# Myocardial Technetium-99m-Tetrofosmin and Technetium-99m-Sestamibi Kinetics in Normal Subjects and Patients with Coronary Artery Disease

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This study was designed to compare the tracer kinetics between $^{99m}$Tc-sestamibi and $^{99m}$Tc-tetrofosmin in a heterogeneous group of 24 patients admitted for routine perfusion imaging. **Methods:** Twelve patients were studied with $^{99m}$Tc-tetrofosmin and 12 with $^{99m}$Tc-sestamibi. In each group, six patients had a low likelihood for coronary artery disease, and six patients had angiographically proven coronary artery stenoses of >75% or previous myocardial infarction. Analysis of myocardial and liver uptake and clearance as well as target-to-organ contrasts were performed with planar stress images. **Results:** Myocardial uptake of $^{99m}$Tc-tetrofosmin was higher from 5 min (0.37 ± 0.12 counts/pixel × $MBq^{-1}$, p = 0.008) to 60 min (0.32 ± 0.10 counts/pixel × $MBq^{-1}$, p = 0.04) compared to $^{99m}$Tc-sestamibi. Biological half-life for $^{99m}$Tc-tetrofosmin (278 ± 32 min) in normal myocardium was significantly shorter (p = 0.008) than for $^{99m}$Tc-sestamibi (680 ± 45 min). Biological liver half-life for $^{99m}$Tc-tetrofosmin (67 ± 16 min) was also significantly shorter (p = 0.02) than for $^{99m}$Tc-sestamibi (136 ± 18 min). Heart-to-lung ratios for $^{99m}$Tc-tetrofosmin (2.49 ± 0.43 at 5 min to 2.66 ± 0.55 at 60 min) and $^{99m}$Tc-sestamibi (2.52 ± 0.37 at 5 min to 2.95 ± 0.50 at 60 min) were similar. Whereas heart-to-liver ratios for $^{99m}$Tc-tetrofosmin (1.04 ± 0.24 at 5 min, increasing to 1.51 ± 0.44 at 60 min) were significantly higher from 30–60 min postinjection (p = 0.05 at 30 min to p = 0.02 at 60 min) compared to the $^{99m}$Tc-sestamibi (0.83 + 0.16 at 5 min to 1.08 ± 0.27 at 60 min). **Conclusion:** Technetium-99m-tetrofosmin displays a shorter myocardial half-life compared to $^{99m}$Tc-sestamibi. The rapid liver clearance of $^{99m}$Tc-tetrofosmin, combined with comparable myocardial retention, resulted in higher heart-to-liver ratios but similar heart-to-lung contrasts compared to $^{99m}$Tc-sestamibi from 30–60 min.

**Key Words:** technetium-99m-tetrofosmin; technetium-99m-sestamibi; liver clearance; myocardial uptake

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Thallium-201 stress myocardial perfusion imaging is widely used for the diagnosis of coronary artery disease (CAD) (*1–3*). However, $^{201}$Tl has several disadvantages when compared to $^{99m}$Tc-labeled compounds because of its longer half-life and lower photon energy which affects image quality. Technetium-99m-teboroxime displays high myocardial extraction but very rapid myocardial washout, limiting its clinical application (*4,5*). Technetium-99m-sestamibi (MIBI) has suitable myocardial kinetics but delineation of regional tracer distribution, especially in the inferior wall, which can be compromised by high liver uptake (*5,6*). More recently, the cationic diphosphine complex $^{99m}$Tc-tetrofosmin has become available in a freeze-dried kit, which allows preparation at room temperature with high radiochemical purity and with an 8 hr stability of the complex (*7*). Rapid myocardial uptake without significant redistribution, good blood clearance (*8*), high heart-to-lung ratios and relatively rapid liver clearance (*9*) are promising characteristics for myocardial scintigraphic imaging and may allow image acquisition as early as 5 min postinjection (*10*).

When using tetrofosmin as a perfusion tracer, the myocardial distribution correlates well to the blood flow (*11*). Safety and reliability of tetrofosmin for detection of CAD comparable to $^{201}$Tl was shown in promising Phase I and II studies (*8–10,12*). Continued research in a recent Phase III multicenter trial determined the accuracy of diagnosis of coronary artery stenosis with tetrofosmin comparable to that of $^{201}$Tl, both in planar images (*13*) and SPECT imaging (*14*). Recently, intraindividual comparisons of SPECT images for tetrofosmin and MIBI were performed (*15*). Varying heart-to-liver ratios and comparable heart-to-lung ratios were found, however, only one time point was analyzed.

