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Evaluation of Coronary Artery Disease Using Technetium-99m-Sestamibi First-Pass and Perfusion Imaging with Dipyridamole Infusion

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The aims of this study were: (1) to test whether first-pass radionuclide angiocardiography (FPRNA) adds useful information to perfusion scintigraphy; and (2) to assess the relative accuracy of perfusion and functional imaging in combination with dipyridamole for the evaluation of CAD. **Methods:** Thirty patients with angiographically proven CAD (17 with prior infarction) were studied on separate days at rest and with dipyridamole infusion (0.7 mg/kg over 4 min). Tomographic images were evaluated using an uptake score. Dipyridamole FPRNA was considered positive in case of stress-induced wall motion abnormality or ejection fraction decrease. **Results:** The CAD detection rate of perfusion imaging was 100%, while that of FPRNA was 70% using wall motion criteria, 63% using ejection fraction response and 77% considering any abnormality. For CAD localization, perfusion imaging showed 76% sensitivity, 96% specificity and 82% accuracy. FPRNA results were 50%, 100% and 60%, respectively. Perfusion imaging was significantly superior to FPRNA also excluding from the analysis the infarct-related vessels. FPRNA did not identify multivessel CAD, which was correctly detected by perfusion imaging in most cases. Both techniques were more sensitive in case of ≥90% stenosis, but the difference was more remarkable for FPRNA (sensitivity 65% versus 14%, $p < 0.0005$). **Conclusions:** Dipyridamole FPRNA did not add noteworthy clinical information to perfusion imaging regarding CAD detection and evaluation of disease extent. The main contribution of a positive FPRNA was its relation with coronary obstruction severity. These results confirm the superiority of perfusion over functional imaging in combination with coronary vasodilators.

Key Words: coronary artery disease; dipyridamole; first-pass radionuclide angiocardiography; perfusion imaging; technetium-99m-sestamibi

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Coronary vasodilation by dipyridamole or adenosine has been demonstrated to induce significant blood flow heterogeneity in the presence of vessel obstruction (*1–3*), which is detected by myocardial perfusion imaging (*4–6*). At present, dipyridamole and adenosine are the most commonly employed pharmacological stress testing agents in patients who are unable to perform adequate dynamic exercise (*7,8*). The results of both adenosine and dipyridamole ^{201}Tl myocardial imaging are comparable to those of exercise studies for the detection and risk stratification of coronary artery disease (CAD) (*6–10*). More recently, dipyridamole and adenosine have been employed with good results in conjunction with ^{99m}Tc-labeled perfusion agents (^{99m}Tc-sestamibi, ^{99m}Tc-teboroxime) (*11–17*).

Through induced blood flow heterogeneity, dipyridamole and adenosine may also produce true myocardial ischemia (*18–19*), which can be recognized by the presence of angina, ischemic ST-T changes on the electrocardiogram and wall-motion abnormalities. Therefore, several groups employed dipyridamole or adenosine echocardiography for the detection of CAD, its evaluation and prognostic stratification (*20–25*). The published studies, however, report variable results, probably because several factors influence the actual induction of ischemia by dipyridamole and adenosine. Therefore, studies performed in the same patient population and possibly during a single pharmacological stimulus are still needed. Until now, relatively few reports fulfilled these requirements (*26–31*), and ^{99m}Tc-sestamibi perfusion imaging was used for the comparison in one study only (*32*).

Furthermore, by using ^{99m}Tc-labeled perfusion agents, a new approach for the simultaneous evaluation of perfusion and function is given by the collection of first-pass radionuclide angiocardiography (FPRNA) at the moment of tracer injection (*33–35*). This approach has been proposed and validated only for exercise FPRNA (*36–38*), but its use in combination with dipyridamole and adenosine should be even easier due to the absence of interferences from increased heart rate, patient motion and breathing.

The aims of the present study were: (1) to test the feasibility of the simultaneous evaluation of perfusion and left-ventricular function using ^{99m}Tc-sestamibi in combination

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TABLE 1
Demographic, Clinical, Angiographic and Scintigraphic Findings of the Patient Population

				SPECT			FPRNA			
Patient no.	Age/Sex	MI	CAD	RCA	LAD	LCX	LAD	LPD	EF rest	EF dipy
1	56/F	0	1-v	0	+	0	0	0	0.65	0.74
2	70/F	A	2-v	+	⊕ +	0	⊕	+	0.43	0.40
3	63/M	0	1-v	0	+	0	+	0	0.57	0.50
4	66/M	0	1-v	0	+	0	+	0	0.65	0.60
5	67/M	A	3-v	+	⊕ +	+	⊕ +	0	0.54	0.43
6	62/M	0	1-v	0	0	+	0	+	0.68	0.60
7	62/M	A	2-v	0	⊕ +	0	⊕	0	0.50	0.56
8	37/M	A	2-v	0	⊕ +	+	⊕	0	0.50	0.50
9	54/M	A	3-v	+	0	0	0	0	0.64	0.77
10	57/M	I	1-v	0	0	⊕ +	0	⊕ +	0.41	0.36
11	51/M	0	3-v	0	0	+	0	0	0.64	0.66
12	63/F	0	1-v	0	0	+	0	⊕ +	0.57	0.64
13	39/M	0	1-v	0	+	0	+	0	0.56	0.48
14	47/M	A	3-v	+	⊕ +	+	⊕ +	0	0.56	0.50
15	47/M	I	3-v	⊕ +	0	+	0	⊕ +	0.52	0.52
16	39/M	I	3-v	⊕ +	0	0	0	0	0.59	0.62
17	52/M	A	2-v	0	+	0	0	0	0.65	0.76
18	46/M	A	3-v	+	⊕ +	0	+	0	0.67	0.56
19	51/M	0	3-v	+	+	+	+	0	0.60	0.53
20	54/F	0	1-v	0	+	0	0	0	0.65	0.74
21	50/F	0	1-v	+	0	0	0	+	0.63	0.62
22	48/M	A	2-v	⊕ +	⊕ +	0	+	0	0.71	0.74
23	47/M	I	2-v	⊕ +	0	0	0	⊕	0.51	0.53
24	72/M	I	2-v	⊕ +	0	+	0	⊕ +	0.54	0.48
25	45/M	I	3-v	⊕ +	+	⊕ +	+	⊕ +	0.47	0.42
26	70/M	0	3-v	+	+	0	0	0	0.61	0.65
27	56/M	0	2-v	+	0	+	0	0	0.47	0.47
28	65/M	I	3-v	⊕ +	+	0	+	⊕ +	0.48	0.42
29	67/M	0	3-v	+	⊕ +	0	+	0	0.52	0.49
30	71/M	I	2-v	+	0	⊕ +	0	0	0.68	0.65

