Comparative myocardial uptake of technetium-99 m sestamibi and technetium-99m tetrofosmin one hour after stress injection

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Abstract. Technetium-99m sestamibi and ^{99m}Tc-tetrofosmin are at present the preferred tracers for simultaneous assessment of myocardial perfusion and function by gated single-photon emission tomography (SPET). The aim of this work was to compare sestamibi and tetrofosmin myocardial uptake 1 h after stress injection. Consecutive unselected patients were studied either with sestamibi or with tetrofosmin on a random basis, until at least 100 patients had been enrolled for each gender and tracer. Stress was obtained by dipyridamole or exercise or combined dipyridamole + exercise; in the latter cases, exercise was sustained for at least 1.5 min after tracer injection. Injected activity was similarly adjusted to body weight. For each patient, imaging began 60–75 min after injection. All SPET projections were summed; due to the acquisition technology ("roving zoom", i.e. a mobile zoom), the heart always appeared at the centre of the frame in all projections and in the sum image. Thus minimal lung background contamination could be assumed in an elliptic region of interest placed over the heart on the sum image. Three indexes were analysed: total myocardial counts (Sum), mean myocardial pixel (Mean) and maximum myocardial pixel (Max). Four patient groups were analysed: males with sestamibi or tetrofosmin (MS: n = 189 and MT: n = 157), females with sestamibi or tetrofosmin (FS: n = 101 and FT: n = 104). MS and MT groups were comparable for physical variables, maximum heart rate and stress type, as were the FS and FT groups. Sum, Mean and Max were significantly higher with sestamibi (P = 0.0001 by ANOVA). Comparing MS vs MT and FS vs FT, mean values ± SD were as follows: for Sum (kcounts) 750±184 vs 652±166, and 707±202 vs 594±189; for Mean (counts) 4517±1171 vs 4107±898, and 4908±1119 vs 4144±1025; and for Max (counts) 6471±1654 vs 5794±1312, and 7318±1886 vs 6152±1684. The mean gain with sestamibi was +15%, +10% and +12% in males, and +19%, +18% and +19% in females. Similar differences were found within each stress type subgroup. No gender-specific effect was found for Mean, so the overall mean gain was calculated for Mean: +13% for sestamibi vs tetrofosmin. These findings are consistent with other published smaller sample series. Possible differences between tracers with regard to residual activity in syringes were ruled out by an additional experiment. In summary, we found significantly higher myocardial counts with sestamibi than with tetrofosmin, in males as well as in females.

Key words: Technetium-99m sestamibi – Technetium-99m tetrofosmin – Myocardial uptake – Comparison

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Introduction

Dual-isotope protocols are being more and more widely used for myocardial single-photon emission tomography (SPET) imaging [1–3]. In this context a choice has to be made for stress injection between the available technetium-99m labelled myocardial tracers. This choice cannot be considered independently of the imaging time, especially when left ventricular resting function is assessed by ECG gating the post-stress SPET acquisition, a now routinely feasible procedure [4–18]. On the one hand post-stress imaging should not be performed less than 1 h after stress completion because of possible exercise-induced myocardial stunning [19]. On the other hand imaging should not be too much delayed because of possible tracer redistribution [20–22]. Acquiring post-stress ECG-gated SPET 60–75 min after tracer injection seems to be an acceptable compromise. Moreover counts requirements are a priori more critical with ECG-gated SPET than with ungated SPET, especially if not only the global left ventricular ejection fraction but also regional systolic thickening is assessed.

Thus if left ventricular resting function is to be assessed by ECG gating the post-stress SPET acquisition in the context of a dual-isotope protocol, relative myocardial uptake of competing ^{99m}Tc-compounds 60–75 min after stress injection is of interest. Few papers have directly compared sestamibi and tetrofosmin myocardial

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uptake [23–27] and none have done so in a large sample. The aim of this work was to perform such a comparison in a large unselected patient sample.

