exhaustion, development of angina, sustained ventricular tachyarrhythmias, severe dyspnea, or fatigue.

All anti-anginal drugs were discontinued the night before both SPECT studies, while therapy with digitalis, diuretics, and anti-arrhythmic agents were left unaltered. Selective coronary angiography was performed within 1 mo of the nuclear medicine investigations. Informed consent was obtained from all patients.

Tomoscintigraphic Acquisition and Processing

SPECT was performed by means of a rotating gamma camera with an acquisition matrix of 64 × 64. A general-purpose (LEGP) and a high-resolution collimator (LEHR) were employed for ^{201}Tl and ^{99m}Tc-MIBI, respectively. Thallium tomography was performed with a 180° rotation (from left posterior oblique 45° to right anterior oblique 45°), in 30 steps of 20″ each, in order to reduce acquisition time and avoid early redistribution. However, for MIBI tomography, the entire 360° revolution was used to obtain the best count statistics from the 140-keV technetium photons.

For reconstruction, a standard Hanning filter with a slice thickness of two pixels (1.2 cm) was used. No attempt was made to correct for tissue attenuation. A complete set of oblique projections, realigned along both the long- and short-axis, was obtained.

Tomographic Interpretation

For each study, 11 tomographic segments (segments 2, 3, and 5 from the long-axis; 1, 2, 4, and 5 from the short-axis, and 1, 3, 4, and 6 from the vertical long-axis) were referred to different myocardial regions (Fig. 2) and qualitatively evaluated. Myocardial segments evaluated in two different projections were assigned to six regions of interest or myocardial walls: anterior (segment 1), septal (segment 2), apical (segment 3), inferior (segment 4), and lateral (segment 5) plus a basal region (segment 6), which was studied only in the vertical long-axis projection. The six regions of interest were related to the three major coronary vessels: the left anterior descending (LAD) included the anterior and septal walls, the right coronary artery (RCA) the inferior, and the left circumflex (LCX) the lateral and basal walls. The apical segment was not related to any coronary vessel and was considered only for evaluation of possible ischemia.

Perfusion was considered to be: (a) normal; (b) moderately; or (c) severely reduced. A region was considered abnormal if two segments in two adjacent slices in the same projection or one segment in two slices in different projections were judged hypoperfused. Only middle slices were considered, because of uncertainty about the anatomical relationship of the apex and low count statistics of basal slices (Fig. 2). Segmental perfusion was classified as normal if there was good and homogeneous distribution of tracer following exercise or dipyridamole infusion. Zones of decreased uptake showing substantial improvement on rest or delayed studies were considered to be transient defects (TD) due to ischemia. Unchanging lesions were considered to be persistent defects (PD) and attributed to myocardial scar or very severe myocardial ischemia. Overall interobserver disagreement (evaluated on 50 scans) was 7% (6% for exercise, 9% for redistribution, and 8% for rest images, respectively). Discrepancies were resolved by consensus agreement.

Cardiac Catheterization

Left ventriculography and selective coronary angiography were performed by the Judkin's technique. Multiple projections (at least five for the left coronary vessel and three for the right coronary) were evaluated by two cardiologists not participating in the investigation.

