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Primer on Cardiac Imaging

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PRIMER ON CARDIAC IMAGING

STATEMENT OF OBJECTIVES

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

1. Explain the physiologic basis of myocardial perfusion imaging.
2. Compare and contrast the radiopharmaceuticals used in myocardial perfusion imaging.
3. Compare and contrast the methods used to induce cardiac stress in myocardial perfusion imaging.
4. Describe the methods used to perform myocardial perfusion imaging.
5. List the agents used to induce pharmacologic stress and discuss their side effects, precautions, and limitations of use.
6. Describe the radiopharmaceuticals and methods used in myocardial ventriculography studies.
7. Describe the biochemical mechanisms involved with radiopharmaceuticals used in myocardial viability and metabolism studies.
8. Describe the mechanisms of localization of radiopharmaceuticals used in myocardial perfusion imaging and infarct-avid imaging.
9. Describe the strengths and limitations of SPECT and PET myocardial imaging agents for the diagnosis of heart disease.

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INTRODUCTION

Cardiac imaging has played a key role in the diagnostic workup of patients with heart disease. The use of radiotracers in nuclear medicine for the diagnosis of heart disease began its major development in the 1970's. During this time agents were introduced for infarct-avid imaging and myocardial perfusion imaging. Initially, infarct-avid imaging with ^{99m}Tc-pyrophosphate, was widely used. It provided an important contribution to the workup of patients who sustained an acute cardiac event because at the time there was a lack of sensitive diagnostic tests for identifying MI. Today, serum enzyme assays, such as CK-MB, myoglobin, and troponin, can provide the necessary information soon after the MI event. While infarct-avid imaging in nuclear medicine has declined over the years, perfusion imaging has expanded. Thallous chloride ^{201}Tl was introduced for myocardial perfusion imaging in 1975 and has remained an important radiopharmaceutical for this application despite the later introduction of ^{99m}Tc-labeled complexes. ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are currently the major myocardial perfusion agents used in single-photon emission computed tomography (SPECT) imaging. While these agents have significant imaging advantages over thallium, such as improved image resolution and the ability to assess ventricular function, thallium is still used for myocardial perfusion imaging and has an important role in the assessment of myocardial viability with SPECT.

In more recent years positron emission tomography (PET) imaging has commanded a greater role in cardiac imaging due to the establishment of cyclotrons in regional nuclear pharmacies and PET cameras in nuclear medicine facilities. Fluorodeoxyglucose labeled with fluorine-18 (^{18}F-FDG) is a glucose metabolism agent which is principally used for assessing myocardial viability, while ^{13}N-ammonia and ^{82}Rb-rubidium chloride are used for measuring myocardial perfusion. Other PET agents, such as ^{11}C-acetate and ^{11}C-palmitate, are used in the assessment of myocardial metabolism.

The radiopharmaceuticals for heart imaging fall into four main groups (1) blood flow agents to evaluate coronary artery blood flow and ischemia, (2) blood pool agents to evaluate heart function, (3) infarct-avid agents for myocardial infarction, and (4) metabolism agents to assess myocardial viability and metabolic processes (Table 1).

MYOCARDIAL IMAGING

The goals of cardiac imaging in nuclear medicine are broad, encompassing the assessment of the cardiac chambers, myocardial perfusion, metabolism, and infarction, with the major focus in current practice on the assessment of myocardial perfusion and ventricular function. 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 (revascularization), and monitoring the effects of treatment.

Table 1. Myocardial Imaging Agents

SPECT Agents	Application
^{99m}Tc-Red Blood Cells	Blood Pool Markers
^{99m}Tc-Pyrophosphate ^{111}In-Imciromab Pentetate* ^{99m}Tc-Glucaric Acid ^{99m}Tc-Annexin V	Infarct Avid Agents
^{201}Tl-Thallous Chloride ^{99m}Tc-Sestamibi ^{99m}Tc-Tetrofosmin ^{99m}Tc-Teboroxime* ^{99m}Tc-Nitrido dithiocarbamate [Tc-N-$(NOEt)_2$]	Perfusion Agents
PET Agents	**Application**
^{82}Rb-Rubidium Chloride ^{15}O-Water ^{13}N-Ammonia	Perfusion Agents
^{11}C-Acetate ^{11}C-Palmitate ^{18}F-Fludeoxyglucose (FDG)	Metabolism Agents

* No longer marketed in the U.S. (Reprinted by permission from Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine. © 2004 by the American Pharmacists Association).

The majority of clinical nuclear medicine studies today use SPECT methods for data acquisition; however, PET is increasing as centers with these capabilities become established. Approximately 30 to 60% of all nuclear medicine procedures involve cardiac studies. The majority (~84%) of these studies involve myocardial perfusion imaging, 15% are for radionuclide ventriculography, and the remainder are for miscellaneous studies, e.g., infarct imaging and metabolism studies.[1] Myocardial perfusion imaging provides information regarding coronary artery blood flow, an indirect measure of oxygenation and metabolism in the myocardium, while ventriculography studies provide information about cardiac function.

MYOCARDIAL BLOOD FLOW

Coronary artery disease (CAD) 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. 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 tissue dies. Clinically, it is important to distinguish between ischemic and infarcted myocardium because ischemic, and therefore, viable myocardium can be restored to health by medical and surgical intervention.

Resting myocardial blood flow to most regions of the left ventrical ranges from 0.6 to 0.8 mL/min/g.[3] At rest, the oxygen extraction efficiency of the heart is about 70%, compared with 20% for skeletal muscle.[4] Consequently, an increased myocardial oxygen demand necessitates increased coronary blood flow. Coronary blood flow can increase in almost direct proportion to the metabolic consumption of oxygen by the

heart. Under normal conditions and following appropriate stimuli, such as exercise or the administration of specific pharmacologic agents, blood flow can increase 5 to 6 fold, or up to 3 to 4 mL/min/g[3]. However, in the clinical setting with healthy volunteers and patients, maximal induced flows are typically in the range of 2 to 4 times baseline.[5-7] The difference between baseline flow and maximal flow is known as *coronary flow reserve*. This reserve is progressively lost as vessels become stenosed and hardened by atherosclerosis.

Studies in dogs have shown that *resting* coronary blood flow does not change until coronary arterial stenosis exceeds 85%, whereas *maximal* coronary blood flow begins to decrease when stenosis exceeds 45%.[8] Thus, only the most severe coronary obstruction will likely be detected by perfusion imaging under resting conditions. It follows then that assessment of regional myocardial perfusion under conditions of cardiac stress would substantially increase the sensitivity for detecting obstructive CAD. Indeed, perfusion abnormalities can be detected in patients whose coronary arterial lumen diameter is reduced by 50%, but patients are usually asymptomatic.[1] When lumen diameter is reduced by 70%, however, clinical symptoms of chest pain (angina) become evident during myocardial stress because tissue oxygenation is temporarily below that required for myocardial function. Therefore, nuclear medicine procedures are typically conducted in conjunction with cardiac stress, induced either by exercise or through the use of pharmacologic agents, to identify regions of subcritical coronary arterial stenoses that may be candidates for reperfusion.

During maximal coronary artery dilatation following exercise or pharmacologic stress, a greater portion of the increased blood flow to the heart goes to normally perfused myocardial regions, with lesser amounts going to those regions of the myocardium supplied by stenosed coronary vessels due to their limited vasodilatory reserve (Figure 1).[8] The basis for detecting CAD with cardiac stress imaging is founded on the ability to detect the difference in blood flow between well-perfused and poorly-perfused myocardium. Early on it was shown with ^{201}Tl-thallous chloride that imaging defects are detectable during induced hyperemia when flow into normal coronary vessels exceeds that into stenotic vessels by a ratio of 2.4 or greater.[9] The methods for inducing cardiac stress used in nuclear medicine imaging procedures are capable of achieving this blood flow differential.

VIABILITY

Myocardial cells are considered to be nonviable when some basic aspect of cell behavior no longer functions.[8] The uncorrected progression of atherosclerosis and myocardial ischemia can result in electrical conduction abnormalities with loss of contractile function in the affected tissue. However, the loss of functional integrity can be reversed if blood flow is restored to the ischemic regions of viable myocardium. Two primary cellular functions can be used to measure viability: membrane ion transport and intermediary metabolism.[8] Under normal circumstances the Na-K-ATPase membrane pump maintains cell function and volume by maintaining high extracellular Na^+ and high intracellular K^+ concentrations (Figure 2).[9] During ischemia it is believed that the energy available for the pump is decreased so that Na^+, along with Cl^- and water, accumulate within the cell, while K^+ leaks out into the extracellular space. This process decreases the intracellular-extracellular K^+ concentration differential and produces a marked effect on membrane polarity and cardiac muscle function. This disparity in ion shift forms the basis for using potassium analogs such as $^{201}Tl^+$ and $^{82}Rb^+$ for imaging. These agents participate in the ion

Figure 1. Schematic representation of the principle of rest/stress myocardial perfusion imaging. (Top) Two branches of a coronary artery are shown; one is normal (left) and one has a significant stenosis (right). (Middle) Myocardial perfusion images of the territories supplied by the two branches. (Bottom) Schematic representation of coronary blood flow in the branches at rest and during stress. At rest, myocardial blood flow is equal in both coronary artery branches. When a myocardial radiotracer is injected at rest, uptake is homogeneous (normal image). During stress, coronary blood flow increases 2.0 to 2.5 times in the normal branch, but not to the same extent in the stenosed branch, resulting in heterogeneous distribution of blood flow. This heterogeneity of blood flow can be visualized with ^{201}Tl, ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin as an area with relatively decreased uptake (abnormal image with a myocardial perfusion defect). (Modified from original and reprinted by permission of the Society of Nuclear Medicine from: Wackers FJTh. Exercise myocardial perfusion imaging. *J Nucl Med* 1994;35: 726-29.)

