Technetium-99m tetrofosmin rest/stress myocardial SPET with a same-day 2-hour protocol: comparison with coronary angiography

A Spanish-Portuguese multicentre clinical trial

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Received 1 September and in revised form 12 December 1995

Abstract. Technetium-99m tetrofosmin (Myoview) has unique properties for myocardial perfusion imaging very early after injection of the tracer. We used a very short same-day rest/stress protocol, to be performed within 2 h and evaluated its diagnostic accuracy. The study included 144 patients from seven Spanish and four Portuguese centres with a diagnosis of uncomplicated coronary artery disease (CAD); 78 patients (54%) had no history of prior myocardial infarction. Patients were injected with ≤300 MBq ^{99m}Tc-tetrofosmin at rest and ≤900 MBq approximately 1 h later at peak exercise. Single-photon emission tomographic (SPET) acquisitions were initiated within 5–30 min post injection. The results were compared with those of coronary angiography (CA). The data of 142 patients were completely evaluable (two with non-evaluable images were excluded). The quality of rest images was excellent or good in 86%, regionally problematic in 7%, poor but well interpretable in 5% and non-evaluable in 2%. The overall sensitivity for the detection of CAD was 93%, the specificity 38% and the accuracy 85%. The localization of defects by SPET in relation to the perfusion territories of stenosed vessels (≥50%) was achieved with a sensitivity of 64% for the left anterior descending artery, 49% for the left circumflex artery and 86% for the right coronary artery, and an accuracy of 71%, 72% and 73% respectively. Concordance of SPET and CA was 62% for single-vessel disease and 68% for multivessel disease. In conclusion, this Spanish-Portuguese multicentre clinical trial confirmed, in a considerable number of patients who underwent coronary angiography, the feasibility of ^{99m}Tc tetrofosmin (Myoview) rest/stress myocardial SPET using a very short protocol (2 h).

Key words: Myocardial perfusion single-photon emission tomography – Coronary angiography – Technetium-99m tetrofosmin – Same-day 2-hour rest/stress protocol – Coronary artery disease

Eur J Nucl Med (1996) 23:639–647

Introduction

Three technetium-99m compounds are now commercially available for single-photon emission tomography (SPET) of myocardial perfusion: ^{99m}Tc-teboroxime,

The results contained herein were presented in part at the 2nd International Conference of Nuclear Cardiology, held in Cannes, France, on 23–26 April 1995

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^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin. The biokinetics of ^{99m}Tc-teboroxime differ essentially from those of the other two ^{99m}Tc compounds: it has a very rapid myocardial washout, which may be advantageous using a multidetector camera [1]. Both ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are lipophilic compounds. Their myocardial uptake shows a correlation to microsphere flow [2] similar to thallium-201; however, they remain fixed in the myocardium without substantial washout [3]. ^{99m}Tc-sestamibi has already been widely used in clinical practice, a variety of separate- and same-day, rest/stress and stress/rest protocols having been employed with very similar diagnostic accurary for coronary disease [4, 5]. In comparison to ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin shows some characteristic differences making it suitable for early imaging after injection: background and liver clearance is high [6], with myocardium to liver ratios increasing to >1.0 between 15 and 30 min post injection (p.i.) at rest [7, 8] whereas they remain constant at about 0.5 with ^{99m}Tc-sestamibi [9].

Multicentre phase III clinical trials directly comparing ^{99m}Tc-tetrofosmin and ^{201}Tl have been reported, using planar imaging techniques in 55 [10] and 252 patients [11] and SPET in 355 patients [12]. Diagnostic accuracy was found to be comparable, with concordance ratios between 81% and 89% for normal versus abnormal segmental analysis and without significant differences in estimations of reversible ischaemia. Comparison of ^{99m}Tc-tetrofosmin SPET results with findings of coronary angiography has been undertaken in relatively small numbers of patients in clinical trials, i.e. 22 in the European Multicenter Report [4], and 26 and 25 patients respectively in two Japanese single-centre reports [8, 13]. The possibility of performing ^{99m}Tc-tetrofosmin SPET with a very short same-day rest/stress protocol was concluded from the biokinetics of this new myocardial perfusion tracer [3, 7]. The aim of this Spanish-Portuguese phase III multicentre clinical trial was to evaluate in a sufficiently large number of patients ^{99m}Tc-tetrofosmin myocardial SPET using such a protocol in comparison to coronary angiography.

Materials and methods

Multicentre trial patients. Eleven institutions from six different geographical locations in Spain and Portugal participated in the clinical trial evaluation (Table 1). Various systems of single-head SPET cameras and on-line computers (Elscint, General Electric, Siemens, Sopha) were utilized. A total of 167 patients [age (mean±SD)=58±10 years; 87% males and 13% females] with suspected or documented coronary artery disease (CAD) were included in the study population. The numbers of patients per centre were: >20 from three centres (31, 29 and 21 patients), between 10 and 12 from four centres, five from three centres and two from one centre.