This study was, therefore, designed to compare myocardial and liver uptake, clearance kinetics and heart-to-organ ratios for tetrofosmin and MIBI between two similar patient populations. Stress planar images were analyzed in normal subjects and patients with CAD to establish a time course for best image acquisition of myocardial scintigraphy for tetrofosmin in comparison with MIBI.

## MATERIALS AND METHODS

### Patient Population

Twenty-four patients (20 men, 4 women; mean age 56 yr) referred for routine myocardial perfusion scintigraphy were included in this study. The patients were separated into groups: 12 tetrofosmin, 12 MIBI. Patient characteristics are listed in Table 1. The population consisted of patients with a low likelihood of CAD as defined by <5% and patients with angiographically proven coronary stenoses of >75% of at least one vessel or previous myocardial infarction. The CAD patient population consisted of four patients with single-vessel disease, three with two-vessel disease, three with triple-vessel disease and one patient with a previous myocardial infarction. There was no difference in the extent of CAD in this patient population.

Exclusion criteria for the study were: childbearing potential, previous myocardial infarction within the last 2 mo, unstable angina, intravenous nitrates or inotropic substances, severe primary valvular disease, left ventricular aneurysm, left bundle branch block, congenital heart defect, history of primary cardiomyopathy or belonging to a group with increased exposure to radioactivity (>15 mSv per year).

### Radiopharmaceutical Preparation and Quality Control

Tetrofosmin was supplied in a commercially available ready-to-use kit (Myoview, Amersham Intl., Braunschweig, Germany). Each vial contained 0.23 mg tetrofosmin, 0.03 mg stannous chloride dehydrate, 0.32 mg sodium sulfosalicylate and 1.00 mg sodium-D-gluconate. Each vial was reconstituted with 6 GBq sodium [$^{99m}$Tc]pertechnetate in 4–8 ml saline. The vial was shaken gently until complete dissolution of the lyophilized powder

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**TABLE 1**
Patient Clinical Data*

| Study groups | No. of patients | Male | Female | Age (yr) | Body weight (kg) | Height (cm) | RPP/100 | No. diseased vessels |
|---|---|---|---|---|---|---|---|---|
| All subjects | | | | | | | | |
| Tetrofosmin | 12 | 11 | 1 | 56 ± 3 | 79 ± 2 | 173 ± 2 | 220 ± 22 | |
| MIBI | 12 | 9 | 3 | 63 ± 4 | 77 ± 4 | 172 ± 2 | 227 ± 24 | |
| p value | | | | 0.26 | 0.51 | 0.53 | 0.92 | |
| Low likelihood for CAD | | | | | | | | |
| Tetrofosmin | 6 | 5 | 1 | 57 ± 5 | 77 ± 3 | 173 ± 3 | 230 ± 3 | |
| MIBI | 6 | 4 | 2 | 63 ± 7 | 77 ± 7 | 172 ± 3 | 241 ± 35 | |
| p value | | | | 0.29 | 0.72 | 0.75 | 0.35 | |
| Proven CAD | | | | | | | | |
| Tetrofosmin | 6 | 6 | – | 55 ± 3 | 81 ± 3 | 174 ± 2 | 213 ± 30 | 2-1 VD, 2-2VD, 2-3VD |
| MIBI | 6 | 5 | 1 | 64 ± 7 | 76 ± 5 | 172 ± 3 | 211 ± 35 | 2-1 VD, 1-2 VD, 1-3 VD, 1 MI |
| p value | | | | 0.65 | 0.69 | 0.40 | 0.68 | |

*The p values for differences between tetrofosmin and MIBI are listed.
VD = vessel disease; MI = myocardial infarction.

and allowed to stand for 15 min at room temperature. This preparation yields a tetrofosmin complex with high radiochemical purity and a stability of 8 hr (*7*).

MIBI was supplied in a sealed vial containing 24.675 mg dried powder consisting of 1 mg tetrakis(2-methoxy-2-methylpropanisocyanid) copper (*1*+)-tetrafluoroborat, 0.075 tin(II)-chloride 2 $H_2O$, 1 mg cysteinhydrochloride-monohydrate, 2.6 mg sodiumcitrate and 20 mg mannitol. Each vial was prepared with 5.55 GBq sodium [$^{99m}$Tc]pertechnetate in 3 ml saline. The vial was shaken and complete reaction of the complex was achieved at 100°C for 10 min by incubating the vial in boiling water. The preparation was completed after 15 min to allow the vial to cool to room temperature. Both the tetrofosmin and MIBI solutions were stored at room temperature and used on the same day of preparation. The radiochemical purity of each sample was assessed as previously described (*7*) and only a purity >90% was considered sufficient quality for use in patients.

