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*Technetium Agents and Thallium
for
Myocardial Perfusion Imaging*

by: Richard J. Kowalsky, Pharm.D.

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Myocardial Perfusion Imaging**

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TECHNETIUM AGENTS AND THALLIUM FOR MYOCARDIAL PERFUSION IMAGING

STATEMENT OF OBJECTIVES

The primary goal of this correspondence course is to increase the reader's knowledge and understanding of cardiac imaging agents used in the assessment of myocardial perfusion, namely Tc-99m sestamibi, Tc-99m teboroxime, and Tl-201 thallous chloride. In this regard the course discusses myocardial blood flow and perfusion imaging, the requirements of myocardial perfusion imaging agents, and the properties and use of these radiopharmaceuticals.

Upon successful completion of this material, the reader should be able to:

1. Describe the underlying cause of coronary artery disease (CAD) and be able to differentiate myocardial ischemia from infarction.
2. List the principal clinical applications for myocardial perfusion imaging.
3. Define coronary flow reserve.
4. Describe the underlying principle behind cardiac stress imaging.
5. Describe the Tl-201 stress-redistribution study for the differential diagnosis of myocardial ischemia versus infarction.
6. Describe exercise-stress in cardiac imaging and the advantages and disadvantages of this method.
7. Describe pharmacologic-stress in cardiac imaging and the advantages and disadvantages of this method.
8. List and discuss two fundamental differences between dipyridamole and adenosine used in cardiac imaging.
9. Describe the diffusional barriers a tracer must traverse to localize in the heart.
10. List three important requirements of a tracer used for myocardial perfusion imaging.
11. List five factors that affect myocardial extraction of diffusion-limited perfusion agents.
12. Rank order Tl-201, Tc-99m sestamibi, and Tc-99m teboroxime regarding cardiac extraction fraction and myocardial clearance.
13. Explain the relationship between myocardial blood flow and extraction of Tl-201, Tc-99m sestamibi, and Tc-99m teboroxime.
14. Describe the mechanism of myocardial uptake of Tc-99m sestamibi, Tc-99m teboroxime, and Tl-201.
15. List the critical organ and effective dose equivalents for Tc-99m sestamibi, Tc-99m teboroxime, and Tl-201 thallous chloride.
16. List the advantages of Tc-99m over Tl-201 for myocardial perfusion imaging.
17. Describe the biological property of Tl-201 that may affect diagnostic accuracy in the evaluation of CAD.
18. Describe the role that Tl-201 thallous chloride reinjection plays in the diagnosis of CAD.
19. Describe the preparation and chemical properties of Tc-99m sestamibi and Tc-99m teboroxime.
20. Compare and contrast the biologic properties of Tc-99m sestamibi and Tc-99m teboroxime.
21. Discuss the clinical advantages and limitations of Tc-99m sestamibi and Tc-99m teboroxime for myocardial perfusion imaging.

COURSE OUTLINE

TECHNETIUM AGENTS AND THALLIUM FOR MYOCARDIAL PERFUSION IMAGING

- I. INTRODUCTION
- II. BLOOD FLOW TO THE HEART
 - A. Coronary Perfusion and Cardiac Imaging
 - B. Coronary Vasodilator Methods
- III. REQUIREMENTS OF MYOCARDIAL PERFUSION IMAGING AGENTS
 - A. Radiotracer Transport and Uptake
 - B. Extraction Fraction
- IV. Tc-99m SESTAMIBI
 - A. Chemistry
 - B. Biologic Properties
- V. Tc-99m TEBOROXIME
 - A. Chemistry
 - B. Biologic Properties
- VI. Tl-201 THALLOUS CHLORIDE
 - A. Chemistry
 - B. Biologic Properties
- VII. RADIATION ABSORBED DOSE
- VIII. COMPARISON OF Tl-201 THALLOUS CHLORIDE, Tc-99m SESTAMIBI, AND Tc-99m TEBOROXIME
 - A. Thallium-201 versus Technetium-99m
 - B. Extraction Fraction and Myocardial Uptake
 - C. IMAGING CONSIDERATIONS
 - 1. Tl-201 Thallous Chloride Imaging
 - 2. Tc-99m Sestamibi Imaging
 - 3. Tc-99m Teboroxime Imaging
 - 4. Tl-201/Tc-99m Dual-Isotope Imaging

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INTRODUCTION

Coronary artery disease (CAD) ranks third behind accidents and cancer as the most important cause of years-of-potential-life-lost before age 65 in the United States. A 1985 compilation of age-standardized mortality from CAD indicates that out of 100,000 persons aged 30-69, 235 men and 80 women die annually (1,2). Considering the entire US population, this translates into approximately 750,000 deaths each year due to CAD alone--more than one-third of all deaths. Approximately 1.2 million persons with CAD are hospitalized annually with direct annual costs close to 20 billion dollars and indirect costs of 10 billion dollars.

Coronary artery disease arises principally from a gradual narrowing of coronary arterial lumen due to atherosclerotic deposits. The progressive narrowing of lumen diameter eventually predisposes one to myocardial ischemia, a condition where coronary blood flow decreases to a level below that needed to meet oxygen demand. When coronary arterial lumen diameter is reduced by 50%, perfusion abnormalities can be detected but patients are usually asymptomatic. When lumen diameter is reduced by 70%, clinical symptoms of chest pain (angina) become evident during myocardial stress because tissue oxygenation is temporarily below that required for adequate function. In advanced ischemic CAD where blood flow and tissue oxygenation is so low that it cannot sustain cardiac function at rest, myocardial infarction results and the affected muscle dies. Clinically, therefore, it is important to be able to distinguish between ischemic and infarcted myocardium because ischemic, viable myocardium can be restored to health by medical and/or surgical intervention.

Cardiac imaging has played a key role in the diagnostic workup of patients with CAD. While the goals of cardiac imaging are broad, encompassing the assessment of the cardiac chamber, myocardial perfusion, metabolism and infarction, the major focus has been the assessment of myocardial perfusion. Precise measurement of regional myocardial perfusion in humans has clinical applicability for identifying ischemia, defining the extent and severity of disease, assessing myocardial viability, establishing the need for medical and surgical intervention, and monitoring the effects of treatment.

The majority of clinical nuclear medicine studies today use Single Photon Emission Computed Tomography (SPECT)

methods for data acquisition. On the upswing, however, are centers that also use Positron Emission Tomography (PET) methods. The PET methods offer the advantage of being able to assess myocardial metabolism. A variety of radiopharmaceuticals are utilized to meet the goals of cardiac imaging. The principal agents used in SPECT imaging are Tc-99m red blood cells for blood pool studies, Tl-201 thallous chloride for perfusion studies, and Tc-99m pyrophosphate for infarct avid imaging. The main agents used in PET imaging are Rb-82 rubidium chloride, O-15 water and N-13 ammonia for perfusion studies, and C-11 palmitate, C-11 acetate and F-18 fluorodeoxyglucose for metabolism studies. The Rb-82 generator was approved for routine use by the Food and Drug Administration (FDA) in December 1989.

Since its introduction into medical use in 1975 (3-5), Tl-201 thallous chloride has evolved as the principal radiopharmaceutical used to evaluate myocardial perfusion because of its favorable biological properties. However, its less than ideal physical properties stimulated the development of agents labeled with technetium-99m. These efforts have produced two new agents for myocardial perfusion imaging, Tc-99m sestamibi and Tc-99m tetroxime, which received FDA approval for routine use in December 1990. Each of these agents has unique properties as applied to myocardial perfusion imaging. Because the technetium-99m agents are new, it is not clear at this time how they will fit into the radiopharmaceutical armamentarium to diagnose ischemic heart disease.

BLOOD FLOW TO THE HEART

Blood flow to the normal heart varies, with the greatest flow per gram to the left ventricle and the least flow per gram to the atria. Because of its substantially greater mass compared to other heart chambers, the left ventricle receives about 80% of total flow to the heart. Because of its greater thickness, the left ventricle is the predominant region seen in cardiac imaging while the atria are almost never seen and the right ventricular wall cannot be visualized well unless it is thickened.

Resting myocardial blood flow to most regions of the left ventricular myocardium ranges from 0.6 to 0.8 ml/min/g (6). At rest the oxygen extraction efficiency of the heart is about 70%, compared with 20% for skeletal muscle (7). Because not much oxygen is left, little additional oxygen can be removed from the blood unless the blood flow increases. Fortunately, coronary blood flow does increase in almost direct proportion to the metabolic consumption of oxygen by the heart. With a normal heart and under appropriate stimulus, such as exercise or the administration of specific pharmacologic agents, blood flow can increase 5 - 6 fold, i.e., to 3.0 - 4.0 ml/min/g (6). Several investigators, however, report maximally induced flows in the range of only 2 to 4 times baseline for healthy volunteers and patients (8-10). The difference between baseline flow and maximal flow is known as *coronary flow reserve*. While cardiac imaging studies do not measure coronary flow reserve per se, the diagnostic utility of radionuclide studies is based on observing the

difference in blood flow to normal and diseased myocardium under conditions of myocardial stress (maximal flow) and at rest (baseline flow).