Patients eligible for inclusion had a history of chest pain suggestive of CAD associated with positive signs of ischaemia (e.g.

Table 1. Multicentre trial sites and investigators

Code	Institute	Location	Investigators
001	Universidad Complutense, Facultad de Medicina, Servicio de Medicina Nuclear y Instituto de Cardiología de Madrid	Madrid, Spain	J.L. Carreras, M.J. Pérez-Castejón, A. Jurado, F. Taboada, R. Ruiz, I. Díaz, J.C. Recio
002	Hospital Reina Sofía, Servicios de Medicina Nuclear y de Cardiología	Córdoba, Spain	J.M. Latre
003	Clínica Puerta de Hierro, Servicios de Medicina Nuclear y de Cardiología	Madrid, Spain	J. Ortíz-Berrocal, M.J. Tabuenca
004	Hospital de Bellvitge, Servicios de Medicina Nuclear y de Cardiología	Hospitalet, Spain	J. Martín Comín, E. Esplugues, V. Vallejos, R. Granja, M. Ramos, M. Roca, J. Mauri
005	Hospital Clínico y Provincial, Servicios de Medicina Nuclear y de Cardiología	Barcelona, Spain	A. García, J. Magriñá, F.J. Setoaín
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009	Facultad de Medicina, Hospital Santa María Institutos de Medicina Nuclear y de Cardiología	Lisbon, Portugal	G. Cantinho
010	Hospitals da Universidade de Coimbra, Servicios de Medicina Nuclear y de Cardiología	Coimbra, Portugal	A.L. Ferrer, J. Pedrosa
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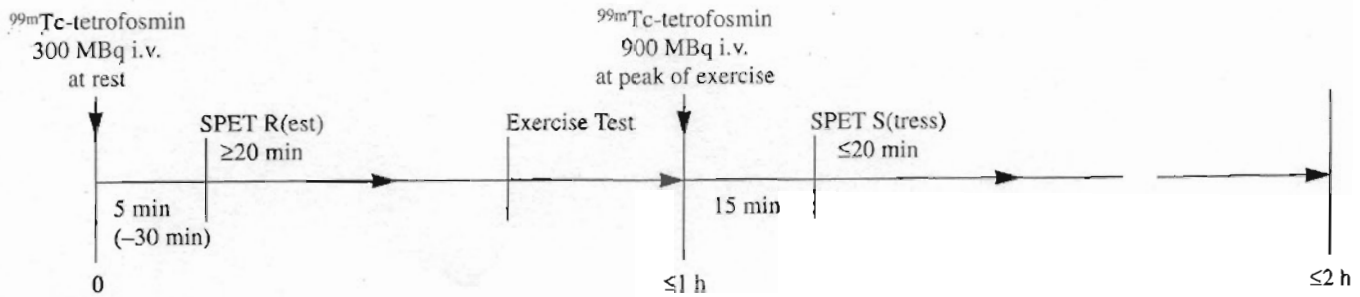

Fig. 1. Scheme of the same-day 2-h rest/stress protocol using a 1:3 split dose of ^{99m}Tc-tetrofosmin (Myoview) for myocardial perfusion SPET

abnormal exercise ECG or angiogram), were at least 30 year old, were receiving either no medication or medication stabilized for at least 2 weeks, and had given written informed consent. The following were excluded from the study: (a) females of child-bearing potential, (b) patients with recent myocardial infarction or unstable coronary disease, congestive heart failure, significant primary valvular pathology or congenital heart defect, cardiomyopathy, left bundle branch block, any significant vascular incident or coronary intervention between the invasive and non-invasive studies, or other significant pathologies likely to interfere with the success of the study (e.g. by causing inability to perform bicycle or treadmill exercise), and (c) persons classified as highly exposed to radiation due to their occupation (>15 mSv/year).

Coronary angiography, defined as the reference technique for the global and territorial evaluation of myocardial SPET with ^{99m}Tc-tetrofosmin, was performed in 144 patients using standard techniques as established in each cardiological department of the participating centres, usually within 2 months prior to or after the SPET study (mean±SD=–18±45 days; range –180 to +132 days). Sixteen patients with long intervals between angiography and tetrofosmin SPET (more than 67 days) had stable disease and no intercurrent events. The degree of luminal narrowing (≥75% and ≥50%) of the coronary arteries [left main (LM), left anterior descending (LAD), left circumflex (LCX) and right coronary (RCA) arteries] was determined by visual analysis.