### Study Protocol

In the tetrofosmin patient group, rest imaging was performed approximately 60 min after injection of 330 ± 14 MBq tetrofosmin. Four hours later, a stress protocol was performed with treadmill exercise and injection of tetrofosmin (1115 ± 40 MBq) at peak exercise with continued exercise for one additional minute after injection. For the MIBI patients, the same rest/stress protocol was followed as for tetrofosmin The mean of the injected dose of MIBI was 270 ± 15 MBq at rest and 967 ± 30 MBq during stress. Endpoints for exercise termination in both groups were fatigue, hypotension, chest pain, dyspnea, significant ST-segment depression of >0.2 mV or induction of arrhythmias.

After injection at peak exercise, dynamic planar images were acquired at 5, 10, 20, 30, 40, 50 and 60 min. One planar image per time point was obtained in the true anterior position with a 200-sec acquisition time. Imaging was performed using a dual-head camera with a parallel-hole, low-energy, high-resolution collimator (LEHR). Images were acquired in a 128 × 128 matrix with a zoom of 1.45. The camera energy window was set at 140 keV (15% width) for the $^{99m}$Tc peak.

### Data Analysis

For comparison of tetrofosmin and MIBI kinetics, myocardial and liver uptake and washout were measured. For normal values, individual ROIs were manually drawn over myocardial areas with visually highest uptake. Identical ROIs were used for each time point for the individual patient and similar ROIs were used between patients (Fig. 1). For comparison of myocardial uptake of these normal regions versus ischemic myocardium, corresponding ROIs were drawn in the myocardium of the same patients with stress induced perfusion abnormalities. After decay correction for $^{99m}$Tc, myocardial and liver activity in counts/pixel were normalized by the injected dose of tracer activity in MBq. Biological half-life for tetrofosmin or MIBI was calculated by exponential curve fitting from the decay corrected washout curves from ischemic and normal myocardium or liver.

Contrast between tracer accumulation in the heart and surrounding organs is essential for good image quality. Thus, the heart-to-lung ratios and heart-to-liver ratios were calculated. Individual ROIs were drawn over heart, lung and liver (Fig. 1). These ROIs included the anterior wall or the liver parenchyma, avoiding activity from the gallbladder or hepatic duct. The same ROIs were used for each time point for an individual patient and similar ROIs between patients. The activity in respective organs was analyzed as counts per pixel and ratios were calculated. Two experienced observers without knowledge of clinical data independently drew standardized ROIs and analyzed the data. If conflicting results between observers occurred, discrepancy was resolved by consensus.

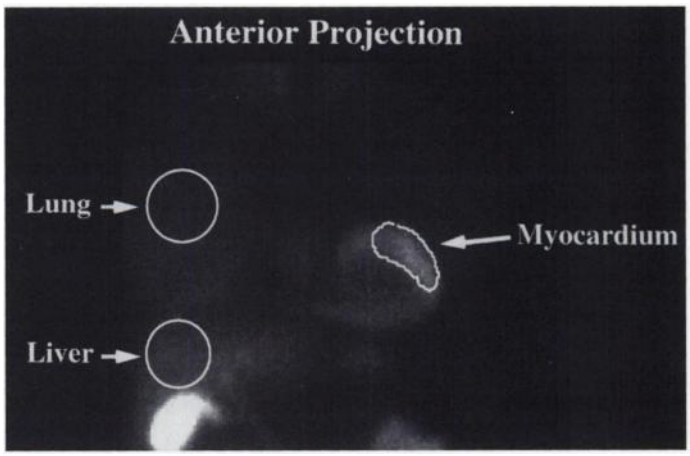


**FIGURE 1.** Planar image with heart-to-liver and heart-to-lung ROIs. The same ROIs were used for each time point for the individual patient and similar ROIs were used for all patients.