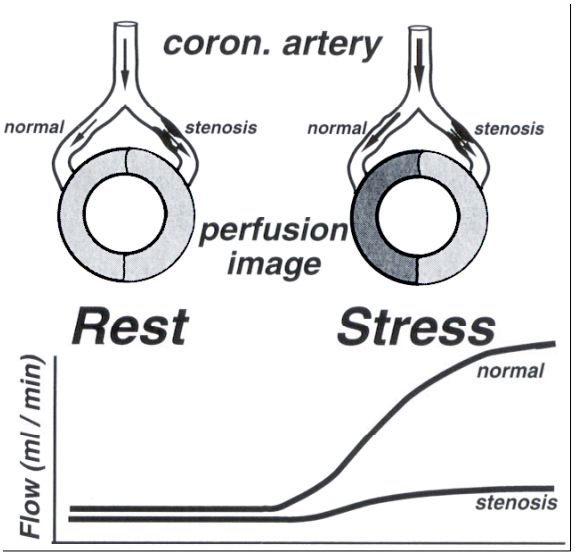
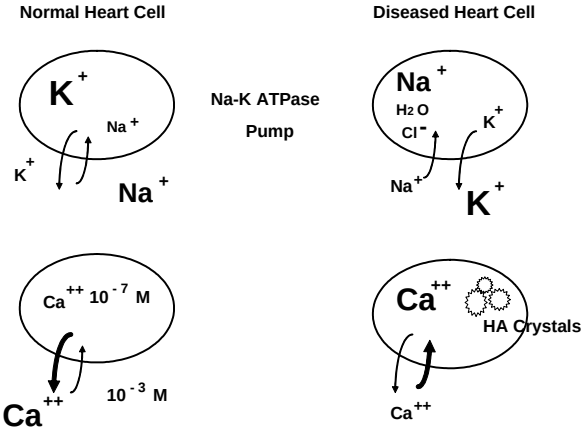


Figure 2. Diagrammatic representation of sodium, potassium, and calcium ion transport between myocyte cytoplasm and interstitial fluid demonstrating alterations in ion concentration in normal and necrotic cells. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).



transport process similar to potassium and are able to assess membrane integrity and cellular viability.[8]

Under resting conditions the myocardium derives the majority of its energy by the aerobic metabolism of fatty acids.[9] More than 95 percent of the energy liberated during metabolism is in the form of ATP. However, during hypoxia or ischemia, glucose becomes an important source of energy. There are several functions involved in intermediary metabolism that can be exploited for assessing myocardial viability. They include glucose utilization measured by FDG uptake, fatty acid metabolism measured by ^{11}C-palmitate uptake, and oxygen consumption measured by ^{11}C-acetate uptake.[10] Each of these agents has been used with PET, but the most useful of them is FDG. Thallium, as a membrane viability agent has been compared with FDG as a metabolism marker and these agents were shown to be equivalent for assessing myocardial viability under the proper conditions.[11]

CARDIAC STRESS METHODOLOGY

Two conditions are required for valid measurement of coronary blood flow deficit: (1) maximum coronary blood flow and, (2) use of a radiotracer whose myocardial extraction is proportional to coronary artery blood flow. The key aspect of perfusion imaging is the induction of a disparity of flow between well perfused and poorly perfused myocardium. Under these circumstances, radiotracer uptake will be increased in normally perfused regions of the heart whereas regions supplied by stenosed arteries will demonstrate a decreased uptake of radiotracer (Figure 1). The current methods employed to achieve maximal coronary dilatation are intense exercise or administration of pharmacologic agents that increase blood flow either through coronary vasodilatation or increased cardiac output.

Exercise Stress

Exercise is a natural method of stress that increases cardiac work and metabolic demand on the heart. When challenged by an increased physical workload, segments of the myocardium perfused by stenotic arteries are likely to become ischemic because of inadequate blood flow to meet oxygen demand. Ischemic cells lose their ability to retain ion-transport radiotracers (e.g., $^{201}Tl^{+}$) because of altered membrane integrity. Therefore, ischemia is readily detected following exercise because less tracer is localized in these regions due to reduced tracer delivery (low blood flow) and reduced tracer extraction (leaky cells).

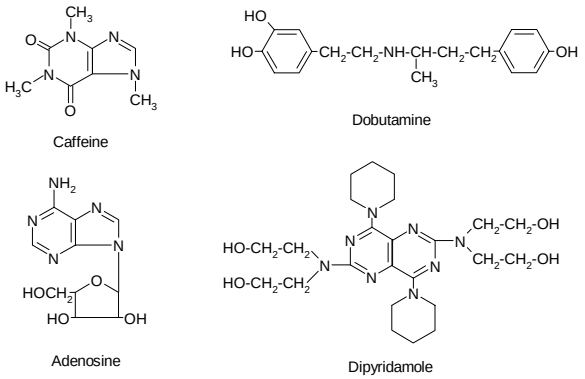
In general, treadmill exercise is used according to the modified Bruce protocol.[12] The method increases the speed and grade of the exercise in a stepwise manner to achieve the required workload on the heart. The desired endpoints are an age-related heart rate ≥ 85% of maximal predicted rate (220 minus the patient's age in years) and a double-product (heart rate x systolic BP) of ≥ 25,000. Heart rate[13] and double-product[14] have been shown to increase linearly with workload, and coronary blood flow is closely related to the double-product.[15] In general, exercise stress under this protocol increases blood flow to about 2 times the resting flow which is adequate for diagnostic evaluation. Exercise stress provides important prognostic information. Experience has shown that patients with CAD have a better survival rate if they can exercise longer than Stage IV of the Bruce protocol, achieve a heart rate >160 bpm at peak exercise, and show no ST-segment depression on an exercise ECG.[16]

A maximal increase in coronary blood flow following exercise may be difficult to achieve clinically because patients suspected of having heart disease often cannot achieve the intense level required to produce maximal coronary dilatation. Additionally, exercise cannot be used in some patients for reasons such as claudication, cerebrovascular accidents, arthritis, amputation, severe anxiety, or current use of beta-blocking medications.

Pharmacologic Stress

An alternative to exercise stress is pharmacologic stress with agents such as dipyridamole, adenosine, or dobutamine (Figure 3).[17-22] Dipyridamole and adenosine are coronary vasodilators. Following administration of either of these agents, normal vessels dilate maximally while stenosed, non-compliant vessels fail to dilate sufficiently, creating a pefusion deficit. Hence, a heterogeneity of blood flow to the heart is created relative to the severity of CAD. Maximal coronary dilatation is more consistently achieved with these agents than with exercise.

Figure 3. Chemical structures of caffeine and the pharmacologic interventional agents adenosine, dipyridamole, and dobutamine. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. © 2004 by the American Pharmacists Association).



Dobutamine is a predominant beta-1 agonist, increasing heart rate and myocardial contractility and systolic blood pressure.[22] Consequently, dobutamine increases myocardial oxygen demand, being more akin to exercise. Normal coronary arteries dilate to increase perfusion in order to meet the demand while stenotic arteries may not be able to increase flow to the same degree as normal vessels, creating a perfusion deficit similar to exercise stress.

Adenosine

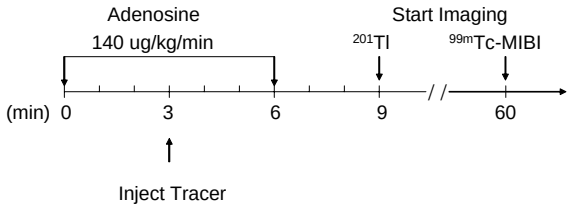
Adenosine is an endogenous nucleoside present in all cells of the body including the myocardium. In the heart it is involved with the autoregulation of coronary artery blood flow. It is produced by enzymatic dephosphorylation of ATP by 5′ nucleotidase. It has been shown that interstitial concentrations of adenosine rise in response to increased metabolic oxygen requirements or ischemia in the heart.[23] Adenosine readily diffuses into the interstitial space where it causes vasodilation by activating receptors on coronary endothelial cells and by increasing intracellular cAMP. Its half-life is very short, reported to be between 4 and 10 seconds.[24,25]

Adenosine's stimulatory effect is blocked by methylxanthine compounds such as caffeine, theophylline, and aminophylline.[26] Food or beverages containing caffeine or methylxanthine medications must be discontinued for at least 12 hr prior to adenosine administration. Patients taking oral dipyridamole should discontinue this medication for 12 hours before adenosine stress testing because of potentiation.[18]

Adenosine also causes a slowing of electrical conduction through the atrioventricular node, potentially causing mild to severe heart block. Thus, the use of adenosine (and dipyridamole) in patients with these conditions should be approached with caution or may be contraindicated.[27] Adenosine has been shown to cause bronchospasm in asthmatic patients. Both dipyridamole and adenosine are contraindicated in these patients.[28,29]

For cardiac imaging, adenosine is administered at a standard dosage of 0.14 mg/kg/min for a total of 6 minutes (Figure 4). The radiotracer is injected 3 minutes into the infusion when maximum vasodilation is predicted. Adenosine infusion is continued for 3 additional minutes to facilitate tracer uptake and localization in the myocardium under the stress condition. Following cessation of the adenosine infusion, imaging can begin within a few minutes with ^{201}Tl, or at later times (30 to 60 minutes) with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin, to allow for hepatobiliary clearance of these agents.[30] Thallium imaging must commence and be completed before significant redistribution occurs, whereas the ^{99m}Tc agents are more firmly fixed in the heart and imaging can begin once background activity clears. With the standard dosage of adenosine, it is reported that 84% of normal patients achieve an average coronary vasodilation equal to 4.4 times the resting coronary blood flow.[23]

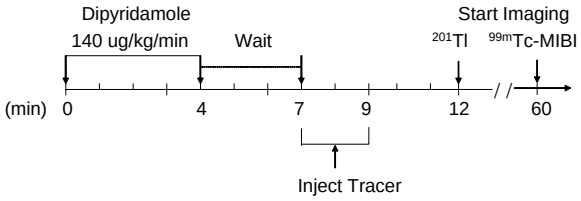
Figure 4. Adenosine dosing, radiotracer injection, and imaging protocol during pharmacologic stress imaging. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).



Dipyridamole

Dipyridamole increases plasma adenosine levels indirectly by inhibiting adenosine's metabolism. The standard dosage of dipyridamole is 0.56 mg/kg administered over 4 minutes. Because its action is indirect, dipyridamole is predicted to achieve its maximum dilator effect 6 to 8 minutes after the start of infusion. This dilator effect is sometimes indicated by a drop in blood pressure and a rise in heart rate.[31] It increases coronary blood flow about 4 times baseline, similar to adenosine. The radiotracer should be injected when maximal effect is anticipated, about 7 minutes after the start of infusion (Figure 5). Imaging with ^{201}Tl is begun at about 12 to 15 minutes from the start of infusion and at later times (approximately 60 minutes) with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin. The plasma half-life of dipyridamole is about 30 minutes.[28] Therefore patients must be monitored following administration of dipyridamole for about 20 minutes because ischemia may be induced.[17] Some institutions routinely administer 50 to 100 mg of aminophylline intravenously 5 minutes after tracer injection to reduce the incidence of dipyridamole-induced ischemia. If a patient complains of shortness of breath or wheezes, dipyridamole administration should be halted and aminophylline administered immediately.[17]

Figure 5. Dipyridamole dosing, radiotracer injection, and imaging protocol during pharmacologic stress imaging. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).

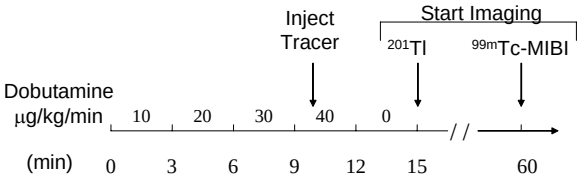


Technetium-99m agents have more uptake in the splanchnic bed than ^{201}Tl.[17] An intervention to reduce this uptake is mild hand-grip exercise or walking, which stimulates the release of catecholamines that will reduce sphanchnic blood flow and activity accumulation in this area when dypyridamole is used.[17]

Dobutamine

Being principally a beta-1 agonist, dobutamine causes a combined positive ionotropic and chronotropic effect on the myocardium, increasing contractility and oxygen demand and causing coronary vasodilation. A general imaging protocol is to administer the dosage slowly, ramping up in 10 μg/kg/min steps every 3 minutes for 12 minutes to a maximal dose of 40 μg/kg/min (Figure 6).[22] The radiotracer is injected 1 minute after the highest dose is begun (~ 10 minutes from start of infusion) and the dobutamine infusion is continued for 2 minutes while tracer is localizing in the myocardium. If heart rate is less than 85% of the predicted rate after the maximal dose of dobutamine, atropine 0.2 to 1 mg IV may be administered.[32] [32] Imaging with ^{201}Tl is begun at about 3 minutes following cessation of infusion while imaging with ^{99m}Tc agents is begun in 60 minutes. The plasma half-life of dobutamine is 2 minutes.