A = anterior; CAD = coronary artery disease; dipy = dipyridamole; EF = left ventricular ejection fraction; FPRNA = first-pass radionuclide angiocardiography; I = inferior; LAD = left anterior descending artery; LCX = left circumflex artery; LPD = left posterior descending circulation; MI = myocardial infarction; RCA = right coronary artery; rest = baseline study; 1-v = one-vessel CAD; 2-v = two-vessel CAD; 3-v = three-vessel CAD; 0 = no prior MI or normal perfusion or wall motion, respectively; ⊕ = baseline perfusion or wall motion abnormality; and + = dipyridamole-induced perfusion or wall motion abnormality.

with dipyridamole infusion; (2) to verify whether dipyridamole FPRNA adds useful data to perfusion scintigraphy for the assessment of CAD extent and severity; and (3) to gain new insight into the effectiveness of functional imaging in conjunction with coronary vasodilators.

METHODS

Patient Population and Study Protocol

The study population consisted of 30 patients, prospectively recruited from those with known CAD, who were referred to our nuclear medicine department for evaluation of angina which was refractory to medical treatment. Patients with cardiac conditions other than CAD (i.e., valvular disease, cardiomyopathy, etc.) or with history of previous coronary angioplasty or bypass grafting were excluded from the study population. There were 25 males and 5 females, with ages ranging from 37 to 72 yr (mean 55.8 ± 10.2 yr). Seventeen patients had a history of previous myocardial infarction (anterior in 9 and inferior in 8). Table 1 lists the main features of the patient population. Antianginal drugs were discontinued for 24 hr (nitrates), 48 hr (calcium channel blockers) or 1 wk (beta-blockers) before entering the study. All subjects were instructed not to consume drugs containing xanthine or substances for 36 hr before the dipyridamole test. The clinical status of all patients remained unchanged for the duration of the study. The study protocol was approved by the ethics committee of our institution and all patients gave informed consent to participate in the study.

The patients underwent a baseline FPRNA study at the time of ^{99m}Tc-sestamibi injection. Patients then had a light meal and myocardial perfusion scintigraphy was performed beginning at least 1 hr after tracer injection (60–92 min). Twenty-four hours later after overnight fasting, the patients underwent the dipyridamole test (infusion of 0.7 mg/kg body weight over 4 min) (*13,39*). Patient conditions during dipyridamole infusion were checked by continuous electrocardiographic monitoring and blood pressure measurements at 1-min intervals. As soon as the patient's typical angina developed and/or horizontal depression of ST segment was observed on the electrocardiogram, or 3 min after the end of dipyridamole infusion, ^{99m}Tc-sestamibi was injected and FPRNA acquired. Intravenous aminophylline (100 mg) was given to all patients 5 min after the administration of ^{99m}Tc-sestamibi, inde-

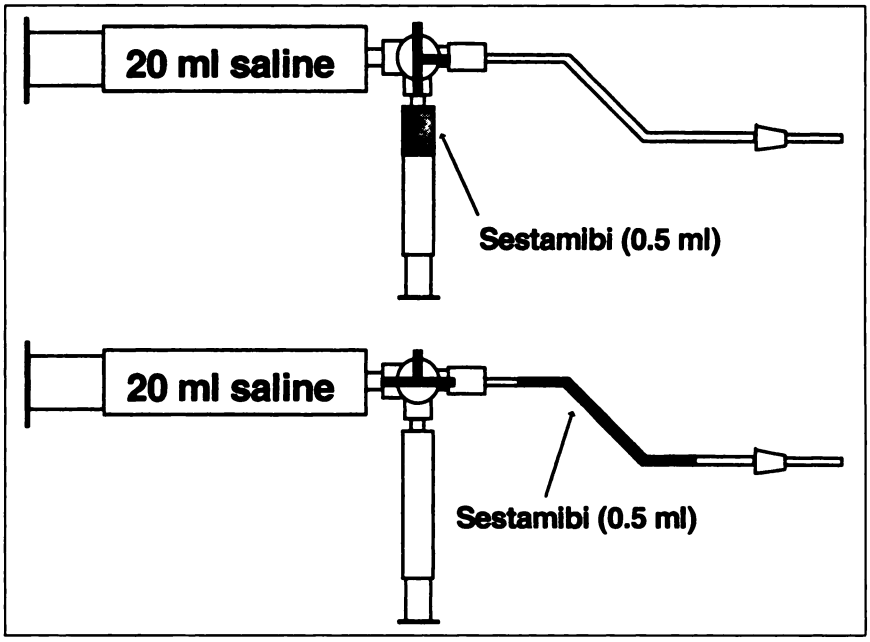

FIGURE 1. Schematic drawing of the method used to obtain a good quality bolus injection for FPRNA.

pendent of adverse reactions. Myocardial scintigraphy was performed using the same procedure described for the rest study (acquisition delay: 62–94 min after injection). Biplane coronary angiography performed within 15 days of the scintigraphic studies was available in all patients.

Coronary Angiography

Heart catheterization was performed using either the brachial or the transfemoral approach. Biplane left ventricular cineangiography was performed in the 30 degrees right anterior oblique projection and in the 60 degrees left anterior oblique projection using a pig-tail catheter. Left and right coronary angiograms were acquired in multiple projections in order to identify the presence and severity of the lesions. A stenosis was classified as significant whenever the vessel narrowing was ≥50% and was classified as severe whenever it was ≥90%. All studies were visually evaluated by an experienced observer who had no knowledge of the patient's identity or the results of the other examinations.