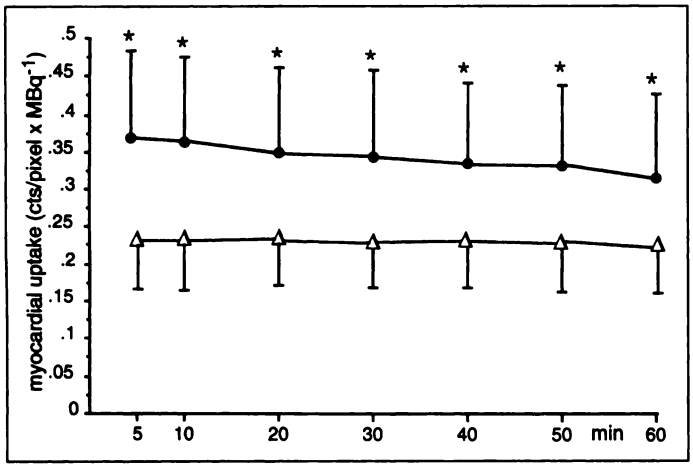


**FIGURE 2.** Comparison of $^{99m}$Tc-tetrofosmin (●) and $^{99m}$Tc-sestamibi (△) tracer kinetics in stress planar images. Myocardial uptake index of normal myocardial areas from 5 to 60 min postinjection as counts per pixel activity per injected dose. The means ± s.e.m. of 12 patients are presented. *p < 0.05 significant differences.

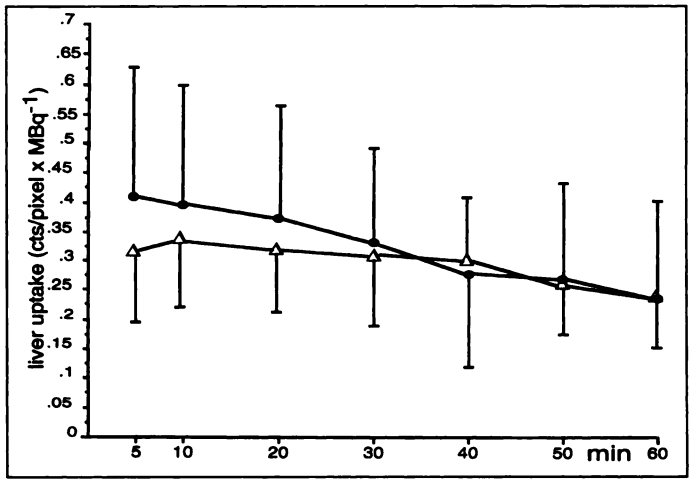


**FIGURE 3.** Comparison of $^{99m}$Tc-tetrofosmin (●) and $^{99m}$Tc-sestamibi (△) liver uptake kinetics in stress planar images. Liver uptake index from 5 to 60 min postinjection as counts per pixel activity per injected dose. The means ± s.e.m. of 12 patients are presented. *p < 0.05 significant differences.

### Statistical Analysis

The mean ± s.e.m. were presented. Uptake values are expressed in counts/pixel × MBq$^{-1}$. Heart-to-organ ratios are given without units. Statistical differences were calculated with a Mann-Whitney test; p values of < 0.05 were considered significant.

## RESULTS

### Exercise Data

The rate pressure products/100 achieved during treadmill exercise are given in Table 1. There was no significant difference in rate pressure product, age and body habitus, neither between the tetrofosmin and MIBI groups or between patients with known CAD and patients with low likelihood for CAD. None of the patients developed severe arrhythmias or angina nonresponding to nitrates during or after exercise.

### Imaging Results

Figure 2 shows the comparison of tetrofosmin and MIBI myocardial uptake index in visually normal myocardium. In all 12 patients, myocardial uptake index at rest approximately 60 min postinjection was 0.25 ± 0.07 counts/pixel × MBq$^{-1}$ for tetrofosmin. After stress, the myocardial uptake of tetrofosmin was 0.37 ± 0.12 counts/pixel × MBq$^{-1}$ at 5 min postexercise and declined to 0.32 ± 0.10 counts/pixel × MBq$^{-1}$ at 60 min postinjection. Myocardial uptake for MIBI at rest (0.20 ± 0.08 counts/pixel × MBq$^{-1}$) was similar to the rest uptake of tetrofosmin. After stress, the myocardial uptake of MIBI was 0.23 ± 0.06 counts/pixel × MBq$^{-1}$ at 5 min and declining to 0.22 ± 0.06 counts/pixel × MBq$^{-1}$ at 60 min. The stress values for MIBI were significantly (p = 0.008 at 5 min, to p = 0.04 at 60 min) lower compared to tetrofosmin for the entire 60 min.