Figure 6. Dobutamine dosing, radiotracer injection, and imaging protocol during pharmacologic stress imaging. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).



Precautions, Side Effects, and Contraindications

Adenosine, dipyridamole, and dobutamine are potent pharmacologic agents that should be administered with caution and full awareness of their side effects and potential toxicities. Blood pressure, heart rate, and a 12-lead ECG should be monitored continuously. An electronic infusion pump should be used to administer these agents to provide precise control.[33]

The relative merits of adenosine and dipyridamole have been compared[34] and their adverse effects have been reported.[35-37] The most common side effects of dipyridamole and adenosine are chest pain, headache, dizziness, flushing, dyspnea, ST-T changes on ECG, and ventricular extrasystoles. Other effects occurring with less incidence include nausea, hypotension, and tachycardia (Table 2). These effects are related to the plasma level of vasodilator and may be readily reversed, in the case dipyridamole by giving intravenous aminophylline (50 to 100 mg IV), or for adenosine by simply stopping the infusion because of its short plasma half-life. Because of dipyridamole's long half-life patients who receive it should be monitored for potential drug-induced ischemia before being released from the nuclear medicine department. Adenosine and dipyridamole should be used with caution in patients with heart block and both agents are contraindicated in asthma and COPD.

Table 2. Percent of Reported Side Effects of Pharmacologic Agents

Effect	Adenosine[a]	Dipyridamole[b]	Dobutamine[c]
Flushing	36.5	3.4	14
Dyspnea	35.2	2.6	14
Chest Pain	34.6	19.7	31
Gastrointestinal	14.6	5.6	-
Headache	14.2	12.2	14
Dizziness	8.5	11.8	4
Palpitation	-	-	29

Data from; a. Ref 34; b. Ref 32; c. Ref 35 (Reprinted by permission from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).

The distribution of cardiac output to various organs is different with adenosine and dipyridamole than with exercise stress.[2] The relative blood flow to abdominal viscera increases with these agents, whereas with exercise it decreases. Thus, perfusion imaging agents, particularly ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin, will tend to accumulate in the liver and spleen areas to a greater extent with adenosine and dipyridamole than with exercise. This visceral activity may interfere with assessing perfusion of the inferior wall of the left ventricle.[2] Additionally, adenosine and dipyridamole will not work effectively if patients have taken caffeine or other methylxanthine substances as noted above and these substances are contraindicated for vasodilator studies.

Dobutamine is not affected by caffeine or methylxanthine drugs and is an alternative if adenosine or dipyridamole are contraindicated. The principal side effects of dobutamine are chest pain, palpitation, headache, flushing, and dyspnea (Table 2).[38] These effects should readily abate with cessation of the infusion. However, the beta-1 blocking

agent esmolol should be available if problems arise. Its recommended loading dose is 0.5 mg/kg/min for 1 minute followed by 0.05 mg/kg/min for 4 minutes as a maintenance dose. Dobutamine is contraindicated for the same conditions that apply to exercise stress.

MYOCARDIAL EXTRACTION

The principal uptake mechanisms of perfusion tracers are active transport, via the Na-K ATPase pump by monovalent cations, and passive diffusion of lipophilic compounds. A primary requirement for a useful myocardial perfusion tracer is high extraction efficiency proportional to blood flow over the range of flows seen clinically and heart retention long enough to conduct imaging studies. Myocardial extraction versus flow has been measured for several perfusion tracers.[39-41] Most diffusible tracers used clinically have extraction fractions that decline as blood flow increases because the time available for tracer exchange at the capillary surface is shortened. Thus, tracer uptake becomes diffusion-limited at higher flows.[40-43] This diffusion limitation, however, does not present a problem with the clinical use of flow markers in nuclear medicine procedures.

Once a radiotracer is localized it must remain fixed for the period of time required for imaging, otherwise a correction must be made for back-diffusion of tracer. For example, imaging with ^{201}Tl must be completed within about 45 minutes following injection because of its redistribution over time. ^{99m}Tc-teboroxime requires completion of imaging within 10 to15 minutes of injection due to rapid back-diffusion. However, this agent is no longer marketed. Technetium-99m-labeled sestamibi and tetrofosmin have relatively long myocardial retention, which is an advantage if repeat imaging is required.

Uptake of activity by the myocardium is a function of tracer delivery and extraction. Retention of activity is a function of tracer back-diffusion and binding to myocytes. Each of these processes can be affected by disease. The mechanism of localization of perfusion imaging agents is different and will be discussed later in the text. While thallium is taken up by active transport via the Na-K-ATPase membrane pump, it is retained longer than potassium. Thallium is not bound to myocytes and eventually diffuses back out of these cells proportional to blood flow.[44] Technetium-99m-labeled sestamibi, as a lipophilic mono-valent cation, is taken up into myocytes by passive diffusion associated with negative plasma and mitochondrial membrane potentials. Sestamibi retention is dependent on maintenance of these membrane potentials.[45] Technetium-99m tetrofosmin uptake is also associated with membrane potential-driven transport mechanisms and its retention is long.

SPECT RADIOPHARMACEUTICALS

Myocardial perfusion imaging agents, or "cold spot" markers, demonstrate decreased accumulation of activity in poorly perfused regions of myocardium. Early on, several radioisotopes of potassium and its monovalent cation analogs were investigated for myocardial perfusion studies.[46] Potassium-43 had the disadvantages of beta particle decay and high photon energy (619 keV) that degraded image resolution. Of the potassium analogs, ^{201}Tl gained clinical acceptance because it has rapid blood clearance, high myocardial extraction, and a reasonable shelf-life. However, its low-energy photons produce poor quality images compared to ^{99m}Tc agents, and its long retention time in the body limits the amount of activity that can be administered safely.

The limitations of thallium led to the development of ^{99m}Tc-labeled complexes that would allow administration of larger amounts of activity with improved image quality and lower radiation dose. Early studies with ^{99m}Tc-DMPE, a phosphine com-

pound, demonstrated that this complex could image the human myocardium but intense liver uptake obscured the cardiac apex. Heart-to-liver ratios in man were much less than in the dog, creating inferior images to those obtained with thallium. In 1982 Jones prepared ^{99m}Tc-sestamibi.[47] This stable Tc(I) complex was easy to prepare, and achieved myocardial uptake proportional to blood flow when compared to ^{201}Tl.[48] Technetium-99m-teboroxime was developed in 1989.[49] It is a complex of Tc(III) known as a boronic acid adduct of technetium dioxime (BATO). The complex is neutral and lipophilic with very high extraction by the myocardium proportional to blood flow. However, its rapid washout presented logistical problems for imaging. ^{99m}Tc-sestamibi and ^{99m}Tc-teboroxime were approved for routine use by the Food and Drug Administration (FDA) in December 1990. Subsequently, ^{99m}Tc-tetrofosmin was developed and approved for use by the FDA in 1996. It is a phosphine complex of Tc(V), that exhibits similar biological properties to ^{99m}Tc-sestamibi.[50,51] The sestamibi and tetrofosmin agents were shown to be comparable to ^{201}Tl-thallous chloride in myocardial perfusion imaging but their heart activity was fixed and did not show redistribution as did thallium. Thus, while a thallium stress-rest imaging protocol can be accomplished with one dose of thallium because of its redistribution in the myocardium, two separate doses of the technetium agents must be administered, one at stress and one at rest.

Thallous Chloride Tl 201 Injection

Thallium is a potassium analog localizing in the heart in proportion to myocardial blood flow. Following intravenous administration ^{201}Tl disappears rapidly from the blood. In the resting state, 90 percent of the plasma activity disappears by 20 minutes, but under stress the same percentage of activity disappears by 1.5 minutes.[52] Maximum myocardial uptake occurs in 10 to 30 minutes in the resting state and by 5 minutes during exercise stress. In humans about 4% of the injected dose (ID) is localized in the heart. The heart activity is sustained long enough after exercise stress so that imaging can be performed, but by 30 minutes after injection thallium's rate of release from the heart parallels the loss of activity from the blood pool. Consequently, redistribution of thallium activity from the heart requires that imaging be completed within this time frame following radiotracer injection.The half-life from the heart following intravenous injection in clinical studies is 4.5 to 8 hours.[44] Under normal coronary blood flow thallium's extraction fraction is about 85%. However, its extraction is not proportional to blood flow, being only 60% higher when blood flow is increased 3 to 4 times normal following dipyridamole[53] or adenosine[54] administration. Nonlinear extraction begins to occur when blood flow is increased 2 to 2.5 times normal, which is about the level that flow increases with exercise stress during thallium imaging.[53]

Total body elimination of thallium is slow, with a biologic half-time of 10 days.[52] Only about 5% is excreted in the urine by 24 hours accompanied by insignificant fecal excretion. These factors plus the long physical half-life (73 hours) are undesirable properties of ^{201}Tl and contribute to its high radiation absorbed dose. The critical organs are the thyroid (2.3 rad(cGy)/mCi) and the testes (3 rad(cGy)/mCi). The effective dose is 1.3 rad(cGy)/mCi injected.

Following transcapillary diffusion from blood into the interstitial space, thallium is taken up into myocytes by the membrane-bound sodium/potassium ATPase pump due to a monovalent cationic charge and hydrated ionic radius similar to K^+.[54] While there is a close relationship between thallium uptake and blood flow, adequate tissue oxygenation to support cellular metabolism is also required for uptake.[55] A significant