First-Pass Radionuclide Angiocardiography

FPRNA was acquired in the 30 degrees right anterior oblique projection, with the patient supine, using an Elscint Apex SP4 gamma camera (Haifa, Israel) equipped with low-energy, all-purpose collimator and a 20% window centered on the 140 keV photopeak of ^{99m}Tc. In order to obtain a high quality bolus injection, the following procedure was carried out. First, an 18-gauge indwelling cannula was inserted into an antecubital vein of the right arm (possibly the basilic vein) and connected with a saline-filled tubing extension ending with a three-way stop-cock. Second, a 0.5-ml solution containing the dose of 20 mCi (740 MBq) of ^{99m}Tc-sestamibi was injected into the tubing through the lateral opening of the stop-cock, preceded and followed by a small air bubble. Third, a syringe with 20 ml of saline solution was connected to the straight opening of the stop-cock. Fourth, after having switched the stop-cock, the saline solution was smoothly but forcefully injected, pushing the tracer bolus in front of it into the patient (Fig. 1). The bolus quality was controlled by the time-activity curve obtained in a region of interest (ROI) drawn on the superior caval vein with good results (FWHM < 1 sec).

The study was acquired in frame mode (24 frames/sec), using a ×2 zoom factor and an electrocardiographic gating for the reconstruction of the representative cardiac cycle. In the gamma camera used, a 20% count rate loss is observed at count rates over 150,000 counts/sec. A typical study collected approximately 120,000 cps during the right phase and 80,000 counts/sec during the left phase. Therefore, no significant count losses were expected.

The left ventricular ejection fraction was calculated from the background-subtracted time-activity curve. Two measurements were performed for each study and the mean of the two values, which never differed by more than 2 ejection fraction units, was adopted for the data analysis. The reproducibility of FPRNA in our laboratory had been previously tested in another patient population by acquiring two separate studies a few days apart under stable clinical conditions and had been proven to be satisfactory (Pearson's r = 0.94, s.e.e. = three ejection fraction units) (*35*, DuPont: Data on File). The regional wall motion was analyzed using the left ventricular end diastolic and end systolic outlines with the aid of the representative cycle cine movie display of the regional ejection fraction images and of the Fourier amplitude images.

Myocardial Perfusion Scintigraphy

Myocardial perfusion scintigraphy was performed using a double-headed gamma camera (Rotacamera, Siemens, Erlanger, Germany) equipped with ultra-high resolution collimators and interfaced with a Hewlett Packard A900 computer system. A 20% window centered on the ^{99m}Tc 140 keV photopeak was used. SPECT was acquired using both heads, a 360° rotation arc in the step-and-shoot mode with 90 projections of 20 sec each, and recorded on 64 × 64 matrices. The SPECT images were reconstructed using an iterative algorithm according to the conjugate gradient method (*40,41*), and were then reoriented according to the heart axes so that short-axis and horizontal and vertical long-axis slices were obtained.

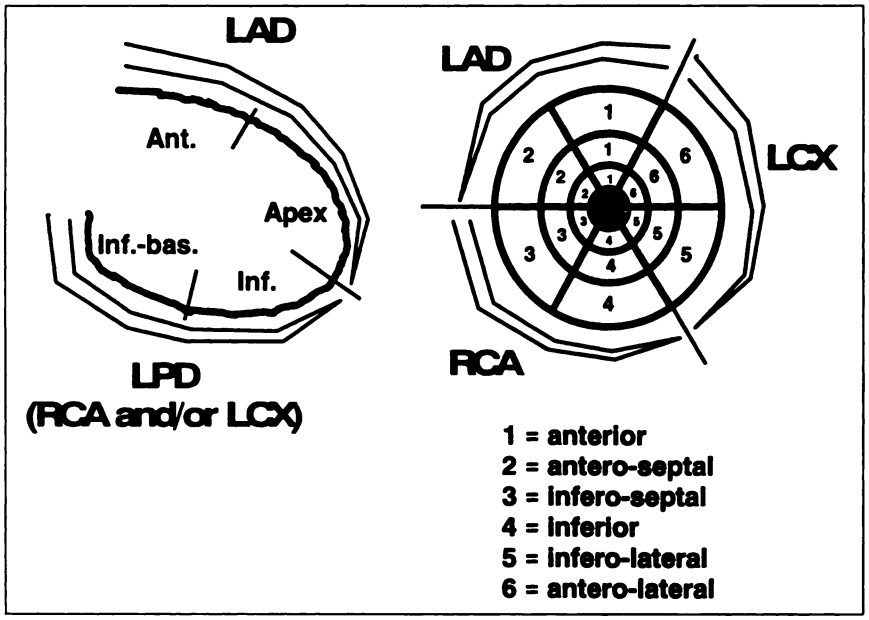

FIGURE 2. Diagram showing the adopted segment division for FPRNA (left panel) and perfusion imaging (right panel). The attribution of the segments to the different vascular territories is also shown. The gray area in the middle of the three short-axis slices of perfusion imaging represents the two apical segments of the mid-ventricular vertical long-axis slice, which were used to evaluate the apical perfusion and were assigned to the LAD. Ant. = anterior, Inf. = inferior; Inf.-bas. = infero-basal; LAD = left anterior descending artery; LCX = left circumflex artery; LPD = left posterior descending artery; and RCA = right coronary artery.

Image Evaluation

The studies were independently evaluated by two experienced observers who had no knowledge of the patient's history or the results of the other examinations. In case of disagreement, the images were reviewed with the help of a third observer and finally classified by consensus.

For FPRNA analysis, the left ventricular wall was divided into four segments (anterior, apical, inferior, infero-basal) (*34*) (Fig. 2). On the basis of a qualitative evaluation, the regional wall motion of each segment was classified normal, mildly hypokinetic, severely hypokinetic, akinetic or dyskinetic. The dipyridamole study was judged positive for CAD in the presence of either a lack of increase in left ventricular ejection fraction (*39,42,43*) and/or a transient regional wall motion abnormality that was absent or of lesser degree in the baseline study. For individual diseased vessel localization, the results of FPRNA were evaluated by considering only two vessel distributions (i.e., the left anterior descending artery and the left posterior descending circulation, the latter including both the right coronary and the left circumflex artery) (Fig. 2).