Study design. The design of the study is illustrated in Fig. 1. The myocardial SPET at rest (R) and stress (S) was to be completed within 2 h. Initially at rest each patient received an intravenous injection of (185–)300 MBq [(5–)8 mCi] ^{99m}Tc-tetrofosmin. SPET acquisition (R) had to be started between 5 and 30 min p.i. with a single-head gamma camera rotating 180° around the anterior and left lateral cardiac area of the patient in the supine position. Data were acquired by 60 projections with acquisition times of ≥20 s per view and total counts of at least 4000 kcounts. Total acquisition times of SPET (R) ranged from 13 to 31 min (mean=18 min). Thereafter, at the latest 1 h p.i., the patient proceeded to exercise on a bicycle or treadmill according to the standard protocol of each centre. Exercise was symptom limited (anginal pain, severe fatigue or dyspnoea, ST segment depression etc.) or heart rate limited (≥85% of the maximal predicted rate). At peak exercise a second tracer dose of 3 times the first one [555–900 MBq (19–24 mCi)] was administered, and exercise was continued for 1–2 min. After control of heart rate and blood pressure during 15 min of patient recovery, the second SPET (S) acquisition was started using the same technique as for SPET (R), except allowing for a shorter time per projection (≤20 s). Total acquisition times of SPET (S) ranged from 10 to 25 min with a mean of 15 min.

^{99m}Tc-tetrofosmin (Myoview, Amersham International plc) was prepared from a freeze-dried solid supplied in a 10-ml vial sealed under an inert nitrogen atmosphere. Each vial was reconstituted with 4–8 ml of no more than 1100 MBq/ml sterile sodium [^{99m}Tc]pertechnetate. After adequate mixing the vial was allowed to stand at room temperature for 15 min, after which it was stored at 2°–8° C. Radiochemical purity was controlled by thin-layer chromatography using Gelman ITLC/SG strips (2.0×20 cm) and a 35:65 acetone/dichloromethane solution. Only preparations with ≥90% labelling were used, this within 8 h of preparation.

Tomographic image processing and analysis. Three series of slices parallel to the axis of the left cardiac ventricle (vertical long axis, short axis and four-cavity long axis) were obtained by reorientation of transverse slices as reconstructed by filtered backprojection of the acquired scintigraphic data. No attenuation correction was used. Each of the participating centres applied its current imaging procedure with respect to the filters used for reconstruction, the number and thickness of tomograms, colour or grey scale documentation, and the additional use of polar maps from short-axis slices. The images were interpreted visually by consensus of two experts in nuclear cardiology, and in the case of discordance a third reader decided. The readers were blinded to clinical, ECG and coronary angiographic results. The images were read in pairs of rest-stress. Image quality was judged as excellent, good, poor or nonevaluable. Defects in R(est) and S(tress) images were scored on a 1- to 4-point scale: 1=normal; 2=infarction (R=S); 3=ischaemia (S) only); 4=mixed defect. All readers kept in mind their experience that with ^{99m}Tc-sestamibi and ^{201}Tl myocardial SPET the normal count rate in the inferior wall region is somewhat less (about 20%) than in the lateral, anterior and septal regions. The defects were allocated to the territories of the main coronary arteries (Fig. 2): LAD territory=anterolateral, anterior, anteroseptal and midseptal wall regions; LCX territory=midlateral and posterolateral regions with facultative extension to the inferolateral region; RCA territory=inferior and inferoseptal region with facultative extension to the midseptal region. The apical region, when affected alone, was allocated to the LAD territory; if, however, there was extension of one of the territory defects to the apex, the apical region was allocated to that vascular territory.

Statistical analysis. For overall detection of disease, sensitivity was defined as the percentage of patients with at least one significant coronary artery stenosis demonstrating any kind of abnormal ^{99m}Tc-tetrofosmin defect (reversible as well as fixed or mixed defects), specificity as the percentage of patients without significant coronary artery stenosis and normal SPET results, and accuracy as the percentage of all patients with a correct diagnosis as judged from SPET results versus coronary angiography. Sensitivity, specificity and accuracy for localization of SPET defects to vascular territories were compared by the chi-square test in the following subgroups: (a) patients with coronary artery stenosis ≥75% and

