Dipyridamole and exercise SPET provide different estimates of myocardial ischaemic areas: role of the severity of coronary stenoses and of the increase in heart rate during exercise

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Abstract. In patients unable to perform a maximal exercise test, dipyridamole single-photon emission tomography (SPET) has a higher capacity than exercise SPET to detect coronary artery disease (CAD). However, in patients with myocardial ischaemia who are able to perform a maximal exercise test, it is not known whether these two tests may be equally used to assess the areas of myocardial ischaemia. This study was aimed at comparing the results provided by dipyridamole and exercise SPET in CAD patients with documented exercise myocardial ischaemia. Forty CAD patients who had undergone exercise thallium-201 SPET and who had myocardial ischaemia documented by an unequivocally positive exercise test underwent an additional ^{201}Tl SPET study after dipyridamole infusion and low-level (40 W) exercise. The extent of defects was compared between the two tests and predictors of discrepant results were sought among data from exercise testing and coronary angiography. The extent of SPET defects was equivalent between the two tests in only 11 patients (28%), larger defects being observed with exercise in 18 [average difference: 12%±5% of left ventricle (LV)] and with dipyridamole in 11 (average difference: 15%±11% of LV). The best independent predictors of discrepancies between the two tests were: (1) increase in heart rate at exercise SPET, with defects being smaller at exercise than after dipyridamole in none of the patients with an increase >60 bpm (0/14), but in 42% of the others (11/26; P=0.004); and (2) an ischaemic territory related to a <70% coronary stenosis, for which SPET defects were always induced at exercise (10/10) but in only 30% (3/10) with dipyridamole (P=0.0004). Exercise and dipyridamole SPET provide different estimates of myocardial ischaemic areas. Dipyridamole allows the unmasking of perfusion abnormalities in patients who have low increases in heart rate at exercise SPET. However, dipyridamole is also much less efficient at inducing perfusion abnormalities in the ischaemic areas supplied by coronary stenoses of intermediate severity at rest angiography.

Key words: Myocardium – Ischaemia – Dipyridamole – Exercise – Scintigraphy

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Introduction

Dipyridamole or adenosine single-photon emission tomography (SPET) is generally used instead of exercise SPET to detect coronary artery disease (CAD) in patients unable to perform a maximal exercise test. Such practice is strongly supported by the findings that performing additional dipyridamole SPET may unmask perfusion abnormalities in patients having a sub-maximal exercise SPET [1, 2] and may also increase the sensitivity of the test for the detection of coronary stenoses [3]. However, exercise SPET may also be useful to assess prognosis in patients already identified as having CAD. In patients having significant CAD, indeed, the presence of a normal exercise SPET ("false-negative" result) has been shown to correlate with an excellent prognosis [4, 5]. Moreover, the extent of the underperfused left ventricular (LV) area determined by exercise SPET has been shown to be a major prognostic indicator [6, 7, 8, 9, 10, 11] that complements conventional predictors from exercise testing and coronary angiography [6, 7, 8, 9].

Up to now, however, dipyridamole and exercise SPET have mainly been compared in the setting of detection of CAD and in the particular population of patients unable to perform a maximal exercise test [1, 2, 3]. Therefore, it is not known whether these two tests are of equal value for assessment of the extent of underperfused areas in CAD patients who have both a good physical capacity and suspected myocardial ischaemia.

This prospective study was designed to compare the extent of myocardial ischaemic areas ascertained by dipyridamole and exercise SPET in patients with proven CAD and identified as having a strong likelihood of myocardial ischaemia on the basis of an unequivocally positive ECG exercise test.

Materials and methods

Selection of patients

The study population comprised 40 patients prospectively selected from patients referred for exercise thallium-201 SPET in our department, who had: (1) a proven history of CAD (>50% coronary stenosis on coronary angiography and/or history of myocardial infarction); (2) an unequivocally positive exercise test (sustained typical angina and/or ≥2-mm ST segment depression) at the time of the exercise ^{201}Tl SPET; (3) no contra-indications to dipyridamole infusion (asthma, respiratory insufficiency, recent history of stroke etc.) and no medication including theophylline or aminophylline and (4) given written informed consent to participation in the study.

In the 3 weeks following the exercise ^{201}Tl SPET, at the same hour of the day and with a drug regimen that was kept unchanged, the patients underwent an additional ^{201}Tl SPET study after dipyridamole infusion combined with low-level exercise testing. The patients were also asked to avoid taking coffee, tea, chocolate or cola during the 48 h preceding the dipyridamole test. This protocol was approved by the local ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Nancy).

Stress protocols and radionuclide imaging

Exercise testing. For the baseline exercise SPET, the exercise test was performed on a bicycle ergometer, with the patient in the upright position. Blood pressure and a 12-lead ECG were recorded at rest and at each minute of exercise, with continuous monitoring on the leads V1, V5 and aVF.

The protocol began at 20 W and increased by 20-W increments every minute. Exercise end-points were physical exhaustion, sustained angina pectoris, >2-mm ST segment depression, sustained ventricular tachyarrhythmia, exertional hypotension or achievement of maximal predicted heart rate (220 – age) [12].

Dipyridamole test. Dipyridamole was given intravenously at a standard dose of 0.56 mg/kg body weight and over a 4-min period [13]. In order to provide an enhanced image quality, equivalent to that achieved with exercise SPET, low-level exercise was added [14]: bicycle exercise was started at 20 W at the third minute of dipyridamole infusion, and at the end of the infusion the workload was increased to 40 W and maintained at this level for 4 min. A minimum of 1 min after ^{201}Tl injection, 62.5 mg of aminophylline was given intravenously. Blood pressure and a 12-lead ECG were recorded before and at each minute of the test, and continuous monitoring was performed on leads V1, V5 and aVF.