SPECT perfusion images were evaluated qualitatively and the tracer uptake was defined as normal, slightly reduced, severely reduced or absent. Three short-axis slices (basal, mid-ventricular and sub-apical) were divided into six segments each and considered together with the antero-apical and the infero-apical segments of the mid-ventricular long-axis slice (*44*) (Fig. 2). A fixed defect seen unchanged on both rest and dipyridamole studies was classified as an infarct scar. A decrease in uptake in the dipyridamole myocardial scintigraphy as compared to the baseline pattern was considered inducible hypoperfusion in that territory. For individual coronary artery localization, the various segments were attributed to the three main coronary territories as proposed by Kiat et al. (*44*) (Fig. 2).

To evaluate the agreement between the two radionuclide techniques in the same vascular territories, SPECT and FPRNA segments assigned to the left anterior descending artery were directly compared, whereas the SPECT segments assigned to the right coronary or left circumflex arteries were considered together and compared with the segments attributed to the left posterior circulation in FPRNA.

Statistical Analysis

Since our patient population included only subjects with known CAD, we did not estimate the diagnostic sensitivity or specificity of the radionuclide studies, but only the CAD detection rate. Sensitivity for the identification of individual diseased vessels was defined as the number of territories with abnormal findings divided by the total number of diseased territories. Specificity was defined as the number of territories with normal results divided by the total of territories without angiographic CAD. Data were expressed when appropriate as the mean ± s. d. The comparison of baseline and dipyridamole hemodynamics was performed using the two-tailed signed rank test for paired data. For the comparison of proportions, the Fisher's exact test was employed. The agreement of the two radionuclide techniques in evaluating the same coronary territories was assessed by the McNemar's test. The relation of the left ventricular ejection fraction response with CAD extent and severity was analyzed by one-way analysis of variance and by the Spearman's rank correlation coefficient. A probability value of $p < 0.05$ was considered significant.

RESULTS

Left Ventricular and Coronary Angiography

Of the 17 patients with a history of prior myocardial infarction, 16 had abnormal wall motion by left ventricular cineangiography. An inferior and infero-lateral akinesia was demonstrated in an additional patient, who had an occluded left circumflex branch, but no history of previous infarction. By coronary angiography, 9 patients had one-vessel CAD, 9 had two-vessel CAD and 12 had three-vessel CAD. Therefore, a total of 63 vessels presented a ≥50% stenosis. The left anterior descending artery was involved in 23 cases, the left circumflex artery in 21 and the right coronary artery in 19 (with a total of 25 left posterior descending circulations with CAD). A high grade (≥90%)

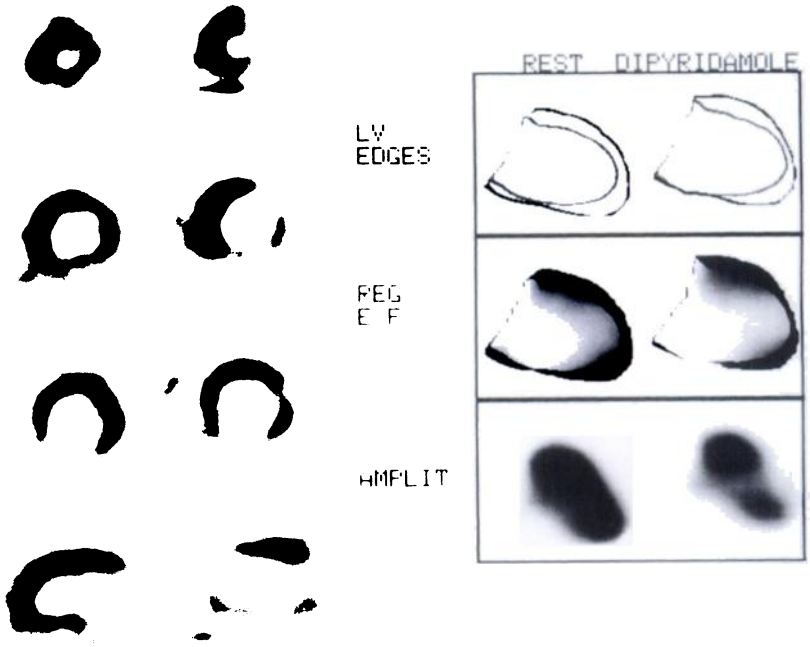

FIGURE 3. From left to right: baseline and dipyridamole perfusion images; three short-axis slices from subapical (top row) to basal, plus the midventricular vertical long-axis slice; and baseline (rest) and dipyridamole FPRNA images; left ventricular end-diastolic and end-systolic outlines (LV edges), regional ejection fraction (reg. e.f.) and Fourier amplitude (amplit). An infero-lateral defect is seen in the baseline study, corresponding to an infero-basal severe hypokinesis. After dipyridamole, this defect worsens and enlarges and the region becomes akinetic; furthermore an apical defect appears, accompanied by hypokinesis in the FPRNA images.

stenosis was observed in 29 arteries; if the left posterior descending circulation was considered instead of the right coronary artery and the left circumflex artery, however, a total of 26 territories showed a ≥90% obstruction.

Hemodynamics and Adverse Reactions

The heart rate, systolic blood pressure values and rate-pressure product at the moment of the baseline study were respectively: 66.4 ± 13.2 bpm, 137 ± 18.8 mmHg and 9,149 ± 2,606 bpm × mmHg. At the end of dipyridamole infusion, the heart rate was 85.4 ± 16.9 bpm ($p < 0.00001$ versus baseline), the systolic blood pressure was 129 ± 25.5 mmHg ($p < 0.005$ versus baseline) and the rate pressure product was 11,118 ± 3,963 ($p < 0.0001$ versus baseline). Mild and noncardiac adverse reactions (headache, flushing and nausea) developed in 10 patients. In six patients ischemic ST-segment changes on the electrocardiogram were noted. In five of these patients typical angina occurred. Both the noncardiac and the ischemic symptoms and signs disappeared promptly after the routine administration of intravenous aminophylline.

Detection of Coronary Artery Disease

Table 1 shows the results of FPRNA and perfusion imaging. Figures 3 and 4 show two examples of studies obtained in our patient population.

