Technetium-99m Tetrofosmin: A New Myocardial Perfusion Agent

Stephanie Jones and Robert C. Hendel

Departments of Nuclear Medicine and Medicine, Northwestern University Medical School, Chicago, Illinois

This is the fifth article in a series of five on new radiopharmaceuticals. Upon completion, the technologist will be able to (1) list the characteristics of tetrofosmin, (2) describe the clinical images, and (3) compare tetrofosmin to other myocardial perfusion agents.

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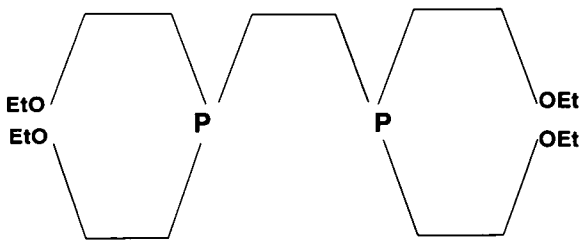
Myocardial perfusion imaging is an established technique for the detection and assessment of coronary artery disease. Although electrocardiographic exercise testing is a useful method, improved sensitivity and specificity are present when exercise is combined with perfusion imaging. At present, the most frequently used perfusion agent is thallium-201 (^{201}Tl). However, despite the wide acceptance of thallium as a perfusion agent, it is far from an ideal tracer, possessing significant limitations, such as low-energy photons (69–83 keV), which are easily attenuated by soft tissue and may result in artifact production and decreased image resolution. Additionally, the relatively long half-life (73 hr) limits the dosage that can be given to the patient, leading to reduced photon flux and lower count statistics.

Technetium-99m (^{99m}Tc) agents have many advantages, including a higher photon energy (140 keV), which is optimal for gamma camera imaging. The short physical half-life (≈6 hr) permits a larger dose to be administered, which results in greater photon flux. Furthermore technetium can be produced on site by a generator, which makes it readily available and relatively inexpensive.

CHARACTERISTICS OF TETROFOSMIN

Tetrofosmin (1,2-bis[bis(2-ethoxyethyl)phosphino]ethane) is a recently developed ligand which forms a lipophilic, cationic complex with technetium (Fig. 1). Early experimental work has demonstrated good heart uptake and rapid blood, lung, and liver clearance in animal studies, making tetrofosmin a promising imaging agent (*1*). No toxicity or mutagenicity has thus far been demonstrated with tetrofosmin, even in doses up to 1500 times the maximum single human dose (*1*). Tetrofosmin distributes within the heart proportionately to blood flow, clearing rapidly from the blood and slowly from the heart (*1,2*). At normal resting blood flows, a linear relationship exists between tetrofosmin uptake and blood flow as determined by microspheres. However, as with other tracers, tetrofosmin appears to overestimate true blood flow at low flow rates and underestimates blood flow at higher flow rates (*3*). The precise mechanism of transport of the tracer into the myocardial cells is unknown, but it is likely to be similar to sestamibi. Like sestamibi, it appears that tetrofosmin localizes within the mitochondria of the cells.



The structure of the ligand 1,2-bis[bis(2-ethoxyethyl)phosphino]ethane = tetrofosmin

FIG. 1. Molecular structure of tetrofosmin.

EARLY CLINICAL STUDIES

Initial experience in human subjects demonstrated the rapid heart uptake of tetrofosmin, approximately 1.2% of the injected dose at 5 min postinjection. The blood clearance of tetrofosmin is also rapid, with less than 5% of the injected dose remaining 10 min postinjection (*2*). Excretion is shared almost equally between urinary and fecal routes, and 80% of the administered dose is removed within 48 hr. The organs receiving the highest dose are those of the excretory pathway (gallbladder, lower large intestine, upper large intestine, small intestine, urinary bladder, and kidneys) (*2*).

For reprints contact: Robert Hendel, MD, 250 E. Superior Street, Suite 726, Chicago, Illinois 60657.

TABLE 1. Technetium-99m Tetrofosmin Preparation

Step 1:	Elute up to 100 mCi of ^{99m}TcO4- (4–8 ml; <30 mCi/ml) from a generator with 0.9% saline.
Step 2:	Add to freeze-dried kit, dilute up to 6 ml with 0.9% saline.
Step 3:	Shake gently.
Step 4:	Allow to stand at room temperature (25°C) for 15 min.
Step 5:	Perform quality control, utilizing thin-layer chromatography.
Step 6:	If radiochemical purity exceeds 95%, the reconstituted injectate is ready for use.
Step 7:	Administer within 8 hr.