^{201}Tl SPET imaging. For both tests, an activity of 37 MBq of ^{201}Tl per 25 kg body weight (without exceeding 130 MBq) was injected intravenously 1 min before the termination of exercise. SPET imaging was initiated 10 min later. A rest SPET acquisition was performed on the day of exercise SPET, using a technique of ^{201}Tl rest-reinjection [15]: 3–4 h after the exercise, a second dose of ^{201}Tl, corresponding to one-third of the dose injected at exercise, was reinjected at rest and SPET imaging was initiated 60 min later. In order to limit the amount of injected ^{201}Tl activity, the rest-reinjection acquisition was not repeated on the day of the dipyridamole test and the initial rest-reinjection acquisition was used as the reference for both exercise and dipyridamole tests.

All tomographic acquisitions were performed in the prone position (to prevent artefacts due to upward creep and inferior attenuation [16]), using a rotating gamma camera equipped with a low-energy, high-resolution parallel-hole collimator, interfaced with a computer system (Sopha Medical Systems, Inc., Columbia, Md.). The technique for the acquisition and reconstruction of the tomographic images has been described elsewhere [17].

Data analysis

^{201}Tl SPET. Analysis of the reconstructed tomographic slices was performed visually by consensus of two experienced observers who were unaware of the clinical data. Among the three SPET acquisitions from each patient (exercise, dipyridamole and rest acquisitions), only the rest acquisition was identified, so that the observers could not know whether the stress acquisitions corresponded to exercise or to dipyridamole testing.

As previously described [17, 18, 19], the myocardial uptake was scored on a 20-segment division of the LV using a 4-point grading system: 0, normal uptake; 1, equivocal; 2, moderate reduction of uptake and 3, severe reduction of uptake. For each stress acquisition, the extent of the total stress defect was determined by the percentage of segments showing an uptake score ≥2 on the stress acquisition, and the extent of the reversible stress defect was determined by the percentage of segments with stress defect which had a ≥1-point decrease in their uptake score on the rest acquisition.

As described previously [19], the reversible perfusion defects were assigned to the normal distribution of individual coronary vessels, while taking into account the dominance of the coronary circulation identified on the angiograms. Thus anterior, anteroseptal, anterolateral and apical segments were assigned to the left anterior descending coronary artery, inferolateral segments to the left circumflex coronary artery, and inferior and inferoseptal segments to the right coronary artery or to the left circumflex artery, depending on the right or left dominance of the circulation [20]. A vascular territory was considered to be ischaemic when a reversible defect was documented by using either exercise or dipyridamole SPET.

A difference in defect extent of ≥5% of the LV (≥1 segment) between exercise and dipyridamole SPET was considered significant. This threshold value was found to be close to the mean+1.5 SD of the variability in the determination of the extent of SPET defects. For our two observers' visual analysis, this variability was

assessed as follows: 20 abnormal exercise ^{201}Tl SPET acquisitions were rescored at least 2 months apart, and the mean±SD of the absolute values of the differences in defect extent between the two analyses was calculated.

The influence on our results of the definition of a significant difference in defect extent between the two tests was assessed by an additional analysis. This analysis was performed with a higher threshold value of ≥10% of the LV, only differences in stress defects which were ≥2 segments then being considered significant.

Coronary angiography. Coronary angiograms could be analysed in 35 patients (88%) in whom coronary angiography had been performed within no more than 2 months from the SPET study (mean interval: 20±16 days).

The number of diseased coronary vessels was determined according to the Coronary Artery Surgery Study criteria for stenosis location [21] and calculated using two different cut-off values for a significant stenosis: ≥70% and ≥50% reduction in diameter. The TIMI score [22] was determined for occluded or sub-occluded vessels and the Rentrop score [23] for collateralised vessels.

For each ischaemic vascular territory determined at ^{201}Tl SPET, an ischaemia-related stenosis was determined on the corresponding coronary vessel. When multiple stenoses were located on the same vessel, only the most severely narrowed segment was taken into account.

The percentage of diameter reduction and the minimal luminal diameter of the ischaemia-related coronary stenoses were determined using the Cardiovascular Angiography Analysis System (CAAS, Pie Medical, Maastricht, The Netherlands), which is an automated contour detection technique [19, 24].

The ischaemia-related stenoses were classified into three categories: (1) those with mild to moderate narrowing (40%–69% diameter reduction); (2) those with severe narrowing (≥70% diameter reduction) but with normal flow (TIMI score = 3); and (3) the totally or sub-totally occluded vessels (TIMI score ≤2).

Statistical analysis

Comparisons between discrete variables were performed using the chi-square test and, when inappropriate, the Fisher exact test for two-group comparisons and the rank-sum test for three-group comparisons, groups being used as an ordinal variable.

Continuous variables were expressed as mean±SD and compared with non-parametric tests: the Wilcoxon test was used for paired series and for unpaired series, the Mann-Whitney test for two-group comparisons and the Kruskal-Wallis test for three-group comparisons.

A P value <0.05 was considered to be indicative of a significant difference. Multivariate analysis was performed using a stepwise linear regression analysis (StatviewTM II, Abacus Concepts, Inc., Berkeley); at each step, variables were entered at a P value of 0.05 and removed at a P value of 0.10.

Results

Characteristics of patients

The study population comprised 38 men and two women; their mean age was 61±8 years (range 43–73) and nine (23%) had diabetes mellitus. A history of coronary angioplasty or of bypass grafting was documented in 17 (43%) and three (8%) cases, respectively, and 17 patients (43%) had had a myocardial infarction.

Among the 35 patients who had undergone coronary angiography, 14 (40%) had (≥50%) single-vessel disease, 15 (43%) had two-vessel disease and six (17%) had three-vessel disease.

Twenty-six patients (65%) had angina and 32 (80%) were receiving anti-anginal treatment at the time of the stress tests: 21 (53%) were receiving beta-blockers, 16 (40%) calcium antagonists and 13 (33%) nitrates or molsidomine.