Eighteen perfusion defects in the baseline study were observed in 16 subjects, involving 15 asynergic scars of prior infarction and 3 territories related to diseased vessels, but with normal wall motion in the contrast left ventriculography. Dipyridamole myocardial perfusion scintigraphy was positive for stress-induced perfusion defects in all patients (100% CAD detection rate) (Fig. 5).

Baseline FPRNA showed a wall-motion abnormality in 12 patients, 4 of whom also had an abnormal baseline ejection fraction. The baseline abnormal territories involved 11 asynergic infarct scars and the already mentioned asynergic territory without history of infarction. Dipyridamole induced a wall-motion abnormality in 18 patients. Therefore, considering the baseline and/or the dipyridamole-induced wall-motion abnormalities, FPRNA was positive in 21 patients (CAD detection rate: 70%, $p < 0.001$ versus perfusion imaging). The ejection fraction criteria for an abnormal response to dipyridamole were fulfilled in 19 patients (CAD detection rate: 63%, $p < 0.0002$ versus perfusion imaging). Overall, dipyridamole FPRNA was positive in 23 patients (CAD detection rate: 77%, $p < 0.01$ versus perfusion imaging) (Fig. 5).

In the 13 patients without prior myocardial infarction, dipyridamole FPRNA detected a wall-motion abnormality in 8 (CAD detection rate: 62%, $p < 0.02$ versus 100% of perfusion imaging). In seven of these eight patients and in an additional patient, the ejection fraction response to dipyridamole was abnormal (CAD detection rate using the ejection fraction criteria: 62%, $p < 0.02$ versus perfusion imaging). Overall, wall motion or the ejection fraction criteria for CAD was fulfilled in 9 of 13 patients without previous infarction (CAD detection rate: 69%, $p < 0.05$ versus perfusion imaging) (Fig. 5).

In the 6 patients with typical angina and/or ischemic ST segment changes in the electrocardiogram induced by dipyridamole infusion, the overall CAD detection rate of FPRNA was not significantly different from the value observed in the other patients (83% versus 75%).

Localization of Diseased Coronary Arteries

Of all territories (infarcted or not) with significant CAD, perfusion imaging recognized 48 as diseased (sensitivity 76%) and was abnormal in one without significant stenoses

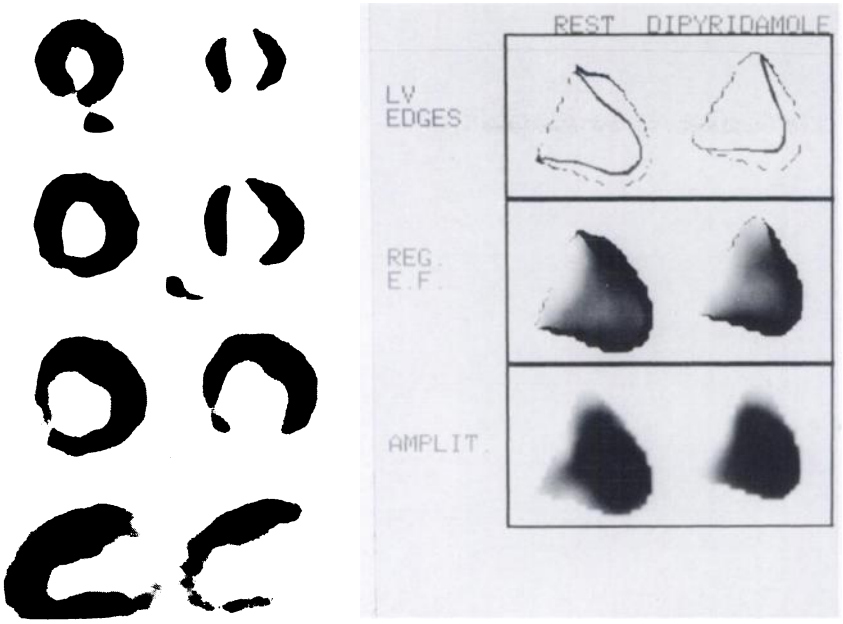

FIGURE 4. Same image disposition as in Figure 2. Baseline perfusion and FPRNA are normal. After dipyridamole, both an antero-apical and an inferior defect appear, whereas FPRNA remains normal.

(specificity 96%); thus, the overall accuracy was 82%. FPRNA was abnormal in 24 of the 48 evaluated coronary artery territories (sensitivity 50%, $p < 0.005$ versus perfusion imaging), but was never abnormal in a territory without significant coronary stenosis (specificity 100%, NS versus perfusion imaging). The overall accuracy of FPRNA was 60% ($p < 0.0005$ versus perfusion imaging) (Fig. 6).

A separate analysis was performed after excluding the coronary arteries related to infarcted territories: thus, 73 vessels (46 with significant obstruction) were considered for perfusion imaging and 43 (31 with significant obstruction) were considered for FPRNA. The sensitivity of perfusion imaging was 67% and that of FPRNA 35% ($p < 0.01$); the specificity was 96% and 100%, respectively (NS), and the accuracy 78% and 53%, respectively ($p < 0.01$) (Fig. 6).

Figure 7 shows the agreement of SPECT perfusion scintigraphy and FPRNA for the evaluation of the same coronary artery territories. The significant difference between the two techniques is apparent, taking into account all territories and excluding those with previous infarction.

Assessment of Extent of Coronary Artery Disease

In 15 of 21 patients with multivessel CAD, uptake defects were demonstrated by perfusion imaging in more than one territory. More specifically, of the 9 patients with two-vessel CAD, 6 were correctly classified by SPECT and 3 were found to have one-vessel disease. Of the 12 patients with three-vessel CAD, 4 were correctly classified, 5 were found to have two-vessel disease and 3 showed a single-vessel involvement. FPRNA detected a wall-motion ab-