TABLE 1
Patient's Clinical, Angiographic, and Perfusion Data

Patient no	Age (yr)	Coronary arteriograms (% stenosis)				^{201}Tl						^{99m}Tc-MIBI					
		MI	LAD	LCx	RCA	AN	S	AP	I	L	B	AN	S	AP	I	L	B
1	67	N															
2	53	N															
3	58	N				P		P				P	T	P			
4	54	N															
5	65	N	90%			P	T	T	P			P	T	T	P		
6	44	N	90%			T	T	P				T	T	P			
7	33	Y		80%						P	P					P	P
8	55	Y		100%					P	P					P	P	
9	53	N		90%					T	T					T	T	
10	57	N			75%				T	T	T				T		T
11	66	Y			95%				P						P	T	P
12	48	Y			100%				P		P				P		P
13	49	Y	90%		90%		T		P		P		T		P		P
14	61	N	70%		80%		P		P				T		P		
15	49	Y	50%		100%				P	P	P	T			P	T	P
16	62	Y	70%		100%		T		P	P					T		P
17	62	N	80%		95%	T	T	T	T		P		T	T	P		P
18	57	Y	80%		90%				T		T	T				T	P
19	72	Y	100%	60%		P		P					P	P			
20	70	Y	100%	90%		P	T	T				P	T	P	T		
21	58	N		50%	85%						T						T
22	62	Y		90%	100%				P	T	P				P	T	P
23	63	Y		75%	50%				T		P				T		P
24	59	N		90%	100%					T	T				T		P
25	63	Y	90%	65%	100%		P	P	P				P	P	P		
26	65	Y	75%	95%	90%			P	P	T	P				P	P	P
27	68	N	75%	60%	70%	P					P	P				P	P
28	64	Y	95%	80%	100%		P	P	P		P		P	P	P		P
29	64	Y	75%	100%	90%		P	P	P		P		P	P	P		P
30	61	Y	90%	85%	60%				P	P	P				P	P	P
Mean ± s.d.	58.7 ± 8.3																
Total P						5	4	7	14	5	12	4	4	7	14	5	16
Total T						2	6	3	5	5	4	3	7	2	6	5	2

AN = anterior; AP = apical; B = basal; I = inferior; L = lateral; LAD = left anterior descending; LCx = left circumflex; MI = myocardial infarction; P = persistent defect; RCA = right coronary artery; S = septal; and T = transient defect.

Data Analysis

Sensitivity and specificity were calculated according to the number of vessels with significant lesions identified by the two nuclear studies.

Agreement between ^{201}Tl and ^{99m}Tc-MIBI was defined as the sum of concordant myocardial segments or walls divided by the total number considered. The significance of the differences in sensitivity and specificity was assessed by means of McNemar's test. Probability (p) values ≤5% were considered significant. Confidence limits (95%) for proportions were derived from apposite tables (*12*).

RESULTS

Patient data and scintigraphic results are reported in Table 1. Seventeen patients suffered from a previous myocardial infarction.

Coronary Angiography

Twenty-six of the 30 patients presented significant stenosis in at least one of the major coronary arteries; a total of 50 vessels were involved. Eight patients had single-, 12 double-, and 6 triple-vessel disease. Altogether, 16 diseased LAD arteries, 19 RCA, and 15 LCX were found. Isolated lesions of LAD, RCA, and LCX were found in two, three, and three cases, respectively. Association of lesions in LAD and RCA, LAD and LCX, RCA and LCX were found in six, two, and four cases, respectively.

Clinical and Hemodynamic Effects Related to Provocative Tests

Peak effects of both ergometric stress and dipyridamole infusion were as follows: heart rate 123 ±18 versus 89 ± 16 ($p < 0.001$); systolic blood pressure 174 ± 25 versus 146 ± 24 ($p < 0.001$); double product 21 ± 5 × 10^3 versus 13 ± 3 × 10^3 ($p < 0.001$). Seven patients complained of chest pain during exercise and seven complained during drug infusion. ST depression ≥2 mm was recorded in 18 patients after ergometric stress and in four following dipyridamole infusion. Typical chest pain was reported in 14 and 3 patients, respectively. The most common side-effects during DPD infusion were headache in 7 patients (23%), dizziness in 3 (10%), and facial flushing and nausea in 1 (3%).

Sensitivity and Specificity for Identification of CAD and Diseased Vessels

Overall sensitivity and specificity for ischemic heart disease were 100% and 75%, respectively, for both ^{201}Tl and MIBI tomography. Identification of diseased vessels by both radiopharmaceuticals is reported in Figure 3. No statistically significant differences were found between the two studies regarding diseased vessel identification. Lesions on LAD were identified with a lower sensitivity than lesions on RCA and LCX. Diagnostic accuracy was superior when RCA and LCX were assigned to the same inferoposterior territory (sensitivity: 92% for ^{201}Tl versus 96% for ^{99m}Tc-MIBI; specificity: 83% for both ^{201}Tl and ^{99m}Tc-MIBI).