Data from the baseline exercise SPET are shown in Table 1. Heart rates ranged from 54 to 107 bpm at rest (mean: 72±14 bpm) and from 83 to 166 bpm at maximal exercise (mean: 127±19 bpm). In 16 patients, the ischaemic signs (angina and/or ≥2-mm ST segment depression) occurred after they had reached 85% of the maximal predicted heart rate. In the remaining 24 patients, by contrast, the exercise was stopped before this level had been reached. This was because of early occurrence of >2-mm ST depression or angina in 15 cases and occurrence of physical exhaustion in nine patients, all of these nine patients having 2-mm ST segment depression at maximal exercise.

Comparison between exercise and dipyridamole SPET

Dipyridamole SPET was performed an average of 10±4 days after exercise SPET. Comparisons between the two tests are detailed in Table 1. Since the dipyridamole tests only included a 40-W bicycle exercise, maximal heart rate and maximal blood pressure were lower at dipyridamole than at exercise. Moreover, ST segment depression was markedly greater at exercise (2.2±1.3 mm) than at dipyridamole (1.3±1.3 mm, P=0.0001), and the percentage of positive tests (chest pain or ST segment depression) was higher at exercise (100%) than at dipyridamole (73%, P=0.0004).

Overall, the ^{201}Tl SPET results looked comparable between the two tests: the rates of abnormal SPET were 95% for exercise (38/40) and 88% for dipyridamole (35/40), all patients having an abnormal SPET either at dipyridamole or at exercise. The average extent of reversible defects, as well as that of total defects, was similar when compared between the two tests (Table 1).

However, when the analysis was applied to individual patients, discrepancies were extremely common (Fig. 1). In fact the extent of stress defects was similar for the two tests in only 11 patients (28%). Larger defects were observed after exercise in 18 patients (45%), for whom the average difference in defect extent between the two tests was 12%±5% of LV (range 5%–20% of LV), while larger defects were observed after dipyridamole in 11 patients (28%), for whom the average difference in defect extent between the two tests was 15%±11% of LV (range 5%–35% of LV). The individual variations in the extent

Table 1. Comparison between data from exercise SPET and those from dipyridamole/low-level exercise SPET in the overall population

	Exercise test	Dipyridamole/ low-level exercise	*P* value
Haemodynamic parameters			
Heart rate (bpm)			
Maximal	127±19	98±17	0.0001
Increase	55±18	26±11	0.0001
Systolic pressure (mmHg)			
Maximal	182±26	155±23	0.0001
Increase	46±25	24±18	0.0001
Double product (×100)			
Maximal	232±52	152±35	0.0001
Increase	135±49	57±24	0.0001
Exercise testing results			
ST segment depression (mm)	2.2±1.3	1.3±1.3	0.0001
≥1 mm	32 (80%)	23 (58%)	NS
Chest pain	19 (48%)	14 (35%)	NS
Chest pain or ST depression	40 (100%)	29 (73%)	0.0004
^{201}Tl SPET results			
Abnormal SPET	38 (95%)	35 (88%)	NS
Reversible defects	36 (90%)	33 (83%)	NS
Extent of stress defects (% LV)	21±15	20±16	NS
Extent of reversible defects (% LV)	16±10	15±14	NS

bpm, Beats per minute; LV, left ventricle; NS, non significant

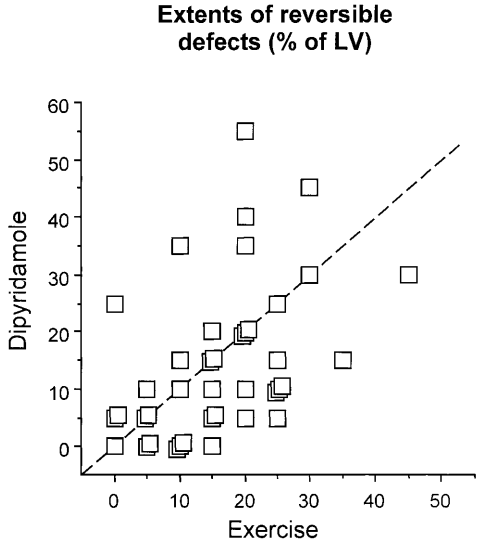

Fig. 1. Comparison of the extent of ischaemic areas (reversible ^{201}Tl SPET defects) using exercise or dipyridamole in individual patients

of defects between the two tests are illustrated in Figure 1 and examples of discrepant results are given in Figs. 2, 3, 4 and 5.

Predictors of the discrepancies between the two tests

Analysis of patients. The patients were classified into three groups: (1) those with larger defects at exercise; (2) those with equivalent defects between the two tests, and (3) those with larger defects at dipyridamole. Correlations with variables from the case history, stress tests and coronary angiography were sought. The results are detailed in Tables 2 and 3.

Only two variables were significantly related to the discrepancies between the two tests: the number of ≥50% stenosed vessels (patients with larger defects at exercise than at dipyridamole having less extensive CAD) and the increase in heart rate at exercise SPET compared with baseline, for which a lower value was related to larger defects at dipyridamole compared with exercise.

When patients for whom the defects were larger at dipyridamole (and thus possibly underestimated at exercise) were compared with the others, the sole significant variable was a lower increase in heart rate at exercise SPET (P=0.04). This result is illustrated in Fig. 6.

In a retrospective analysis, an increase in heart rate higher than 60 beats per minute (bpm) during the initial exercise test was the best criterion for prediction of the absence of larger defects at dipyridamole: none of the 14 patients who had an increase >60 bpm had smaller defects at exercise than at dipyridamole, whereas this was the case with 11 out of the 26 remaining patients (42%) (P=0.004). By contrast, there was no such significant relationship using the conventional criterion of having achieved ≥85% of predicted maximal heart rate at exercise: eight of the 24 patients (33%) who did not reach this level had smaller defects at exercise, but this was also the case with three out of the 16 remaining patients (19%).