Coronary Perfusion and Cardiac Imaging

Coronary vascular resistance and oxygen consumption are tightly coupled in normal hearts. Changes in vascular resistance in response to oxygen deficit are very rapid, on the order of a few hundred milliseconds. A maximal coronary dilation can occur in 10 to 15 seconds following intense metabolic stimulus (6).

The diagnosis of obstructive coronary disease is made by assessment of coronary perfusion in the heart. Studies in dogs have shown that *resting* coronary blood flow does not change until coronary diameter stenosis exceeds 90%, whereas *maximal* coronary blood flow begins to decrease when diameter stenosis exceeds 50% (11). Thus, only the most severe coronary obstructive lesions will likely be detected by perfusion imaging under resting conditions. It follows, then, that assessment of regional myocardial perfusion under conditions of stress would substantially increase the likelihood of detecting obstructive coronary disease during cardiac imaging. The basis for cardiac stress imaging is that during induced maximal coronary dilation, the increased blood flow goes largely to normally perfused myocardial regions, while myocardium supplied through significantly stenosed coronary vessels has limited vasodilatory reserve and therefore little or no increase in perfusion (11). With Tl-201 thallous chloride, imaging defects are detectable during induced hyperemia when flow into normal coronary vessels exceeds that into stenotic vessels by a ratio of 2.4 (12).

In the nuclear medicine clinic the perfusion imaging study with Tl-201 thallous chloride is traditionally done in two parts. The first part, the stress study, is designed to produce near maximal dilatation of the coronary vessels just prior to administration of the Tl-201 thallous chloride. Dilatation is achieved either through exercise or by the administration of a pharmacologic agent such as dipyridamole or adenosine. Under these conditions, the Tl-201 ion, which is a biological analog of potassium ion, will be extracted by the myocardium in proportion to blood flow. Thus, normally perfused myocardium will take up the radiotracer well, i.e., appear "hot," whereas poorly perfused (ischemic) or non-perfused (infarcted) myocardium will show decreased or no radiotracer uptake, i.e., appear as a deficiency or defect ("cold" area) in the myocardial image. After a period of rest, usually 4 to 24 hours after the stress study, the second part, or redistribution study, is performed. At this time the patient is re-imaged to assess myocardial redistribution of the Tl-201 radioactivity administered during the stress study. During the rest phase Tl-201 ion redistributes in the myocardium, washing out of normal myocardium well, but less well from areas of compromised flow during the stress. Thus, the redistribution image of the heart will demonstrate "filling-in" of activity in ischemic areas, but no "filling-in" of infarcted areas. Hence, the differential diagnosis of ischemia versus infarction. It is worthy to note that a normal stress perfusion imaging study precludes the need for doing the rest perfusion study unless triple vessel CAD is suspected. In the latter situation all areas

of the myocardium may have received similar but diminished blood flow. The only clue to triple vessel CAD may be retarded washout of Tl-201. Thus, some kind of quantitation is needed to detect this.

Coronary Vasodilator Methods

Two conditions must exist to make sensitive coronary flow deficit measurements in cardiac imaging: (1) the achievement of near maximal coronary flow and (2) a myocardial extraction of the radiotracer which is proportional to blood flow. The current methods used to achieve maximal coronary dilation are intense exercise, using a bicycle ergometer or treadmill, or administration of the coronary vasodilators, dipyridamole or adenosine. Exercise stress is the preferred method because it increases the work and, therefore, metabolic demand of the heart. Under such physiologic conditions, myocardial cells perfused by stenotic arterioles are likely to demonstrate blood flow inadequate to meet oxygen demand, i.e., become ischemic. Thus, such cells lose their ability to concentrate radiotracer. Theoretically then, exercise stress is the more sensitive condition for detecting ischemia because both myocardial blood flow and tracer extraction are more likely to be decreased. Maximal increase in coronary flow following exercise is oftentimes difficult to achieve clinically because patients suspected of having heart disease can rarely achieve the intense exercise level required to produce maximal dilation. Additionally, this method cannot be used in some patients for reasons such as claudication, cerebrovascular accidents, arthritis, amputation, severe anxiety or a previous non-diagnostic submaximal stress test such as with CAD patients on beta-blocking medication who are unable to adequately increase their heart rate by exercise. Also, certain imaging protocols that require rapid acquisition of data, such as with Tc-99m tetrofosmin, may not be feasible with exercise stress because of logistical problems, i.e., time delays in getting the patient from the exercise equipment to the imaging equipment.

An alternative to exercise stress is pharmacologic stress using dipyridamole (13) or adenosine (14). The word "stress" in this context is really a misnomer because heart work is actually not increased with these agents; they only cause coronary dilation and hence only measure heterogeneity of blood flow between stenosed and normal vessels. True ischemia may develop but usually in only a small proportion of patients. Although only differential blood flow is measured, maximal coronary dilation is more consistently achieved. Studies with these agents indicate that both adenosine and dipyridamole Tl-201 imaging provide diagnostic information comparable with that of exercise Tl-201 imaging (15-20). Both of these drugs are administered intravenously, although dipyridamole has been used orally (21). Rapid onset of action and ease of control of possible side effects are the benefits of the intravenous route.

Dipyridamole is believed to act by inhibition of cellular uptake and metabolism of endogenous adenosine, a potent coronary vasodilator. The usual dosage of dipyridamole is 0.56 mg/kg (0.142 mg/kg/min infused over 4 minutes). Dipyridamole achieves its maximal dilator effect 6 to 8 minutes after start of infusion, indicated by a sustained drop

in blood pressure and a rise in heart rate (21). After intravenous administration plasma concentrations decline in a triexponential manner with half-lives of 12 ± 10 min, 62 ± 29 min and, 11.6 ± 2.2 hours (22).

Adenosine is an endogenous nucleoside that is synthesized in the myocardium and is present in all cells in the body. It has been shown that interstitial concentrations of adenosine rise in response to increased metabolic oxygen requirements or ischemia (23) and adenosine is believed to play a physiologic role in regulating coronary blood flow. For cardiac imaging, adenosine is administered at a dosage of 0.85 mg/kg (0.142 mg/kg/minute over 6 minutes) to achieve maximum vasodilation of coronary vessels. At this dosage, 84% of normal patients achieve maximal vasodilation (23). Infusion rates above this dosage fail to elicit greater vasodilation and infusion rates below this level may cause a cyclical rise and fall in coronary blood flow (23). At an infusion rate of 140 ug/kg/min the average time from onset of infusion until maximal vasodilation is achieved is 84 ± 46 seconds. The time from offset of infusion until coronary blood flow velocity returns to baseline levels is 145 ± 67 seconds. At this dosage rate in normal patients the heart rate rises 24 ± 14 beats/min, and mean arterial pressure falls 6 ± 7 mm Hg (23).

The relative merits of adenosine and dipyridamole have been compared (24). Adenosine differs from dipyridamole by acting directly on coronary vessels and having a plasma half-life of less than 10 seconds. Its direct effect causes a prompt pharmacologic response which has the potential for more rapid onset of side effects as well. Thus, close monitoring is needed. The short half-life is an advantage because any adverse effects produced by adenosine can be reversed easily by stopping the infusion. Adverse effects from use of dipyridamole require administration of aminophylline which is believed to act by blocking specific adenosine receptors. The dose of aminophylline is 50-100 mg intravenously over 30-60 seconds in a dosage range of 50-250 mg. Other methylxanthines, such as caffeine and theophylline, also antagonize the effects of adenosine. Caffeine has been shown to reduce the effects of dipyridamole during cardiac imaging with Tl-201 (25). The plasma half-life of caffeine in normal adults is 3.5 hr but clearance of methylxanthine drugs vary according to patient age, disease state, and type of drug (26). The duration of caffeine abstention prior to pharmacologic stress studies has not been determined thoroughly. Thus, based on the plasma half-life of caffeine, a safe, practical recommendation is that patients should not consume caffeine-containing medications, beverages or foods for 18 to 24 hours nor long-acting theophylline medications for 36 to 48 hours prior to study.

