Biokinetics of Technetium-99m-Tetrofosmin: Myocardial Perfusion Imaging Agent: Implications for a One-Day Imaging Protocol

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Tetrofosmin is a ^{99m}Tc-labeled myocardial perfusion imaging agent that has shown encouraging results in Phase I and II clinical trials. The purpose of this study was to determine the biokinetics of this agent following administration during exercise and at rest in order to determine an optimal imaging protocol. Twenty patients with suspected coronary artery disease underwent symptom-limited treadmill exercise. Six to 8 mCi of ^{99m}Tc-tetrofosmin was injected at peak exercise and 22–24 mCi was injected 4 hr later at rest. Serial 5-min planar images were obtained in the left anterior oblique view at 5, 10, 15, 30, 60, 120 and 180 min after the radiotracer injection. Regions of interest were drawn on the serial images around the entire heart and portions of liver, lung, spleen, gallbladder and gastrointestinal tract. Average decay-corrected counts per pixel in each organ were plotted against time. In addition, heart-to-adjacent organ ratios were also determined. On stress images, the heart had the highest activity at all times, with the exception of gallbladder in the first 15 min. On rest images, the gallbladder, liver and gastrointestinal tract initially had higher activity than the heart; but the activity in these organs cleared rapidly over the subsequent 30–60 min. Heart-to-adjacent organ ratios were >1.0 at all times in the stress images. Heart-to-organ ratios were <1.0 in the first 15 min on the rest images for the liver and gastrointestinal tract. However, 30 min later, all ratios on the rest images were ≥1.0. Technetium-99m-tetrofosmin images were considered to be of good to excellent quality with good myocardial delineation and adequate contrast between the heart and background. These These observations indicate that a convenient one-day tetrofosmin imaging protocol similar in duration to conventional ^{201}Tl imaging is feasible.

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Stress radionuclide myocardial perfusion imaging is an integral part of the clinical evaluation of suspected or known coronary artery disease (CAD) (*1–4*). Thallium-201 has been the traditional myocardial perfusion imaging agent since its clinical introduction in 1976. However, this agent has important physical limitations which include a low energy emission and a relatively long half-life (73 hr). These factors result in significant soft-tissue attenuation and scatter, limitation of allowable dose and technical difficulties with both planar and SPECT imaging.

To address these issues, ^{99m}Tc-labeled agents have been developed and evaluated over the past 5 yr. Sestamibi (*5–8*) and teboroxime (*9–11*) have been approved for clinical use. Sestamibi generally provides good quality images. However, a high initial hepatic sestamibi activity with relatively slow clearance necessitates a delay of 0.5–2 hr before imaging can be started after injection (*12*). This increases the total time a patient is required to spend in the imaging laboratory and consequently impacts upon laboratory logistics. Moreover, in some cases residual high hepatic and gastrointestinal tract activity can make image interpretation impossible. In contrast, teboroxime has a very short residence time in the myocardium and rapidly washes out after initial uptake (*9,10*). There is a very narrow time window during which imaging should be completed and images are often of suboptimal quality (*9*). In addition, hepatic activity increases progressively within a few minutes after injection of ^{99m}Tc-teboroxime which also interferes with image interpretation.

Tetrofosmin (Myoview™) is a newly developed compound of the diphosphine group labeled with ^{99m}Tc (*13–16*). The chemical name of this compound is 1,2-bis [bis (2-ethoxyethyl) phosphino] ethane. After intravenous administration, this compound is rapidly cleared from the blood and is taken up by the heart, skeletal muscle, liver, spleen and kidneys in proportion to the blood flow (*14–16*). The biodistribution of this compound suggests its suitability for use as a myocardial perfusion imaging agent. Once it is taken up by the myocardium, there appears to be little, if any, redistribution over the subsequent 3–4 hr (*17,18*). Initial Phase I and II clinical studies indicate that ^{99m}Tc-tetrofosmin compares well to ^{201}Tl as far as detection of CAD is concerned (*16–17*).

The purpose of this study was to evaluate and define the

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biokinetics of ^{99m}Tc-tetrofosmin at rest and following exercise. To achieve this goal, serial quantitative imaging was performed in patients. Data generated in such a manner can then be used to define an optimal timing for imaging under varying physiologic circumstances with this agent.