The Phase II clinical studies revealed that high quality images of the heart can be obtained as early as 5 min postinjection, owing to the rapid myocardial uptake. There is excellent myocardial retention of this tracer, with stable myocardial distribution over 4 hr postinjection (*1,4*). Comparisons of serial planar views, up to 3 hr after tetrofosmin administration, show no visual or quantitative evidence for redistribution (*4*). This lack of redistribution necessitates the use of two separate injections (stress and rest) for the examination of defect reversibility (ischemia), but also allows for a delay between drug delivery and imaging.

Tetrofosmin appears to be a safe agent, as no serious adverse reactions related to drug administration have been reported. Some patients describe a "metallic" taste immediately after the intravenous injection (*2*), similar to that noted with sestamibi. No changes in vital signs have been noted and the only hematologic, blood chemistry, or urinalysis alterations noted have been a transient, mild elevation in the white blood cell count.

PREPARATION AND QUALITY CONTROL

The freeze-dried kit formulation of tetrofosmin (PPN1011; Myoview) (Amersham Healthcare, Arlington Heights, IL) enables rapid complex formation at room temperature with stability of at least 8 hr following reconstitution (*1*). The preparation of ^{99m}Tc-tetrofosmin is straightforward, as outlined in Table 1. The agent should be administered within 8 hr of reconstitution.

Radiochemical purity (RCP) is determined by thin-layer chromatography, using a method similar to that of other technetium-labeled compounds (Table 2). Microchromatographic methods, which substantially reduce the time required to perform the quality control, have been used successfully and are expected to be used when this agent becomes commercially available.

IMAGING METHODOLOGY

The studies performed to date have coupled the use of ^{99m}Tc-tetrofosmin imaging with maximum treadmill exercise. At peak exertion, 5–8 mCi (185–296 MBq) of tetrofosmin is administered and imaging is begun 15–30 min later. A separate rest injection of 15–24 mCi (555–888 MBq) of tetrofosmin is administered 4 hr later. A dosage ratio of approximately 1:3 has been used for the first and second tetrofosmin injections, to minimize interference on the second set of images due to residual activity.

Myocardial perfusion imaging utilizing tetrofosmin is then performed 10–15 min postinjection, with a large-field-of-view gamma camera. Both planar and single-photon emission computed tomography (SPECT) imaging have been performed with good to excellent image quality results, using the acquisition protocol described in Table 3.

Processing and display procedures are similar to those used with other technetium-labeled agents and are dependent on camera systems. Overall, imaging protocols that are used for thallium scintigraphy should not be used for the processing of tetrofosmin scans.

MULTICENTER TETROFOSMIN TRIAL

The efficacy of tetrofosmin compared with thallium for the detection of coronary artery disease was recently evaluated in a Phase III, multicenter, international, clinical trial. Exercise and resting images were acquired the same day on 218 patients (*5*). Imaging was performed approximately 15 min postinjection and exercise/rest images were separated by about 4 hr (*5*).

Overall, there was agreement between the tetrofosmin and thallium images in 76% of patients for the detection of perfusion abnormalities (*5*). There was a concordance of 68% for reversible, ischemic perfusion defects and 78% agreement for fixed defects (*5*). Each patient study was then divided into five regions, which correspond to the myocardial territories: anterior, inferior, apex, septum, and lateral walls of the heart. Out

TABLE 2. Technetium-99m Tetrofosmin Quality Control Procedure

1. Fill the chromatography tank, to a depth of 1 cm, with a fresh solution of 36:65 acetone/dichloromethane mixture.
2. Place 10–20 μl of tetrofosmin at the origin position, on the quality control strip (2.0 × 20 cm).
3. Immediately place the strip in the prepared ascending chromatography tank.
4. Wait, approximately 20 min, for the free technetium to move up the solvent front.
5. Cut the strip at the three indicated positions, yielding three pieces.
6. Count each piece, individually, in a well counter.
7. Activity localizes in the following way:

Top Portion	Middle Portion	Bottom Portion
free pertechnetate	^{99m}Tc-tetrofosmin complex	reduced hydrolyzed ^{99m}Tc and other hydrophilic complexes

8. Calculate the % radiochemical purity as follows:

% Radiochemical Purity = Activity on the middle portion/total activity of all three pieces