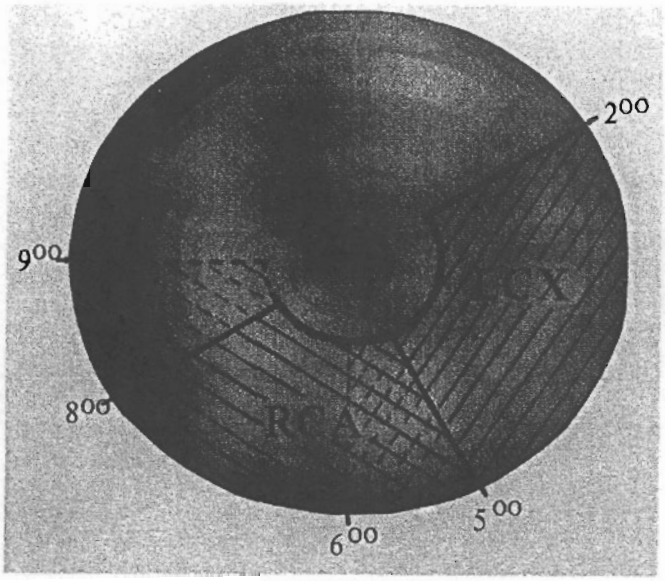

Fig. 2. Distribution of the myocardial territories related to the coronary arteries LAD, LCX and RCA, designed on a polar map from SPET short-axis tomograms: centre=apex, periphery=basis, top=anterior, bottom=inferior, left=septal, right=lateral wall region of the left ventricle

versus those with stenosis ≥50%, (b) patients with strictly symptom- or heart rate-limited stress versus all patients, including those with symptomless stress not reaching 85% of predicted maximal heart rate; and (c) patients without prior myocardial infarction (non-MI) versus all patients. Coronary angiography and ^{99m}Tc-tetrofosmin SPET concordance for the detection of single-vessel and multivessel disease was defined as the sum of the concordant myocardial regions or vascular territories as a percentage of the total number of segments or territories, respectively. Kappa statistical values were also calculated.

Results

Adverse events attributable to ^{99m}Tc-tetrofosmin

None of the patients experienced any adverse reaction after the administration of ^{99m}Tc-tetrofosmin.

Image quality of ^{99m}Tc-tetrofosmin SPET with the 2-h protocol

Two patients from two different centres (both of whom underwent coronary angiography, one showing no vessel stenosis but hypokinesia and the other, two-vessel disease with >75% stenosis) had to be excluded from further evaluation because of non-valuable image quality due to minimal myocardial tracer uptake at both rest and stress in one case (both doses administered from the same vial) and only at rest in the other case (repetition of the study on a separate day yielded excellent image quality). Chromatographic quality control prior to the injection showed ≥90% radiochemical purity in both cases, precluding any non-speculative explanation. Excellent or good image quality (Fig. 3a) was found in 86% of rest images and 95% of stress images. The readers reported interpretational difficulties in 12 patients, i.e. 7% (only R images in seven cases; R and S in five cases), due to interference by subdiaphragmatic tracer accumulation with inferior myocardial activity. In eight patients, i.e. 5% (R=7, R+S=1), the image quality was considered "poor, but evaluable" because of a very high ratio of hepatic to myocardial activity (Fig. 3b). In one case poor image quality at rest was explained by partial extravasation of the injected dose. The aforementioned instances of limited rest image quality mainly occurred in a subgroup with extremely short time intervals between tracer injection and start of SPET acquisition [20 of 85 patients from six centres with intervals of 7±4 min (mean±SD), in comparison to 1 of 82 patients from five centres with intervals of 31±14 min].

Coronary angiography

One hundred and nine patients had one or more coronary lesions with stenosis ≥75% (≥50% for left main artery) as graded by visual analysis. One hundred and twenty-two patients had significant coronary lesions, using the criterion of ≥50% luminal diameter narrowing. Of 20 patients without stenosed vessels (<50%), four nevertheless had an abnormal exercise reaction; thus only 16 patients could be regarded as "normal". Stenosis ≥50% involved one (n=39) or more (n=83) arteries. Of 78 patients (55%) with no previous myocardial infarction, 59 showed one (n=21) or more (n=38) stenosed (≥50%) arteries.

Overall detection of coronary artery disease

Exercise level (Table 2). Out of 92 patients with coronary artery stenosis of ≥75% and strictly symptom/heart rate-limited stress (subgroup "stress A"), 89 (sensitivity=97%) were identified as having fixed or reversible stress/rest perfusion defects by ^{99m}Tc-tetrofosmin myocardial SPET. Inclusion of patients with symptomless exercise not reaching 85% of predicted maximal heart rate (subgroup "stress B") did not affect the results: the rate of false-positive results was similarly high and the accuracy identical. Employing the criterion of ≥50% luminal narrowing for stenosis, the number of false-positive SPET results diminished considerably, to ten for subgroup "stress A" and to 13 when subgroup "stress B" was also considered (the difference between subgroups "stress A" and "stress A+stress B" was not significant). In consequence, the patients with symptomless exercise not reaching 85% of predicted maximal heart rate ("stress B") were included in all further evaluations. When patients with an abnormal stress reaction but without evidence of coronary artery stenosis were also con