METHODS

Patient Population

The study population consisted of 20 patients (16 men and 4 women; mean ± s.d. age 55 ± 12 yr), entering a Phase III ^{99m}Tc-tetrofosmin clinical trial who underwent additional serial imaging following stress and rest injections of tetrofosmin (*19*). Thirteen patients had symptoms suggestive of CAD supported by at least one or more of the following: (a) an abnormal exercise test defined by chest pain with reversible ST-segment depression of >1.5 mm, (b) evidence of reversible myocardial ischemia on exercise ^{201}Tl scintigraphy, (c) presence of 70% or greater occlusion of at least one major coronary vessel on coronary angiography performed within the last 6 mo. The remaining seven patients had atypical chest pain syndrome but with negative stress ^{201}Tl images.

Three of the 20 patients had diabetes, 8 had hypertension, 9 had prior documented myocardial infarction. Six patients had undergone prior percutaneous coronary angioplasty, but none had undergone prior coronary artery bypass grafting. Patients continued their routine medication during the test. Five patients were receiving beta blockers, 11 were receiving calcium channel blockers, 6 were receiving long-acting nitrates, 8 were receiving diuretics and 4 patients were receiving no medications.

Radiopharmaceutical Preparation

Tetrofosmin was supplied by Mediphysics Amersham Healthcare (Arlington Heights, IL) as freeze-dried vials, with each vial containing 0.23 mg of tetrofosmin, 0.32 mg of disodium sulphosalicylate, 0.03 mg stannous chloride dihydrate and 1.00 mg of sodium D-gluconate sealed under an inert nitrogen atmosphere. Each vial was reconstituted at room temperature with 4–8 ml of sterile ^{99m}Tc as sodium pertechnetate containing no more than 30 mCi of ^{99m}Tc per ml. The vial was shaken to ensure adequate mixing and then allowed to stand at room temperature for 15 min. Radiochemical purity was determined by thin-layer chromatography and only preparations with ≥90% labeling were used. The preparation was stored at room temperature and was used within 8 hr of labeling.

Study Protocol

This study was designed as a one-day ^{99m}Tc-tetrofosmin imaging protocol. Exercise imaging was performed first, followed by rest imaging 4 hr later utilizing a second injection of the radiopharmaceutical (see Fig. 1). The study was approved by the Human Investigation Committee of Yale University School of Medicine.

Exercise Testing

Patients underwent a symptom-limited treadmill exercise test with continuous 12-lead ECG monitoring. Exercise was conducted in the morning either in the fasting condition or at least 2 hr after a light breakfast. Exercise was terminated by the appearance of limiting symptoms of angina, dyspnea or fatigue, or if there was a drop in blood pressure or appearance of significant arrhythmia, or if maximum age-related heart rate was achieved. Standard American Heart Association safety recommendations for exercise testing were followed (*20*).

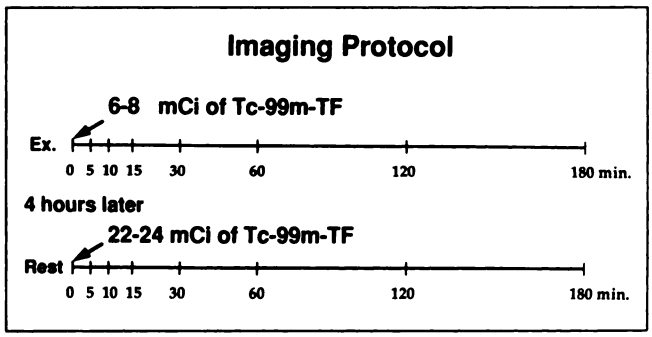

FIGURE 1. Schematic representation of the imaging protocol. Imaging was commenced 5 min after both stress and rest ^{99m}Tc-tetrofosmin injections in the left anterior oblique view. Each image was acquired for 5 min.