TABLE 3. Tetrofosmin Imaging Parameters

	PLANAR	SPECT
Collimator	High resolution	High resolution
Photopeak	140 keV	140 keV
Window	20% symmetric	20% symmetric
Matrix	128 × 128, word mode	64 × 64, word mode
Zoom	none (1.2–1.5 if LFOV)	1.0–1.5
Views/Projections	3–4	32
Time per view	5 min	40 sec (stress), 25 sec (rest)
Orbit		180°, circular

of 1080 regions, there was excellent concordance between the thallium and tetrofosmin scans, with 83% and 88% agreement for transient and fixed defects, respectively (*5*). Image quality was superior with tetrofosmin, and subdiaphragmatic activity infrequently interfered with the tetrofosmin image analysis. The aforementioned study utilized planar imaging. Preliminary results also point to the value of tetrofosmin as a useful agent for tomographic imaging, yielding a 76% concordance with thallium images (*6*). Examples of planar and tomographic scans are shown in Figures 2 and 3.

COMPARISON TO OTHER PERFUSION AGENTS

Thallium

Thallium was the only myocardial perfusion agent until approximately 3 yr ago. A large body of evidence points to the value of this agent for a variety of diagnostic and prognostic applications. Improvements in camera systems and the advent of quantitation have improved the clinical value of this perfusion agent. Additionally, thallium remains the standard for viability detection, especially in view of studies