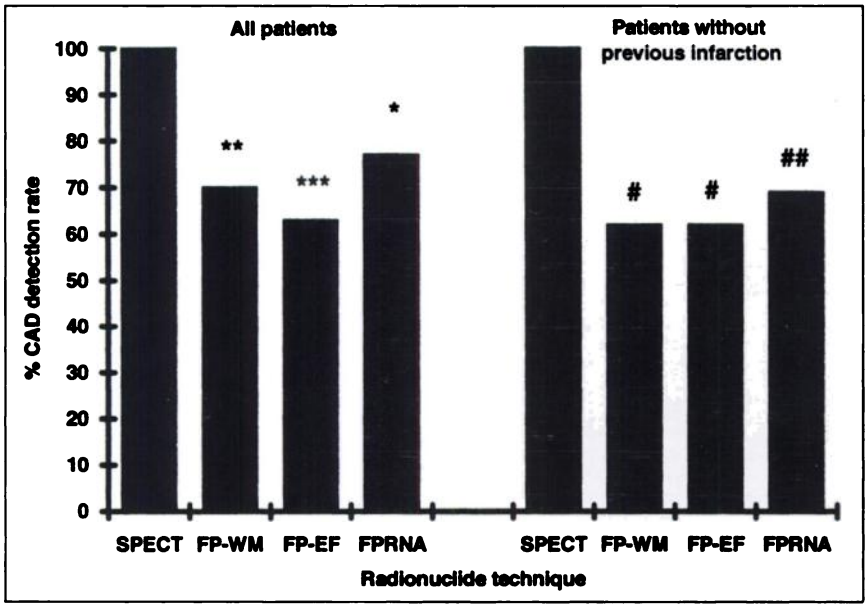

FIGURE 5. Bar histogram showing the CAD detection rate of perfusion imaging (SPECT) and FPRNA, considering respectively the wall motion criteria (FP-WM), the ejection fraction response (FP-EF) or the presence of any abnormality (FPRNA). * = $p < 0.01$; ** = $p < 0.001$; *** = $p < 0.0002$; # = $p < 0.02$; ## = $p < 0.05$; (all versus perfusion imaging).

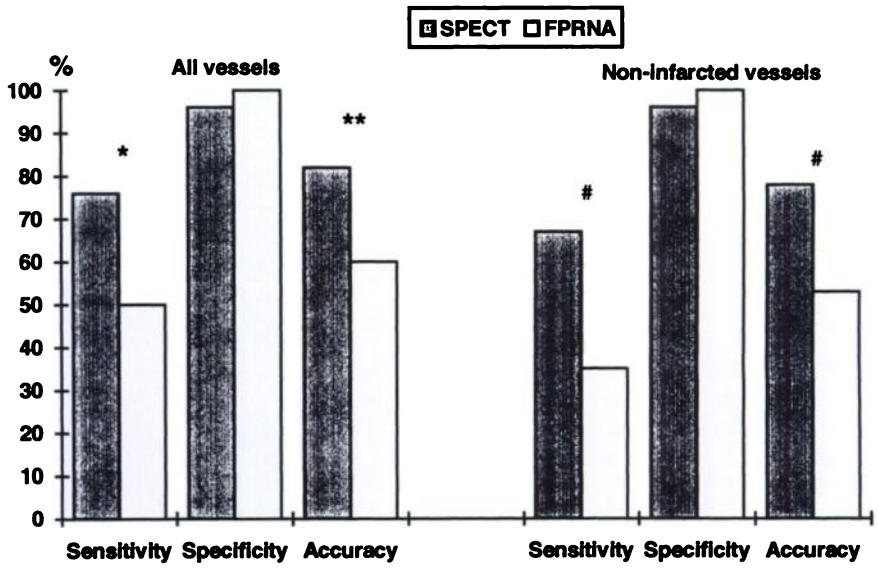

FIGURE 6. Bar histogram showing the results of dipyridamole perfusion imaging (SPECT) and FPRNA for CAD localization, respectively, considering all vessels (left group of bars) and excluding the infarct-related arteries (right group). * = $p < 0.005$; ** = $p < 0.0005$; # = $p < 0.01$.

normality of both examined territories in only 3 patients ($p < 0.001$ versus perfusion imaging). Examining only the patients without previous infarction, perfusion imaging correctly classified 4 of 5 multivessel patients and FPRNA classified none of them ($p < 0.05$ versus perfusion imaging). Neither the analysis of variance nor the Spearman's correlation coefficient demonstrated any relation between the dipyridamole-induced changes of the left ventricular ejection fraction and the number of diseased vessels.

Assessment of Coronary Stenosis Severity

A perfusion defect was observed in 26 of the 29 arteries with a high-grade stenosis (≥90% of vessel lumen) (sensitivity 90%) and in 22 of the 34 with a <90% obstruction (sensitivity 65%, $p < 0.02$). A wall-motion abnormality was detected by FPRNA after dipyridamole in 17 of the 26 territories considered for this investigation which presented a ≥90% lesion (sensitivity 65%), and in only 3 with a <90% obstruction (sensitivity 14%, $p < 0.0005$). Limiting the analysis to the diseased vessel in territories without prior infarction, perfusion imaging was positive in 15 of 19 with ≥90% obstruction (sensitivity 79%) and in 16 of 27 with <90% narrowing (sensitivity 59%, NS). FPRNA was positive in 8 of 16 vessels with ≥90% (sensitivity 50%) and in 3 of 15 with <90% obstruction (sensitivity 20%, NS).

Figures 8 and 9 show the agreement of the two radionuclide techniques in the detection of coronary involvement, taking into account the severity of vessel narrowing and either including or excluding the territories with prior infarction. A significant difference between perfusion and FPRNA was found in stenoses ≥50% and <90%, but was no longer observed in obstructions ≥90%, independently from the presence of previous infarction. Both the one-way analysis of variance ($p = 0.08$) and the Spearman's correlation coefficient (-0.31, $p = 0.09$) showed a trend to a different response of left-ventricular ejection fraction to dipyridamole infusion in the patients with at least one severe stenosis compared to the others, although the statistical significance was not attained.