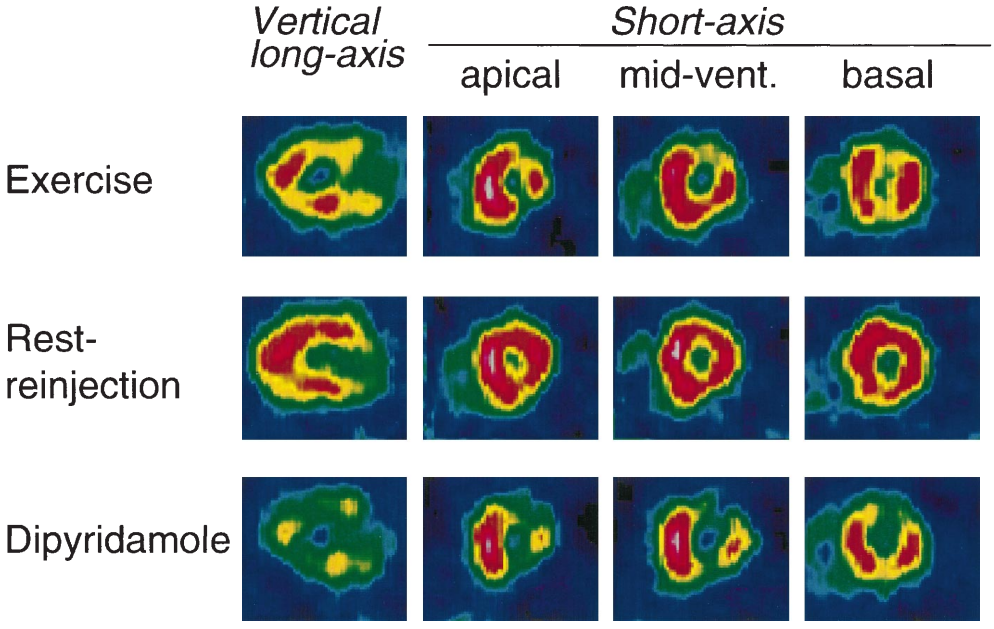

Fig. 2. Example of a much larger (^{201}Tl SPET) ischaemic area at dipyridamole compared with exercise in a 72-year-old man with typical exercise angina and 4-mm ST segment depression at exercise testing. The discordant areas are located in territories supplied by a large intermediate branch (90% stenosis) and by a dominant left circumflex coronary artery (80% stenosis). At exercise SPET, maximal heart rate was 83% of the maximal predicted value and the increase in heart rate was only 40 bpm

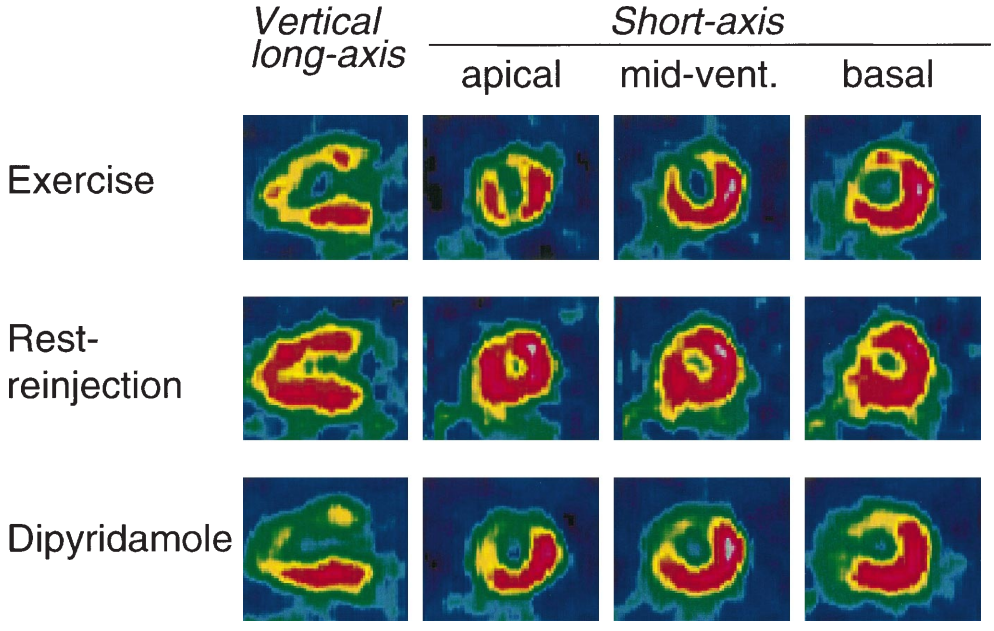

Fig. 3. Example of a much larger (^{201}Tl SPET) ischaemic area at dipyridamole compared with exercise in a 71-year-old man with typical exercise angina, 3-mm ST segment depression at exercise testing and a totally occluded (but well-collateralised) left anterior descending artery. At exercise SPET, maximal heart rate was 89% of the maximal predicted value and the increase in heart rate was 53 bpm

Analysis of vascular territories. Among the 35 patients who had undergone coronary angiography, a single ischaemic vascular territory was observed in 25, while two territories were identified in ten. The 45 ischaemic territories were classified into three categories: (1) defects larger at exercise [18 territories (40%)]; (2) equivalent defects between the two tests [16 territories (36%)]; and (3) larger defects at dipyridamole [11 territories (24%)]. Variables from coronary angiography were correlated with this classification (Table 4).

Three variables were significant univariate predictors: the percentage of diameter reduction (P=0.015) and the minimal luminal diameter (P=0.04) of related coronary stenoses, and the presence of a mildly to moderately narrowed (<70%) stenosis (P=0.003). Reversible defects were documented at exercise in all ten cases with stenoses with <70% narrowing, but in only three cases (30%) after dipyridamole (P=0.0004).