In the six CAD patients studied with tetrofosmin, the uptake in stress images over normal myocardium was 0.39 ± 0.11 counts/pixel × MBq$^{-1}$ at 5 min and declined to 0.33 ± 0.09 counts/pixel × MBq$^{-1}$ at 60 min. Ischemic myocardial uptake with tetrofosmin was 0.29 ± 0.08 counts/pixel × MBq$^{-1}$ at 5 min and declined to 0.24 ± 0.06 counts/pixel × MBq$^{-1}$ at 60 min, which was significantly lower compared to normal myocardium at all time points (p = 0.03 at 5 min, to 0.05 at 60 min) excluding 40 min p.i. (p = 0.14). In six patients with CAD in the MIBI group, the normal myocardial uptake for only the 5, 10 and 40 min time points were significantly (p = 0.04) higher than in stress induced hypoperfused myocardium. All uptake values for MIBI were lower than those for tetrofosmin The decay-corrected biological half-life for tetrofosmin for both normal and ischemic myocardium, 278 ± 32 min and 224 ± 28 min, respectively, were significantly lower (p = 0.008) than that for MIBI, 680 ± 45 min and 1045 ± 56 min, for normal and ischemic myocardium, respectively.

Figure 3 shows the comparison between the liver uptake index of tetrofosmin and MIBI. Liver uptake for tetrofosmin in stress images was 0.41 ± 0.19 at 5 min and declined to 0.24 ± 0.11 at 60 min. The decay corrected biological half-life of tetrofosmin in the liver was 67 ± 13 min. For MIBI, the liver uptake was 0.31 ± 0.14 at 5 min and declined to 0.24 ± 0.08 at 60 min, which was not significantly different from tetrofosmin. The decay-corrected biological liver half-life for MIBI was 136 ± 18 min, which was significantly longer than for tetrofosmin (p = 0.02).

The heart-to-lung and heart-to-liver ratios are presented in Figures 4 and 5. The heart-to-lung ratios showed no significant differences between the two tracers at all time points. The heart-to-liver ratio (p = 0.05 at 30 min to 0.02 at 60 min) showed varying significance at different time points, with tetrofosmin having higher overall uptake values.

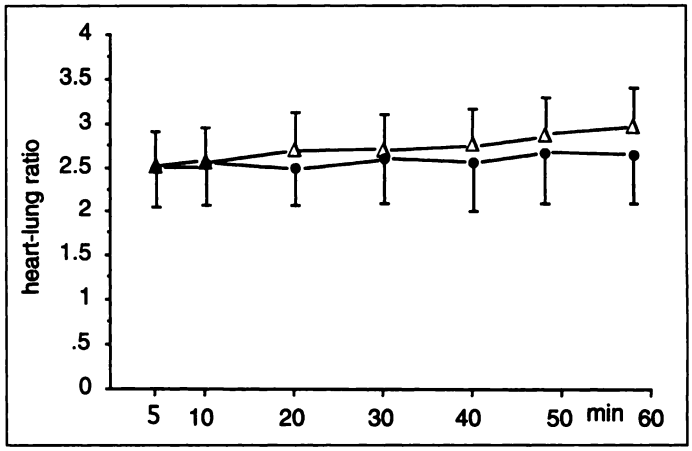


**FIGURE 4.** Comparison of $^{99m}$Tc-tetrofosmin (●) and $^{99m}$Tc-sestamibi (△) tracer kinetics in stress planar images. Heart-to-lung ratios from 5 to 60 min postinjection on a counts per pixel basis are given. The means ± s.e.m. of 12 patients are presented. *p < 0.05 significant differences.