Material and methods

Patients. Patients were enrolled from February 1997 to August 1997. All the patients referred to our institution for routine myocardial imaging (performed 4 days a week) were eligible. Studies performed as an emergency were not considered. The end-point for each tracer was fixed at a minimum of 100 patients of each gender. The two tracers were used on an alternating weekly basis: sestamibi on odd weeks, tetrofosmin on even weeks. The weekly alternation was planned to continue until at least 100 patients of each gender had been enrolled for one tracer or the other. Due to random fluctuations in recruitment and sex ratio, this criterion was first met for tetrofosmin; thereafter only sestamibi was used until the criterion was again met, which took an additional 4 weeks. All consecutive patients were enrolled except one, who was excluded because a technical problem on the gamma camera led to him being imaged 3 h post-injection. Finally the group sizes were: males with sestamibi (MS) = 189, females with sestamibi (FS) = 101, males with tetrofosmin (MT) = 157, females with tetrofosmin (FT) = 104, i.e. a total of 551 patients.

Acquisition protocol. All the patients were imaged according to our routine dual-isotope protocol [28], closely derived from previous descriptions [1–3]. After rest thallium-201 injection and delayed (>1 h) SPET imaging, the stress was performed as a rule on a cyclo-ergometer. When the patient was supposed to be unable to perform adequate exercise because of physical limitations or therapy, dipyridamole infusion was used (0.56 mg/kg over 4 min) followed by a low- or mid-level exercise. In the case of left bundle branch block (permanent or previously known as frequency-dependent) or when the patient was unable to perform any significant exercise, dipyridamole infusion was used alone. The ^{99m}Tc agent was injected at peak stress [23 mCi (= 851 MBq) + 1 mCi (= 37 MBq) /10 kg body weight]; in the case of exercise or combined stress, exercise was sustained for at least 1.5 min after injection. ECG-gated SPET was acquired 60–75 min post-injection with an ADAC Vertex gamma camera (ADAC, Milpitas, Calif.): this delay was strictly observed for all patients. Milk chocolate (50 g) was given 15–20 min prior to imaging. Imaging parameters were: 32 projections over 180°, 45 s/projection, eight segments/cardiac cycle, no beat rejection, 64×64 matrix, 38 cm field of view (6.43 mm/pixel). The two camera heads were placed at right angles and equipped with ultra-high resolution collimators (ADAC VXUR).

Image analysis. Myocardial uptake was directly assessed from the ungated projection images and not from the reconstructed gated or ungated SPET slices, to avoid any possible interference from the reconstruction process (e.g. counts normalization, filter). Projection images were systematically corrected for possible vertical heart motion [29]. A sum image of the ungated projections was then computed. Due to the acquisition technology ("roving zoom"), the heart always appeared near the centre of the frame in all projections, and on the sum image it looked like a centered ovoid shape and not like a horizontal ribbon, as is usually the case with other imaging systems. Thus an elliptic region of interest (ROI) could be easily placed over the heart on the sum image and was considered as almost pure myocardium with little background (lung) contamination. Obviously this assumption would not have been valid with other imaging systems and a rectangular ROI placed over the "heart ribbon". From this elliptic ROI, manually sized and placed (Fig. 1), the following parameters were obtained: total counts, ROI area in pixels, mean pixel count and maximum pixel count. To avoid any user dependence on ROI sizing and positioning and possible interference with tracer, this task was performed on a daily alternating basis by the authors.

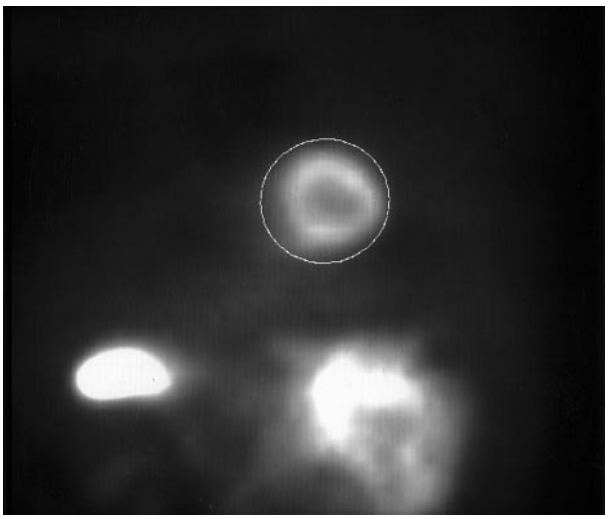

Fig. 1. A typical example of a summed projections image with an elliptic ROI placed over the heart

Data collection. For each patient the following data were recorded: gender, age, height, weight, stress type (exercise, dipyridamole or combined), maximum heart rate achieved (MHR) as a percentage of maximum predicted heart rate, total counts (Sum), number of ROI pixels (NP), mean pixel count (Mean) and maximum pixel count (Max). Furthermore additional parameters were computed: body mass index (BMI) in kg/m^2 and body surface area (BSA) in m^2.