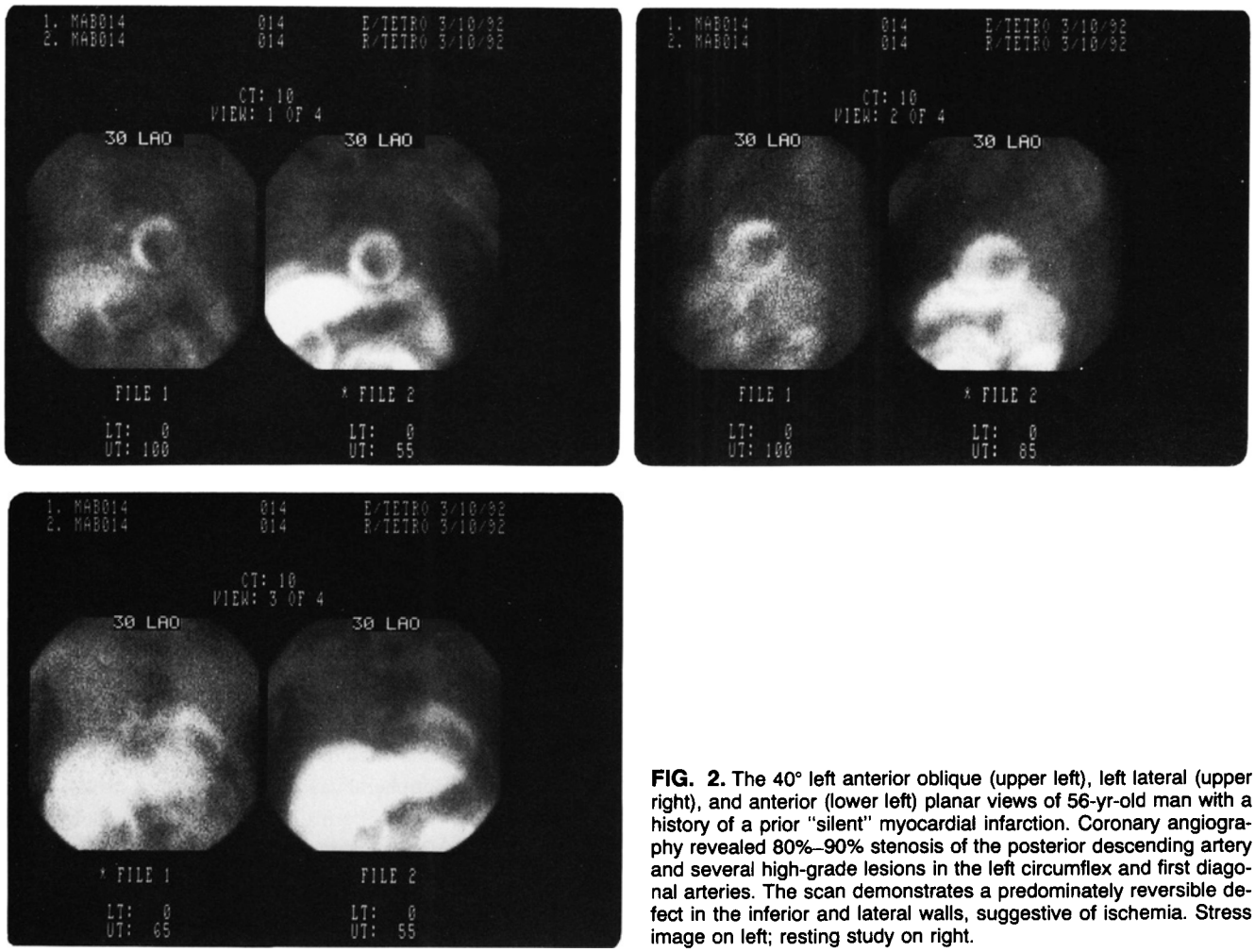


FIG. 2. The 40° left anterior oblique (upper left), left lateral (upper right), and anterior (lower left) planar views of 56-yr-old man with a history of a prior "silent" myocardial infarction. Coronary angiography revealed 80%–90% stenosis of the posterior descending artery and several high-grade lesions in the left circumflex and first diagonal arteries. The scan demonstrates a predominately reversible defect in the inferior and lateral walls, suggestive of ischemia. Stress image on left; resting study on right.