Adverse effects of dipyridamole have been reported (27). The most common effects are chest pain (19.7% of all patients), headache (12.2%), dizziness (11.8%), ST-T changes on ECG (7.5%), and ventricular extrasystoles (5.2%). Other effects occurring in lesser incidence include nausea, hypotension, flushing and tachycardia. Similar adverse effects have been reported for adenosine but with higher incidence of occurrence (28). These effects are related to the plasma level of vasodilator and are usually readily reversed by intravenous

aminophylline or, in the case of adenosine, cessation of infusion. Since adenosine also causes slowing of electrical conduction through the AV node, first, second or third degree AV block may occur. Thus, use of dipyridamole or adenosine in patients with these conditions should be approached with caution or may be contraindicated.

The distribution of cardiac output in various organs is much different with dipyridamole (and adenosine) than with intense exercise. The relative blood flow to abdominal viscera increases with these agents, whereas with exercise it decreases. Thus, perfusion imaging agents will tend to accumulate in the liver and spleen to a greater extent with use of pharmacologic agents than with exercise and this may interfere with assessing perfusion of the inferior wall of the left ventricle (6).

REQUIREMENTS OF MYOCARDIAL PERFUSION IMAGING AGENTS

The first step in imaging any organ in the body is the delivery and localization of an appropriate radiotracer to that organ. This requires the transport of radiotracer molecules through several biological membranes in the body including the capillary endothelial membrane, the parenchymal cell membrane, and perhaps membranes of intracellular organelles. The principal transport mechanisms through biological membranes are (1) passive diffusion, (2) active transport via energy-consuming enzyme systems, (3) facilitated transport and (4) filtration through membrane pores and intercellular spaces.

Radiotracer Transport and Uptake

The main mechanisms associated with uptake of radiotracers into the heart are active transport and passive diffusion. The active transport mechanism in the myocardial cell membrane is the sodium/potassium ATPase pump. This mechanism has been exploited to develop heart localizing radiotracers, the first being radioactive Potassium-43. The sodium/potassium ATPase pump is not selective for potassium ions but instead has affinity for monovalent cations of a certain ionic radius. Thus, several radionuclide cations with similar properties to potassium have been used to measure myocardial perfusion, most notably Thallium-201 for planar and SPECT imaging and Rubidium-82 for PET imaging. The physical limitations of Tl-201, mainly low photon energy and long half-life, prompted the development of Tc-99m labeled tracers. Initial work centered on development of monovalent cationic compounds with limited success. Many different types of compounds were produced and tested by several investigators with the most successful agents having a lipophilic character, most notably the isonitriles and the boronic acid adducts of technetium dioxime (BATOs). Uptake studies of these agents demonstrate that they most likely do not localize in the heart by the sodium/potassium ATPase pump but rather by passive diffusion.

Figure 1 illustrates a simple model of radiotracer (drug) uptake from the blood by the heart, however it can be applied to other organs as well. In this model, drug is delivered to

the heart via arterial blood. Drug in the blood exists as free drug or as drug bound to plasma proteins. In general, only free drug can pass through the capillary endothelium into the interstitial space and subsequently through the parenchymal cell membrane into the intracellular space. Drug may be retained, bound to the cell membrane or intracellularly by some process of entrapment, or it can diffuse out of the cell. Drug not extracted initially and drug that back-diffuses into the blood is removed from the heart by the venous system.

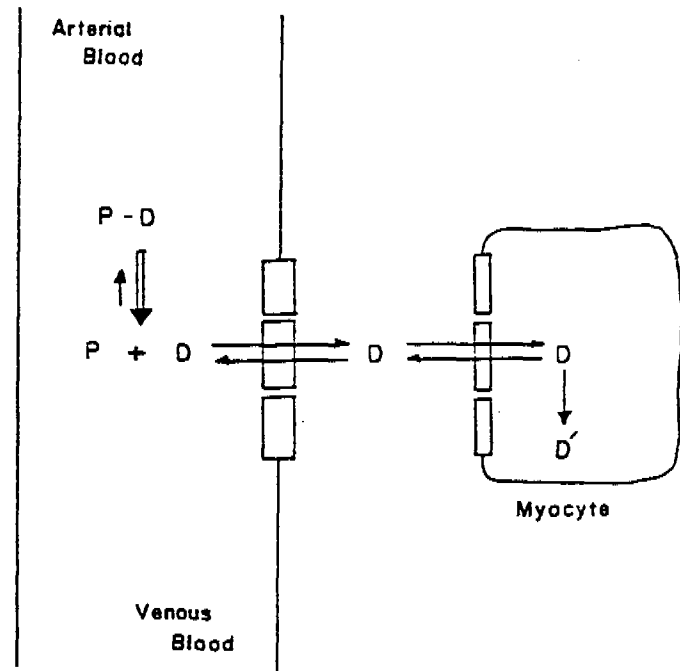


Figure 1. Myocardial uptake model. P = plasma proteins; D = free drug; P-D = drug bound to plasma protein; D' = myocyte bound drug.

Extraction Fraction

The principal requirement of a perfusion imaging tracer is that its extraction fraction by the heart is high and is proportional to blood flow over the range of flow seen clinically. If a tracer's extraction falls off at high flow rate, the ratio of activity in normal myocardium to that in ischemic myocardium will decrease, thereby reducing the sensitivity of the perfusion imaging study. Extraction fraction (EF) is defined as the fraction of a drug removed from the blood first-pass by an organ. It is usually determined in one of two ways: (1) by measuring the arterio-venous difference of steady state plasma concentrations of drug entering and exiting the organ or, (2) by the indicator dilution method whereby the ratio of diffusible-to-nondiffusible or reference tracer (albumin) exiting from the organ is measured following a simultaneous bolus arterial injection of both tracers (29,30). Extraction fraction, using the first method, is calculated using Equation [1] below, where C_a and C_v are arterial and venous tracer concentrations, respectively. Extraction fraction using the latter method is calculated using Equation [2], where H_{Df} and H_{Rt} are the fractions of injected diffusible and reference tracers, respectively, emerging from the heart per unit time.

Equation [1]

$$\text{Extraction Fraction} = \frac{C_A - C_V}{C_A}$$

Equation [2]

$$\text{Extraction Fraction} = 1 - [H_{Dt}/H_{Rt}]$$

The principal disadvantage of the steady state infusion method is that extraction and back-diffusion of diffusible tracer cannot be distinguished from each other. In other words, this method yields an *apparent* first pass extraction fraction because back-diffusion is not accounted for. The indicator-dilution method obviates this problem because samples are obtained before back-diffusion becomes significant.

The extraction fraction of drugs which localize by passive diffusion is influenced by several factors such as lipophilicity, protein binding, molecular size and charge. In general, neutral, lipophilic molecules that are not protein bound in plasma (i.e., free drug) can readily pass through biological membranes, whereas charged, hydrophilic species cannot. Studies conducted during the development of radiotracers for uptake by the brain (31) and heart (32) have demonstrated a parabolic relationship between tracer lipophilicity and organ uptake. That is, uptake increases in proportion to lipophilicity to a point, however continued increases in lipophilicity cause a decrease in uptake. The explanation for this is that at low values of lipophilicity the drug is too hydrophilic for uptake and at high values of lipophilicity increased plasma protein binding of drug occurs, lowering the concentration of available free drug.

Another factor which may affect EF is blood flow. While it is desirable that EF be proportional to blood flow, several heart imaging agents demonstrate flow limited or linear extraction only at low flows. At high flows, a nonlinear relationship occurs where tracer uptake becomes diffusion limited.

In addition to a high extraction fraction, two other factors are important in the assessment of myocardial perfusion: organ retention of tracer and tracer metabolism. A radiotracer that quickly washes out of an organ, even after high initial extraction, will require a fast imaging system. If SPECT imaging is used, especially with single-headed systems, some tracer binding in the organ is desirable because of the long acquisition times during imaging. Fast tracer kinetics is more acceptable with PET or multi-headed SPECT systems because faster acquisition of data is possible. The extent of tracer metabolism should be limited only to that required to bind it within the organ. Extensive metabolism, producing metabolites that subsequently diffuse away from the initial accumulation site of the parent drug, will diminish the accuracy of assessing regional myocardial perfusion.

Tc-99m SESTAMIBI

Chemistry

Tchnetium-99m sestamibi is a monovalent cationic,

lipophilic complex comprised of one atom of Tc-99m in the 1+ oxidation state and six molecules of 2-methoxy isobutyl isonitrile (MIBI) (33). Its structural formula is shown in Figure 2. It is prepared by the addition of up to 150 millicuries of sodium pertechnetate to a lyophilized kit containing the ligand, tetrakis (2-methoxy isobutyl isonitrile) copper (I) tetrafluoroborate, stannous chloride as reducing agent and additional adjuvants, adjusted to pH 5.3 to 5.9. Labeling is effected by incubation of the Tc-99m pertechnetate/kit mixture in a boiling water bath for 10 minutes. The complex is stable at room temperature for 6 hours after preparation. Radiochemical purity, checked by thin layer chromatography, must be 90% or greater for patient administration.