Data analysis. Tracer and gender were considered as control variables; age, height, weight, NP, MHR, BMI and BSA as descriptive variables, stress type as a mixed control-descriptive variable, and Sum, Mean and Max as result variables. Statistical analysis was performed with Statview II (Abacus Concepts Inc., Berkeley, Calif.), using ANOVA for quantitative variables and chi-square test for qualitative variables. Probability levels (P)<0.05 were considered significant.

Results

Descriptive variables

Age, height, weight, NP, BMI and BSA were analysed in the four groups MS, MT, FS and FT (Table 1). Differences were analysed by ANOVA, using tracer and gender as control variables: significance levels are listed in Table 1. No difference was significant between tracers for these six measured variables. Significant gender differences were found for age, height, weight, NP and BSA: females were on average older, smaller and lighter and had a smaller heart ROI and a smaller BSA than

Table 1. Descriptive physical variables

	Sestamibi, males	Tetrofosmin, males	Sestamibi, females	Tetrofosmin, females	Tracer, effect (*P*)	Sex effect (*P*)
Age (yr)	62.0±11.3 (34–87)	60.3±10.0 (39–88)	65.7±9.9 (43–88)	65.0±9.1 (41–81)	NS	0.0001
Height (cm)	170.8±6.9 (150–190)	170.8±6.7 (151–190)	158.5±6.2 (142–172)	158.9±5.9 (143–172)	NS	0.0001
Weight (kg)	78.2±13.6 (49–119)	78.6±13.6 (50–125)	68.0±13.4 (45–114)	69.7±12.6 (41–107)	NS	0.0001
NP	167.5±31.7 (102–287)	160.5±31.3 (93–265)	144.9±25.1 (91–244)	146.1±25.8 (98–249)	NS	0.0001
BMI (kg/m^2)	26.7±4.0 (17.7–42.9)	26.9±3.8 (17.9–39.1)	27.1±5.1 (18.0–43.4)	27.7±5.0 (18.2–46.3)	NS	NS
BSA (m^2)	1.90±0.18 (1.42–2.37)	1.90±0.18 (1.48–2.51)	1.69±0.16 (1.37–2.18)	1.71±0.15 (1.32–2.06)	NS	0.0001

Data are displayed as mean ±SD, with range in parentheses
Probability levels (*P*) were obtained by ANOVA

Table 2. Mean maximum heart rate (MHR)

	Exercise	Dipyridamole	Combined
Sestamibi, males	86.9	61.8	73.5
Tetrofosmin, males	86.2	57.7	71.6
Sestamibi, females	91.2	63.2	75.0
Tetrofosmin, females	89.5	66.9	79.6

MHR is expressed as a percentage of maximum predicted heart rate
ANOVA showed significant differences for gender ($P = 0.0002$) and stress type ($P = 0.0001$) but not for tracer ($P = 0.9978$)

Table 3. Stress type distribution in males

	Sestamibi	Tetrofosmin	Total
Exercise	126	111	237
Dipyridamole	19	15	34
Combined	44	31	75
Total	189	157	346

Chi-square test was not significant

males. There was no difference between males and females for BMI.

MHR, expressed in percent of maximum predicted heart rate, was analysed by ANOVA using tracer, gender and stress type as control variables. A significant difference was found for gender and stress type (Table 2). Mean MHR values for males and females were, respectively, 86.6 and 90.4 for exercise, 60.0 and 65.0 for dipyridamole, and 72.7 and 77.7 for combined stress. These findings had no consequences for tracer comparison: the significance level for a possible tracer effect was $P = 0.998$.

Thus globally, the groups MS and MT on the one hand, and FS and FT on the other, were similar with regard to descriptive variables.