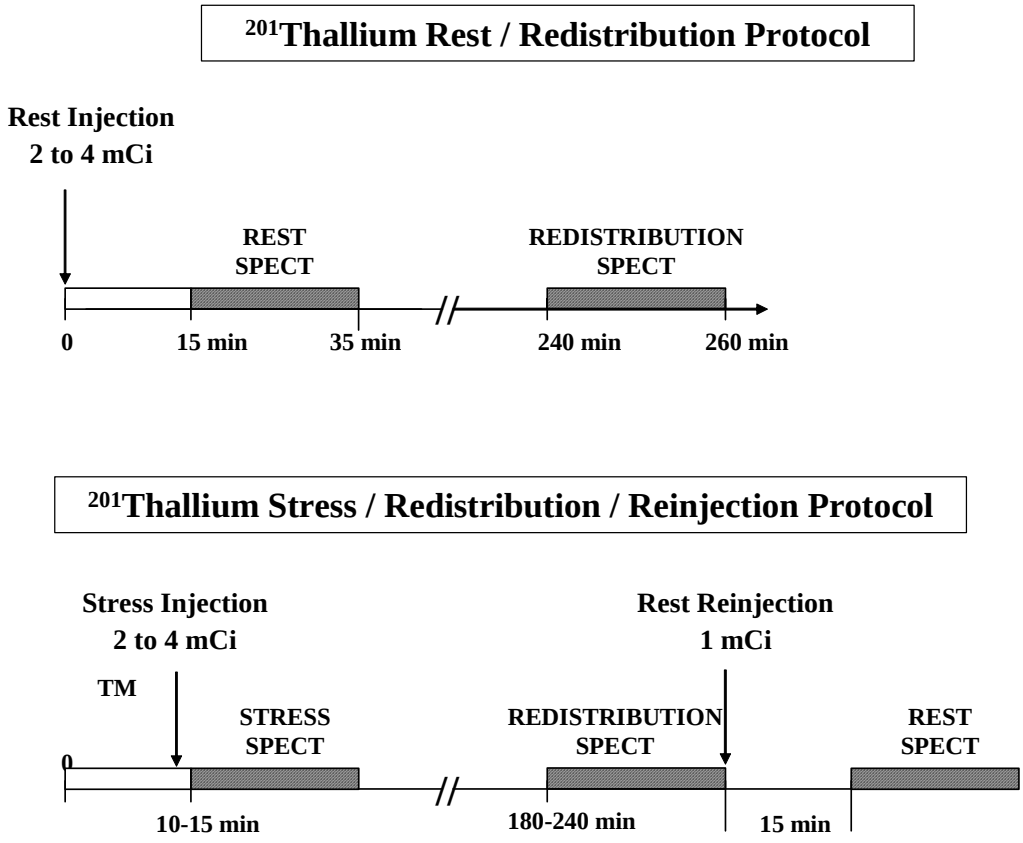
reduction in blood flow and an oxygen deficit leading to necrosis will impair this cellular uptake function. Since thallium uptake is dependent on adequate blood flow for its delivery to the myocardium and active transport across an intact sarcolemma, it is well suited as a marker of myocyte viability.

Thallium has been used as a marker of myocardial perfusion and viability for many years beginning in the mid 1970s.[56] The first thallium procedures were conducted with two separate injections; one injection for the exercise stress study and one injection for the rest study. The rest study was conducted 1 to 2 weeks after the stress study because of thallium's long effective half-life in the body. The thallium procedure changed to a 1-day protocol when it was observed that thallium redistributed in the heart over time. By 3 to 4 hours following an exercise study it was observed that normal myocardial regions demonstrated a decrease in thallium activity while ischemic regions increased in activity.[57] Subsequently, the standard procedure became a one-day thallium protocol (exercise study followed by a 3 to 4 hour redistribution study) to differentiate ischemia from infarction. This procedure was shown to provide an accurate assessment of myocardial viability when perfusion defects on the exercise study showed redistribution on delayed imaging. While this procedure had high sensitivity for predicting viability of reversible defects, its specificity for predicting non-viability of irreversible defects was found to be low.[58,59] Incomplete redistribution of thallium was believed to have occurred on the initial redistribution image, causing an overestimation of infarct size. Henceforth, late (8 to 24 hour) redistribution imaging was instituted to allow more time for thallium to redistribute.[60] Kiat demonstrated that 61% of irreversible thallium defects on 3- to 4-hour images reversed on late redistribution at 18 to 72 hours.[61] However, a high percentage of patients (37%) with apparent irreversible defects were able to achieve restored perfusion following myocardial revascularization procedures. Thus, although late imaging improved diagnosis, it still overestimated the frequency and severity of myocardial fibrosis.[61]

To improve specificity, a thallium reinjection technique was introduced to increase plasma levels of thallium during the redistribution phase of the study. Reinjection of 1 mCi (37MBq) of ^{201}Tl, either after the standard 3- to 4-hour redistribution study or after a late 24-hour redistribution study, facilitates uptake of thallium into many viable regions of myocardium with apparently irreversible defects. With this technique, up to 49% of apparent irreversible defects on the 4-hour redistribution study [62] and 39% of such defects on the 24-hour redistribution study [63] improved or showed normal uptake after thallium reinjection. A number of studies have also shown the ability of thallium reinjection to predict improved ventricular function following revascularization.[62,64-66] Thus, the thallium stress-redistribution-reinjection protocol has become a standard procedure for evaluating myocardial perfusion and viability.

A routine perfusion study with thallium is conducted in two parts. One of two protocols is typically used, depending on the information required (Figure 7). If only viability information is sought in a patient with known CAD and left ventricular dysfunction, a rest/redistribution protocol is preferred with a quantitative method of reversibility assessment. If viability is questionable on the 4 hour redistribution image, a repeat image at 24 hours is often done. If inducible ischemia and viability is the goal a stress-redistribution-reinjection protocol is preferred for assessment of the extent and severity of myocardial ischemia. Some institutions perform only a stress-reinjection protocol electing to skip the 4 hour redistribution image.

Figure 7. Thallium rest/redistribution imaging protocol and stress/redistribution/ reinjection imaging protocol. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).



In the rest-redistribution protocol the thallium dose is injected into a patient who has fasted for at least 4 hours. Imaging is begun 15 to 20 minutes post injection and proceeds for about 20 minutes. Perfusion deficits seen on the resting study that reverse on the 4-hour redistribution study may result from clearance of ^{201}Tl from normal regions and accumulation of ^{201}Tl in the defect region during the redistribution phase. Reversiblity of perfusion deficits indicates viable myocardium.

The first part of the stress-redistribution-reinjection protocol is designed to produce near maximal dilatation of the coronary vessels just prior to administration of the thallium dose (2 to 4 mCi [74 to 148 MBq]). Dilatation is achieved either through exercise or by administration of a pharmacologic agent (dipyridamole, adenosine, or dobutamine). Exercise stress should continue for 30 to 60 seconds following tracer injection to ensure heart uptake. Imaging should commence as soon as possible following tracer injection and by no later than 15 minutes. With pharmacologic stress, tracer injection and the start of imaging should follow the protocols given in Figures 4, 5, and 6. Under these conditions, thallium ion will be extracted by the myocardium in proportion to regional blood flow. Normally perfused myocardium will take up the radiotracer well, whereas poorly perfused (ischemic) or non-perfused (infarcted) myocardium will show decreased or absent radiotracer uptake, appearing as a perfusion

defect (Figure 8). After a 3- to 4-hour period of rest the redistribution study is performed. At this time the patient is re-imaged to assess myocardial redistribution of the ^{201}Tl activity administered during the stress study. Images of the heart are usually displayed in three planes as short axis, vertical long axis, and horizontal long axis views (Figure 9), with the stress images on top and the corresponding rest images underneath. During the rest phase, ^{201}Tl ion redistributes in the myocardium, washing out of normally perfused 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 (reversibility) in ischemic areas (Figure 10). When a stress perfusion defect does not reverse, thallium reinjection is done to improve specificity of the study (Figure 11). The patient is reimaged 15 minutes following the reinjection. The reinjection study can also be done the next day. A lack of reversibility on the reinjection image would indicate myocardial infarction (scar).

Technetium Tc 99m Sestamibi Injection

Technetium Tc-99m sestamibi (Cardiolite™, Dupont) is a monovalent cationic lipophilic complex comprised of a Tc(I) core coordinated by six monodentate, 2-methoxy-isobutylisonitrile (MIBI) ligands (Figure 12). Since the MIBI ligands are neutral, the ^{99m}Tc-sestamibi complex retains the single positive charge of the Tc^{+} core.

Figure 8. Model of the left ventricle (short axis view) at stress and at rest following a 4-hour redistribution of thallium ^{201}Tl in the normal heart, in heart with a region of significant stenosis, and in heart with a region of infarction. At stress, heart activity is at high count density in normal well perfused myocardium, at less density in stenotic regions that are poorly perfused, and absent in infarcted regions that are scarred. At rest (redistribution), normal myocardium washes out thallium more quickly than stenotic regions, appearing as a "filling in" of the stress defect in stenotic areas. A persistent defect remains in areas of infarct. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).

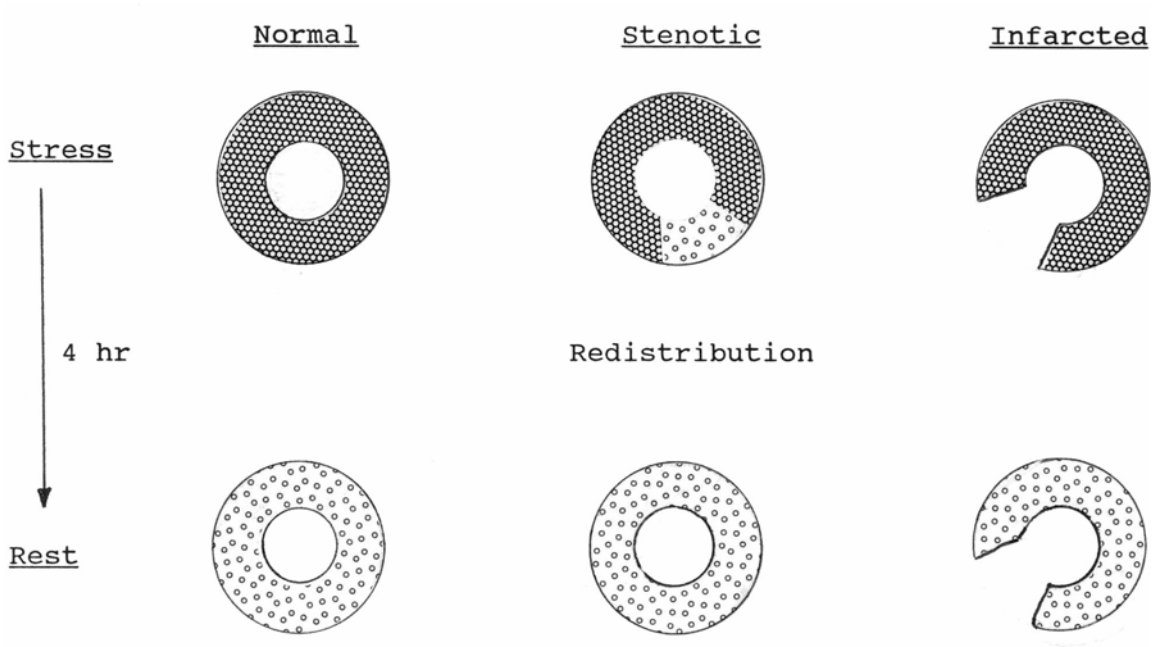
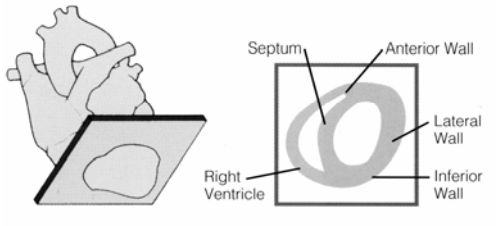
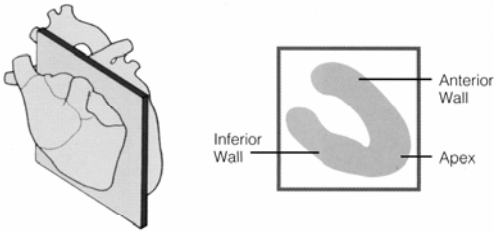


Figure 9. Cardiac tomography. Pictorial illustration of short-axis, vertical long-axis, and horizontal long-axis views of myocardial walls on SPECT imaging. (Reprinted by permission of Bristol-Meyers Squibb Medical Imaging).