Cardiac Imaging

Patients received an intravenous injection of 6–8 mCi of ^{99m}Tc-tetrofosmin at peak exercise through an indwelling intravenous canula and were then encouraged to exercise for an additional 2 min. Patients received a second injection of 22–24 mCi of radiotracer for rest imaging 4 hr later. Serial planar cardiac imaging was begun 5 min after injection of the radiotracer (see Fig. 1). Imaging was performed using Siemens LEM or Picker CX 240 small field of view gamma cameras, each equipped with a low-energy, all-purpose collimator. For the purpose of the analysis of organ biokinetics, serial images were obtained in the left anterior oblique view. The same gamma camera was used for obtaining a complete set of serial images in all patients. The heart was positioned in the center of the field of view without zoom, so that parts of the liver, gallbladder, spleen, gastrointestinal tract and lungs were also included in the field of view. The images were obtained at 5, 10, 15, 30, 60, 120 and 180 min after both exercise and rest injections. Figure 1 is a schematic representation of the study protocol and imaging sequence. Each image was obtained for 5 min. The angle of the camera and position of the cardiac activity in the field of view were kept unchanged for all the images. The 5-, 10-, 15- and 30-min images were obtained without moving the patient from the imaging table. In the interval between the subsequent images, patients were allowed to move from the table. They were, however, carefully repositioned prior to imaging. In addition, standard anterior and left lateral views were also acquired in the interval between 15–60 min after injection of the radiotracer, both following exercise and at rest. This provided images for the analysis of three standard planar views employed for diagnostic interpretation. Images were stored on magnetic disc for subsequent analysis.

Image Analysis

The images were transferred to a Picker PCS 512 computer using a common format and were displayed on the computer screen. Regions of interest (ROIs) were manually drawn around the entire heart, liver, spleen, gallbladder, gastrointestinal tract and lungs (Fig. 2). The counts per pixel in each organ were determined in the serial images and were plotted against time after decay correction in order to define the average time-activity curve over each organ. In addition, small ROI (3–5 pixel wide) were drawn over the left ventricular myocardium and contiguous parts of the liver, lung, spleen and gastrointestinal tract to determine the ratio of average pixel activity between the myocardium and the surrounding organs [i.e., heart to liver, heart to lung, heart to

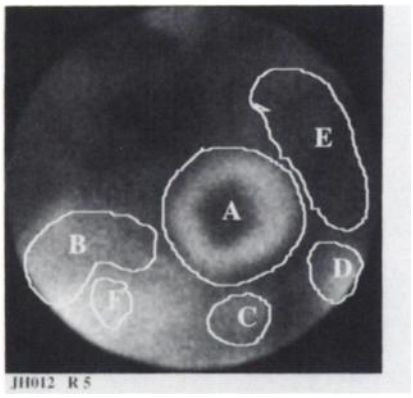

FIGURE 2. ROIs on the left anterior oblique view for assessment of organ biokinetics. Regions: heart (A), liver (B), gastrointestinal tract (C), spleen (D), left lung (E) and gallbladder (F).

gastrointestinal tract and heart to spleen ratios (Fig. 3)]. All images were also examined visually to assess overall image quality and relative activities in the heart and surrounding organs. In addition, the three standard planar views were analyzed visually and quantitatively for evidence of regional myocardial perfusion abnormalities (*4*).

Data Analysis

The decay-corrected average pixel activity over the different organs was plotted against time. The average activity in the heart in the initial 5-min image was arbitrarily assigned a value of 100% and the activities in the heart and other organs over time were all expressed relative to this maximum. All values are expressed as mean ± s.d.

RESULTS

All 20 patients in the study group had good quality images suitable for clinical interpretation, as well as for analysis of kinetics. Specifically, there was no interpretative problem due to subdiaphragmatic uptake in any of the patients. Visual analysis of three-view planar stress and rest ^{99m}Tc-tetrofosmin images showed reversible ischemia in 12 patients, a fixed defect in 1 and were normal in the remaining 7. The average organ activity of ^{99m}Tc-tetrofosmin over time following exercise and rest injections are

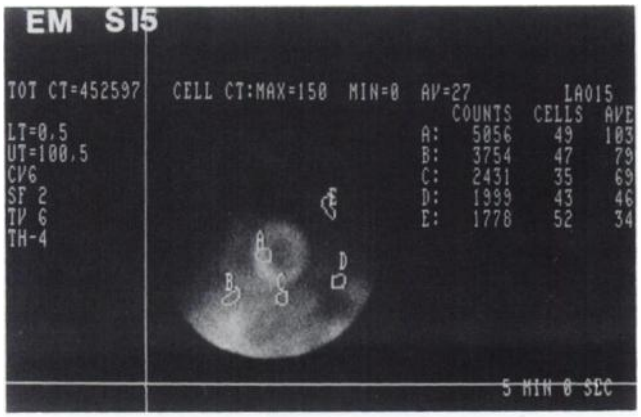

FIGURE 3. ROIs on the left anterior oblique view for assessment of heart-to-adjacent organ ratios. Regions: left ventricular myocardium (A), liver (B), gut (C), spleen (D) and left lung (E).