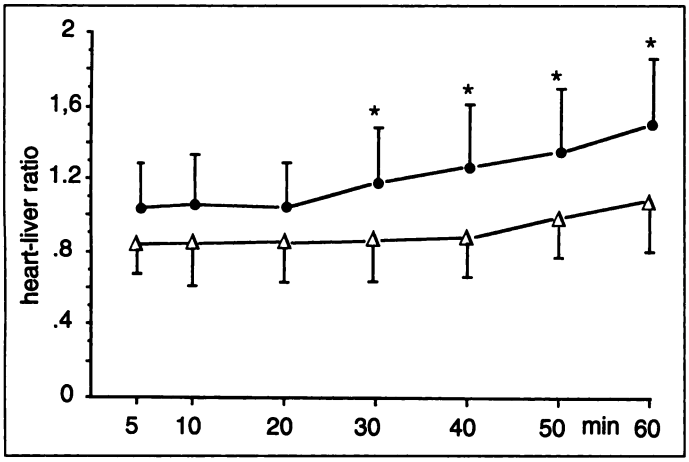


**FIGURE 5.** Comparison of $^{99m}$Tc-tetrofosmin (○) and $^{99m}$Tc-sestamibi (△) tracer kinetics in stress planar images. Heart-to-liver ratios from 5–60 min after injection on a counts per pixel basis are given. The means ± s.e.m. of 12 patients are presented. *$p < 0.05$ significant differences.

## DISCUSSION

### Myocardial Kinetics

In this study, the myocardial uptake and retention characteristics of both tetrofosmin and MIBI were compared by evaluation of the dynamic myocardial uptake index over 1 hr at various time points. Tetrofosmin displayed higher myocardial uptake but also a more rapid washout. The mechanism of myocardial uptake and retention of MIBI is explained by a passive diffusion across the plasma membrane driven by the negative membrane potential of the intact cell (*16*). First reports on uptake mechanisms of tetrofosmin demonstrated a membrane-potential driven diffusion mechanism independent of cation channel transport (*17*) depending on the metabolic status of the cell (*18*). In addition to the charge of the tracer complex, lipophilicity of tracers is correlated with uptake as previously described (*19*). Therefore, the higher lipophilicity of tetrofosmin, resulting in better diffusion across the cell membrane, may explain the higher initial uptake and faster washout of this tracer. The faster washout of tetrofosmin must be considered with delayed imaging, a characteristic not as critical for MIBI. In contrast to tetrofosmin, however, MIBI clearance half-time in ischemic myocardium is lower compared to nonischemic myocardium. As tracer retention in the myocardium is not only dependent on the myocardial extraction but even more importantly on myocardial washout, diminished clearance from ischemic myocardial areas due to low perfusion flow, could explain this overestimation of myocardial perfusion of ischemic areas in accordance with previous experimental studies (*20*). A comparable study with tetrofosmin, however, is lacking and future investigations have to clarify the characteristics of tetrofosmin in ischemic myocardium. In this study, similar retention times for tetrofosmin in normal and ischemic myocardium were observed.

### Liver Kinetics

In addition to high myocardial accumulation and retention, high background clearance is of major importance for good image quality with respect to heart background contrast. Particularly, high liver uptake and slow liver clearance has been a problem for MIBI (*6*). Therefore, the liver uptake characteristics of both tracers were also compared by evaluation of the dynamic liver uptake. In this study, liver clearance for tetrofosmin is faster compared to MIBI, resulting in a clearance half-life twice as fast in accordance with previous studies (*10*). As tetrofosmin demonstrated also higher initial liver uptake, the implication of liver and myocardial kinetics on the target-to-background ratio is discussed below.

### Target-to-Background Ratio Kinetics

The high myocardial retention and faster liver washout resulted in significantly better heart-to-liver ratios for tetrofosmin compared to MIBI from 30–60 min after tracer injection, but not from 0–30 min postinjection. Our data are similar to the heart-to-liver ratios in the previous studies of Wackers et al. (*6*) and a very recent study of Flamen et al. (*15*). These investigators performed intraindividual comparisons between MIBI and tetrofosmin, at one time point 1 hr after tracer injection. Although these results are also similar to the study of Jain et al. at one time point (*10*), their conclusion, which suggests favorable heart-to-backgound ratios for tetrofosmin as early as 5 min postinjection, cannot be confirmed by the present kinetic data. Therefore, the importance of kinetic studies becomes obvious in this point, as tetrofosmin develops advantages over MIBI with regard to heart-to-liver ratios not before 30 min postinjection.

Discrepancies with the study of Nakajima et al. (*9*), who found lower heart-to-liver ratios than we did, can be explained by the different analysis procedures. We compared individual ROIs from parts of respective organs, resulting in higher heart-to-organ ratios in our study, whereas Nakajima et al. (*9*) used overall heart activity to calculate heart-to-organ ratios, including areas of reduced tracer uptake. On the other hand, Higley et al. (*8*) used planar imaging and had significantly higher heart-to-liver ratios in planar images than we did. However, in their study, young, healthy volunteers were investigated, whereas a mixed population of older patients were investigated in our study. As tetrofosmin shows good correlation between blood flow and myocardial distribution (*11*), it is likely that our patient data showed an overall decreased myocardial uptake due to decreased coronary reserve caused by coronary artery disease in older patients compared to young volunteers. Similarly, our MIBI heart-to-liver ratios were also lower compared to previously published data with healthy volunteers (*8,10*). However, because we studied a similar patient population with both tracers, tetrofosmin and MIBI, the observed differences in tracer kinetics are more likely due to tracer characteristics.