Short Axis



Vertical Long Axis



Horizontal Long Axis

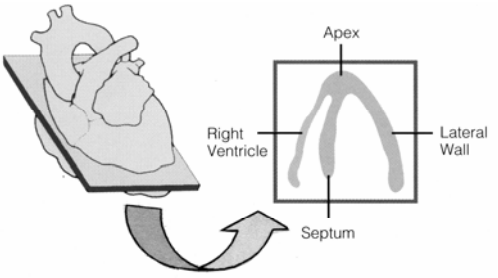


Figure 10. Adenosine stress and rest redistribution study following injection of 3 mCi (111 MBq) of ^{201}Tl-thallous chloride. Horizontal long-axis views demontrate normal perfusion evidenced by uniform uptake of activity throughout the left ventricle at stress and rest. Ischemia is noted by reduced perfusion and uptake of activity in the lateral ventricular wall during the stress image that fills-in at the 4-hour rest redistribution image. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).

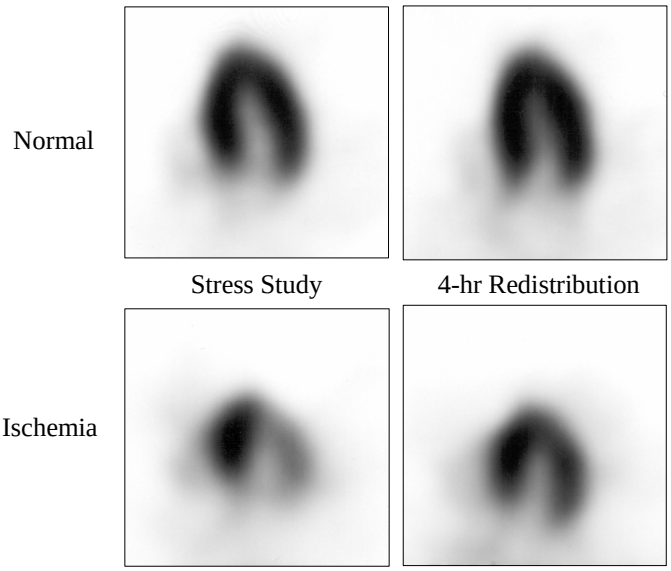


Figure 11. Adenosine ^{201}Tl stress/rest/reinjection myocardial perfusion study. The top two rows of short axis images show the stress images (top row) and redistribution images (second row) obtained 4 hours later. The images demonstrate perfusion defects involving the septum and inferior walls of the heart with poor washout over the 4-hour period. Reinjection images (bottom row) were obtained 24 hours later just after reinjection with 1 mCi (37 MBq) ^{201}Tl at rest. There is improvement in the septum and inferior walls consistent with ischemia and viable myocardium in these regions. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).

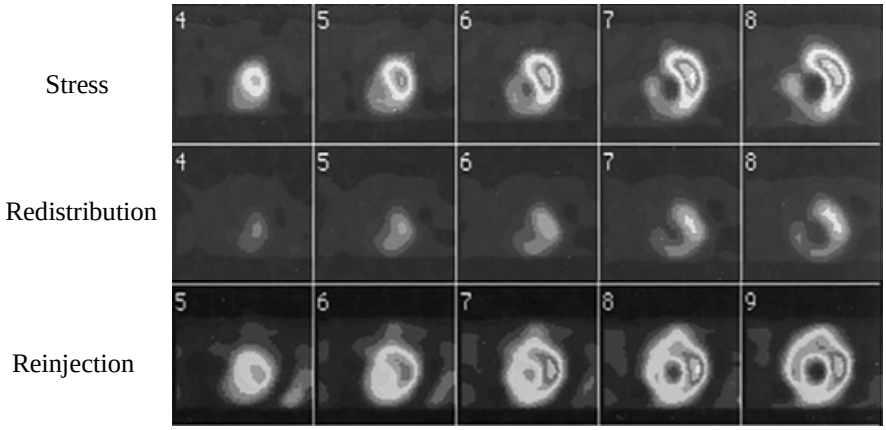
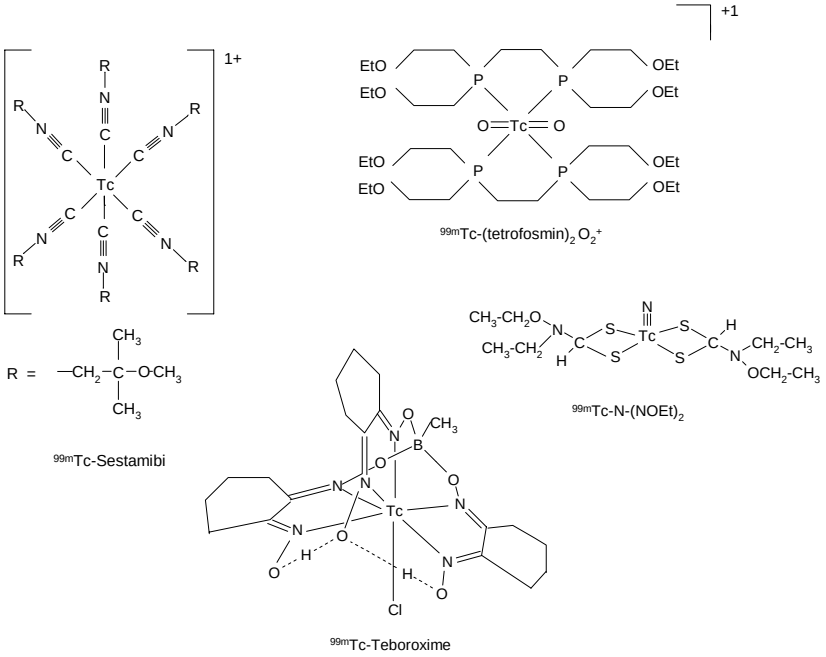


Figure 12. Chemical structures of various ^{99m}Tc-complexes used in mycocardial perfusion imaging. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).



Technetium Tc-99m sestamibi (Cardiolite, Dupont) injection is a sterile, aqueous solution prepared from a kit consisting of a lyophilized mixture of tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate (1.0 mg), sodium citrate dihydrate (2.6 mg), L-cysteine HCl monohydrate (1.0 mg), mannitol (20 mg), and stannous chloride dihydrate (0.025 to 0.075 mg) sealed under nitrogen. Following package insert instructions, ^{99m}Tc-sestamibi is prepared by adding 25 to 150 mCi (925 to 5550 MBq) of ^{99m}Tc sodium pertechnetate in 1 to 3 mL to the kit and mixing vigorously to dissolve the powder. The vial is then placed into a boiling water bath for 10 minutes. During this time the following reactions take place:

Step 1.

$$TcO_4^- + citrate \xrightarrow{Sn^{2+}} Tc - Citrate$$

Step 2:

$$\left[Cu(I)(MIBI)_4 + Tc - Citrate\right] \xrightarrow{heat} \left[Tc(I)(MIBI)_6\right]^+$$

The vial is allowed to cool 15 minutes before use. The labeled product is stored at 15 to 25°C and is stable for 6 hours. Its radiochemical purity must be ≥ 90%.

It is not uncommon for sestamibi kits to be compounded with amounts of ^{99m}Tc-sodium pertechnetate activity greater than the package insert limit, however this practice should be appropriately validated.

Technetium-99m sestamibi is indicated for imaging the heart to assess myocardial perfusion. Following intravenous injection, ^{99m}Tc-sestamibi clears rapidly from the blood and is extracted by the myocardium in proportion to blood flow up to 2.5 mL/min/g, or approximately 3 times resting flow. Its extraction fraction at rest is about 65%.[67] About 1% of the ID localizes in the heart at rest and remains relatively fixed in the myocardium. The uptake of ^{99m}Tc-sestamibi is about one-fourth that of ^{201}Tl, but the administered activity of ^{99m}Tc-sestamibi is much higher (10 to 30 mCi [370 to 1110 MBq]), improving count density in the heart during

imaging. When compared to thallium's low photon energy (69 to 80 keV) the 140 keV photons of ^{99m}Tc-sestamibi have less tissue attenuation and produce sharper, higher contrast images. Table 3 compares the general properties of ^{201}Tl and ^{99m}Tc for myocardial imaging studies and Table 4 compares the properties of myocardial perfusion imaging agents.

Table 3. Comparison of Tl-201 and Tc-99m for Myocardial Perfusion Imaging

Property	Thallium-201	Technetium-99m
Photon Energy	69 – 80 keV Scatter and absorption Low resolution	140 keV Less scatter and absorption High resolution
Half-life	73 hr Low dosage (2 – 3 mCi) Long collection times Low count densities	6 hr High dosage (20 – 30 mCi) Short collection times High count densities
Effective Dose	1.3 rad(cGy)/mCi	1.1 rad(cGy)/mCi
Availability	Cyclotron-Commercial Mfr	Generator-local
First-pass Study	No	Yes
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Table 4. Myocardial Perfusion Imaging Agent Properties

Property	Tl-201 Chloride	Tc-99m Sestamibi	Tc-99m Tetrofosmin
Chemistry	+1 Cation Hydrophilic	+1 Cation Lipophilic	+1 Cation Lipophilic
Shelf Life	6 days after calibration	6 hours	12 hours
Photon Energy (abundance)	68 – 80 keV (94%)	140 keV (88%)	140 keV (88%)
Uptake Mechanism	Active Na-K ATPase Pump	Passive Diffusion (associated with intact membrane potentials)	Passive Diffusion (associated with intact membrane potentials)
Extraction Fraction	~ 85%	~ 65%	~60%
Heart Uptake (% Injected Dose)	~ 4%	~ 1.2%	~ 1.0%
Administered Activity	2 – 4 mCi (74 - 148 MBq)	10 – 30 mCi (370 – 1110 MBq)	10 – 30 mCi (370 – 1110 MBq)
Heart Distribution	Redistributes	Fixed (mitochondria associated)	Fixed (cytosol associated)
Effective Dose	1.3 rad(cGy)/mCi	0.056 rad(cGy)/mCi	0.041 rad(cGy)/mCi
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Myocardial uptake studies indicate that ^{99m}Tc-sestamibi enters the myocardium by passive diffusion due to its lipophilicity and is retained for a prolonged period of time. In isolated, cultured chick myocytes, uptake was shown to be related to the integrity of myocyte plasma and mitochondrial membrane potentials.[68] Subcellular distribution studies in rat heart demonstrate that approximately 90% of ^{99m}Tc-sestamibi is associated with mitochondria in an energy-dependent manner as a free cationic complex.[69] The attraction of ^{99m}Tc-sestamibi to mitochondria is promoted by a negative potential generated in the mitochondrial membrane of viable myocytes, implying that ^{99m}Tc-sestamibi is a marker of myocardial viability and perfusion.[68,69] Other studies show that the uptake of ^{99m}Tc-sestamibi by the heart is not affected by oubain. This suggests that the localization in the myocytes is not exclusively due to the action of the sodium/potassium ATPase membrane pump.[70]

In humans, the mean heart retention of ^{99m}Tc-sestamibi is 1 ± 0.4% of the ID 60 minutes after intravenous injection at rest, and 1.4 ± 0.3% following exercise.[48] Activity that is fixed in the myocardium demonstrates insignificant redistribution.[71-73] Following intravenous injection, over 90% of ^{99m}Tc-sestamibi clears from the blood in less than 5 minutes. Compared to ^{201}Tl, ^{99m}Tc-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.[48] Technetium-99m sestamibi is excreted intact principally by the kidneys and the hepatobiliary system. By 24 hours, urinary excretion is 30% and 24% of the ID following rest and exercise studies, respectively. By 48 hours fecal excretion is 37% at rest and 29% after exercise.[48] The lower fecal excretion after exercise is due to reduced splanchnic blood flow and lower liver uptake during exercise. The biologic half-life is about 6 hours from the heart and approximately 0.5 hr from the liver following rest or exercise.[74] Thus, the heart-to-liver ratios at 30, 60, and 120 minutes are 0.5 , 0.6, and 1.1, respectively after a rest injection, and 1.4, 1.89, and 2.3 after exercise injection. Therefore, rest imaging is best begun at 60 minutes or later after injection of ^{99m}Tc-sestamibi; however some practitioners shorten the dose-to-image time to 15 to 30 minutes for SPECT exercise studies because of higher heart-to-liver ratios. Dose-to-image time should be 45 to 60 minutes if adenosine or dipyridamole stress is used to allow more time for splanchnic activity to be cleared.