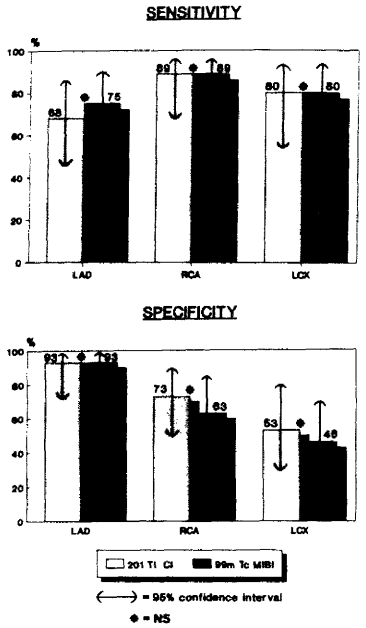

FIGURE 3
Sensitivity and specificity of the two radiotracers for identification of diseased vessels (LAD = left anterior descending; RCA = right coronary artery; LCx = left circumflex artery).

Previous myocardial infarction was detected with a sensitivity of 94% by ^{201}Tl and of 100% by ^{99m}Tc-MIBI. Specificity was 54% for both examinations. Apical defects were detected 10 and 9 times, respectively. Single-vessel disease was correctly diagnosed by both methods in all instances. However, in four cases with ^{201}Tl and in six with ^{99m}Tc-MIBI, it was not possible to say whether RCA and LCX lesions were isolated or combined.

In 13/18 of the patients with double- or triple-disease (72%), vessel disease at least two of the diseased vessels were identified. In a patient with mitral valve prolapse and normal coronary arteries (Patient 3), two defects were identified by ^{201}Tl and three by MIBI/SPECT.

Segmental Agreement for Presence of Persistent or Transient Defects

A total of 330 segments were analyzed. Initial defects were found in 72 segments with ^{201}Tl (32%) and in 75 with MIBI (33%). Partial or complete reperfusion oc-

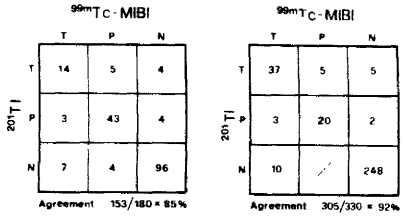

FIGURE 4
Agreement for identification of myocardial regions (n = 180) and of myocardial segments (n = 330) with normal perfusion (N), transient (T), or persistent defects (P).

curred in 25 segments with both radiotracers. Concordance between the two exams for identification of perfusion status in the 180 regions or the 330 myocardial segments is reported in Figure 4. In 13 cases, an hypoperfused segment was detected by only one of the two compounds.

Agreement in identifying fixed or transient hypoperfusion in each of the six myocardial walls is reported in Figure 5.

DISCUSSION

Preliminary data in the literature have demonstrated the utility of ^{99m}Tc-MIBI in identifying and localizing significant coronary stenosis (*13–17*). Due to the absence of redistribution, however, two injections of ^{99m}Tc-MIBI on separate days are usually suggested to differentiate acute from chronic ischemia. This may result in low outpatient compliance. Consequently, different approaches based on split dose injections of ^{99m}Tc-MIBI have been proposed for "same day" studies, using either ergometric exercise (*18–20*) or dipyridamole (*21*) as provocative tests.

Taillefer demonstrated that short- and long-time intervals between rest and stress injections have the same diagnostic accuracy (*18*), suggesting that a rest-stress sequence should be preferred since more segments with reversible ischemia are detected (*20*). Although in our experience this method showed satisfying results overall, it failed to detect segments with low-grade hypoperfusions, so that mild ischemia or small myocardial infarctions were overlooked (*22*). Since it has been shown that myocardial extraction of MIBI is relatively