Table 4. Stress type distribution in females

	Sestamibi	Tetrofosmin	Total
Exercise	58	50	108
Dipyridamole	15	14	29
Combined	28	40	68
Total	101	104	205

Chi-square test was not significant

Stress type

The number of patients for each stress type is listed in Table 3 for males and in Table 4 for females. Chi-square test showed no statistical significance in either case with regard to a possible experimental fortuitous link between tracer and stress type. Thus globally, the groups MS and MT on the one hand, and FS and FT on the other, were similar with regard to stress type.

Result variables

ANOVA was performed using tracer, gender and stress type as control variables, and Sum, Mean and Max as measured variables. Mean values for each of the 12 subgroups are listed in Table 5 and displayed in Figs. 2–4. The significance levels associated with tracer, gender, stress type, tracer × gender interaction, tracer × stress type interaction, gender × stress type interaction and global interaction are listed in Table 6. Tracer effect was always highly significant; gender effect and stress type effect were significant for Sum and Max but not for Mean. Gender×stress type interaction was always significant: significant interactions are usually difficult to interpret in ANOVA but here it seemed that the finding was due to the fact that the results were higher with di-

Table 5. Myocardial counts

		Exercise	Dipyridamole	Combined	Mean
Sestamibi, males	*n*	*n* = 126	*n* = 19	*n* = 44	*n* = 189
	Sum	745±162	738±180	769±239	750±184
	Mean	4422±911	4626±1388	4742±1640	4517±1171
	Max	6367±1300	6562±2072	6731±2268	6471±1654
Tetrofosmin, males	*n*	*n* = 111	*n* = 15	*n* = 31	*n* = 157
	Sum	660±159	639±207	628±172	652±166
	Mean	4177±944	3973±846	3923±727	4107±898
	Max	5865±1358	5493±1341	5685±1126	5794±1312
Sestamibi, females	*n*	*n* = 58	*n* = 15	*n* = 28	*n* = 101
	Sum	726±192	790±287	624±136	707±202
	Mean	5014±1085	5218±1273	4523±1040	4908±1119
	Max	7539±1842	7938±2222	6528±1578	7318±1886
Tetrofosmin, females	*n*	*n* = 50	*n* = 14	*n* = 40	*n* = 104
	Sum	658±174	493±136	549±199	594±189
	Mean	4444±1071	3799±464	3889±1018	4144±1025
	Max	6748±1722	5512±943	5631±1610	6152±1684

Units are kcounts for Sum, counts for Mean and Max (see text for abbreviations)
Values are shown as mean ±SD
Associated significance levels are listed in Table 6

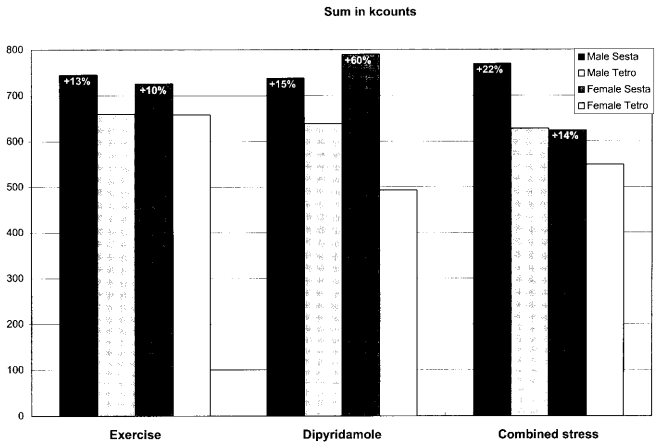

Fig. 2. "Sum" values according to gender, tracer and stress type. The relative difference of sestamibi vs tetrofosmin is shown in percent

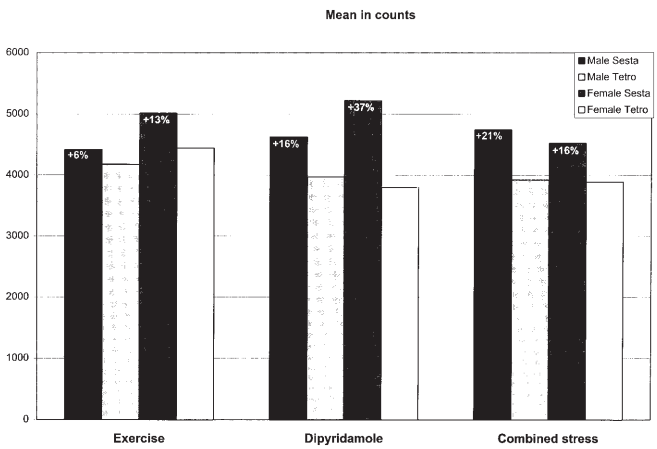

Fig. 3. "Mean" values according to gender, tracer and stress type. The relative difference of sestamibi vs tetrofosmin is shown in percent