The critical organ following a rest injection is the upper large intestinal wall (3.7 rad(cGy)/20 mCi) and the effective dose is 1.11 rad(cGy)/20 mCi.[75]

Imaging with ^{99m}Tc-sestamibi is typically begun 60 minutes after a rest injection and about 30 minutes after an exercise injection. Because ^{99m}Tc-sestamibi does not redistribute appreciably, separate rest and stress injections are required to differentiate myocardial ischemia from 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.[30,76] With the 2-day protocol the patient is stressed, injected with 20 to 25 mCi (740 to 925 MBq) 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.[30] If the 1-day protocol is used, a rest-stress sequence is preferred (Figure 13). This is the most common procedure. A rest dose of 8 to 10 mCi (296 to 370 MBq) is injected and imaging is begun in 45 to 60 minutes. Following the rest dose image treadmill exercise is performed and a stress injection of 25 to 30 mCi (925

to 1110 MBq) is given followed by imaging in 15 to 30 minutes. The activity in the heart during the stress study overwhelms the residual activity from the rest dose because of the increased blood flow to the heart and the large stress dose administered. The 1-day procedure may take up to 2 to 3 hours to complete depending on the time needed to acquire patient images. 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.[30] If there are no perfusion abnormalities during the stress study, homogeneous uptake of radiotracer throughout the myocardium will be seen. In a normal study using a ^{99m}Tc agent, no perfusion abnormalities are seen on either the stress or rest images (Figure 14). Myocardial regions with relatively reduced radiopharmaceutical uptake on the stress portion of the myocardial perfusion study that normalize or partially normalize on the rest study represent regions of stress induced ischemia associated with flow-limiting coronary artery disease (Figure 15). Myocardial regions with fixed perfusion defects on both the stress and rest portions of the exam can represent either scarring from prior myocardial infarction (Figure 16) or possibly an attenuation artifact usually caused by the diaphragm or breast. Since ^{99m}Tc-sestamibi (and ^{99m}Tc-tetrofosmin) is fixed in the myocardium, a gated SPECT study would allow evaluation of fixed perfusion defects by examining myocardial wall motion and thickening. Fixed perfusion defects with associated normal wall motion and thickening are likely related to attenuation artifacts. Fixed defects with abnormal focal wall motion abnormalities and decreased thickening are generally associated with scar.

To improve patient throughput a 1-day stress-rest procedure was initially proposed, however it was shown to have a higher incidence of misinterpreting reversible defects as fixed when compared with the rest-stress procedure.[77] This problem was ascribed to stress dose crosstalk interfering with the later resting study[78] and to a lower count density from the low-activity stress dose administered.[30] Therefore this procedure is not recommended, but if done should be reserved for those patients with a low probability of disease in whom a normal initial stress study is anticipated.[78]

To improve patient throughput without compromising diagnostic accuracy a dual-isotope procedure has been developed (Figure 17).[30] In this procedure, ^{201}Tl is injected at rest and a ^{201}Tl-SPECT acquisition is made. The patient is then stressed on a treadmill and 25 to 30 mCi (925 to 1110 MBq) of ^{99m}Tc-sestamibi is injected. A SPECT stress image is then acquired 15 minutes after injection. The entire procedure can be completed in 1.5 to 2.0 hours.

There are several advantages afforded by ^{99m}Tc-sestamibi's lack of redistribution. Image acquisition can be repeated in the event of a positioning error, patient motion, or instrument malfunction. A second advantage is the ability to inject a patient during an acute ischemic event with imaging performed later at a more convenient time. An example of this is being able to rule out myocardial ischemia in patients with unstable angina who have spontaneous chest pain.[79] Technetium-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 scan strongly suggests that the pain is not of coronary origin. An abnormal scan may suggest 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 to determine the amount of myocardium

Figure 13. ^{99m}Tc-sestamibi one-day rest/ stress imaging protocol. (Modified and reprinted by permission of the Society of Nuclear Medicine from: Berman DS, et al. Myocardial perfusion imaging with technetium-99m-sestamibi: comparative analysis of available imaging protocols. *J Nucl Med* 1994;35:681-688.)

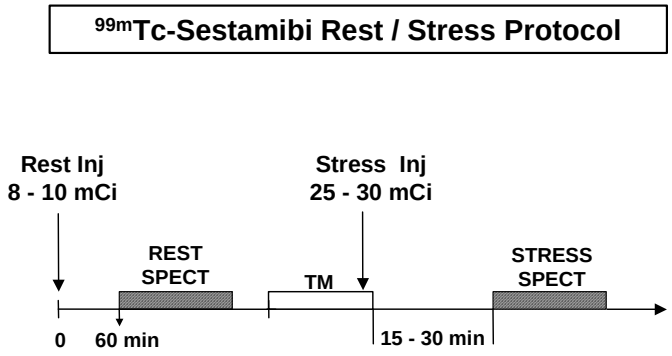


Figure 14. Normal ^{99m}Tc-sestamibi myocardial perfusion study. Images of the heart are shown in three planes. The top row represents short-axis views of the heart from apex on the left to mid-heart on the right at stress. Matching views on the rest portion of the study are shown on the next row. The third and fourth rows are continuation of the short axis views at stress and rest from the mid-heart to the base or valve plane. The next two rows (frames 29 – 37) are the vertical long axis views, stress on top and rest underneath. These views are from the septum on the left to the lateral wall on the right. The last two rows are the horizontal long axis views, stress on top and rest underneath. These views run from the inferior wall on the left to the anterior wall on the right. There are no significant perfusion defects seen either during stress or at rest to suggest flow-limiting coronary artery disease. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).

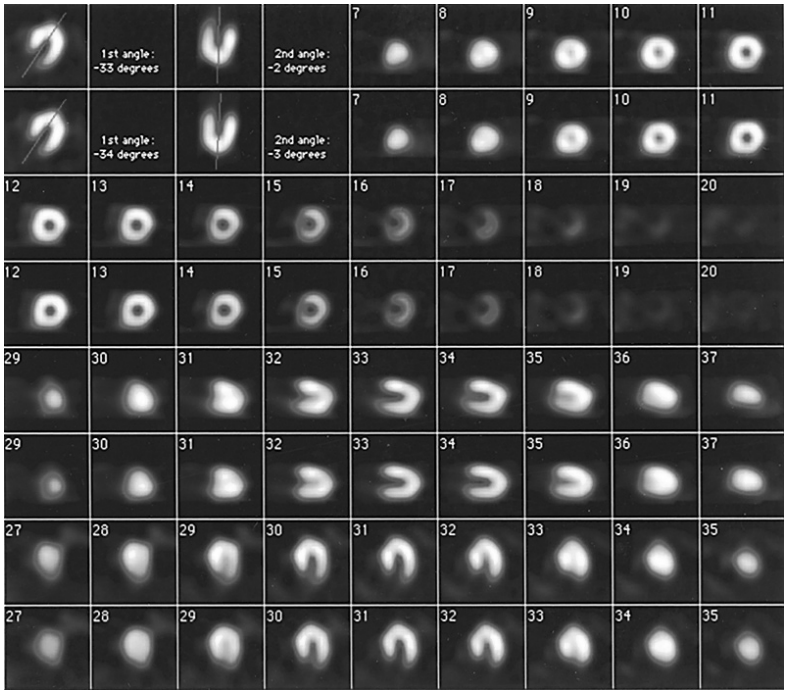


Figure 15. ^{99m}Tc-sestamibi study demonstrating myocardial ischemia. Short axis views at stress (top row) and at rest (bottom row). There are significant perfusion defects seen on the stress portion of the study that are not present at rest, consistent with multi-vessel flow-limiting coronary artery disease. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).

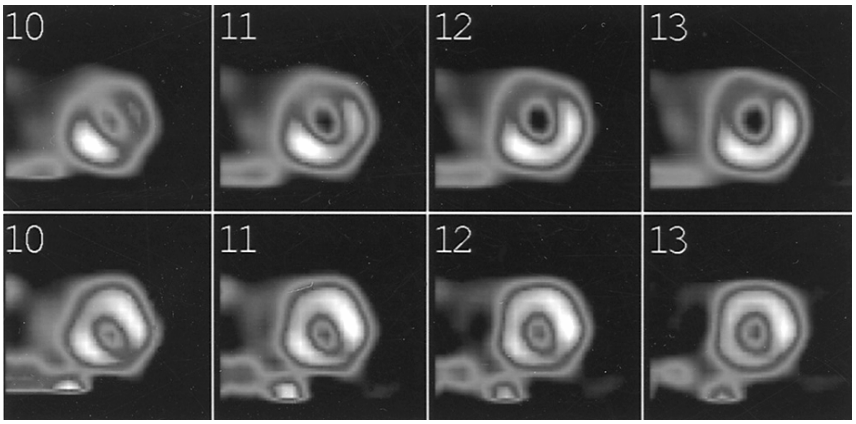


Figure 16. ^{99m}Tc sestamibi study demonstrating a fixed defect in the inferior wall both at stress and at rest. There was hypokinesis in the inferior wall on the gated images as well as decreased thickening in the inferior wall during systole most consistent with scarring from a prior myocardial infarction. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).