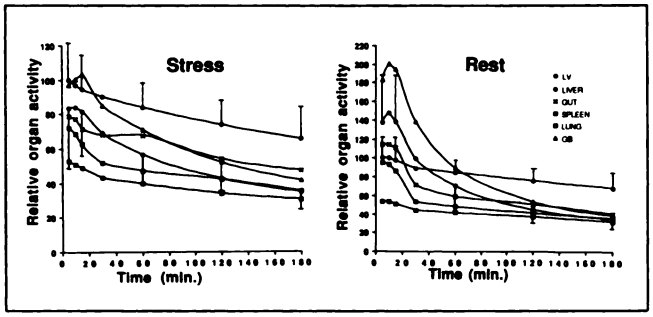

FIGURE 4. Mean (± s.d.) decay-corrected organ activities over time following injection of ^{99m}Tc-tetrofosmin at peak exercise and at rest. Mean organ activity is normalized to activity in the heart at 5 min postinjection. For clarity, s.d. bars are only indicated for 5-, 15-, 60-, 120- and 180-min values in the left ventricle (LV) and liver.

shown in Figure 4. It is apparent that in the stress images, the heart has the highest activity of all organs at all times (except the gallbladder in the images acquired during the first 15 min). In comparison, in the rest images, the liver, gastrointestinal tract as well as gallbladder initially have higher activity than the heart. However, tetrofosmin clears rapidly from the liver, gallbladder and gastrointestinal tract. At 60 min after injection, the heart has higher activity than the remaining organs. Figure 5 shows the stress and redistribution ^{201}Tl and stress and rest ^{99m}Tc-tetrofosmin images of a patient with atypical chest pain. Myocardial perfusion is normal with both imaging agents. Stress and rest ^{99m}Tc-tetrofosmin images were acquired 15 and 30 min, respectively, after injection of the radiotracer. There is excellent myocardial delineation with minimal background activity.

Table 1 shows the heart-to-organ ratios at various time intervals following the stress and rest injections of ^{99m}Tc-tetrofosmin. Again, the ratio is >1.0 for all organs at all times after the stress injection. For rest images, it is <1.0 for the liver and gastrointestinal tract in the 5-, 10- and

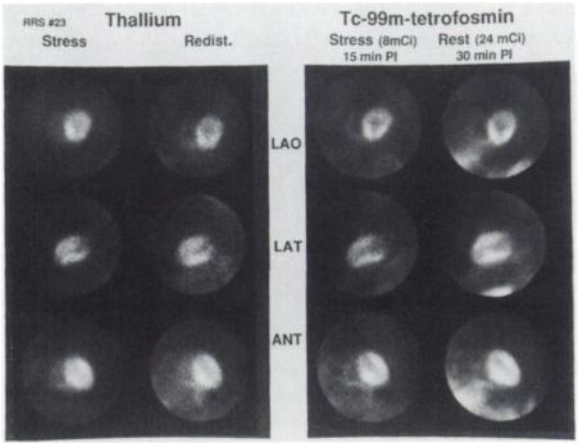

FIGURE 5. Left anterior oblique (LAO), left lateral (LL) and anterior (ANT) ^{99m}Tc-tetrofosmin stress and rest images and corresponding ^{201}Tl stress and redistribution images in a patient with atypical chest pain. Both sets of images show normal myocardial perfusion. Note the excellent image quality and low extra cardiac activity of the ^{99m}Tc-tetrofosmin images.

TABLE 1
Ratios Between Tetrofosmin Activity in the Left Ventricular Myocardium (H) and Adjacent Organs at Various Time Intervals Following Injection at Stress and at Rest (Values are expressed as mean ± s.d.)