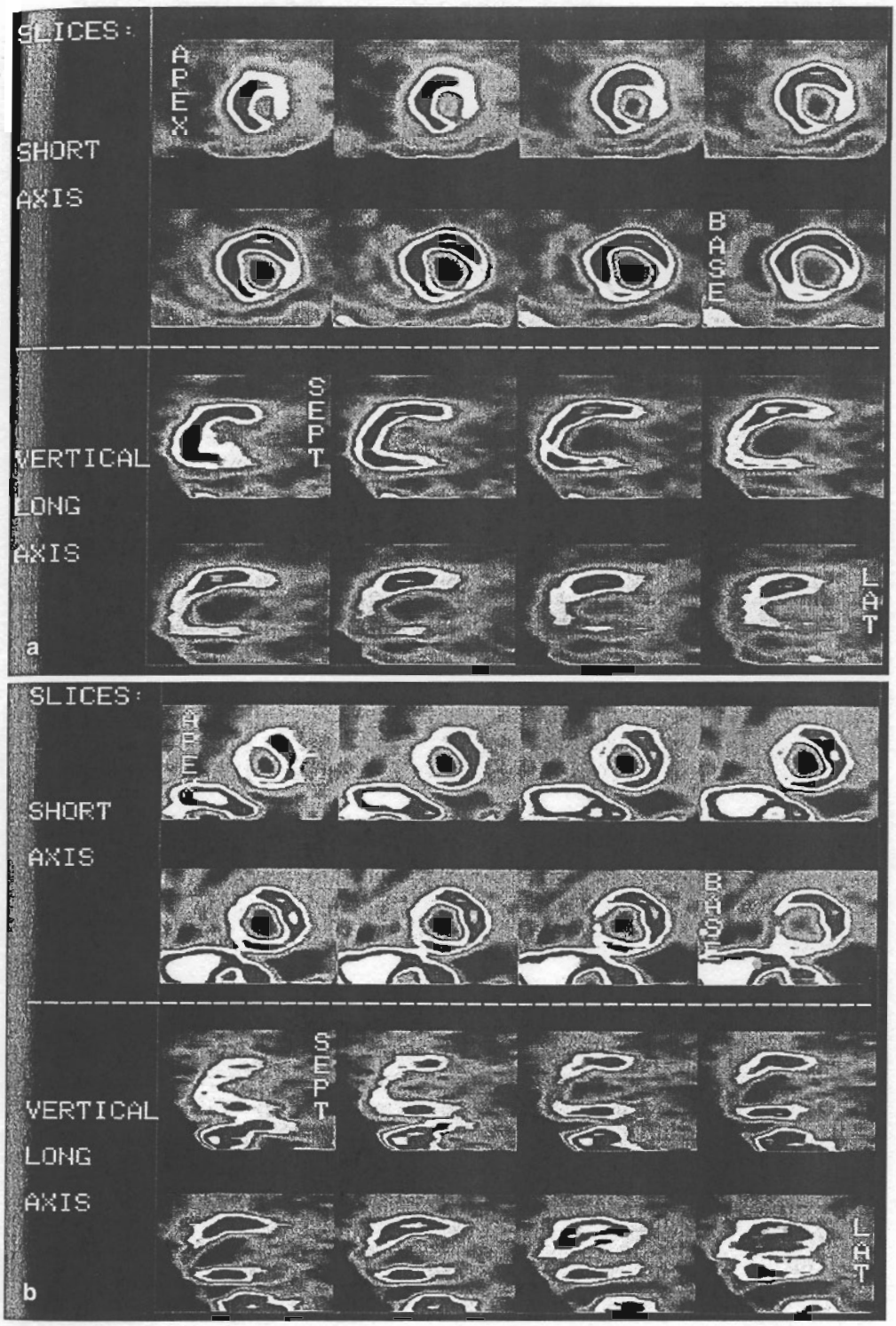

Fig. 3. Myocardial low-dose rest images of "excellent" (a) and "poor, but evaluable" (b) quality. **a** Acquisition started 19 min p.i. Patient with severe three-vessel disease and a history of anterior and inferolateral infarctions. **b** Very high hepatic and relatively low myocardial activity; the myocardial images were nevertheless interpretable through adequate data processing. Acquisition started 11 min p.i. Patient with two-vessel disease (LAD and LCX) and a history of anterior and inferolateral infarctions

sidered as possibly having CAD, false-positives were considerably reduced for both degrees of stenosis: 10 versus 22 for ≥75% and 8 versus 13 for ≥50% stenosis.

Patients without prior myocardial infarction (Table 3). Sensitivity and accuracy for the overall detection of CAD by ^{99m}Tc-tetrofosmin myocardial SPET was inferior in the subgroup of patients without a history of prior myocardial infarction (non-MI) in comparison to the whole patient population, though the difference did not reach statistical significance. Most of the false-positive and all of the false-negative results were observed in the non-MI subgroup, thus conditioning the low specificity value for all patients.