Surprisingly, tetrofosmin presented with similar heart-to-lung ratios as MIBI, despite previous reports emphasizing the favorable heart-to-lung ratios for MIBI (*21*). Our heart-to-lung ratios for tetrofosmin were slightly higher than those found by Jain et al. (*10*) but were similar to those published by Nakajima et al. (*9*), despite their superior SPECT imaging technique. As described earlier, the selection of ROIs may explain the differences in reported values. Finally in comparison to the heart to liver ratios of Higley and co-workers (*8*), our results were lower, which can be explained by the differences in the study subjects.

### Study Limitations

A major limitation of this study was the lack of intraindividual comparisons. In this study, a heterogeneous population of patients were investigated admitted for routine myocardial perfusion scintigraphy. Although the physical characteristics of both the MIBI and tetrofosmin populations were not significantly different, i.e., age, height, weight and body habitus, it cannot be excluded that the reported differences between MIBI and tetrofosmin myocardial uptake could be due to this population difference. For a direct comparison of the two tracers. A study designed to administer both tracers in the same patient population is needed. However, a double investigation with both tracers would be difficult to perform due to time constraints and radiation dose.

## CONCLUSION

The present kinetic study revealed faster initial myocardial uptake and liver clearance of tetrofosmin in comparison to MIBI. This leads to a favorable time window for image acquisition with tetrofosmin between 30 and 60 min after tracer injection. However, the faster clearance may represent a disadvantage for delayed myocardial imaging, since the tracer distribution may not only reflect blood flow. Future experimental and clinical studies are required to define the tetrofosmin kinetics in ischemic myocardium in order to exclude the possibility of redistribution by differential washout in normal and ischemic myocardium.


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# Myocardial Perfusion and Function Imaging at Rest with Simultaneous Thallium-201 and Technetium-99m Blood-Pool Dual-Isotope Gated SPECT


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We present a simultaneous gated SPECT (G-SPECT) dual-isotope technique using $^{201}$Tl for perfusion and $^{99m}$Tc blood-pool labeling for function imaging. **Methods:** Seventeen patients (13 with previous myocardial infarction, MI) and a control group of three normal volunteers were investigated. They received, 15 min after a $^{201}$Tl stress/redistribution protocol with reinjection, 900–950 MBq $^{99m}$Tc-HSA for blood-pool labeling. Eight frames per R-R interval were recorded in the G-SPECT mode with three windows: window A with 20% centered at 71 keV for $^{201}$Tl, window B with 10% centered at 105 keV for Tc scatter contamination and window C centered at 140 keV with 20% for $^{99m}$Tc. Nongated, crosstalk-corrected $^{201}$Tl SPECT perfusion images were reconstructed according to normalized projection-by-projection subtraction from data from windows A and B. G-SPECT data from window C were reconstructed with the same reconstruction limits to allow topographic correlations of left ventricular perfusion and wall motion abnormalities. Polar maps of perfusion and function were used to divide the myocardium into 20 segments. Perfusion was expressed as the percentage of thallium uptake and function corresponding to diastolic to systolic shortening normalized by end diastolic volume. **Results:** Segmental comparison of uncontaminated-to-contaminated and corrected $^{201}$Tl patient images demonstrated an overall agreement score of 93%, with a kappa statistic of 0.76 ± 0.06 when normal perfused segments were excluded. Segmental matching of perfusion against function at rest showed no correlation for the 10 patients with preserved ejection fraction of 59% ± 8% nor for the control group. For the remaining seven patients with an ejection fraction of 34% ± 10%, there was linear correlation between perfusion and function ($r^2$ = 0.61). **Conclusions:** The feasibility of dual Tl-Tc G-SPECT was examined at rest and suggests low perfusion hypokinesis that matches linear dependence for CAD patients with low ejection fraction.



**Key Words:** myocardial perfusion; dual-isotope imaging; thallium-201; technetium-99m; gated SPECT; left ventricular function

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