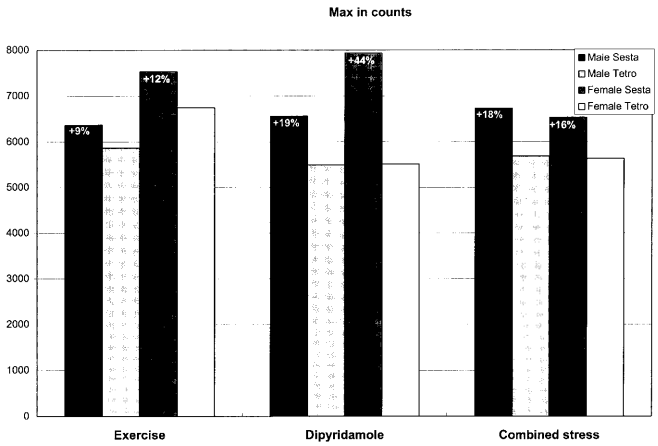

Fig. 4. "Max" values according to gender, tracer and stress type. The relative difference of sestamibi vs tetrofosmin is shown in percent

pyridamole than with exercise and combined stress for FS, and lower with dipyridamole than with exercise and combined stress for FT, while this was not the case for males; it is important to note, however, that the small size of the two subgroups (n = 15 for FS with dipyridamole, n = 14 for FT with dipyridamole) must be taken into account. Tracer×stress type was merely significant for Max: the same kind of explanation was likely and more generally it was debatable whether, in this context of multiple statistical tests, a level of P = 0.01 would not have been more appropriate.

Globally, myocardial counts were found to be higher with sestamibi than with tetrofosmin: +10 to +15% in males, and +18 to +19% in females, depending on the parameter (Sum, Mean or Max).

Table 6. ANOVA significance levels for myocardial counts

	Sum	Mean	Max
Tracer	0.0001	0.0001	0.0001
Gender	0.0042	NS	0.0022
Stress	0.0118	NS	0.0115
Tracer×Gender	NS	NS	NS
Tracer×Stress	NS	NS	0.0429
Gender×Stress	0.0248	0.0376	0.0021
Tracer×Gender×Stress	NS	NS	NS

See Table 5 for mean values in each group

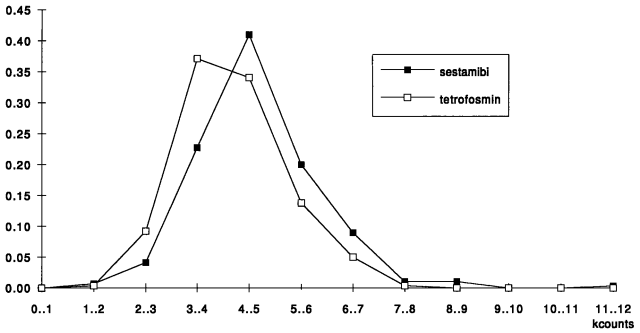

Fig. 5. "Mean" values distribution with both tracers; data for males and females were pooled; vertical axis units are fractions of total

Discussion

Analysis of results

Analysis of descriptive variables, including stress type, clearly showed that the MS and MT groups on the one hand, and the FS and FT groups on the other, were perfectly comparable. This is probably a direct consequence of the very large sample sizes. As was to be expected, gender-related differences were found for most physical variables (age, height, weight, NP, BSA) but not for BMI. On average, females reached a higher MHR than did males, and there were differences for stress type: exercise gave a higher MHR than combined stress, and combined stress gave a higher MHR than dipyridamole, an unsurprising finding. More important was the lack of difference in MHR between tracers.