Single-vessel versus multivessel disease. The sensitivity for overall detection of CAD in patients with single-vessel disease was 90% (35/39 patients), the four false-neg-

Table 2. Overall detection of CAD by ^{99m}Tc-tetrofosmin SPET using the same-day 2-h rest/stress protocol, in relation to exercise levels

	CA stenosis ≥75%		+Stress pos.	CA stenosis ≥50%		+Stress pos.
	Stress A	Stress A +stress B	Stress A +stress B	Stress A	Stress A +stress B	Stress A +stress B
SPET results						
True +	89	105	115	98	113	118
True −	10	11	11	7	8	8
False +	19	22	10	10	13	8
False −	3	4	6	6	8	8
Total no.	121	142	142	121	142	142
Sensitivity (%)	97	96	95	94	93	94
Accuracy (%)	82	82	89	87	85	89

Stress A=patients with symptom- or heart rate-limited exercise; stress B=patients with symptomless exercise not reaching 85% of maximal heart rate

+Stress pos.=Results when patients with an abnormal stress reaction but no evidence of CA stenosis were considered possibly to have CAD

Table 3. Overall detection and localization of CAD by ^{99m}Tc-tetrofosmin SPET in individual coronary arteries with stenosis ≥50%

	Overall CAD		LAD		LCX		RCA	
	All patients	Non-MI	All patients	Non-MI	All patients	Non-MI	All patients	Non-MI
SPET results								
True +	113	51	59	21	33	13	68	27
True −	8	8	42	28	69	42	36	22
False +	13	11	8	5	6	2	27	20
False −	8	8	33	24	34	21	11	9
Total no.	142	78	142	78	142	78	142	78
Sensitivity (%)	93	86	64	47*	49	38	86	75
Specificity (%)	38	42	84	88	91	98	57	49
Accuracy (%)	85	76	71	63	72	85	73	63

Non-MI, Patients without prior myocardial infarction; * $P<0.05$, significant difference, chi-square test

ative results occurring in the non-MI subgroup (sensitivity 17/21=81%). The corresponding results in patients with multivessel disease were 79/83 (95%) in the whole group and 34/38 (89%) in the non-MI subgroup.

Identification of individual diseased coronary arteries (Table 3)

Considering a ≥50% luminal diameter narrowing as the criterion of stenosis, the diagnostic accuracy was moderately good, at around 70%, for the three vessels LAD, LCX and RCA. A relatively high number of false-negative results (33 of 92 stenosed LADs) caused a moderately low sensitivity of 64% for LAD stenosis. Sensitivity was even lower for LCX stenosis (49%: false-negative results obtained for 34 of 67 stenosed vessels). RCA stenosis was correctly identified in 68 of 79 vessels, for a corresponding sensitivity of 86%, but specificity was low because of a high false-positive rate (27 of 63 vessels without significant stenosis). These sensitivity and accuracy values for the detection of LAD and RCA stenoses tended to be somewhat worse among patients without prior myocardial infarction, but the differences were not statistically significant. Detailed data analysis of the false-positive rates revealed the following observations: Of the eight patients with false-positive results in respect of the LAD territory, three were female, and in these patients the false-positive findings were assumed to be caused by attenuation artefacts due to breast tissue; one of the male patients had been diagnosed to have a prior anterolateral infarction and a further two without significant stenosis nevertheless showed pathological exercise test results. Four out of six false-positive SPET defects relating to the LCX territory coexisted with severe RCA stenosis. Correspondingly, 8 out of 27 false-

Table 4. Classification of CAD extent: concordance of SPET defects with coronary artery stenosis ≥50% in all patients and in those without myocardial infarction

	CA	SPET			CA	SPET			CA	SPET		
	Normal	Normal	SVD	MVD	SVD	Normal	SVD	MVD	MVD	Normal	SVD	MVD
All patients												
No.	20	8	10	2	39	4	27	8	83	4	32	47
Concordance (%)		86					62					68
Kappa		0.36					0.23					0.38
Non-MI patients												
No.	17	8	6	3	21	4	14	3	38	4	20	14
Concordance (%)		78					57					61
Kappa		0.31					0.17					0.21

CA, Coronary angiography; SVD, single-vessel disease; MVD, multivessel disease

positive RCA localizations occurred in patients with severe LCX or left main artery stenosis; two other patients had prior inferior or posterior infarction, and four without vessel stenosis had pathological stress reactions. Thus, after exclusion of these cases with possible explanations, the numbers of unexplained false-positive results in respect of the LAD, LCX and RCA territories were 2, 2 and 13, respectively. Nine of the 13 false-positive RCA localizations corresponded to inferior region defects on SPET classified as infarction (n=5) or mixed ischaemia+infarction (n=4).