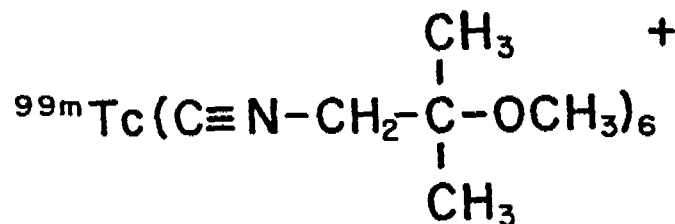


Figure 2. Structural formula of Tc-99m Sestamibi

Biologic Properties

Following intravenous administration, Tc-99m sestamibi is extracted by the myocardium in proportion to blood flow up to 2.5 ml/min/g, or approximately 3 times resting flow (34). At resting blood flow of 0.8 ml/min/g the extraction fraction measured in canine myocardium is 65%, but above resting flow the extraction decreases (34). By comparison, the extraction fraction of Tl-201 in the same canine model is 82%. In a rabbit perfused heart model, Tl-201 also shows higher extraction than Tc-99m sestamibi (35). The higher extraction of Tl-201 relative to Tc-99m sestamibi is due to higher transcapillary exchange, i.e. the plasma-to-interstitial space transport of Tl-201 is greater. Thus, capillary exchange dominates the first pass extraction kinetics. However, Tc-99m sestamibi has higher parenchymal cell permeability and volume of distribution, contributing to a slower cellular washout compared to Tl-201 (35). This difference may be due to the high lipophilicity of Tc-99m sestamibi.

Myocardial uptake studies indicate that Tc-99m sestamibi enters the myocardium by passive diffusion and is retained for a prolonged period of time. Subcellular distribution studies in guinea pig heart demonstrate that Tc-99m sestamibi is bound to cytosolic substances, but that under hypoxic conditions a major portion of the cytosolic activity is shifted to the mitochondria (36). Other studies show that the uptake of Tc-99m sestamibi by the heart is not affected by ouabain and thus it is not extracted by the sodium/potassium ATPase pump (37). Therefore, it is not a potassium analog.

In humans, the mean heart retention of Tc-99m sestamibi is $1 \pm 0.4\%$ of the injected dose (ID) 60 minutes after intravenous injection at rest, and $1.4 \pm 0.3\%$ following exercise (38). The activity is fixed in the myocardium for a prolonged period of time demonstrating insignificant redistribution (39-41). Following intravenous injection, over 90% of Tc-99m sestamibi clears from the blood in less than 5 minutes. Compared to Tl-201, Tc-99m sestamibi blood levels immediately after injection are higher, presumably because of lower extraction, whereas late blood levels are lower, presumably because of the lack of redistribution (38). It is excreted intact principally by the kidneys and hepatobiliary system. By 24 hours, 30% and 24% of the ID are excreted in the urine following rest and exercise studies, respectively. By 48 hours fecal excretion is 37% at rest and 29% after exercise (38). This difference in hepatobiliary excretion is due to reduced splanchnic blood flow and lower liver uptake during exercise. The highest activity is achieved in gallbladder and liver, followed by the heart, spleen and lungs. However, activity in the liver, lungs, and spleen decreases more rapidly with time than heart activity and more so with exercise studies than at rest. At 3 hours after a rest injection, 27% of the initial activity is cleared from the heart, whereas 76% is cleared from the liver (38). Thus, the heart:liver ratios at 30, 60, and 120 minutes are 0.5, 0.6, and 1.1, respectively after a rest injection and 1.4, 1.8, and 2.3 after exercise injection. Best imaging is achieved at 60 minutes or later after injection of Tc-99m sestamibi, mainly because higher heart:liver, heart:lung, and heart:spleen ratios are achieved at these times. However, for expediency, some investigators shorten the dose-to-image time to 30 minutes for exercise studies with SPECT because of higher heart:liver ratios after exercise. Because of accumulated activity in subdiaphragmatic structures, particularly with rest studies or when coronary vasodilators such as adenosine are used, one must normalize the image set to the hottest pixel in the myocardium instead of that below the diaphragm (42). This significantly improves visualization in the myocardium. High concentration of this tracer in subdiaphragmatic structures, e.g., the liver or in biliary excretions localized within bowel just below the heart, can cause severe artifacts in SPECT reconstruction, especially if there is respiratory motion. Some clinical investigators have found that imaging these patients in the prone position has helped to increase the distance between myocardium and the "hot" structure, thus diminishing the SPECT reconstruction artifact. Other investigators have advocated imaging the patient while upright, seated on a rotating chair.

Tc-99m TEBOROXIME

Chemistry

Tc-99m teboroxime is a neutral lipophilic complex of the general class of compounds known as boronic acid adducts of technetium dioxime (BATO) (43). It is prepared by the general method of template synthesis wherein a metal ion serves as a template to organize the course of complex multistep reactions. Tc-99m teboroxime is unique from other

Tc-99m complexes in that the ligand is not present in the vial before addition of pertechnetate, but is formed around technetium as the template atom. The essential reactants in the kit are cyclohexanedione dioxime, chloride as axial ligand, and methyl boronic acid. The kit also contains stannous chloride as reducing agent and other adjuvants. It is prepared by heating the kit reactants with up to 100 millicuries of Tc-99m sodium pertechnetate in a volume of 1 ml for 15 minutes at 100°C. The final complex is one of a heptacoordinate Tc(III) atom bound to a chlorine atom and to the six nitrogens of the three vicinal dioximes. One end of the molecule is capped by a boron atom covalently bound to one oxygen atom from each of the dioximes (Figure 3). The complex is stable at room temperature for 6 hours after preparation. Radiochemical purity, determined by thin layer chromatography, must be 90% or greater for patient administration. The preparation volume should not exceed 1 ml and if dilution of the dosage is desired it should be done with preservative-free saline just prior to injection, otherwise the radiochemical purity may decline. The complex has a tendency to bind to the rubber plunger of disposable syringes and therefore a significant loss of activity may result upon injection. Ideally, the tracer should be drawn into the syringe immediately before injection into the patient to minimize binding losses. Depending on the brand of syringe used, a slight overfill of activity in the syringe may be necessary to deliver the required dosage. An expiration time may be necessary for a teboroxime-loaded syringe.

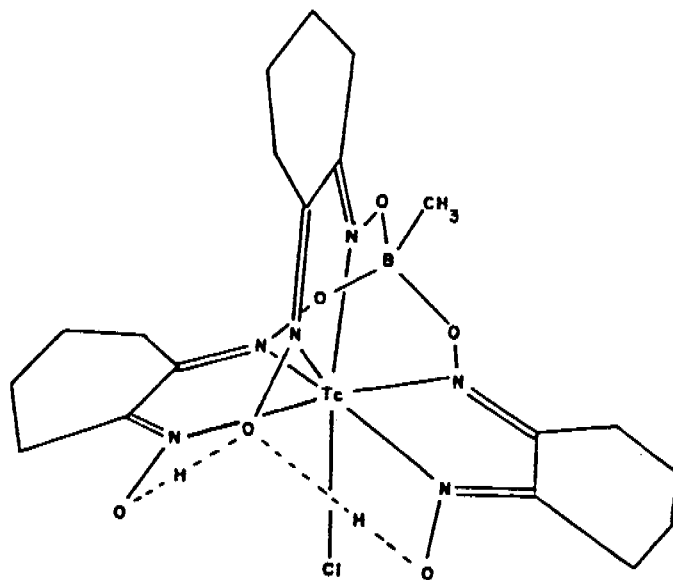


Figure 3. Chemical structure of Tc-99m Teboroxime

Biologic Properties

Following intravenous injection Tc-99m teboroxime is highly extracted by the myocardium. Experimental studies in various animal models report its first pass extraction fraction ranges from 62 to 96% (30, 44-46). The 96% value is probably an overestimate because it was determined in

buffer-perfused rabbit heart, whereas the other studies used blood. When incubated with blood, Tc-99m teboroxime binds readily to blood cellular elements, decreasing its extraction fraction with time (45). Similar experiments with Tc-99m sestamibi or Tl-201 thallos chloride showed that extraction of these agents was neither affected by the length of time in circulation nor the presence of blood. In comparative studies with Tl-201 or Tc-99m sestamibi, Tc-99m teboroxime usually demonstrates higher extraction (47). Studies of the relationship between extraction fraction and blood flow indicate an inverse relationship (30) or no demonstrable effect (46). The differences in these studies may be due to the different methods used for measuring extraction. Despite its high first pass extraction, Tc-99m teboroxime quickly back-diffuses from myocardial cells into the vascular space. This rapid egress from the heart means that data collection must be performed very quickly after tracer injection in clinical studies.