Against this background it was logical to compare the myocardial counts parameters separately for males and for females. The three myocardial counts parameters (Sum, Mean, Max) were significantly higher with sestamibi than with tetrofosmin, in males as well as in females. Among these three parameters, Mean was supposed to be the more meaningful for overall final image quality: for Mean, the gain with sestamibi compared with tetrofosmin was +10% in males and +18% in females. Actually the gain varied with stress type from +6% to +21% in males, and from +13% to +17% in females. From Table 6 it appeared that gender effect was not significant for Mean, so Mean data were pooled for males and females and the corresponding histograms for sestamibi and tetrofosmin are displayed in Fig. 5: this graph can be considered as a minimal summary of our work, clearly showing a shift towards lower counts for tetrofosmin compared with sestamibi, Mean being on average 13% higher with sestamibi than with tetrofosmin.

An apparently subsidiary but actually important question is: does the observed difference for Mean have a clinically significant impact on final image quality and clinical interpretation? As will be discussed below with reference to published comparative clinical studies, the answer seems to be no, as long as one is concerned with myocardial perfusion assessment. However, from the perspective of left ventricular function assessment by gated SPET, the answer has to be qualified. If one only considers LVEF, then automatic algorithms seem robust enough to process low-counts acquisitions, and in fact two published works [30, 31] suggest the feasibility of left ventricular ejection fraction (LVEF) assessment with ^{201}Tl gated SPET, which yields lower myocardial counts than with either of the two technetium compounds that we have studied. But if one considers local systolic thickening assessment, then measurement of local counts increase from end-diastole to end-systole is the sole experimentally validated and physically sound method with the spatial resolution currently available in SPET [32, 33]. Adequate local counting statistics is then of concern when comparing side-by-side end-diastolic and end-systolic slices. In our study, since the overall average Mean was 4653 counts with sestamibi, 32 projections and 8 time segments result in a mean pixel value in individual gated projections of 18.18 counts, while for tetrofosmin the overall average Mean was 4122 counts, thus resulting in a mean pixel value in individual gated projections of 16.10 counts. Further work is needed to determine the counts requirements for reliable local systolic thickening assessment, whether count-based, geometric or hybrid [33].

Comparison with published comparative studies.

Münch et al. [26] studied 12 subjects (six patients and six normals) with tetrofosmin and 12 subjects (again, six patients and six normals) with sestamibi. A 1-day protocol was used (rest then stress). They studied the time course of uptake by various organs after the stress injection: myocardial uptake was 45% higher at 1 h with tetrofosmin than with sestamibi. Of course, these results stand in contradiction to our own. A possible explanation is that the stress-to-rest injected activity ratio seemed to be lower with tetrofosmin than with sestamibi (3.38 for tetrofosmin and 3.58 for sestamibi: these values were calculated as the ratios of the mean injected activities and could be different from the means of the ratios). Thus residual activity from rest injection could have been more important for tetrofosmin than for sestamibi, especially given that in this study myocardial uptake after rest injec-

tion was already 25% higher with tetrofosmin than with sestamibi. However, this phenomenon probably played a marginal role compared with the possible random fluctuations in a small sample: in our study the overall variation coefficient for Mean was 25% for sestamibi and 23% for tetrofosmin. Random selection of 12 patients in the right-hand side of the tetrofosmin histogram and 12 patients in the left-hand side of the sestamibi histogram in Fig. 5 is far from unlikely.

Valkema et al. [25] compared myocardial uptake of sestamibi and tetrofosmin in the same six patients 1 h post rest injection. The sestamibi/tetrofosmin ratios varied from 0.97 to 1.31, which seems more consistent with our results even if the measurements were performed after rest injection. The limitation of the very small sample size is probably less important than in the previous study, since the same patients received both tracers.

Flamen et al. [23] compared uptake by various organs of sestamibi and tetrofosmin in the same 30 subjects, comprising 25 patients and 5 normals. A 1-day protocol was used (rest then dipyridamole stress). Their results were similar to ours: myocardial counts 1 h post stress injection were 17% higher with sestamibi than with tetrofosmin. Possible residual rest activity in stress measurements was of limited impact since the stress-to-rest injected activity ratios were a priori similar for both tracers and myocardial counts after rest were only 3% higher with sestamibi than with tetrofosmin. Flamen et al. also compared visual, semi-quantitative and quantitative scoring of the reconstructed slices and found no significant difference between sestamibi and tetrofosmin.