DISCUSSION

Dipyridamole or adenosine perfusion scintigraphy has been proven to be accurate for the diagnosis of suspected CAD and effective for prognostic stratification (*6–17*). Since the blood flow heterogeneity produced by these

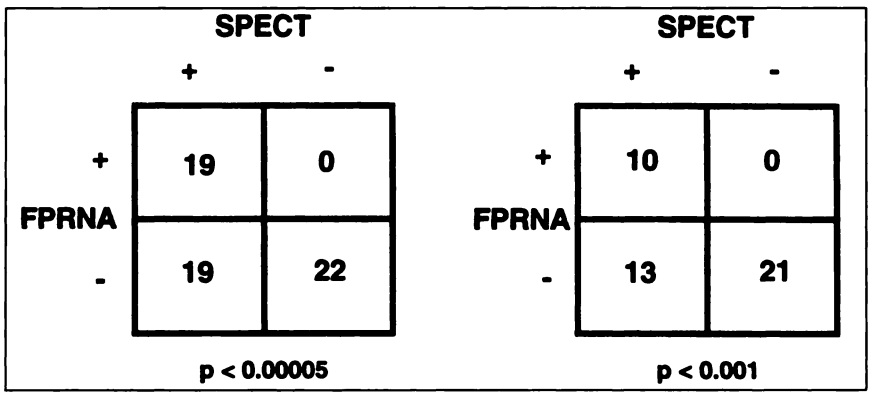

FIGURE 7. Agreement for classification of individual coronary vessels between perfusion imaging (SPECT) and FPRNA in the left anterior and left posterior descending territories. The left diagram includes all territories, the right only those without previous infarction.

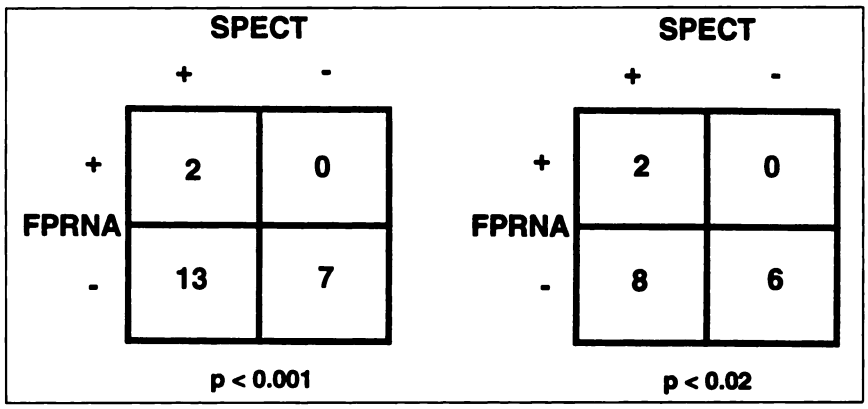

FIGURE 8. Agreement for classification of individual coronary arteries between perfusion imaging (SPECT) and FPRNA in vessels with ≥50% and <90% obstruction; the left diagram includes all of them, the right only those without previous infarction.

agents may induce myocardial ischemia, their use in combination with imaging techniques, which can detect ischemic wall-motion abnormalities, has been proposed (*20*). Unfortunately, dipyridamole and adenosine induce actual ischemia in only a limited number of cases. In an animal model of single-vessel obstruction, Fung et al. (*19*) demonstrated that dipyridamole induced a blood flow heterogeneity in all animals by producing a higher increase of flow in the normal than in the stenosed territory; however, a true reduction of coronary blood flow followed by actual ischemia was observed only in about 50% of cases. In humans, several factors may influence the induction of myocardial ischemia by dipyridamole or adenosine. Among them are the extent and severity of CAD (*43,45*), the concomitant antianginal therapy (*46*) and the dosage of dipyridamole and adenosine (*21*). Therefore, it is not surprising that the value of functional changes induced by dipyridamole or adenosine is far less established than that of perfusion abnormalities. Most data have been obtained employing two-dimensional echocardiography and the reported sensitivity values vary substantially, ranging from 10% (*28*) to 85% (*22*) for the adenosine test and from 40% (*30*) to 90% (*24*) using dipyridamole. With regard to equilibrium radionuclide angiocardiography, Harris et al. (*47*) found only a 13% sensitivity of dipyridamole testing for the diagnosis of CAD. This number increased to 31% in the study of Sochor et al. (*48*), whereas Cates et al. (*39*), using a higher dipyridamole dosage and less stringent positivity criteria, were able to detect CAD in 67% of cases. Even better results were reported by Klein et al. who concluded that a true dipyridamole-induced ischemia is present in most patients (*43*). These authors also suggested a relation between the extent and severity of CAD and the left-ventricular ejection fraction response (*43*). More homogeneous data are reported about the specificity of adenosine and dipyridamole functional imaging, with values constantly over 85% (*21,24,39*).

However, relatively few data are available comparing perfusion and functional changes caused by a single pharmacological stress in the same patient population. Using the collection of echocardiographic images and the injection of ^{201}Tl during a single adenosine infusion, Nguyen et al. (*28*) found a very low sensitivity of echocardiography (10%) compared to perfusion imaging (88%). Using a similar approach and dipyridamole infusion, Labovitz et al. (*26*) demonstrated a 74% sensitivity of echocardiography for the detection of ^{201}Tl perfusion defects. Jain et al. (*27*) performed the comparison after the oral administration of dipyridamole, observing a positive echocardiographic study in 14 of 16 patients with a perfusion defect in ^{201}Tl scintigraphy. Perin et al. (*29*) found a significant superiority of dipyridamole ^{201}Tl over echocardiography both with regard to detection of CAD and to evaluation of its extent. Finally, in the only published study employing ^{99m}Tc-sestamibi perfusion scintigraphy, Marwick et al. (*32*) found that the sensitivity of adenosine echocardiography was

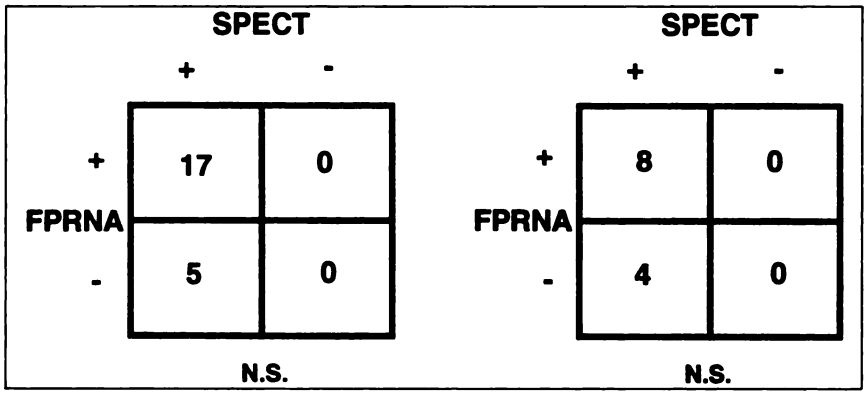

FIGURE 9. Agreement for classification of individual coronary arteries between perfusion imaging (SPECT) and FPRNA in vessels with ≥90% obstruction; the left diagram includes all of them, the right only those without previous infarction.