	Stress				Rest			
	H-to-Liver	H-to-Lung	H-to-GI	H-to-Spleen	H-to-Liver	H-to-Lung	H-to-GI	H-to-Spleen
5 min	1.3 ± 0.4	1.9 ± 0.3	1.3 ± 0.3	1.5 ± 0.4	0.8 ± 0.2	1.8 ± 0.2	0.9 ± 0.2	1.2 ± 0.3
10 min	1.2 ± 0.3	1.9 ± 0.3	1.3 ± 0.3	1.5 ± 0.4	0.7 ± 0.2	1.9 ± 0.2	0.9 ± 0.2	1.2 ± 0.3
15 min	1.2 ± 0.3	1.9 ± 0.3	1.4 ± 0.4	1.6 ± 0.4	0.7 ± 0.1	1.9 ± 0.2	0.9 ± 0.2	1.2 ± 0.3
30 min	1.4 ± 0.3	2.2 ± 0.5	1.4 ± 0.3	1.9 ± 0.5	1.0 ± 0.2	2.0 ± 0.4	1.3 ± 0.3	1.8 ± 0.4
60 min	1.6 ± 0.4	2.1 ± 0.4	1.3 ± 0.3	1.9 ± 0.5	1.3 ± 0.4	2.1 ± 0.3	1.5 ± 0.3	1.9 ± 0.4
120 min	1.8 ± 0.4	2.2 ± 0.3	1.4 ± 0.3	2.0 ± 0.6	1.7 ± 0.3	2.1 ± 0.3	1.6 ± 0.3	2.0 ± 0.5
180 min	2.0 ± 0.4	2.1 ± 0.3	1.5 ± 0.4	2.0 ± 0.6	2.1 ± 0.4	2.1 ± 0.4	1.7 ± 0.4	2.1 ± 0.6

15-min images. In the subsequent images, however, it is ≥1.0. For the remaining organs, it is >1.0 in all images.

Figure 6 shows serial images of a patient with partially reversible perfusion abnormality involving the interventricular septum and apex. The stress images show an excellent visualization of the myocardium with low background activity. The rest images show significant tracer activity in the liver, gastrointestinal tract and spleen in the 5-min image. However, there is rapid clearance of the hepatic and splenic activity in the 10-, 15- and 30-min images.

DISCUSSION

This study indicates that tetrofosmin, a ^{99m}Tc-labeled agent, has biokinetics suitable for clinical use as a myocardial perfusion imaging agent. The hepatic uptake is acceptably low, even at rest. Following injection at peak exercise, hepatic activity is lower than heart activity as soon as 5 min postinjection. Moreover, hepatic activity declines further over time. The gallbladder has slightly higher activity than the heart in the first 15 min. However, the gallbladder is not immediately adjacent to the heart and does not interfere with myocardial perfusion interpretation. In comparison, following the injection of ^{99m}Tc-Tetrofosmin at rest, the liver and gastrointestinal tract have higher activity than the heart in the initial images. Nevertheless, activity in the liver and gastrointestinal tract clear rapidly, and as early as 30–45 min after injection it is lower than that in the heart. The gallbladder again accumulates considerably higher activity than the heart, but the activity also clears rapidly. Serial count density ratios between the heart and adjacent organs are consistent with the above pattern (Table 1).

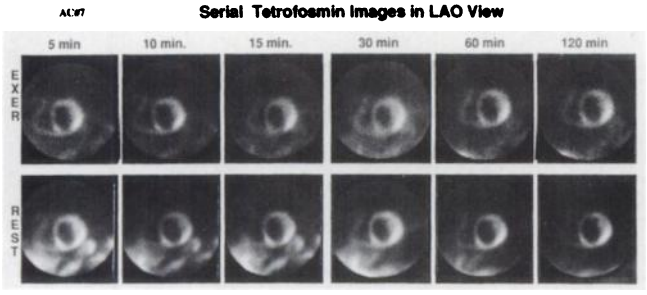

FIGURE 6. Serial images in the left anterior oblique view following exercise and rest injections of ^{99m}Tc-tetrofosmin in a patient with partially reversible septal and apical perfusion abnormality. Each image was obtained for 5 min. Note the low subdiaphragmatic activity as early as 5 min after the exercise injection. Following the rest injection, the first image shows significant hepatic activity, which rapidly clears and concentrates in the gallbladder. By 30 min, most of the subdiaphragmatic activity has cleared.

These observations on organ kinetics indicate that imaging can be started as soon as 5 min after injection during exercise. For rest imaging, a delay of 30 min after tracer injection allows adequate hepatic clearance in most patients. However, a delay of 45 min may be required in a small percentage of patients. Thus, it is possible to perform both stress and rest imaging on the same day within a 4.5–5-hr time period.

For optimal nuclear imaging of an organ, not only is adequate tracer uptake in that organ required, but also a relatively low uptake in adjacent organs. High tracer uptake by the adjacent organs results in scattering and crosstalk of the radiation to the target organ, which makes it difficult to clearly delineate the margins of the target organ. From an imaging point of view, an ideal myocardial perfusion imaging agent should have the following characteristics:

1. High first-pass myocardial extraction that is proportional to myocardial blood flow.
2. A high target-to-background ratio which can be achieved by relatively low uptake and rapid clearance from the contiguous organs, particularly the liver.
3. An adequate time window for obtaining images of the heart following radiotracer administration.
4. Completion of the entire stress and rest imaging on the same day in as little time as possible.