Two other works compared clinical results of sestamibi and tetrofosmin. Naruse et al. [24] compared normal data bases obtained with various tracers: for SPET, marginal differences were found between tetrofosmin and furifosmin and between sestamibi and furifosmin, but no difference was found between sestamibi and tetrofosmin. Widding et al. [27] compared sestamibi and tetrofosmin clinical results in the same 20 patients. Although imaging protocols were different for both tracers (2 days for sestamibi, 1 day for tetrofosmin), they obtained a nearly perfect agreement regarding clinical interpretation.

Possible tracer absorption by rubber bung in syringes

Some concern may be raised about ad- or absorption of tracer by the rubber bung in syringes, and, of course, if such a phenomenon were to be significant and to vary between tracers then our results would be invalid or at least questionable. In order to clarify this point we performed an additional experiment as follows.

One sestamibi vial and one tetrofosmin vial were labelled with a similar amount of ^{99m}Tc drawn from the same generator eluate (5.587 GBq for sestamibi, 5.698 GBq for tetrofosmin). Five syringes were drawn from each vial; the syringes were those which we use routinely (B-D Plastipak 2 ml). At 30, 60, 90, 120 and 150 min, a syringe was counted in a dose calibrator, connected to a three-way stop-cock and an isotonic saline infusion set, voided, flushed 3 times with saline and counted again: this experimental protocol was designed to mimic our real clinical conditions. The whole process was repeated the day afterwards with ^{99m}Tc drawn from another generator and a different amount of activity (12.321 GBq for sestamibi, 12.395 GBq for tetrofosmin). Full syringe activity with the first eluate was (mean ± SD), 672±231 MBq for sestamibi and 645±40 MBq for tetrofosmin; with the second eluate it was 1040±36 MBq for sestamibi and 1044±48 MBq for tetrofosmin. Results were analysed using ANOVA with eluate number, delay and tracer as control variables, and residual activity (absolute and relative) as result variables. No significant difference was found between eluates, between delays and most importantly between tracers. Absolute residual activity in syringe was (mean ± SD) 28±13 MBq for sestamibi and 29±11 MBq for tetrofosmin. Relative residual activity was (mean ± SD) 3.7%±2.0% for sestamibi and 3.5%±1.4% for tetrofosmin. Labelling quality control was performed on all four vials: the radiochemical purity was always higher than 93%.

Consequently, a possible differential ad- or absorption of tracer by the rubber bung in syringes was ruled out.

Heart-to-liver ratio

A high liver activity or, more precisely, a low heart-to-liver ratio, is a potential source of artefactual defects in the inferior or inferoseptal myocardial wall [34, 35]. It has been shown by Nuyts et al. [35] that on the one hand iterative reconstruction minimizes the artefact in comparison to filtered backprojection, and on the other hand that the artefact is partially an attenuation problem since it nearly disappears when attenuation correction is added to iterative reconstruction. Thus not only is the role of a low heart-to-liver ratio in the genesis of the artefact questionable, but also the commercial availability of iterative reconstruction techniques and attenuation correction could soon make this concern irrelevant. In any case, significant artefact was found in a phantom study only when the heart-to-liver ratio was as low as 0.5 [34]. This has been confirmed by previously mentioned clinical studies [23, 24, 27]; in particular, despite the heart-to-liver ratio being less favourable for sestamibi than for tetrofosmin (1.05 vs 1.37 post-stress, 0.96 vs 1.19 post-rest), Flamen et al. [23] found no difference in the inferior and inferoseptal myocardial segments. Reported values for heart-to-liver ratios vary widely among studies: after stress injection, cited values are between 0.92 and 1.9 for sestamibi [26, 36–38] and between 1.3 and 3.1 for tetrofosmin [26, 39, 40], i.e. above the critical threshold of 0.5 determined by phantom studies [34]. The wide range of values reflects the difficulty in reliably quantifying this parameter. This is why we decided not to compute this ratio in our study: preliminary experiments re-

vealed wide inter-observer and even intra-observer variations which would seriously compromise long-term reproducibility, a mandatory requirement for our study, planned to extend over several months.

Limitations of the study

An important limitation of our study should be pointed out: our results are valid only with our imaging protocol, and in particular any generalization to a different delay post stress injection would not be acceptable.