Multivariate analysis. All significant variables from univariate analyses were entered in a multivariate analysis to predict the discrepancies between the two tests, these discrepancies being defined according to the three-group classification of the ischaemic vascular territories.

Only two independent predictors were selected: (1) a coronary stenosis with <70% diameter reduction (P=0.002)

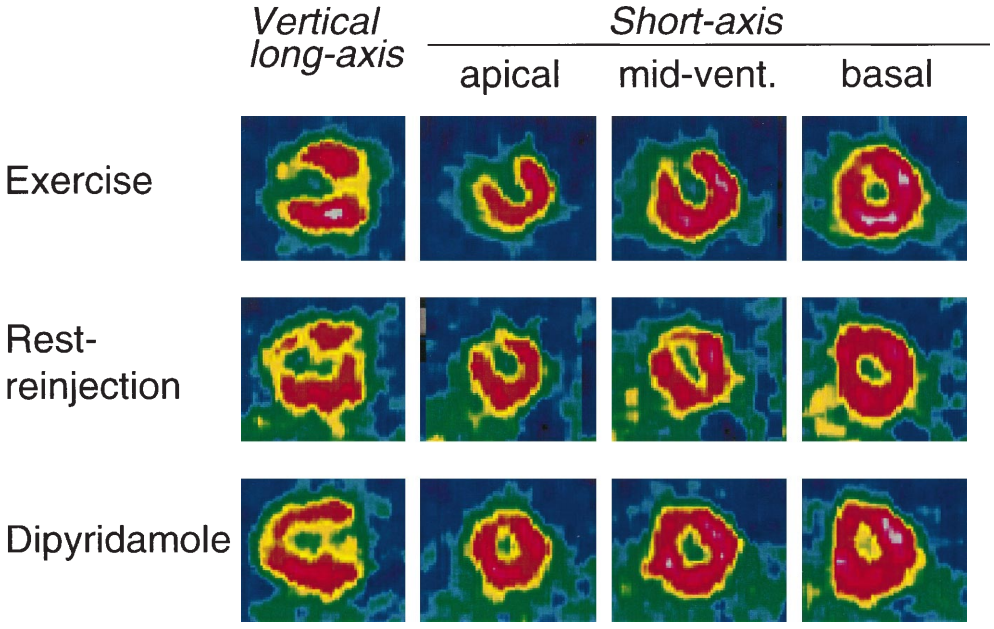

Fig. 4. Example of a much larger (^{201}Tl SPET) ischaemic area at exercise compared with dipyridamole in a 53-year-old woman with typical exercise angina, no ST segment depression at exercise testing and a 60% stenosis of the left anterior descending artery. At exercise SPET, the maximal heart rate was only 78% of the maximal predicted value but the increase in heart rate was high: 71 bpm

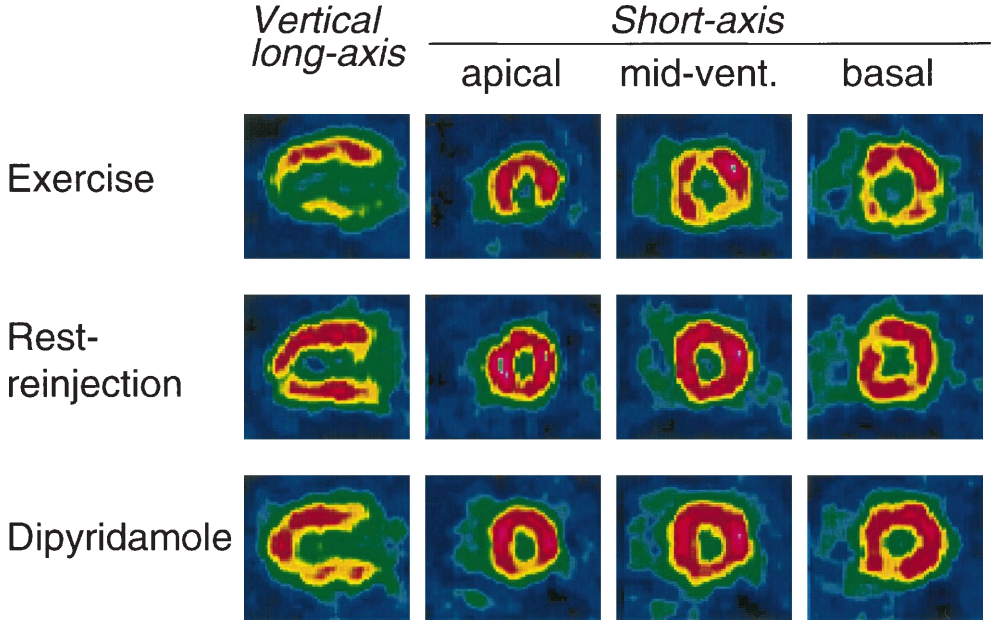

Fig. 5. Example of a much larger (^{201}Tl SPET) ischaemic area at exercise compared with dipyridamole in a 72-year-old man with exercise angina, 1.5-mm ST segment depression at exercise testing and a 60% stenosis of the right coronary artery. At exercise SPET, both the maximal heart rate and the increase in heart rate were high (93% and 79 bpm, respectively)

and (2) the increase in heart rate at exercise (P=0.005). The presence of a <70% stenosis, as well as a higher increase in heart rate at exercise, was related to larger defects at exercise compared with dipyridamole. Figure 7 illustrates the additional predictive values provided by these two variables.

Influence of the increase in the threshold value for the definition of a discrepant result between the two tests. When the differences in stress defects which were ≥10% of LV (≥2 segments), were considered to be significant, there were 21 (47%) discrepant vascular areas (six with larger defects at dipyridamole and 15 with larger defects at exercise). The predictors of discrepancies were unchanged and results provided by the multivariate analysis were identical, the sole independent predictors being a <70% coronary stenosis (P=0.002) and the increase in heart rate at exercise SPET (P=0.005).