In humans, peak myocardial uptake of 2.3% of the injected dose occurs within 2 minutes following intravenous injection (48). Blood clearance is rapid with only 10% of the ID remaining at 10 minutes after injection. Various washout rates of activity from the heart have been reported. Early clinical studies demonstrated a biexponential pattern with a 2 minute fast component (68%) and a 78 minute slow component (32%) (48). Washout from the heart is related to flow. In dog studies, following an intracoronary injection, two-thirds of the ID (fast component) washed out with a half-time of 2.3 minutes at normal flows (0.93 ml/min/g), but in 1.5 minutes after a dipyridamole stimulated increase in flow (4.2 ml/min/g) (46). The slow components had half-times of 20 minutes and 34 minutes, respectively. In the same dog model, following intravenous injection, washout was monoexponential with clearance half-time of 21 minutes at normal flows and 13 minutes at elevated flows. Studies in human subjects following intravenous injection demonstrate a clearance half-time from the myocardium of 11 minutes (49).

Tc-99m teboroxime is excreted by the kidney with 22% of the ID in the urine by 24 hours. The predominant excretion occurs via the hepatobiliary system with 33% of the ID in the liver by 10 minutes. Liver clearance of activity is slow by comparison to myocardial clearance so that heart:liver ratios decrease rapidly, from 0.1 at 5 minutes after injection to 0.05 at 10 minutes and beyond (50). Early studies with Tc-99m teboroxime recommended that best imaging of the heart is achieved from 2 to 6 minutes following injection to minimize interference by hepatic activity projecting over the diaphragmatic surface of the heart (51). Currently, however, some investigators argue that the best images are obtained between 1.5 and 3.5 minutes after injection of teboroxime. Liver interference may become more of a problem following a second injection of tracer, because of the presence of residual activity from the first injection (51).

Tl-201 THALLOUS CHLORIDE

Chemistry

Thallium-201 is produced in a cyclotron by the proton

bombardment of stable natural thallium-203. The product is lead-201 which is allowed to decay to thallium-201. The Tl-201 is isolated by ion-exchange chromatography and the chloride salt is formed by dissolution in HCl. It is available commercially as a sterile, pyrogen-free injection of the simple chloride salt in aqueous solution adjusted to pH 4.5 to 7.5. Radiochemical purity is not less than 95% as the monovalent species.

Biologic Properties

Thallium is a potassium analog that localizes in the heart in proportion to myocardial blood flow. Following intravenous administration Tl-201 blood levels decrease rapidly as the radiotracer distributes into the extravascular space. Five minutes after injection only 5 to 8% remains in the blood (5). Blood disappearance is faster after exercise because of the high blood flow to muscle. Thallium is taken up in highest concentration in the myocardium and kidneys, with lower uptake in liver, lung and skeletal muscle. Although skeletal muscle concentration is low, the large mass of muscle in the body provides a large "sink" for the Tl-201 activity.

Maximum myocardial uptake occurs at 10 to 30 minutes after injection in the resting state and by 5 minutes after exercise. By 30 minutes, in unanesthetized dogs, the ID/g localized in the left ventricle in control animals was 0.0385%, and in dipyridamole treated dogs was 0.0614%. The fact that only a 60% increase in myocardial concentration occurred when coronary blood flow increased 3 to 4 times due to dipyridamole demonstrates that thallium uptake is not related to myocardial blood flow in a linear manner (52). A similar nonlinear relationship between flow and thallium uptake was shown in dogs whose coronary blood flow was increased by reactive hyperemia or adenosine treatment (53). This study demonstrated that the extraction fraction of thallium under normal coronary flow was 88%, but fell linearly with increased flow following vasodilation. The authors suggested that the drop in extraction fraction occurred because coronary flow was in excess of myocardial demand.

Following transcappillary diffusion, thallium is taken up into myocytes by the membrane-bound sodium/potassium ATPase pump. Some of the factors cited for the similarity of action between K^+ and its analogs are monovalent cationic charge, similarly sized hydrated ionic radii, and uptake via the membrane pump. This uptake is known to be partially inhibited by ouabain and hypoxia (37,53,54). The membrane-bound pump's ability to transport ions is a measure of myocyte viability and is known to be affected by conditions which affect the level of tissue oxygenation, such as ischemia and acute infarction. Thus, thallium's mechanism of transport puts it into a position of measuring myocyte viability. Indeed, one study compared Fluorine-18 fluorodeoxyglucose (FDG), which measures intermediary metabolism, with Tl-201 thallos chloride reinjection in patients with chronic coronary artery disease and left ventricular dysfunction. In myocardial regions with severe irreversible thallium defects on standard exercise-redistribution imaging, thallium reinjection identified as viable or nonviable, with few exceptions, the same regions as did PET imaging with FDG (55). Thus, Tl-201 SPECT

imaging may become a prominent modality along with PET in the qualitative assessment of myocardial viability (56).

RADIATION ABSORBED DOSE

The critical organ in Tc-99m sestamibi studies is the upper large intestinal wall, sustaining a radiation absorbed dose of 5.4 rads per 30 millicuries of administered activity. This is followed by the lower large intestinal wall (3.9 rads), small intestine (3 rads), and kidneys, gallbladder wall and urinary bladder wall, each with 2 rads (57).

The critical organ following administration of Tc-99m teboroxime is the upper large intestine with a radiation absorbed dose of 6.15 rads/50 millicurie dosage. This is followed by the gallbladder wall (4.89 rads), the lower large intestine (4.36 rads), the small intestine (3.39 rads) and the liver (3.10 rads) (50).

The total body elimination of Tl-201 is slow with a biologic halftime of 10 days (5). Only a small amount (4 to 8%) is excreted in the urine in 24 hours. Approximately 3% of the injected activity localizes in the kidney, which is the critical organ. The absorbed radiation dose to the kidney is 2.4 rads/2 mCi dosage.

A recent review of these three myocardial imaging agents summarizes their physiologic and pharmacokinetic properties (58). This report compares the radiation dose of these agents in effective dose equivalent units and is shown in Table 1.

COMPARISON OF Tl-201 THALLOUS CHLORIDE, Tc-99m SESTAMIBI, AND Tc-99m TEBOROXIME

The biologic properties of these agents are inherently different, particularly regarding myocardial transport. These differences will dictate, ultimately, how these agents will be used in cardiac imaging and what information they will provide in the diagnosis of heart disease. Many investigative studies have been conducted comparing the Tc-99m agents to Tl-201 in cardiac disease. The results of these studies have elucidated many of the advantages and disadvantages of each of these agents and have led to different protocols for their use in various clinical situations. However, much work needs to be done with these agents, exploring their unique properties, to identify more fully the exact clinical role each will have in the diagnosis of cardiac disease.

Thallium-201 versus Technetium-99m

Despite its widespread use in cardiac imaging, there are several inherent problems with the physical properties of Tl-201 which make it an undesirable imaging radionuclide. Its low photon energy (69 to 80 keV) is easily attenuated in tissue; photon absorption reduces count rate and scatter reduces resolution. By contrast, the photon energy of Tc-99m (140 keV) has less tissue attenuation and is efficiently detected with the gamma camera. The long half-life of Tl-201 (73 hrs) limits the activity which can be administered, because of radiation absorbed dose considerations. The short half-life of Tc-99m (6 hrs) is much more favorable. The effective dose equivalent for Tl-201 is 0.35 rem/mCi to the kidney. This is

10 times greater than that for Tc-99m sestamibi and 6 times that for Tc-99m teboroxime to the GI tract. The low dosage of Tl-201 activity (2-3 mCi) requires long collection times and results in images with lower count densities compared to Tc-99m where much higher activities (20-30 mCi) can be administered producing sharper, higher contrast images. Thallium-201 images have a fuzziness which is caused by backscatter. Better image quality is probably the most significant advantage of the Tc-99m agents over Tl-201.

Other advantages of Tc-99m are that ventricular ejection fractions, volumes, and wall motion can be assessed in addition to myocardial perfusion by first pass and gated planar imaging. SPECT and gated SPECT imaging is possible with Tc-99m sestamibi because of its prolonged retention by the myocardium. Rapid SPECT imaging is possible with Tc-99m teboroxime, but gated SPECT is not because it washes out too quickly from the myocardium. Finally, the ready availability of Tc-99m and radiopharmaceutical kits in the nuclear medicine lab obviates the potential problem of running out of commercially produced Tl-201 late in the week or on weekends.