58% in front of 86% for perfusion imaging. In the same patients, dobutamine echocardiography achieved 85% sensitivity and the authors suggested that this is the best pharmacologic stressor for functional imaging (*32*). All these studies seem to indicate that functional imaging combined with dipyridamole or adenosine infusion is only a moderately sensitive test for the evaluation of suspect CAD.

The use of ^{99m}Tc-labeled perfusion agents has opened the way to the simultaneous assessment by radionuclide imaging of perfusion and function during single stress. Various studies have already demonstrated the feasibility of this approach during dynamic exercise testing (*36–38*). This combined evaluation should be even simpler during dipyridamole or adenosine stress, since the patient may be studied supine and no artifacts due to patient's motion, increased heart rate and increased breathing frequency should be expected. Also, by taking the above mentioned limitations of dipyridamole functional imaging into account, the possibility of achieving additional useful information without increasing the radiation burden for the patient should be considered.

In the present study, the feasibility of a similar approach and its clinical value for the identification of CAD and the definition of its extent and severity in patients with effort angina have been tested. Our study shows that FPRNA with ^{99m}Tc-sestamibi in combination with dipyridamole infusion is easily feasible and that the higher dose compared to the usual protocol for dipyridamole perfusion scintigraphy, which is necessary for a reliable functional study, does not cause any problem in terms of adverse effects, in accordance with previous reports (*13,21,39*). For the identification of CAD, however, our results show that in front of the extremely high CAD detection rate obtained by perfusion imaging, dipyridamole FPRNA-detected wall-motion abnormalities in 70% of patients and reached a slightly higher detection rate only when the changes of the left ventricular ejection fraction were also taken into account.

As for the extent of CAD, which is a major task of imaging techniques in patients with known disease, perfusion imaging allowed correct identification in most patients affected by multivessel CAD and accurate classification of the individual vessel status. On the contrary, FPRNA obtained poor results in both cases. These trends, observed in the whole patient population, were also demonstrated after having excluded the patients with previous infarction, and, respectively, the coronary arteries related to infarcted territories. The left ventricular ejection fraction response, which improved the first-pass detection rate, appeared unable to differentiate reliably between patients with one-vessel disease from those with multivessel disease. Thus, in our patient population and independent of prior infarction, FPRNA data did not improve the coronary disease detection rate and extent evaluation achieved by dipyridamole perfusion imaging. These data support the conclusion that dipyridamole radionuclide angiocardiography alone has no practical role in the work-up of CAD and confirm that the radionuclide technique to be used with coronary vasodilators is perfusion scintigraphy (*49*).

We also tested the influence of the severity of coronary artery stenosis on the perfusion and FPRNA results. Both techniques were more sensitive in cases of high-grade obstruction. The gain was more remarkable for FPRNA, so there was no significant difference of sensitivity compared to perfusion imaging for the detection of ≥90% stenoses. Therefore, the positivity of dipyridamole FPRNA suggested the presence of severe narrowing of coronary arteries related to that territory. Similar data were obtained by taking into account only the vessels without prior infarction. Interestingly, the left ventricular ejection fraction also showed a clear, albeit not statistically significant, trend to respond more abnormally in the patients with at least one severe stenosis compared to the others. Taking these last data into account, however, the technical effort of collecting FPRNA during ^{99m}Tc-sestamibi perfusion imaging with dipyridamole hardly seems justified by the achievable additional information.

Various limitations of the present study must be taken into account. The patient population was relatively small and highly selected, including only patients with known CAD. Therefore, no data could be obtained about the specificity of the employed techniques for the diagnosis of disease. A second selection drawback was that several patients had a history of prior infarction. In our opinion, however, this population represents a more realistic sample for the use of imaging techniques devoted to the definition of CAD extent and severity than a population of subjects in whom the diagnosis itself is still uncertain. Furthermore, the separate analysis of the data, after having excluded the patients or the vessels with prior infarction, fully confirmed the results obtained in the whole population. Finally, our data are in good agreement with those of Marwick et al. (*32*) who examined only patients without a history of infarction. However, caution must be paid in extending our results to other techniques of functional imaging with dipyridamole or adenosine. Indeed, FPRNA has several disadvantages for wall-motion abnormality detection when compared to echocardiography, such as the extremely short time interval which can be examined and the impossibility of evaluating the changes of systolic thickening. More importantly, FPRNA does not allow an accurate evaluation of the wall-motion in the nontangential segments, which are the septum and the lateral wall when the 30° right anterior oblique view is employed. However, the use of regional ejection fraction images improves the analysis of wall-motion changes also in nontangential segments (*50*). On the other hand, FPRNA also offers remarkable advantages, such as allowing a reliable estimate of the quantitative changes in global function induced by the pharmacological stress, being highly reproducible and less observer-dependent (*34,35,51*). Furthermore, the presence of a majority of patients with severe and extensive CAD and the absence of antianginal therapy were both circumstances which should have theoretically increased the rate

of dipyridamole-induced ischemic changes to the highest level (*43,46*). The evaluation of the impact of other advantages of echocardiography such as ease, safety, wide availability and lower costs compared to nuclear medicine techniques was beyond the scope of this study.

In conclusion, dipyridamole FPRNA appeared to be of limited value for CAD detection and assessment of disease extent when compared to perfusion imaging. Specifically, the collection of FPRNA in the context of dipyridamole myocardial scintigraphy with ^{99m}Tc-sestamibi did not add important information to the perfusion images. More generally, this study seems to confirm that, with the exception of the high specificity, the reliability of functional imaging in conjunction with dipyridamole is significantly lower than that of perfusion imaging, even in a population with severe and diffuse CAD studied in therapeutic washout.

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