Discussion

In patients with CAD, exercise SPET gives the opportunity to identify the ischaemic LV areas induced by physi-

Table 2. Relationship between patient characteristics and discordant SPET results between exercise and dipyridamole

	Stress defect extent			*P* value
	Larger at exercise (*n*=18)	Equivalent in the 2 tests (*n*=11)	Larger at dipyridamole (*n*=11)	
Clinical data				
Age (years)	59±7	62±9	64±9	NS
Female gender	1 (6%)	0 (0%)	1 (9%)	NS
Diabetes mellitus	4 (22%)	3 (27%)	2 (18%)	NS
Smoking	14 (78%)	7 (64%)	6 (55%)	NS
Dyslipidaemia	9 (50%)	6 (55%)	5 (36%)	NS
Angina	11 (61%)	8 (73%)	7 (64%)	NS
History of infarction	8 (44%)	6 (55%)	3 (27%)	NS
Q wave	7 (39%)	3 (27%)	3 (27%)	NS
History of revascularisation	8 (44%)	6 (55%)	6 (55%)	NS
Angioplasty	6 (33%)	5 (45%)	6 (55%)	NS
Bypass grafting	2 (11%)	1 (9%)	0 (0%)	NS
Medications during the tests				
Anti-anginal medications	14 (78%)	8 (73%)	10 (91%)	NS
β-blockers	10 (56%)	4 (36%)	7 (63%)	NS
Calcium antagonists	7 (39%)	4 (36%)	5 (45%)	NS
Nitrates or molsidomine	3 (17%)	5 (45%)	5 (45%)	NS
ACE inhibitors	6 (33%)	3 (27%)	2 (18%)	NS
Coronary angiography	(*n*=17)	(*n*=9)	(*n*=9)	
No. of diseased vessels with:				
≥50% stenosis	1.4±0.6	2.2±0.7	2.0±0.7	0.013
≥70% stenosis	1.1±0.8	1.3±0.5	1.7±0.9	NS

ACE inhibitors, Angiotensin converting enzyme inhibitors; NS, non-significant

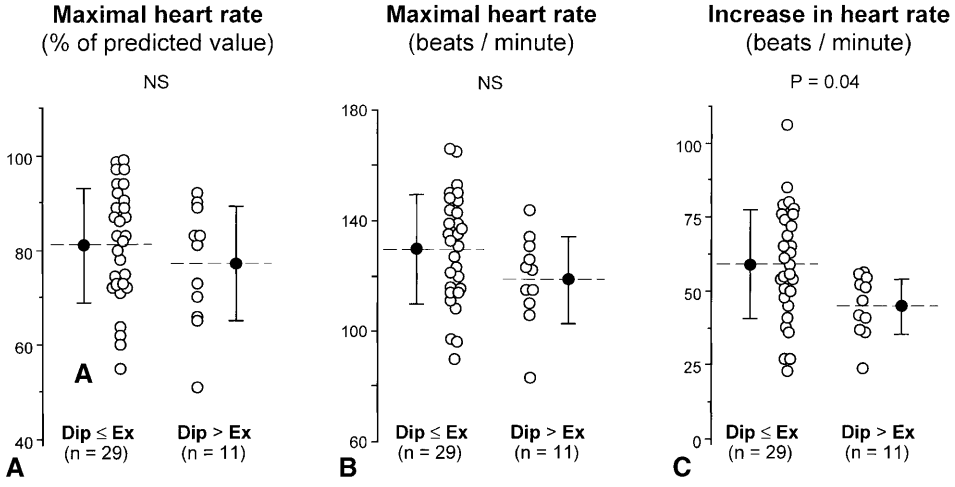

Fig. 6a–c. Comparison of the maximal heart rate achieved at exercise SPET and of the increase in heart rate at exercise SPET between patients for whom the SPET defects were larger at dipyridamole compared with exercise (Dip > Ex) and the others (Dip ≤ Ex)

ological stress, information that may be helpful in assessing the prognosis of patients [6, 7, 8, 9, 10, 11]. However, in patients with a good physical capacity it is not known whether dipyridamole and exercise SPET may be equally used to assess the extent of myocardial ischaemic areas. Indeed, though exercise and dipyridamole SPET have already been compared in the setting of CAD detection [1, 2, 3, 13, 25, 26, 27, 28, 29], no previous report has specifically compared the assessments of myocardial ischaemic areas provided by these two techniques in patients with documented episodes of myocardial ischaemia.

In the present study, these two tests were systematically compared in the same CAD patients who had a

Table 3. Relationship between data from the stress tests and discordant SPET results between exercise and dipyridamole

	Stress defect extent			*P* value
	Larger at exercise (*n*=18)	Equivalent in the 2 tests (*n*=11)	Larger at dipyridamole (*n*=11)	
Exercise testing				
Maximal workload (W)	147±33	136±28	124±25	NS
Heart rate				
Maximal (bpm)	130±20	129±20	119±16	NS
Maximal (%)	81±11	82±14	77±13	NS
Increase (bpm)	63±18	53±19	45±10	0.033
Systolic pressure (mmHg)				
Maximal	187±20	175±35	182±26	NS
Increase	46±21	44±33	49±25	NS
Double product (×100)				
Maximal	244±51	226±55	219±49	NS
Increase	150±49	125±53	120±40	NS
Dipyridamole/low-level exercise				
Heart rate				
Maximal (bpm)	94±19	104±14	99±14	NS
Maximal (%)	58±11	66±11	64±10	NS
Increase (bpm)	25±11	27±14	25±8	NS
Systolic pressure (mmHg)				
Maximal	156±24	160±20	147±24	NS
Increase	23±12	30±22	21±21	NS
Double product (×100)				
Maximal	147±38	166±32	147±33	NS
Increase	55±22	66±29	51±22	NS

bpm, Beats per minute; NS, non-significant

Table 4. Relationship between the characteristics of the coronary stenoses supplying ischaemic myocardium and the discordant SPET results observed between exercise and dipyridamole in the corresponding myocardial territories