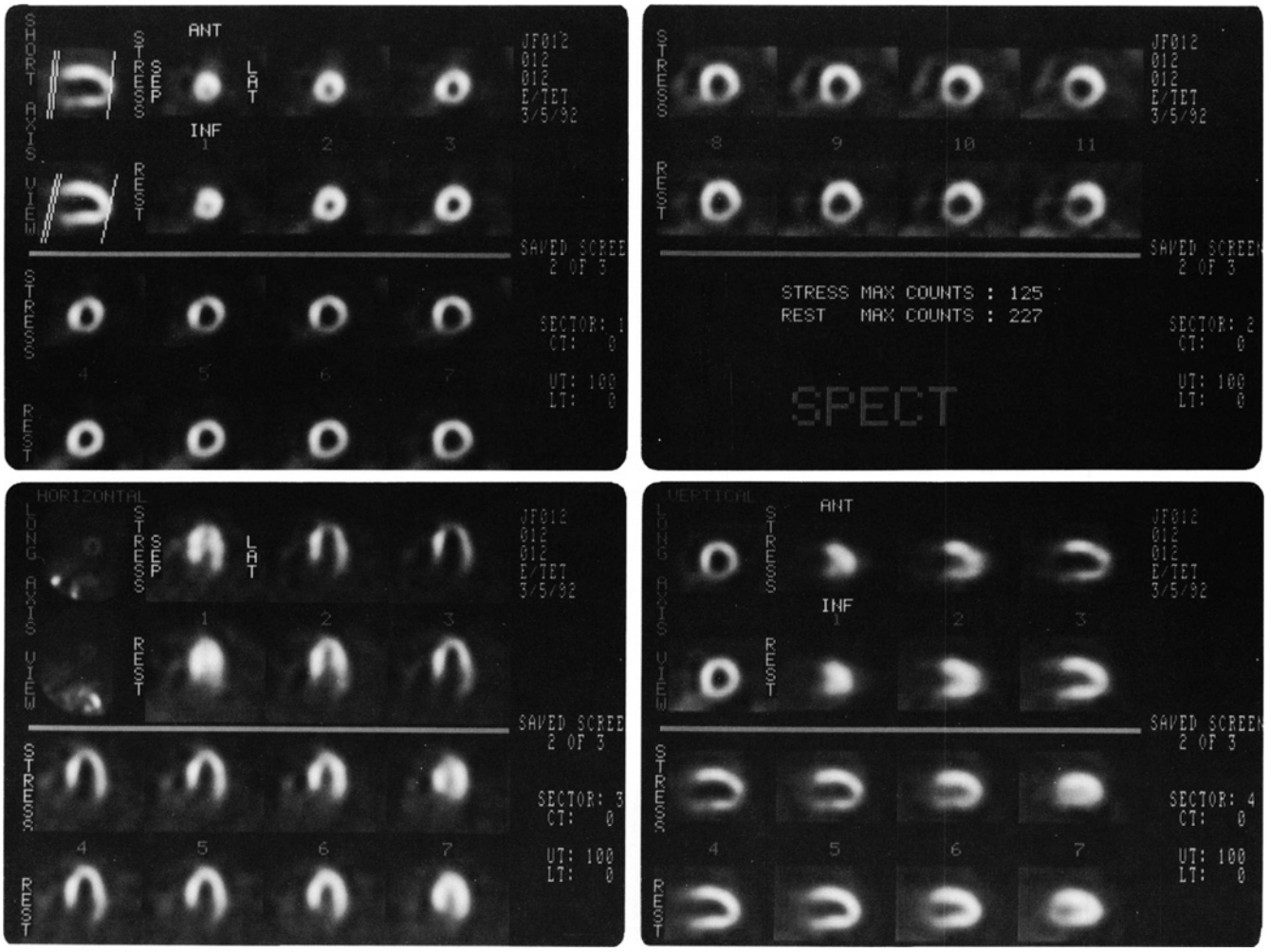


FIG. 3. Tomographic study of a 58-yr-old man with a markedly positive treadmill exercise test. The tetrofosmin scan reveals a small region of inferior ischemia best seen in the vertical long axis.

demonstrating the high correlation of late imaging or reinjection with thallium to the recovery of myocardial function after revascularization and with positron emission tomography (PET) (*7*).

Tetrofosmin has a diagnostic accuracy similar to routine stress/redistribution thallium scintigraphy. The relative value of tetrofosmin compared with thallium reinjection or other methods designed to enhance the detection of viable myocardium is unknown.

Sestamibi

When compared with published data (*8*) about ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin shows similar heart uptake, retention, and blood clearance kinetics (*1*). As with tetrofosmin, two injections of technetium are required, one during exercise and one at rest. However, the clearance from both the lung and liver with tetrofosmin appears significantly faster. Thus, imaging may begin sooner than with sestamibi (15 min. versus 60 min.). The myocardial washout of sestamibi is slow, but some redistribution has been noted; the clinical significance of this is unknown (*9*). In contrast, tetrofosmin appears to have stable myocardial distribution for more than 4 hr.

Teboroxime

Technetium-99m teboroxime is cleared from the blood very rapidly and demonstrates high myocardial uptake, but extremely rapid washout (<10 min). Thus imaging must be performed rapidly, with expeditious patient positioning. Unlike tetrofosmin, if a teboroxime image is lost or there is patient motion, the study cannot be repeated.

FUTURE DIRECTIONS

Pharmacologic Stress

Many patients with suspected coronary artery disease cannot undergo the usual methods for diagnosis, such as exercise stress testing. This is often due to physical limitations, such as severe arthritis, peripheral vascular disease, or a stroke. All of the currently available perfusion agents have demonstrated usefulness in conjunction with pharmacologic stress testing, including dipyridamole, adenosine, and dobutamine. Currently, studies are under way in Europe and the U.S. with tetrofosmin and these pharmacologic stress agents.

Myocardial Viability

The assessment of myocardial viability is currently one of the most active areas of investigation in nuclear cardiology. Thallium, with late (24-hr) imaging or following reinjection, has shown promise and provides much of the metabolic information obtained with PET. The most useful method for this goal is still not known. Studies to determine viability with sestamibi have demonstrated conflicting results. Thus, the usefulness of this agent for the accurate assessment of viability is not clear. No viability studies have been completed to date with tetrofosmin. A quantitative approach and comparison to a normal data file is likely the most useful method. However, we must await the results of trials for the detection of myocardial viability with tetrofosmin.

Acute Cardiac Syndromes

Studies with sestamibi have demonstrated the change in myocardial perfusion before and after thrombolytic therapy for an acute myocardial infarction and may be a promising tool for assessing the efficacy of such therapy (*10*). Additionally, patients presenting with chest pain may have the diagnosis of myocardial ischemia made when sestamibi is injected during the acute episode of pain and then imaged several hours later (*11*). Studies are being planned for the utilization of tetrofosmin due to its similarity to sestamibi.

CONCLUSION

Technetium-99m tetrofosmin is a promising new myocardial perfusion agent, with the inherent imaging superiority of a technetium agent. Studies have demonstrated the safety and efficacy of myocardial perfusion imaging with this agent for the detection of coronary artery disease. The lack of redistribution and rapid clearance from noncardiac tissues allow for flexibility in imaging, which may be started within 15 min of tracer injection. The image quality associated with tetrofosmin is excellent. Studies are currently under way to determine the impact of this agent on departmental throughput, as well as with applications using pharmacologic stress and in acute cardiac syndromes.

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