Extraction Fraction and Myocardial Uptake

The importance of extraction fraction is that it must be high to accurately assess myocardial blood flow. If a radiotracer's extraction is low, the activity deposited in the myocardium will not be a true reflection of regional blood flow. Thus, the ideal perfusion imaging agent should be flow limited over the physiologic range of flow and remain "fixed" in the myocardium during the period of time required to obtain images. Tc-99m sestamibi, Tl-201, and to a lesser extent Tc-99m teboroxime, exhibit diffusion limited uptake because their extraction fractions decrease at high flow rates. Numerous studies have been performed in animal models to investigate the myocardial transport properties of these agents. Some of the results are inconsistent and contradictory, most likely because of differences in the experimental models used to gather data (47). Studies in the isolated perfused rabbit heart comparing the extraction of Tl-201, Tc-99m sestamibi and Tc-99m teboroxime demonstrated an inverse relationship between myocardial extraction of these agents and blood flow (30,35). However, this is compensated for by the linear increase in capillary permeability surface area product with flow. These data show that with increased flow, capillary recruitment occurs, i.e., an increased surface area for exchange is available, and therefore more total tracer is delivered to a larger surface area of capillaries. Thus, more tracer can accumulate in the heart, but only up to a point where a diffusion barrier is reached (Table 1). The extraction fraction decreases with flow, however, because permeability, or the rate of tracer flux through the capillary membrane, is independent of surface area. Thus, while more tracer is available for exchange at higher flows, the portion of total tracer extracted declines because of decreased transit time as the tracer traverses the capillary network (58).

In general these studies indicate that Tc-99m teboroxime has the highest extraction fraction over a wide range of blood flow, followed by Tl-201 thallos chloride, and Tc-99m sestamibi (Table 1). Thus, Tc-99m teboroxime should be more

Table 1.

Properties of Myocardial Perfusion Imaging Agents

Property	²⁰¹ TlCl	^{99m} Tc-Sestamibi	^{99m} Tc-Teboroxime
Chemistry	cationic hydrophilic	cationic lipophilic	neutral lipophilic
Uptake Mechanism	active transport	passive diffusion	passive diffusion
Resting Extraction	~ 85%	~ 65%	~ 90%
Diffusion Limitation (ml/min/g)	2.5 - 3.0	2.0 - 2.5	> 4.0
Resting Heart Uptake (%ID)	~ 4%	~ 1%	~ 2%
Myocardial Clearance T 1/2	3 - 4 hr	> 6 hr	10 - 15 min
Redistribution	variable	insignificant	rapid
Excretion	renal 5% (24 hr)	renal 30% (24 hr) hepatobiliary 37% (48 hr)	renal 22% (24 hr) hepatobiliary 33% (10 min)
Liver Clearance T 1/2	N/A	~ 0.5 hr	~ 1.5 hr
Critical Organ	kidney	upper lg intestine	upper lg intestine
Effective Dose Equivalent	1.05 rem/3 mCi	1.06 rem/30 mCi	1.78 rem/30 mCi
Availability	commercial mfr	on site kit	on site kit
Preparation	ready to use	30 min prep/QC 150 mCi max	30 min prep/QC 100 mCi max
Stability	N/A	6 hr	6 hr

sensitive to flow changes. One study comparing all three agents in the same animal has shown that Tl-201 and Tc-99m tetroxime are similar in approximating blood flow and less diffusion limited than Tc-99m sestamibi (59).

Uptake of activity by the myocardium is a function of tracer delivery and extraction. *Retention* of activity taken up by the myocardium is a function of tracer back-diffusion and binding to myocytes. Each of these processes can be affected by disease. Exercise stress or vasodilators increase myocardial uptake of tracers because of increased blood flow. The myocardial uptake of Tc-99m sestamibi, Tc-99m tetroxime, and Tl-201 thallous chloride as a % of injected dose at rest is 1.0%, 2.3%, and 4.2%, respectively. Although Tl-201 has the highest uptake, clinically the count density is much lower than that seen with the Tc-99m agents because of the low dosage of Tl-201 administered.

The mechanism of uptake of these three agents into myocardial cells appears to be quite different. Tl-201 is transported actively via the sodium/potassium ATPase membrane pump. It washes out at a moderate rate in proportion to regional blood flow (60). Tc-99m sestamibi enters the cell passively, binding to an intracellular moiety with a molecular weight of about 10^4 Daltons (61). It exhibits no significant washout. Tc-99m tetroxime, being highly lipophilic, diffuses rapidly across phospholipid membranes. However, it is not known if this compound enters the myocardial cell or is incorporated into the phospholipid layers of cellular membranes (46).

Cell culture experiments have been conducted to evaluate mechanisms of cellular uptake of heart agents (61-63). When there is mild and reversible metabolic cellular inhibition, there is apparently a slight increase in uptake of Tc-99m sestamibi, a slight decrease of Tl-201, and Tc-99m tetroxime is unaffected. Under more profound cellular damage, resulting in cell death, Tc-99m sestamibi shows a great loss of cellular uptake, whereas Tl-201 and Tc-99m tetroxime are affected in a way similar to moderate cell damage. When cells are exposed to ouabain, only Tl-201 shows any significant decrease in uptake, suggesting that Tc-99m sestamibi and Tc-99m tetroxime uptake is independent of the Na-K ATPase pump. During experiments simulating mitochondrial inhibition, only Tc-99m sestamibi demonstrates significant inhibition in cellular uptake. In addition, "cold" Tc-sestamibi inhibits the uptake of Tc-99m sestamibi but has no effect on Tl-201, suggesting that cellular affinity and saturable binding sites play a role in Tc-99m sestamibi transport. Thus, considering their extraction and uptake properties, it appears that Tc-99m tetroxime has the least degree of sensitivity to cellular dysfunction compared to Tl-201 and Tc-99m sestamibi and may be more reflective of blood flow than these two, whereas Tl-201 and Tc-99m sestamibi may be more sensitive to cellular viability.

IMAGING CONSIDERATIONS

Numerous studies have demonstrated similar sensitivity and specificity of Tl-201, Tc-99m sestamibi, and Tc-99m tetroxime in the diagnosis of ischemic heart disease (64-67).

Since Tl-201, Tc-99m sestamibi, and Tc-99m tetroxime have different cardiac transport properties, imaging protocols must be optimized for each agent for the various clinical settings in which they are used.

Tl-201 Imaging

Two caveats are worth considering regarding the use of Tl-201 in myocardial perfusion imaging. The first is that during stress imaging, Tl-201's washout and redistribution requires that stress image data acquisition must be completed by 45 minutes of injection to avoid missing perfusion defects brought out by the stress. The second is that Tl-201's biologic redistribution has been found to be variable and may affect interpretation of delayed images. Studies have shown that up to 60% of perfusion defects present on the 3 to 4 hour delayed images show redistribution on 8 to 24 hour delayed images (68). In one study 75% of patients having persistent defects on 4 hour delayed images who underwent angioplasty (PTCA) returned to normal, suggesting that persistent defects on 4 hour delayed images may represent viable myocardium (69). These findings of incomplete redistribution are apparently due to variable plasma levels of thallium. To overcome this problem, two injections of Tl-201 thallous chloride have been suggested; one at stress and one during rest to assure adequate plasma levels of Tl-201 during the redistribution phase. This eliminates the reliance of identifying CAD on the time-dependent process of redistribution.

A useful stress-redistribution-resting reinjection imaging protocol involves the intravenous administration of 2 millicuries of Tl-201 thallous chloride at maximal exercise, as evidenced by having achieved 85% of maximum predicted heart rate or pressure-rate product of 25 K, significant ECG changes, or chest pain, with the patient continuing to exercise for 90 seconds at the same level. Following exercise, stress images are obtained beginning at 12 minutes and finishing before 45 minutes with redistribution imaging at 4 hours after the initial injection. During redistribution, the patient is ambulatory and preferably remains in the fasting state. Immediately after the 4 hour redistribution image, the patient receives an additional 1 millicurie dose of Tl-201 thallous chloride at rest, and a third set of images is acquired beginning 20 minutes after the second administered dose. Protocols such as this have identified viable and nonviable myocardium equivalent to PET imaging with FDG (55), suggesting that, when done properly, Tl-201 imaging may be an effective method for assessing myocardial viability.

If a pharmacologic stress protocol is used, dipyridamole (0.56mg/kg) is infused over 4 minutes. Tl-201 thallous chloride is injected between 7 and 9 minutes to coincide with peak effect of dipyridamole. Stress imaging is done at 12 to 35 minutes followed by delayed imaging at 3 to 4 hours (14). Alternatively, if adenosine is used, Tl-201 is injected at 3 minutes into a 6 minute infusion of 0.142 mg/kg/min. Imaging is begun immediately after the adenosine infusion is completed.