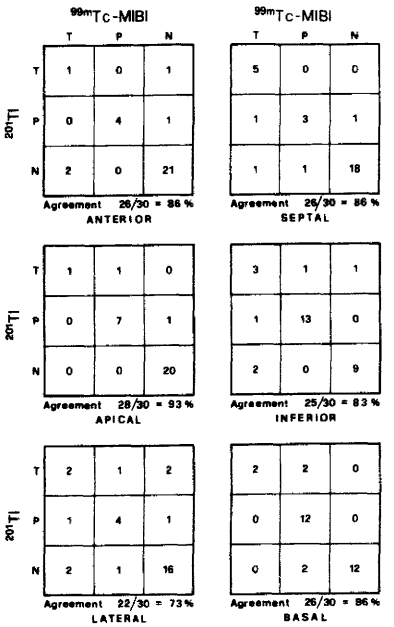

FIGURE 5
Agreement for identification of perfusion in each myocardial territory.

low and non-linear at high flow rates and that it may be decreased during exercise (*23*), physical exercise, therefore, may not be adequate to delineate mild as well as rapidly transient myocardial ischemia. Maximal effort should therefore be maintained for several minutes after tracer administration. Moreover, the effects of severe acute ischemia and body temperature on MIBI cellular extraction are still unclear. These could be limiting factors when injection at rest is planned as the second step of the same-day study.

The infusion of a potent coronary dilator such as DPD allows a perfusion discrepancy that may be maintained for several minutes (*24–27*). The drug potently affects coronary blood flow and may induce discrepancies between coronary flow and poststenotic pressure that may be revealed by ^{99m}Tc-MIBI imaging (*23,28*). The administration of DPD is safe as coronary and systemic vascular effects may be completely reversed by aminophylline infusion (*29,30*). In addition, the prolonged vasodilating effect of DPD on coronary vessels, as compared with the shorter response to physical exercise, may be useful with ^{99m}Tc-MIBI whose blood clearance is longer than that of ^{201}Tl.

With this in mind, we decided to compare exercise thallium scintigraphy, the most widely accepted test in nuclear cardiology, with DPD stress and ^{99m}Tc-MIBI imaging.

Sensitivity and Specifity

The proposed protocol proved easy to perform and detected significantly stenosed vessels with satisfying accuracy. Comparison with ^{201}Tl data yielded similar results with regards to identification of patients with coronary disease, diseased vessels, or defect size.

Although only qualitatively evaluated, our results are in agreement with those obtained by other authors using either exercise- or dipyridamole-^{201}Tl (*31–33*) or ^{99m}Tc-MIBI (*16,34*). However, a lower detection of LAD stenosis was observed. We cannot provide any explanation for this result, except perhaps the fact that we might have favored a higher specificity. Detection of inferoposterior hypoperfusions was, on the contrary, very satisfying (Fig. 6). These results might well depend on the use of SPECT instead of the planar technique and have been previously reported by others (*32,34, 35*).

As expected, single-vessel disease was detected with a greater accuracy since it is easier to identify limited defects when the remaining myocardium is normally perfused (Fig. 7). Although multiple-vessel disease was detected in more than 70% of cases, involvement of the three major coronaries was detected only in a minority and no improvement was found using ^{99m}Tc-MIBI over ^{201}Tl. This limitation, however, is inherent to the scintigraphic technique which cannot discriminate between normally perfused and "less hypoperfused" segments in cases of three-vessel disease. The adoption of other

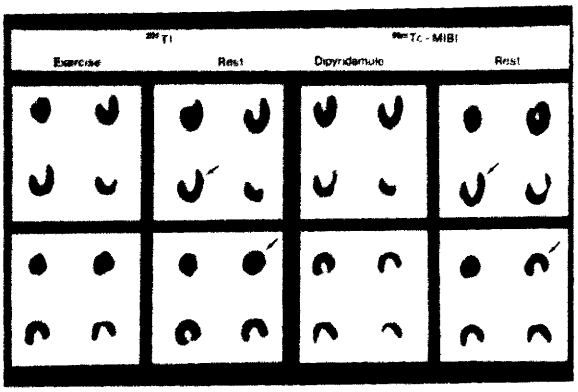

FIGURE 6
Patient with a 90% stenosis of the left circumflex and occlusion of the right coronary artery. Both the provocative tests showed a posterolateral defect with late rest normalization (indicated by the arrow). A mild redistribution in the inferoposterior wall is observed only in the ^{201}Tl study.

imaging criteria such as lung uptake, transient ventricle dilation, or right ventricle visualization might have improved triple-vessel disease identification (*36*). Moreover, the arbitrary attribution of myocardial territories to specific coronary vessels might be misleading, especially in the case of RCA and LCX territories.