Some arguments for a delay shorter than 1 h could be set out. Firstly, the shorter the delay, the easier is patient and camera planning. Secondly, for both tracers a shorter delay would mean higher myocardial counts, and, for tetrofosmin, pharmacokinetics data [40] suggest that post-injection delays as short as 15–20 min still provide acceptable target-to-background (i.e. heart-to-lung and heart-to-liver) ratios. However, a clinical study including 297 patients [41] concluded that the optimal delay for tetrofosmin was 45–60 min, and inferior defects were found in one-third of normal volunteers at 10 min after rest injection whereas images at 1 h were normal [42]. On the other hand, reasons could also be put forward in favour of a longer delay. Firstly, an argument comparable to the aforementioned one for tetrofosmin holds for sestamibi: target-to-background ratios are more favourable if the delay is longer. Secondly, and most importantly, the possibility of post-ischaemic myocardial stunning up to 1 h after stress, and even 2 h after stress when regional function is considered, has been formally demonstrated by Ambrosio et al. [19]; this phenomenon could also partially explain the trend toward underestimation observed when 1-h post-stress rest LVEF from sestamibi gated-SPET was compared with true rest LVEF from ^{201}Tl gated SPET [30, 31].

Data regarding the time course of myocardial tracer distribution also have to be considered. The stability of myocardial sestamibi distribution after stress injection is controversial (no data seem to be available for tetrofosmin). Minimal but significant redistribution in ischaemic segments has been found from 65 min to 190 min [20], from 1 h to 6 h [21] and from 5 min to 2 h [22], but by contrast Villanueva-Meyer et al. [43] found no significant change in defect size from 1 h to 4 h. Differences in defect assessment criteria (roughly: severity or extent) may explain these apparent discrepancies.

The time course of myocardial distribution after rest injection is not directly relevant to our concerns since the studies in question have been aimed at viability assessment. However, they deserve to be mentioned: sestamibi redistribution has been correlated to viability [44, 45], sestamibi reverse redistribution has been correlated to infarct-related artery patency [46], and tetrofosmin reverse redistribution has been found in non-viable segments but not in viable segments within infarct-related artery territory [47].

Thus globally, if we consider the two main constraints, i.e. possible post-ischaemic stunning on the one hand and possible tracer redistribution in ischaemic segments on the other, a post-stress delay of 60–75 min, as employed in our study, seems the best compromise when the goal is to simultaneously assess stress perfusion and rest function by gated SPET.

Another possible limitation is that the patients' coronary status was not taken into account; thus group comparability in respect of this important variable cannot be formally guaranteed. We adopted the hypothesis that if the patients were randomly imaged with sestamibi or tetrofosmin, and if the physical and stress variables were similar with both tracers in paired groups (MS vs MT, FS vs FT), then the large number of patients enrolled in each group would almost certainly ensure that there would not be any significant differences regarding coronary status. Indirect confirmation of the validity of this hypothesis is provided by the fact that the slight counts difference between sestamibi and tetrofosmin was found in females as well as in males: not only is it very unlikely that such large paired groups showing no difference regarding physical and stress variables could exhibit significant differences regarding coronary status, but also it would be extremely unlikely that such hidden differences would by chance be similar in females as well as in males, especially if one further considers that the difference was also observed within each stress type subgroup.

Conclusion

We have compared myocardial counts 60–75 min after stress injection of ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin in males and in females. Groups did not differ with regard to physical variables, stress type and injected activity. Possible differential ad- or absorption of tracer by the rubber bung in syringes was ruled out by an additional experiment. In males as well as in females, significantly higher myocardial counts were obtained with sestamibi than with tetrofosmin: the gain was from +6% to +22% in males, and from +12% to +60% in females, depending upon the index (total counts, mean pixel value or maximum pixel value) and on the stress type (exercise, dipyridamole or combined stress). Since gender differences and stress type differences were not significant for mean pixel value, data could be pooled for this index, probably the most meaningful one: the overall gain with sestamibi was +13%. These findings confirm, on a large-scale basis, previously published smaller sample series. Whether or not this difference is clinically relevant for stress perfusion assessment is doubtful. However, it could be of concern in the context of left ventricular function assessment and especially regional systolic thickening assessment by counts increase from diastole to systole. Further work is needed to clarify to what extent counts requirements are critical for this purpose.

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