Tc-99m Sestamibi Imaging

Following intravenous injection, Tc-99m sestamibi clears rapidly from the blood and remains relatively fixed in the

myocardium. Activity clears steadily from the liver so that heart-to-liver ratios improve with time, being less than 1 at 60 minutes and slightly greater than 1 at 120 minutes after a rest injection and approximately twice these ratios after an exercise injection. Imaging is typically begun at 60-90 minutes after a rest injection and 30-60 minutes after an exercise injection.

Because Tc-99m sestamibi does not redistribute appreciably, separate rest and stress injections are required to identify and differentiate myocardial ischemia and scar. The study can be performed as a 2-day or a 1-day protocol. There is no significant difference in diagnostic accuracy between these protocols (70). With the 2-day protocol the patient is stressed, injected with 20-25 millicuries and imaged. The rest study is performed the next day with a similar dosage. This protocol has appeal in a patient whose pretest likelihood of CAD is low because the rest study can be cancelled if the stress study is normal. If the 1-day protocol is used, a rest-stress sequence is preferred. A rest dose of 8-9 millicuries is injected and imaging is performed in 60-90 minutes. After an interval of 3-4 hours, to allow the resting dose to decay about 33%, stress is performed and a stress injection of 22-25 millicuries is given followed by imaging in 30-60 minutes. Some investigators have estimated that delivery of Tc-99m sestamibi to the myocardium during stress is several times that at rest because of the combination of tripling the dose and augmentation of blood flow by 400 to 600% brought on by stress. The 1-day procedure may take up to 5-6 hours to complete depending on the time interval allowed between rest and stress. This protocol is useful when a rapid diagnosis is needed especially in a patient with high pretest likelihood of CAD, but may present a problem with diabetic patients because of the prolonged fasting requirements.

A 1-day stress-rest sequence may be done but is not preferred because of the higher incidence of misinterpreting reversible defects as fixed (71). This is caused by interference of the high level of residual activity in normal myocardium from the initial stress dose making it difficult for the perfusion defect seen at stress to fill in on the rest study. This procedure should be reserved for those patients with a low likelihood of disease in whom a normal initial stress study is anticipated (58), thus reducing the likelihood of needing to do the rest study.

There are several advantages afforded by Tc-99m sestamibi's lack of redistribution. One is the ability to repeat image acquisition in the event of positioning error, patient motion or instrument malfunction. A second advantage is the ability to inject a patient during an acute ischemic event and image later at a more convenient time or following patient treatment. An example is being able to rule out myocardial ischemia in patients with unstable angina who have spontaneous chest pain (72). Tc-99m sestamibi is injected at the time of pain. A few hours later when the patient has stabilized, a cardiac scan is obtained. A normal Tc-99m sestamibi scan strongly suggests that the pain is not of coronary origin. An abnormal scan suggests significant coronary disease. A subsequent study in the absence of chest pain, demonstrating a decrease in size of an initial perfusion defect, supports the diagnosis of a transient coronary flow

disturbance. Another example involves the evaluation of acute infarction by determining the amount of myocardium salvaged following thrombolytic therapy (73). In this situation the patient is injected upon admission, thrombolytic therapy is given and imaging is performed within 4 to 6 hours to identify infarcted plus jeopardized myocardium at the time of the event. A repeat imaging study at a later date identifies only infarcted myocardium. Analysis of the two studies identifies the amount of salvaged muscle.

A third advantage of Tc-99m sestamibi is the ability to evaluate ventricular function as well as perfusion with a single injection of tracer. Thus, perfusion defects, ventricular ejection fraction, and wall motion studies at rest and stress can be compared to estimate the severity of myocardial disease. For example, an exercise perfusion defect with normal regional wall motion during stress would not imply ischemia. Regional akinesis at rest could be associated with either scar or severely ischemic or stunned myocardium (58). A final application of Tc-99m sestamibi is in the identification and sizing of myocardial infarcts (74).

Tc-99m Teboroxime Imaging

The high extraction of Tc-99m teboroxime at high blood flow coupled with rapid myocardial washout of activity makes this agent potentially attractive for doing multiple studies quickly, enhancing throughput of cardiac imaging procedures. The saying "you can get anywhere in 10 minutes if you go fast enough," has some relevance to Tc-99m teboroxime since its inherent imaging advantages will require procedures and equipment that can handle speedy acquisition. Ideally, because a majority of tracer washes out of the heart quickly, images should begin at 1.5 minutes and be completed by 3.5 to 5.5 minutes after injection to minimize interference by immediate post-injection lung activity and hepatic activity which peaks by 6 minutes. Previous reports on teboroxime imaging recommended later imaging times (58), but current investigations have found that earlier imaging times yield better results. Despite its rapid kinetics, useful imaging with Tc-99m teboroxime has been reported with planar and single-headed SPECT imaging systems (75,76). If planar imaging is used, a bicycle ergometer allows exercise to be performed in close proximity to the camera. If a treadmill is used for exercise, a well planned routine for translocation and positioning of the patient must be in place so that image acquisition can begin in a timely manner. A recommended protocol for planar imaging, developed to minimize liver interference, begins imaging in the steep LAO or lateral projection, where liver overlap is likely to be a problem, to acquire these images before liver activity peaks (75). In this procedure 15 to 20 millicuries of Tc-99m teboroxime is injected at peak exercise and stress imaging in the LLT, LAO, and anterior projections are acquired at early (0-5 min) and delayed (5-10 min) times. A recommended protocol for SPECT acquisition is to start in the 45° LPO position and finish in the 45° RAO position, to minimize liver scattered photon activity contributions in the LPO position. A rest study is then completed 1.5 hours following either the planar or SPECT stress studies.

Time of acquisition is a problem with single-headed

SPECT systems. Minimal distortion of the initial flow distribution due to changing tracer activity will occur if the total acquisition time is equal to or less than the tracer half-time in the organ (77). Thus, with a myocardial clearance half-time in humans following intravenous injection of 11 minutes (49), a SPECT system will be best if it allows study completion by 6 minutes from Tc-99m tetroxime injection. Triple-headed SPECT systems have the capability of completing acquisition in 2 minutes (78), whereas, the equivalent data collection time with a single-headed SPECT system is 3 minutes.

The high extraction of Tc-99m tetroxime at higher blood flow rates compared to Tl-201 and Tc-99m sestamibi (59) matches it well with dipyridamole or with adenosine which causes maximal dilatation. Although not proven clinically, a Tc-99m tetroxime/adenosine combination would theoretically have higher sensitivity detecting mild stenosis because there would be a greater differential in tracer uptake between normal and ischemic myocardium at higher flow rates in this situation. The vasodilator agents also obviate the logistical problems with exercise stress although some benefit of combining mild treadmill exercise with dipyridamole has been reported to diminish splanchnic blood pool and liver uptake of activity with Tl-201 imaging by shunting blood flow away from the abdominal viscera to the exercising musculature (79).

The rapid washout of Tc-99m tetroxime from the heart, which is directly related to blood flow, suggests that a method for measuring differential washout rates from normal and ischemic myocardium may be useful in evaluating coronary artery disease. Rapid washout of Tc-99m tetroxime would be a disadvantage in evaluating patients with acute infarction or unstable angina unless a gamma camera was present at the patient's bedside, whereas, the use of Tc-99m sestamibi would allow the convenience of patient injection remote from the imaging site.

Tl-201/Tc-99m Dual-Isotope Studies

The Tc-99m agents offer the advantages of continuous availability of pertechnetate and cold kits, the opportunity to evaluate function as well as perfusion, the convenience of image acquisition at a time remote from tracer injection in the case of Tc-99m sestamibi, and higher throughput, in the case of Tc-99m tetroxime, so that equipment utilization and patient participation times are minimized.

Another way to increase throughput is with dual-isotope studies. Berman, et al., have shown two possible protocols (80). In the separate rest/stress protocol, 2 to 2.5 mCi of Tl-201 is injected and a rest SPECT study is acquired from 15 to 40 minutes. This is immediately followed by treadmill exercise during which 15 to 20 mCi of Tc-99m sestamibi is injected. Dual-isotope SPECT imaging of Tl-201 and Tc-99m sestamibi is done from 90 to 115 minutes (after Tl-201 injection) to image the stress distribution of Tc-99m sestamibi and correct for photon energy cross-talk between the two radionuclides. Although these studies have not been proven in a large number of patients, preliminary results have shown a high level of diagnostic accuracy and the ability to complete patient studies in 2 hours compared to 5 to 6 hours with same

day rest/stress Tc-99m sestamibi studies. An alternative, quicker method is a simultaneous rest/stress protocol where 3 to 3.5 mCi of Tl-201 is injected with no imaging, followed by a short period of rest and then treadmill exercise with injection of 15 to 20 mCi of Tc-99m sestamibi at 20 minutes. From 60 to 90 minutes, simultaneous dual-isotope acquisition of the rest distribution of Tl-201 and the stress distribution of Tc-99m sestamibi is done with completion of the study in 1.5 hours. More studies are needed to demonstrate the sensitivity and specificity of these imaging protocols, especially with the latter technique, but the introduction of Tc-99m agents has provided more latitude and the opportunity to conduct faster studies with potentially equal or higher accuracy than current protocols used in myocardial perfusion imaging.