Classification of the extent of disease (Table 4)

Analysis of concordance of the results of ^{99m}Tc-tetrofosmin myocardial SPET with those of coronary angiography in identifying normal vessel states, single-vessel disease and multivessel (two- or three-vessel) disease using the >50% stenosis criterion revealed that 8 out of 20 patients without significant coronary artery stenosis were classified as normal by SPET, whereas 114 of 122 patients with one or more stenosed coronary arteries had pathological SPET results. Concordance was thus calculated to 86% (κ=0.36). Twenty-seven out of 39 patients with SVD were correctly classified by SPET (concordance=62%, κ=0.23). Results for categorizing multivessel disease were similar: 47 of 83 cases were correctly identified (concordance=68%, κ=0.38). The subgroup of non-MI patients showed nearly identical results.

Discussion

Since the development of the disphosphine-Tc complex tetrofosmin (Myoview) by Amersham International plc, several phase III multicentre clinical trials have confirmed that its diagnostic accuracy is comparable to that of ^{201}Tl scintigraphy [3, 10–12]. As ^{201}Tl is not an ideal agent for myocardial perfusion imaging, we felt it an interesting aim, additionally, to study the results of ^{99m}-tetrofosmin myocardial SPET in comparison to coronary angiography (CA) in a large multicentre, clinical trial. Similar comparative analyses have previously been carried out in smaller series of patients as a part of trials primarily designed with reference to ^{201}Tl scintigraphy [3, 8, 13]. Although CA alone may not be considered a real gold standard for the detection of CAD, this technique is still the most important reference in reaching therapeutic decisions.

Image quality

Comparisons of separate-day and same-day protocols for myocardial perfusion imaging with ^{99m}Tc-sestamibi [5] and ^{99m}Tc-tetrofosmin [14] did not show significant diagnostic differences. Rapid extramyocardial clearance in combination with minimal myocardial washout of ^{99m}Tc-tetrofosmin suggested the possibility of starting SPET acquisition very early (5–30 min) after injection even at rest, and of continuing the study without a waiting interval, the second injection being given at the peak of exercise at a dose 3 times that of the first one [3, 7]. This allows the study of each patient to be completed within 2 h, and it offers more flexibility in the organization of optimal throughput of patients. The very short same-day 2-h protocol seems especially convenient for out-patients. The present multicentre study confirmed high image quality even in the low-dose rest studies, when SPET was performed shortly after the tracer injection (19±14 min, mean±SD). Inferior quality of mostly rest images acquired extremely early post injection (7±4 min) in some cases caused difficulties but did not ultimately inhibit diagnostic evaluation: difficulties in interpretation occurred in 7% of the patients due to interference by subdiaphragmatic activity, and in 5% due to the presence of high hepatic activity and low myocardial count density.

Concerning image quality, it would be preferable to start with the study at stress, because liver uptake is low-

er and background clearance faster due to rapid accumulation in skeletal muscles [15]. Thus, the contrast of stress defects is optimal with stress/rest protocols. However, defect regions may be photon deficient, and reversibility of apparent fixed defects may be masked due to the fact that no "true" rest image is obtained when superposed on stress activity [14]. Nevertheless, comparative analysis of imaging protocols [5, 14] did not reveal any effect on diagnostic sensitivity from these limitations of stress/rest and rest/stress protocols. The possibility of diminished tracer uptake by hibernating myocardium at rest after previous stress-induced ischaemia is another argument for preferring the rest/stress sequence, at least when using a very short same-day protocol, as in this study.

Overall detection of CAD and identification of individual diseased coronary arteries

The results of the present multicentre clinical trial of 142 patients who underwent ^{99m}Tc-tetrofosmin myocardial SPET in a 2-h rest/stress protocol and CA may require some further comments to permit better understanding in comparison to published data from similar studies. For example, partial data (n=22–26) are available from European [4] and Japanese [8, 13] phase III studies using ^{99m}Tc-tetrofosmin myocardial SPET with same-day 5-h and separate-day rest/stress protocols, from the "UCM 93" [16] single-centre study using a separate-day ^{99m}Tc-sestamibi protocol (the reporting centre is the same as centre 001 of the present multicentre study) and from the "USA 94" multicentre study [17] using a same-day 4- to 5-h rest/stress protocol with ^{99m}Tc-sestamibi.

The results in respect of the overall detection of CAD were quite similar in the present and comparable studies: the senstivities of 90% and 92% for ≥75% and ≥50% stenoses, respectively, in the present study did not differ significantly from reported figures of 86%, 100% and 91% [4, 8, 17], nor did the accuracy of 85% in the present study differ significantly from the figure of 80% reported in the "USA 94" multicentre study [17]. In the current study there was no significant difference between the results in terms of sensitivity and accuracy for all patients and for the non-MI subgroup, despite the fact that most of the false-positive results and all the false-negative were found in non-MI patients, which gave rise to the low specificity and considerably influenced the sensitivity for the overall detection of CAD in the entire group of patients.