Detection of previous myocardial infarctions was very high with both radiotracers, although specificity was low. This might be attributed to the presence of very severe ischemia or of hibernating myocardium. In these cases, standard 3-4-hr delays between ^{201}Tl stress and redistribution imaging might have been insufficient for detecting viable myocardium (*37–38*). On the other hand, the adoption of a rest-stress protocol, as suggested by Taillefer, could have demonstrated a partial filling of the defect.

Limitations of the Study

Two aspects of our study may be open to criticism. First, the use of two different provocative tests (exercise for ^{201}Tl and DPD infusion for ^{99m}Tc-MIBI). Second, the use of different collimators (LEGP for ^{201}Tl and LEHR for ^{99m}Tc) and the adoption of a 360° revolution for ^{99m}Tc-MIBI studies. In making these choices, we assumed that both the higher energy photopeak of ^{99m}Tc and the higher administered dose, together with the use of a LEHR collimator, would have improved image resolution. We also assumed that count statistics, which are also helpful for increasing image resolution, would benefit from the adoption of a 360° revolution.

However, our subsequent experience, as well as literature data (*39*), showed that an 180° revolution would produce images of the same or better quality.

Although DPD infusion was well tolerated, it cannot be referred to as the preferential test, especially in patients with either low blood pressure levels or who are prone to headache or dizziness. Moreover, nonlinear MIBI extraction at the high flow rates induced by DPD infusion, could lead to a decreased sensitivity for the detection of less severe stenoses. Finally, with DPD most of the clinical and ECG information derived from the exercise test is missing.

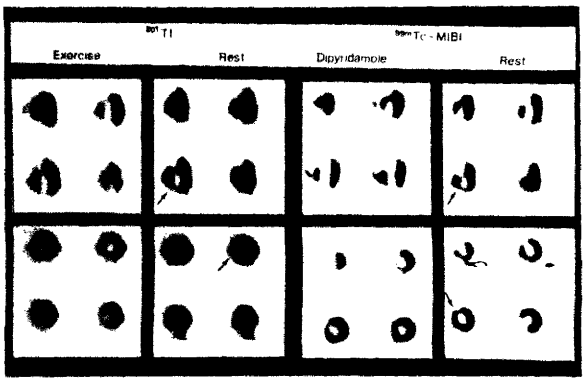

FIGURE 7
A patient with 90% stenosis of the LAD. Reversible defects are present in the anterior and septal walls in the longitudinal long- and short-axes. Diagnostic information obtained by the two tests is similar, although MIBI images are of better quality.

Comparison with Previous Studies

Several studies compared ^{99m}Tc-MIBI and ^{201}Tl. In particular, a good correlation of reversible and irreversible ischemia was demonstrated (*16,33,35*). The former radiopharmaceutical, however, showed a higher sensitivity for vessel identification in three-vessel disease patients. Superiority of SPECT over the planar technique was also demonstrated. These studies were, however, all performed on separate days.

The feasibility of same-day studies using either the rest or the stress injection as the first step of the imaging procedure was also tested (*18,19*). Only patients with proven CAD, most of whom had single-vessel disease were studied. No attempt was made to identify diseased vessels and specificity was not calculated due to the absence of disease-free patients.

Moreover, adoption of the rest-stress sequence as suggested (*20*) would require performing stress tests on patients still carrying radioactivity from the preceding injection, which may decrease sensitivity for the detection of subtle disease.

In conclusion, a ^{99m}Tc-MIBI same-day split injection study, with the first injection given after DPD infusion, may be safely performed, giving results equivalent to those of standard stress-rest thallium studies.

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