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QUESTIONS

1. Clinical symptoms of chest pain first become evident during myocardial stress when coronary arterial lumen diameter is reduced by:

- A. 30%
- B. 50%
- C. 70%
- D. 90%

2. Obstruction to coronary blood flow is most readily detected when:

- A. coronary blood flow is at normal levels
- B. coronary blood flow is at maximal levels
- C. the ratio of flow in stenotic-to-normal vessels is 2.4
- D. coronary flow reserve is at a minimum

3. A diagnosis of myocardial ischemia is supported when:

- A. a perfusion defect is present during a Tl-201 stress study and absent during the distribution study
- B. a perfusion defect is present during a Tl-201 stress study and during the redistribution study
- C. Tl-201 activity washes out of a perfusion defect area faster than a normal area of the myocardium during the redistribution phase
- D. coronary flow reserve in stenotic vessels is greater than that in normal vessels

4. Intense exercise is the preferred method of inducing myocardial stress because it:

- A. constantly produces maximal coronary vasodilation
- B. is a natural method that can be readily performed by all cardiac patients
- C. is more reliable than vasodilator methods
- D. increases the metabolic demand on the heart

5. Which of the following statements about adenosine is true?

- A. maximal vasodilation of coronary vessels is reached when blood pressure increases and heart rate declines
- B. maximal vasodilation of coronary vessels is achieved with a dosage of 0.56 mg/kg body weight
- C. maximal vasodilation of coronary vessels is achieved at a dosage of 0.142 mg/kg/min over 6 minutes
- D. adenosine requires aminophylline as antidote for adverse effects during infusion

6. Which of the following statements about extraction fraction of myocardial perfusion tracers is true?

- A. extraction fraction is linearly related to blood flow up to 5 to 6 times normal
- B. extraction fraction is linearly related to a tracer's lipophilicity
- C. first-pass extraction fraction is best determined by the arterio-venous difference of tracer at steady-state plasma levels
- D. extraction fraction should be proportional to blood flow over the range of flow seen clinically

7. Which of the following is an undesirable property of myocardial perfusion tracers?

- A. uptake proportional to blood flow
- B. high first-pass extraction
- C. myocardial metabolism of the tracer
- D. myocardial retention of the tracer

8. Which of the following best describes the first-pass extraction of myocardial perfusion imaging agents?

- A. Tc-99m Teboroxime > Tl-201 > Tc-99m Sestamibi
- B. Tl-201 > Tc-99m Teboroxime > Tc-99m Sestamibi
- C. Tc-99m Teboroxime > Tc-99m Sestamibi > Tl-201
- D. Tc-99m Sestamibi > Tc-99m Teboroxime > Tl-201

9. Which of the following best describes myocardial clearance rate of perfusion imaging tracers?

- A. Tc-99m Teboroxime > Tc-99m Sestamibi > Tl-201
- B. Tc-99m Sestamibi > Tc-99m Teboroxime > Tl-201
- C. Tc-99m Teboroxime > Tl-201 > Tc-99m Sestamibi
- D. Tl-201 > Tc-99m Teboroxime > Tc-99m Sestamibi

10. Which of the following best describes myocardial uptake as a % of injected dose for perfusion imaging tracers?

- A. Tc-99m Teboroxime > Tl-201 > Tc-99m Sestamibi
- B. Tc-99m Sestamibi > Tl-201 > Tc-99m Teboroxime
- C. Tc-99m Teboroxime > Tc-99m Sestamibi > Tl-201
- D. Tl-201 > Tc-99m Teboroxime > Tc-99m Sestamibi

11. Which of the following best describes critical organ radiation absorbed dose for myocardial perfusion imaging tracers?

- A. Tl-201 > Tc-99m Sestamibi > Tc-99m Teboroxime
- B. Tl-201 > Tc-99m Teboroxime > Tc-99m Sestamibi
- C. Tc-99m Teboroxime > Tc-99m Sestamibi > Tl-201
- D. Tc-99m Sestamibi > Tc-99m Teboroxime > Tl-201

12. The radiochemical purity of Tc-99m Teboroxime or Tc-99m Sestamibi must be greater than _____ % before patient administration.

- A. 97%
- B. 95%
- C. 92%
- D. 90%

13. Which of the following statements regarding Tc-99m Teboroxime is false?

- A. a maximum of 100 mCi can be added to the kit
- B. heating time at 100 degrees C is 10 minutes
- C. some activity may remain bound to the injection syringe
- D. the preparation volume is restricted to 1 milliliter

14. Which of the following statements regarding Tc-99m Sestamibi is false?

- A. a maximum of 100 mCi can be added to the kit
- B. heating time at 100 degrees C is 10 minutes
- C. stability after preparation is 6 hours
- D. the labeled product should be stored at room temperature

15. Which of the following statements is true regarding Tc-99m Sestamibi?
- heart:liver activity ratio decreases with time after injection
 - heart:liver activity ratio is higher after exercise injections than after rest injections
 - highest uptake of activity is seen in heart, gallbladder, liver, spleen and lungs, in that order
 - best imaging is achieved 30 minutes after a rest injection
16. Which of the following statements is false regarding Tc-99m Teboroxime?
- best imaging of the heart is achieved from 1.5 to 5.5 minutes following injection
 - heart:liver activity ratio decreases with time after injection
 - accumulation of liver activity may interfere with imaging the heart
 - redistribution of activity in the heart is relatively slow
17. Which of the following statements is true regarding Tl-201 Thallous Chloride?
- Tl-201's extraction is diffusion-limited above 4 ml/min/g
 - Tl-201 completely redistributes within 4 hours of a stress injection
 - The % injected dose increases in the heart at increased coronary blood flow
 - Tl-201 can assess myocyte viability because it measures intermediary metabolism, similar to FDG
18. Which of the following statements is false? Better quality images are obtained with Tc-99m compared to Tl-201 because:
- Tc-99m produces less scatter in tissue
 - larger activities of Tc-99m can be administered
 - the percent ID of Tc-99m in the heart is higher
 - the attenuation of Tl-201 in tissue is greater
19. Which of the following statements correctly describes Tc-99m Sestamibi?
- being a monovalent cation, it enters the myocyte by the Na-K ATPase mechanism
 - it is bound to intracellular macromolecules and mitochondria
 - it washes out of the heart quickly after intravenous injection
 - its myocyte uptake is readily blocked by ouabain
20. Which of the following statements correctly describes Tc-99m Teboroxime?
- it is bound to intracellular substances in the myocyte
 - it is localized in the heart by active transport
 - it rapidly backdiffuses from the heart
 - it is excreted quickly from the liver
21. Which of the following statements best explains the biologic similarity between Tc-99m Sestamibi and Tl-201 Thallous Chloride?
- their myocardial uptake demonstrate some sensitivity to cellular viability
 - their myocardial extraction is similar
 - their redistribution properties are similar
 - they are both monovalent cations
22. Regarding radiotracer injection during pharmacologic stress imaging, tracer should be injected:
- 3 to 4 minutes after dipyridamole or adenosine infusion
 - immediately after adenosine infusion but during dipyridamole infusion
 - during adenosine infusion but 3 to 4 minutes after dipyridamole infusion
 - during dipyridamole infusion and during adenosine infusion
23. Each of the following statements expresses an advantage of Tc-99m Sestamibi except:
- dosage injection and imaging times can be remote from each other
 - myocardial perfusion and ventricular function can be assessed with one injection
 - ECG-gated wall motion studies can be done
 - a 1-day stress-rest sequence can be done which has the same diagnostic accuracy as a 1-day rest-stress sequence
24. Each of the following statements expresses an advantage of Tc-99m Teboroxime except:
- rapid turnaround of imaging studies is possible
 - first-pass ejection fraction is possible
 - imaging can be done at any convenient time after tracer injection
 - high myocardial extraction occurs at high blood flow rates
25. A patient with unstable angina who comes to the emergency room with chest pain could most conveniently be evaluated for myocardial ischemia by which of the following agents?
- Tc-99m Teboroxime
 - Tl-201 Thallous Chloride
 - Tc-99m Sestamibi
 - Tl-201 Thallous Chloride and Tc-99m Teboroxime