The sensitivity for the correct identification of LAD stenosis was low in the present study as compared with that expected from routine clinical application of myocardial SPET in patients with a single LAD stenosis. The low sensitivity for LAD localization, which was even more pronounced in patients without prior myocardial infarction (non-MI), seems to have been due to the high number of patients with multivessel stenosis (18/24) in the present study. By comparison with the values of sensitivity and specificity in studies with corresponding stenosis criteria, the results of the present study are slightly lower: sensitivity 69% (≥75% stenosis) and 64% (≥50% stenosis) versus 69%–89% [4, 8, 13, 16, 17] and specificity 78% and 84% versus 76%–93% [8, 13, 16, 17].

The rather low sensitivity for the recognition of LCX stenosis and the greater than 90% specificity agreed with the published results except for the higher sensitivities of 85% and 70% and the lower specificities of 83% and 80% from the "UCM 93" [16] and the "USA 94" [17] studies applying territorial quantitation. A striking difference, however, exists for the relation of SPET defects to RCA stenosis: The specificity of about 50% for both ≥50% and ≥75% stenosis criteria and for non-MI patients in the present study is much lower than all published values (60%–86%) [8, 13, 16, 17].

Another recent report of an international multicentre trial [11], is hardly comparable with the present study because planar scintigraphy was used with reference to CA in 181 patients: the results similarly showed a tendency toward lower values for regional sensitivity and specificity.

Thus, as far as the results are comparable, given the application of different imaging techniques (planar scintigraphy or SPET), the use of qualitative or semiquantitative evaluation, and the relatively small number of patients in some of the studies, the common and only convincing difference in diagnostic accuracy seems to be in respect of the detection of RCA stenosis, obviously due to a high rate of false-positive tetrofosmin results for the inferior wall region. There are several possible explanations for this high rate of false-positive results: the well-known variance of overlap between LCX and RCA territories may have been the cause in 12 of our 33 cases. In addition, nine of the false-positive SPET results really could be regarded as false-negative results of CA (three patients with documented infarcts and six with a pathological exercise reaction but normal CA results). The small number of remaining unexplained false-positive results corresponded mostly to fixed or mixed defects, presumably due to attenuation effects.

Different referral bias between centres can influence the results considerably, too [14, 17]: A tendency toward higher diagnostic accuracy that may reach statistical significance has been reported for patients with previous myocardial infarction (MI patients) [10, 14, 16, 17]. In the present study the incidence of MI patients was much less (64/142 patients=45%) than in the "UCM 93" study (78/125=62%) [16] and the "USA 94" multicentre study (56%) [17]. In our multicentre study we observed that most of the false-positive SPET results concerning overall CAD detection occurred in patients without prior myocardial infarctions (non-MI), and correspondingly that the proportion of non-MI patients was significantly higher (P<0.01) in the group with false-positive SPET results for territorial identification (33/42=79%) than in the whole population (78/142=55%); further more, the

two participating centres with the highes rates of false-positives had more non-MI patients (37/59=63%) in comparison with the mean of the other centres (41/83=49%). These observations suggest that there may be a need for more objective, quantitative thresholds for correct territorial evaluation of SPET images, especially regarding the inferior and posterolateral wall regions.

Conclusion

The present study confirms the usefulness of ^{99m}Tc-tetrofosmin (Myoview) for myocardial perfusion SPET. A very short same-day rest/stress protocol using a 1:3 split dose with SPET acquisition shortly after injection offers the possibility of performing the study within ≤2 h. A time interval of 20–30 min between tracer injection and commencement of SPET acquisition seems to be optimal for obtaining high-quality images and avoiding excessive liver activity and overlying bowel activity, even for the low-dose study at rest. Some limitations in diagnostic information and accuracy such as the low sensitivity for the detection of LAD territory disease and a high rate of false-positive results for RCA-dependent disease may be related to referral bias (incidence of multivessel disease and prior myocardial infarction) rather than to the short protocol or the use of ^{99m}Tc-tetrofosmin.

Acknowledgements. The authors wish to thank Dr. Ignacio Carrió for critical revision of the manuscript. The assistance of Gracia Espuela in the management of the multicentre data compilation and the preparation of the tables is greatly appreciated. The ^{99m}Tc-tetrofosmin (Myoview) used in these clinical studies was provided by Amersham Ibérica S.A. and Amersham International plc. The study was supported, in part, by the financing of a sabbatical year for Prof. R. Montz by Dirección General de Investigación Científica y Técnica (DGICYT) del Ministerio Español de Educación y Ciencia.

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