	Stress defect extent			*P* value
	Larger at exercise (*n*=18)	Equivalent in the 2 tests (*n*=16)	Larger at dipyridamole (*n*=11)	
Location of stenosis				
Left anterior descending artery	6 (33%)	7 (43%)	5 (45%)	NS
Right coronary artery	7 (39%)	5 (31%)	3 (27%)	NS
Left circumflex artery	5 (28%)	4 (25%)	3 (27%)	NS
Severity of narrowing				
% reduction in diameter	79±17	86±17	97±7	0.015
MLD (mm)	0.50±0.43	0.26±0.31	0.14±0.27	0.039
Classification:				
Mild to moderate stenosis (40%–69%)	8 (44%)	2 (13%)	0 (0%)	0.003
Severe stenosis (≥70% and TIMI=3)	4 (22%)	5 (31%)	3 (27%)	NS
Vessel occlusion (TIMI ≤2)	6 (33%)	9 (56%)	8 (73%)	NS
Collaterals				
Rentrop score	0.8±1.3	1.1±1.3	1.5±1.3	NS
≥1	5 (28%)	8 (50%)	7 (64%)	NS
≥2	5 (28%)	6 (38%)	6 (55%)	NS

MLD, Minimal luminal diameter; NS, non-significant

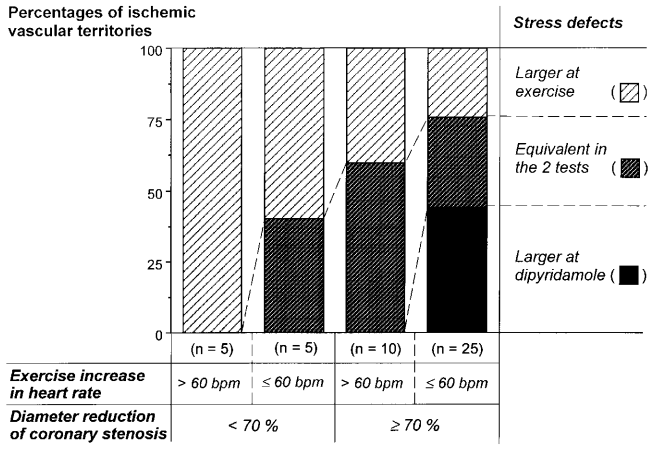

Fig. 7. Percentage of the ischaemic vascular territories with SPET defects larger at exercise, equivalent in the two tests and larger at dipyridamole, as a function of the presence or absence of: (1) a related stenosis with <70% diameter reduction, and (2) an increase in heart rate >60 bpm at exercise SPET. SPET defects were larger at dipyridamole than at exercise only if the ischaemia-related stenosis was ≥70% and the increase in heart rate at exercise SPET was ≤60 bpm

strong likelihood of myocardial ischaemia. The criterion chosen to select patients with a strong likelihood of myocardial ischaemia was an unequivocally positive exercise test, because this criterion was not extracted from the SPET results and, in addition, physical exercise constitutes a physiological stress that may be extrapolated to the stress occurring in daily life. This criterion might, however, disadvantage dipyridamole compared with exercise in the rate of SPET detection of stress ischaemia. Indeed, all patients had a high probability of exercise-induced ischaemia but not of dipyridamole-induced ischaemia. Therefore, our results may not be used to determine a hierarchy between the two tests in this particular setting. The only objective of this study was to determine whether the two tests provided an equivalent assessment of the myocardial ischaemic areas and, if this was not the case, to determine factors that might explain the discrepant results.

Comparison between the two tests

In our CAD patients, rates of abnormal SPET were high and similar for exercise and dipyridamole SPET. Therefore, as already established in a number of previous reports [13, 25, 26, 27, 28, 29], the two tests had comparable sensitivity for the detection of CAD. In addition, they had a similar global ability to detect myocardial ischaemic areas. There were, indeed, similar rates of reversible defects and averaged values of the extent of reversible defects between the two tests. Therefore, despite the fact that the patients had been included on the basis of a positive exercise test, the ischaemic areas documented with exercise SPET had an average severity no higher than with dipyridamole SPET. However, when the ischaemic areas from the two tests were compared in individual patients, we found very high rates of discrepant results: the extent of defects was equivalent between exercise and dipyridamole SPET in only 28% of the patients, and the difference in the extent of defects between the two tests reached up to 35% of the LV area.

In order to support this observation, it may be pointed out that in a multicentre trial comparing adenosine with exercise SPET in patients with suspected CAD [30], a number of markedly discrepant results were also documented with respect to the total extent of stress defects. Nevertheless, our observation, obtained in a very different population of CAD patients with myocardial ischaemia, provides evidence that exercise and dipyridamole SPET do not provide equivalent assessments of the myocardial ischaemic areas. Therefore, when SPET is performed for the purpose of determining prognosis, it must be considered that the choice of the stress test may have a dramatic impact on analysed parameters, i.e. the extent of stress defects and the extent of reversible defects [6, 7, 8, 9, 10, 11].

Predictors of discrepancies between the two tests

Only two variables were independently related to the discrepancies between the two tests: the increase in heart rate at exercise SPET and an ischaemic territory related to a mildly to moderately narrowed coronary stenosis (<70% diameter reduction). It is likely that this result can be explained by differences in the mechanisms by which exercise and dipyridamole induce SPET abnormalities.