The development of ^{99m}Tc-labeled agents for myocardial perfusion imaging is a significant advance over ^{201}Tl imaging. To date, three different categories of ^{99m}Tc-labeled agents have been developed for myocardial perfusion imaging: (a) cationic isonitriles; (b) boronic acid adducts; (c) diphosphines. However, the biokinetics, initial organ distribution and clearance, as well as the mechanism of myocellular uptake and clearance for agents from each group are quite different from each other as well as from

^{201}Tl. These marked differences necessitate unique imaging protocols for agents from each group.

Of the cationic isonitriles, tertiary-butyl isonitrile (TBI) (*21*) and carbomethoxyisopropyl isonitrile (CPI) (*22*) were two of the early isonitrile compounds tested in humans. They were soon abandoned because of unsatisfactory myocardial-to-background ratios. Sestamibi is the currently used agent from this group and has been found to provide good quality images (*5–7,12*). However, there is significant hepatic radiotracer uptake, which is cleared rather slowly over time. This slow hepatic clearance necessitates a delay of 1–2 hr after tracer injection prior to imaging. This significantly increases the time a patient is required to spend in the imaging laboratory. Since two separate injections are required for stress and rest images, it is difficult to obtain satisfactory image sets on the same day. The initial studies with this agent were carried out using two-day protocols where stress and rest imaging were carried out on two consecutive days. However, from a practical and logistic standpoint, this is inconvenient for the majority of referral patients.

A number of strategies have been proposed for same-day imaging (*6,23–25*). Initial rest imaging using a smaller dose (7–10 mCi) followed by stress imaging using a larger dose (25–30 mCi) or vice versa have been evaluated in relatively small series of patients (*6,24*). Computer subtraction techniques have also been proposed for same-day protocols (*23*). However, this does not seem to be a widely applicable approach. Combined use of ^{201}Tl and ^{99m}Tc-sestamibi has also been advocated to complete rest and stress imaging on the same day. In this technique, ^{201}Tl is injected at rest initially for rest imaging followed by exercise imaging using ^{99m}Tc-sestamibi (*25*). However, this approach raises additional issues of cost and radiation dosimetry. In addition, the different physical characteristics of ^{201}Tl and ^{99m}Tc make it difficult to compare the stress and rest images quantitatively. Thus, the issue of a one-day imaging protocol using ^{99m}Tc-sestamibi has not yet been satisfactorily resolved.

Teboroxime, the only BATO derivative in clinical use, was evaluated for performing stress and rest myocardial perfusion studies within an hour (or less) of each other (*9*). However, the images are often of suboptimal quality because of very rapid myocardial washout and hepatic accumulation. This agent may find only a limited use in rapid serial perfusion studies with various interventions and in situations where it is important to track myocardial blood flow.

Recently, a number of ^{99m}Tc-labeled diphosphine ligands have been developed and evaluated in animals as well as humans for use as myocardial perfusion imaging agents (*13–18,26,27*). Of these, tetrofosmin and Q-12 have been evaluated in humans. Preliminary animal studies have shown that first-pass myocardial extraction of ^{99m}Tc-tetrofosmin is comparable to that of ^{99m}Tc-sestamibi (*26*). Moreover, tetrofosmin is available in an easy to label formulation. Labeling can be done simply by mixing tetrofosmin with appropriate quantities of ^{99m}Tc, without the need for boiling. The present study performed stress imaging first using a smaller dose, followed by rest imaging 4 hr later using a larger dose. Further studies are needed to see if it is possible to reduce the interval between the two imaging periods to even less than 4 hr without affecting image quality. In addition, it is worth considering performing rest imaging first using a small dose, followed immediately thereafter by exercise imaging using a higher dose. Moreover, further studies are required to investigate the mechanism(s) of tetrofosmin myocellular uptake, the exact site of myocyte localization, its potential for assessing myocardial viability and the biokinetics following pharmacological stress with dipyridamole, adenosine or dobutamine.

CONCLUSION

This study indicates that ^{99m}Tc-tetrofosmin may be an additional significant advance in myocardial perfusion imaging. Tracer organ biokinetics allow imaging to be started as soon as 5 min after injection during exercise and 30–45 min after injection at rest. This allows a more convenient imaging protocol, which is similar in duration to that with ^{201}Tl.

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