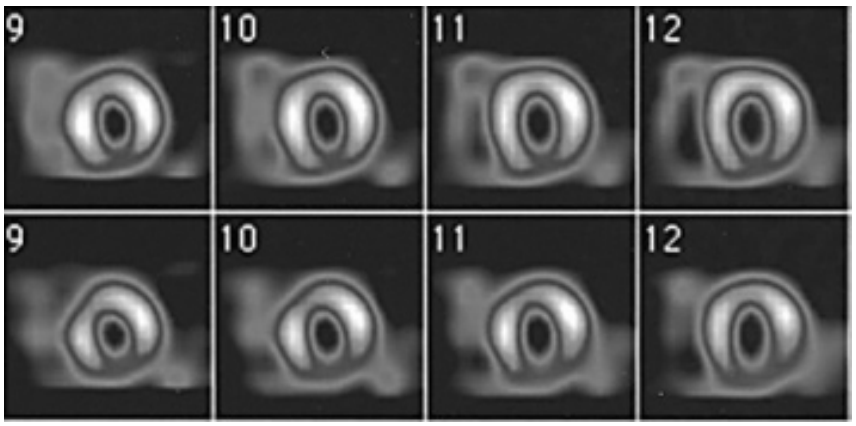
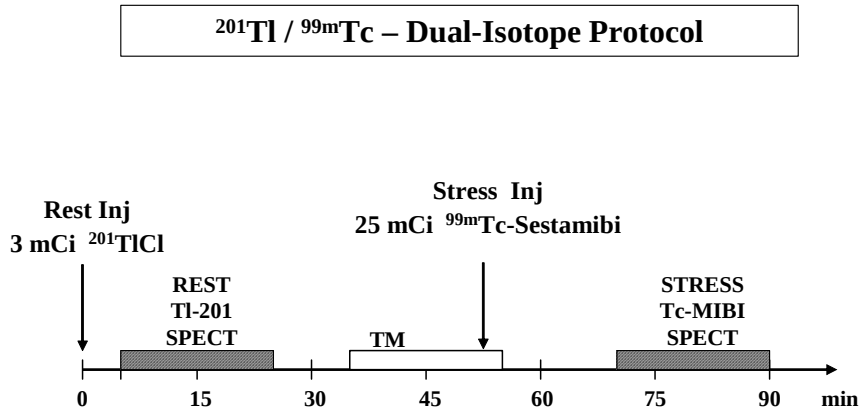


Figure 17. ^{201}Tl/^{99m}Tc dual-isotope imaging protocol. (Reprinted by permission of the Society of Nuclear Medicine from: Berman DS, et al. Myocardial perfusion imaging with technetium-99m-sestamibi: comparative analysis of available imaging protocols. *J Nucl Med* 1994;35:681-688.)



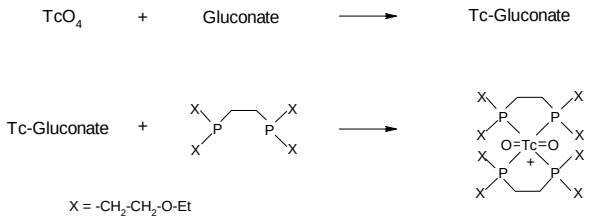
salvaged following thrombolytic therapy.[80] In this situation the patient is injected upon admission, thrombolytic therapy is begun and imaging is performed within 4 to 6 hours to identify infarcted plus jeopardized myocardium at the time of the event. A repeat study at a later date identifies only infarcted myocardium. Analysis of the two studies identifies the amount of muscle salvaged.

A third advantage of ^{99m}Tc-sestamibi is the ability to evaluate myocardial perfusion and ventricular function with a single injection of tracer by means of ECG gating. This permits the simultaneous evaluation of exercise perfusion with resting ventricular function, allowing an estimation of myocardial viability. An exercise perfusion defect with preserved regional wall motion at rest implies ischemia, whereas regional akinesis could be associated with either scar or severely ischemic or stunned myocardium.[78]

Technetium Tc 99m Tetrofosmin Injection

Technetium Tc-99m tetrofosmin (Myoview™, Amersham) is a monovalent cationic lipophilic complex of the Tc(V) dioxo core, $O = Tc = O^+$, and two bis(2-ethoxyethyl)phosphino]ethane ligands [Tc-(tetrofosmin)$_2$O$_2$]$^+$ (Figure 12).[50] Technetium Tc-99m tetrofosmin injection is a sterile, aqueous solution prepared from a kit containing a lyophilized mixture of tetrofosmin (0.23 mg), stannous chloride dihydrate (30 μg), disodium sulfosalicylate (0.32 mg), sodium D-gluconate (1.0 mg), and sodium bicarbonate (1.8 mg) sealed under nitrogen. The kit is stored at 2 to 8°C before reconstitution.

Following package insert recommendations the labeling of tetrofosmin is accomplished by introducing a venting needle into the kit and adding up to 240 mCi (8880 MBq) of ^{99m}Tc sodium pertechnetate (in 4 to 8 mL and not > 30 mCi (1110 MBq)/mL concentration). This is followed by removal of 2 mL of gas from the vial to introduce air and incubation at room temperature for 15 minutes. During this time the following reaction sequence occurs.



This reaction employs a gluconate transfer ligand to facilitate the complexation re-

action between the technetium oxo core and tetrofosmin. Since the tetrofosmin ligand is neutral the ^{99m}Tc-tetrofosmin complex has an overall charge of 1+ from the O = Tc = O^+ core. The labeled product is stored at 2 to 25°C after technetium labeling and is stable for 12 hours. Its radiochemical purity must be ≥ 90%.

Technetium-99m tetrofosmin is indicated for imaging the heart to assess myocardial perfusion. Its application is similar to that of ^{99m}Tc-sestamibi. Following intravenous injection in humans ^{99m}Tc-tetrofosmin clears rapidly from the blood and by 10 minutes post injection, less than 5% of the ID remains, with less remaining following exercise.[51] Uptake in skeletal muscle is the main reason for high background clearance after exercise. Following a rest injection, heart activity declines slowly over time, being 1.2%, 1.0%, and 0.7% of the ID at 1, 2, and 4 hours, respectively. Values are slightly higher after an exercise injection. Liver uptake at these same times are 2.1%, 0.9%, and 0.3% of the ID. Heart-to-liver ratios at 30 and 60 minutes after dosing, respectively, are 0.6 and 1.2 at rest and 1.2 and 3.1 after exercise, reflecting high and rapid hepatobiliary clearance. The rapid clearance of ^{99m}Tc-tetrofosmin from abdominal organs allows images to be performed soon after injection.[81]

Tetrofosmin's uptake in the heart is proportional to coronary blood flow up to 2 mL/min/g.[82] This is similar to the uptake and flow relationship seen with ^{99m}Tc-sestamibi[72] and thallium.[53] All of the SPECT agents underestimate flow at high flow rates and overestimate flow at very low flow rates, which is a function of the time tracer is available for extraction.[82] When compared to thallium extraction in the rabbit heart, tetrofosmin exhibits a myocardial extraction of about 60% that of thallium while the heart uptake of both tracers is correlated with blood flow.[83]

Approximately 66% of the injected activity is excreted in 48 hours, with about 40% in urine and 26% in feces.[84] The critical organ is the gall bladder wall with an absorbed radiation dose of 0.123 rad(cGy)/mCi (stress) and 0.180 rad(cGy)/mCi (rest).

The mechanism of ^{99m}Tc-tetrofosmin uptake in myocytes has been investigated. Data indicate that uptake is by a metabolism-dependent process that does not involve cation channel transport. The most likely mechanism for this is by potential-driven diffusion of the lipophilic cation across the sarcolemmal and mitochondrial membranes.[85] Technetium-99m tetrofosmin appears to be associated more with the cytosol than within mitochondria whereas sestamibi demonstrates a higher concentration within the mitochondria.[86] Quantitative analysis of ^{99m}Tc-tetrofosmin retention in the heart demonstrates that washout is very slow (4%/hour after exercise and 0.6%/hour after rest).[87] Ischemic-to-normal myocardium ratios of tetrofosmin ranged only from 0.75 to 0.72 from 5 minutes to 4 hours following injection, indicating insignificant redistribution of this agent over time. Technetium-99m sestamibi, however, has been shown to exhibit a small degree of redistribution between 1 and 3 hours of dosing due to faster clearance rates from normal segments.[88] Ischemic-to-normal wall ratios with ^{99m}Tc-sestamibi were statistically higher at 3 hours (0.84) than at 1 hour (0.73), which may affect the detection of CAD in cases where the ischemic defect is slight or mild.

Technetium Tc 99m Teboroxime Injection

Technetium Tc-99m teboroxime (CardioTec™, Squibb Diagnostics) is a neutral, lipophilic complex of the general class of compounds known as boronic acid adducts of technetium dioxime (BATO). 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.[89] ^{99m}Tc-teboroxime is unique from other ^{99m}Tc complexes in that the ligand is not present preformed in the kit before addition of pertechnetate, but is formed around technetium as the template atom. The essential reactants in the kit are cyclohexanedione dioxime, chloride as the axial ligand, and methyl boronic acid along with stannous chloride and other adjuvants. The ^{99m}Tc-labeled complex is prepared by heating the kit reactants with up to 100 mCi (3700 MBq) of ^{99m}Tc sodium pertechnetate in a volume of 1 mL for 15 minutes at 100ºC. The final complex is one of a heptacoordinate Tc(III) core 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 12). The complex is stable for 6 hours after preparation. Radiochemical purity must be ≥ 90%. The high lipophilicity of the complex may cause binding with syringe components necessitating an overfill of patient doses to remove the required activity.

Following intravenous administration in humans peak myocardial uptake of 2.3% ID occurs within 2 minutes.[90] Ten minutes after injection only 10% of the dose remains in blood and 33% of the dose is present in the liver due to rapid hepatobiliary clearance. By 24 hours 22% of the dose is excreted in the urine. Liver clearance is slow compared to heart clearance such that heart-to-liver ratios decline rapidly from 0.1 at 5 minutes after injection to 0.05 at 10 minutes and beyond. Residual liver activity may present a problem if a second dose is given. The first-pass myocardial extraction of ^{99m}Tc-teboroxime (80 to 90%) was the highest when compared with ^{99m}Tc-sestamibi (40 to 60%) and thallium (75 to 85%).[91] Consequently, ^{99m}Tc-teboroxime has less diffusion limitation and can more reliably assess higher blood flow levels than ^{99m}Tc-sestamibi or thallium. However, ^{99m}Tc-teboroxime is not fixed in the myocardium and rapidly diffuses out shortly after injection. Its myocardial kinetics are so rapid that imaging must be started within 2 minutes of tracer injection and be completed by 6 to 9 minutes postinjection.[91] While imaging protocols have been worked out to successfully conduct perfusion imaging with ^{99m}Tc-teboroxime, logistical problems hamper its practical usefulness. Presently, the product is no longer on the market.

Technetium Tc 99m NOEt

The nitrido atom N^{3-} was developed by Baldas to complex with Tc(V).[92,93] Subsequently a Tc-nitrido compound, [bis (N-ethyl-N-ethoxydithiocarbamato)nitrido ^{99m}Tc(V), or Tc-N-$(NOEt)_2$, was developed which has shown promise for myocardial perfusion imaging.[94] It is a neutral lipophilic myocardial imaging agent with a $Tc{\equiv}N^{2+}$ core. Its chemical structure demonstrates a Tc(V) atom triple-bonded to a strong pi-electron donor nitride atom (N^{3-}) and four sulfur atoms (Figure 12). The complex is prepared in a 2-step procedure.[94] The first step involves reduction of ^{99m}Tc sodium pertechnetate in acidic conditions by trisodium tri(*m*-sulfophenyl) phosphine in the presence of S-methyl N-methyl dithiocarbazate, $H_2NN(CH_3)C(=S)SCH_3$, as the nitrido nitrogen donating agent. This mixture is heated at 100°C for 20 minutes producing an intermediate species bearing the $Tc{\equiv}N^{2+}$ core. The mixture is cooled and neutralized with buffer and the dithiocarbamate ligand is added, whereupon ligand exchange occurs immediately to form the final ^{99m}Tc-nitrido dithiocarbamate complex, ^{99m}Tc-N-$(NOEt)_2$. A lyophilized kit has been developed (Tc-N-$(NOEt)_2$,CIS Bio-International, France) using stannous chloride that permits labeling at neutral pH.[94]

Following intravenous injection ^{99m}Tc-N-$(NOEt)_2$ localizes in the myocardium proportional to blood flow. Following myocardial uptake ^{99m}Tc-N-$(NOEt)_2$ redistrib-

utes from the heart and has been compared with thallium-201 for myocardial perfusion imaging.[95] Currently, this compound is not marketed in the United States.