Dipyridamole scintigraphic defects are mainly related to the difference in coronary flow reserve between the narrowed and normal arteries [13]. In normal arteries the intravenous administration of dipyridamole leads to a three- to fourfold increase in the coronary flow rate, but for stenotic arteries this increase is lower, depending on the severity of the stenosis [31, 32]. Physical exercise also induces an increase in coronary flow, but this increase is generally more limited than that induced by dipyridamole [13] and depends on the level of cardiac work achieved at exercise [33]. Nevertheless, the exercise scintigraphic defects also depend on the difference in coronary flow reserve between the normal and the narrowed coronary arteries.

There are, however, a number of important differences between the two tests. One is that exercise but not dipyridamole induces a clear increase in oxygen demand and, therefore, the manifestations of ischaemia are more frequent and more pronounced during exercise than during dipyridamole infusion [34]. This point is illustrated by our observation that more severe ECG abnormalities were documented at exercise.

A second difference between the two tests is that exercise, but not dipyridamole, leads to a paradoxical increase in the resistance of narrowed coronary segments. This point has been established by several exercise angiographic studies [35, 36, 37] and might be explained by a malfunctioning of the endothelium in atherosclerotic vessels (especially a lack of NO secretion [35]).

In a population of symptomatic patients who had coronary stenoses with an average 59% diameter reduction, Gage et al. demonstrated that moderate exercise on a bicycle ergometer (allowing coronary angiography to be performed) led to a 30% decrease in the luminal area of narrowed segments, whereas normal vessels had a physiological 20% increase [35]. This indicates that, at least for coronary stenoses not severely narrowed at rest angiography, vasoconstriction participates in the triggering of exercise-induced myocardial ischaemia.

In a very recent report, Becker et al. observed that a high proportion of the myocardial ischaemic areas documented at exercise SPET corresponded to coronary stenoses of mild severity (<50%) at rest angiography, and they also concluded that coronary vasoconstriction might represent a common mechanism of exercise-induced ischaemia [38].

This exercise-induced vasoconstriction of mild to moderate stenoses might explain our observation of a much higher ability of exercise, compared with dipyridamole, to induce SPET defects in the case of <70% ischaemia-related stenoses. The lower ability of dipyridamole may also be explained by the fact that in such low-degree stenoses, coronary flow reserve has been found to be close to that of normal vessels [39]. We recognise, however, that the aforementioned hypothesis cannot be demonstrated by the present data, mainly because the exercise-induced vasoconstriction of low-severity stenoses was not documented by exercise coronary angiography. In addition, the occurrence of defects smaller at dipyridamole than at exercise might be explained by other mechanisms, such as the fact that dipyridamole infusion has an unexplained limited action in certain "non-responder" patients [40, 41]. In our opinion, however, the exercise-induced vasoconstriction at the site of low-severity stenoses, which has already been documented in a number of previous reports [35, 36, 37], constitutes the most satisfactory explanation for the systematic higher ability of exercise SPET, compared with dipyridamole SPET, to induce perfusion abnormalities when the ischaemia-related stenoses are <70% at rest angiography.

No previous report has pointed out the superiority of exercise compared with dipyridamole SPET in the case of <70% ischaemia-related stenosis. This is mainly because none of the previous analyses have focussed on this particular and small sub-group of coronary stenoses. In our population, this sub-group represented only 22% of the total number of ischaemia-related stenoses.

A limiting point was the impossibility of obtaining coronary angiographic data in all cases, the patients being referred for coronary angiography only if it was judged necessary from a clinical point of view. However, recent angiographic data could be obtained in as many as 88% of our patients, and it is therefore unlikely that this point had a real impact on the results.

Another observation was that the exercise defects were smaller than the dipyridamole defects in 11 of our CAD patients, and despite the fact that all patients had an unequivocally positive exercise test, exercise SPET was normal in two cases. In both of them, however, the dipyridamole SPET was abnormal, providing evidence of unmasked perfusion abnormalities. Therefore, it may be considered that the perfusion abnormalities were underestimated by exercise SPET at least in these two patients and possibly also in the remaining nine in whom the stress defects were clearly larger at dipyridamole than at exercise.

These probable underestimations were totally unrelated to the percentage of the maximal predicted heart rate achieved at exercise SPET, although this parameter is commonly used to determine the accuracy of cardiac performance at exercise testing. By contrast, such underestimations could be predicted by the increase in heart rate between rest and maximal exercise. Though this remains to be confirmed in a prospective way, we found that an increase in heart rate higher than 60 bpm allowed the identification of a group of patients in whom the exercise SPET defects were never smaller than those from dipyridamole. The explanation for this observation is probably that the level of heart rate achieved at exercise is markedly dependent on the extremely variable levels of heart rate pre-existing at rest (from 54 to 107 bpm in our patients). Therefore, the increase in heart rate between rest and maximal exercise might be a better correlate of the increase in coronary flow that is required to induce a maximal difference in flow (and thus in ^{201}Tl uptake) between the ischaemic and the normally perfused LV areas. In a population including both patients with and patients without CAD, the increase in heart rate at exercise has been demonstrated to be strongly related to the concomitant increase in total coronary flow [33].

Conclusion

This study, performed on CAD patients with a good physical capacity, provides evidence that exercise and dipyridamole SPET yield different estimates of the myocardial ischaemic area and, therefore, that these two tests are not interchangeable in this setting.

Although dipyridamole SPET allows the unmasking of perfusion abnormalities in patients with low increases in heart rate at exercise SPET, dipyridamole is much less efficient at inducing perfusion abnormalities in the myocardial ischaemic areas supplied by stenoses of intermediate severity. The latter point suggests that, for coronary stenoses showing an intermediate severity at rest angiog-

raphy, the exercise-induced vasoconstriction occurring at the site of stenosis might be a principal determinant in the triggering of exercise-induced ischaemia, a hypothesis which deserves further analysis.

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