PET RADIOPHARMACEUTICALS

PET imaging in myocardial disease offers several advantages over SPECT imaging. In the past, the major advantage of PET over SPECT has been the ability to provide attenuation-corrected images. At present, most SPECT cameras now have attenuation correction capability. Attenuation correction is routinely done with PET, but it may not always be done with SPECT. Attenuation correction decreases the incidence of attenuation artifacts and increases specificity.[96] Other advantages of PET include increased sensitivity and spatial resolution (PET, 6 to 10 mm; SPECT, 10 to15 mm), which translates into a higher degree of accuracy of PET versus SPECT in the detection of CAD with perfusion tracers.[96] Quantification of blood flow is also possible with PET. Additionally, metabolism studies can be done with ^{18}F-FDG, ^{11}C-acetate, and ^{11}C-palmitate. ^{18}F-FDG is considered to be the gold standard for evaluating myocardial viability. The principal disadvantages of PET are availability and cost.

PET Perfusion Agents

Ammonia N 13 Injection

The gold standard for quantitating organ blood flow is radiolabeled microspheres, a non-diffusible tracer that has an extraction fraction of 1.0 at all levels of blood flow.[41] Perfusion measurements in the nuclear medicine clinic are typically made with diffusible tracers that exhibit extraction fractions less than 1.0 because of diffusion limitations of these tracers. Nitrogen-13 ammonia has proven to be one of the most effective perfusion tracers in PET. Its first-pass extraction is high (>90%) due to the rapid diffusion of uncharged lipophilic ammonia across the capillary endothelium and sarcolemma of the myocyte. However, back-diffusion of unfixed tracer occurs so that the amount retained decreases as coronary blood flow increases. At coronary blood flows of 1 and 3 mL/min/g the average first-pass retention is 83% and 60%, respectively.[41] Once taken up into the myocyte ^{13}N-ammonia is rapidly fixed as ^{13}N-glutamine by the enzymatic conversion of glutamic acid by glutamine synthetase. Nitrogen-13 ammonia is cyclotron-produced and its 10-minute half-life restricts its use to facilities with an on-site cyclotron.

Nitrogen-13 ammonia is used for evaluating myocardial blood flow. Typically 10 to 20 mCi (370 to 740 MBq) is administered intravenously with imaging starting about 5 minutes later to allow clearance of excess tracer from the blood. The 10-minute half-life of ^{13}N requires about a 30-minute wait between rest and stress injections to allow for decay.[96]

Rubidium Chloride Rb 82 Injection

Rubidium chloride Rb 82 Injection (^{82}Rb-rubidium chloride) is a generator-produced radionuclide with a half-life of 75 sec. It is the daughter nuclide of ^{82}Sr which has a 25-day half-life, giving the generator a useful life of 4 to 6 weeks. Following intravenous injection of ^{82}Rb-rubidium chloride the rubidium cation is taken up across the sarcolemmal membrane via the sodium/potassium ATPase pump. Rubidium-82, therefore, is a potassium analog. A substantial amount of non-transported tracer back-diffuses from the interstitial space and is washed away in increasing amounts non-linearly as coronary blood flow increases.[41] The mean extraction fraction at 1 and 3 mL/min/g is 59% and 26%, respectively.[41,97]

Administration of ^{82}Rb-rubidium chloride for perfusion imaging is automated and 40 to 60 mCi (1480 to 2220 MBq) is injected intravenously with imaging beginning after a 90 to 120 sec wait to achieve satisfac-

tory heart-to-blood ratios following blood clearance of tracer. The rapid decay of ^{82}Rb permits multiple studies to be performed about every 10 minutes. A disadvantage of ^{82}Rb is its high-energy positron (3.15 MeV_{max}) which travels further from its site of origin before annihilation compared to lower-energy positrons. This effectively decreases intrinsic resolution.[97]

Water O 15 Injection

Oxygen O-15 ($T_{1/2}$ 2 min) as labeled water is a freely diffusible tracer whose first-pass extraction is ~95%. It is independent of blood flow and is metabolically inert and therefore appears to be an ideal tracer for perfusion studies. However, water O 15 injection (^{15}O-water) also distributes into tissues adjacent to the heart (lung and heart blood pool), which complicates imaging by requiring the use of background subtraction techniques.[41] Oxygen-15 water is administered as an intravenous bolus of 30 mCi (1110 MBq) with imaging beginning immediately, or patients inhale ^{15}O-carbon dioxide for 3 to 4 minutes with continuous imaging. In vivo the ^{15}O-carbon dioxide is converted to ^{15}O-water by carbonic anhydrase.[41] Following imaging, and allowing for complete decay, the blood pool is labeled by a single breath dose of ^{15}O-carbon monoxide which labels red blood cells by forming ^{15}O-carboxyhemoglobin. Blood pool images are taken and subtracted from heart perfusion images to assess net myocardial perfusion.

PET METABOLISM AGENTS

Fludeoxyglucose F 18 Injection

Fluorine F-18 ($T_{1/2}$ 110 min) labeled as 2-fluoro-2-deoxyglucose (fludeoxyglucose or ^{18}F-FDG) (Figure 18) is the premier metabolic marker for glucose metabolism in tissues of the body. Fluorine-18 FDG, being a hydrophilic molecule, is taken up into cells via facilitated diffusion similar to glucose, but its metabolism is different (Figure 19). In the first step of glucose metabolism, hexokinase converts glucose and ^{18}F-FDG into glucose-6-phosphate and ^{18}F-FDG -6-phosphate, respectively. While glucose-6-phosphate participates further as a substrate for glycolysis or glycogen synthesis, ^{18}F-FDG-6-phosphate is not a substrate for these pathways. Because it cannot readily diffuse back out of the cell, ^{18}F-FDG-6-phosphate becomes trapped and accumulates in cells that are in active metabolism.

Under normal aerobic fasting conditions, the heart primarily uses fatty acids for is energy needs. After a glucose load elevated insulin levels in blood causes an increase in glucose metabolism in preference to fatty acids. In the ischemic heart, areas of ischemic muscle switch to anerobic glycolysis with glucose as the principal substrate and these areas will demonstrate an increased uptake of ^{18}F-FDG. This forms the basis for using ^{18}F-FDG as a marker of myocardial metabolism and cell viability. Fluorine F-18 FDG is not a useful tracer of myocardial blood flow because its uptake is not related to flow but to phosphorylation. The phosphorylation step is dependent on the rate of glucose metabolism which is independent of blood flow.

The ^{18}F-FDG radiopharmaceutical is supplied as an injection and is used for assessing myocardial viability. At a PET facility with a cyclotron and radiochemistry capability, a typical protocol would be to perform a perfusion/metabolism study with perfusion being evaluated first with ^{13}N- ammonia, ^{82}Rb-rubidium chloride, or ^{15}O-water, followed by an ^{18}F-FDG metabolism study (Figure 20). At PET facilities without a cyclotron or radiochemistry support a ^{99m}Tc-agent is used for the perfusion study followed by an ^{18}F-FDG metabolism study. Because of the difference in physical half-lives, ^{13}N-ammonia is frequently used because it allows longer imaging times with higher count density images compared to

Figure 18. Chemical structures of glucose, deoxyglucose, and fludeoxyglucose (FDG). (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).

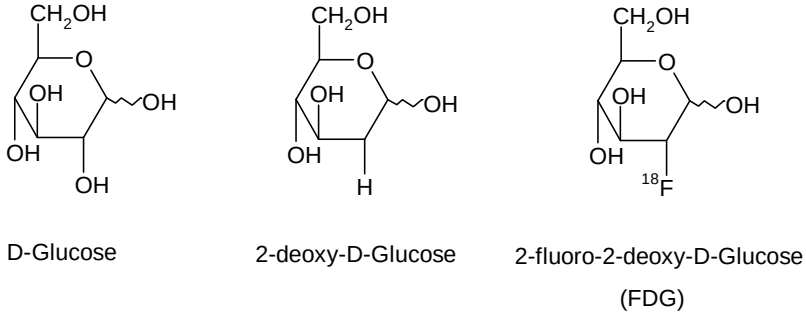


Figure 19. The various metabolic processes occurring in the myocyte illustrating the membrane uptake mechanisms for monovalent cations ($^{201}Tl^{+}$ and $^{82}Rb^{+}$) via Na-K ATPase and FDG and glucose via the glucose transporter. While glucose is metabolized completely, FDG is trapped as FDG-6-phosphate following enzymatic conversion by hexokinase. Fatty acids, as the preferred metabolic substrate for energy, can be converted into triglycerides, phospholipid stores, or shunted, via the carnitine shuttle, into mitochondria for beta oxidation. (Reprinted by permission of W.B. Saunders Co from: Schwaiger M., et al. Evaluation of coronary artery disease with positron emission tomography. *Semin Nucl Med* 1992; 22: 210-223.)

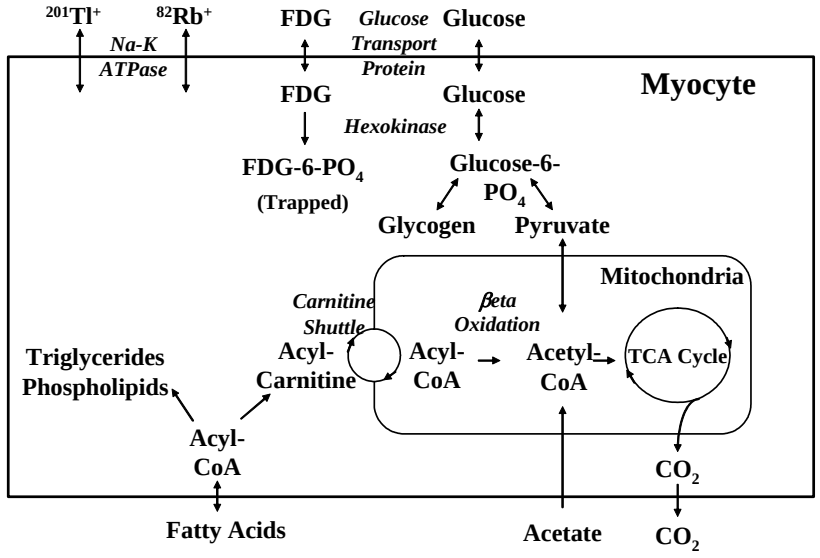
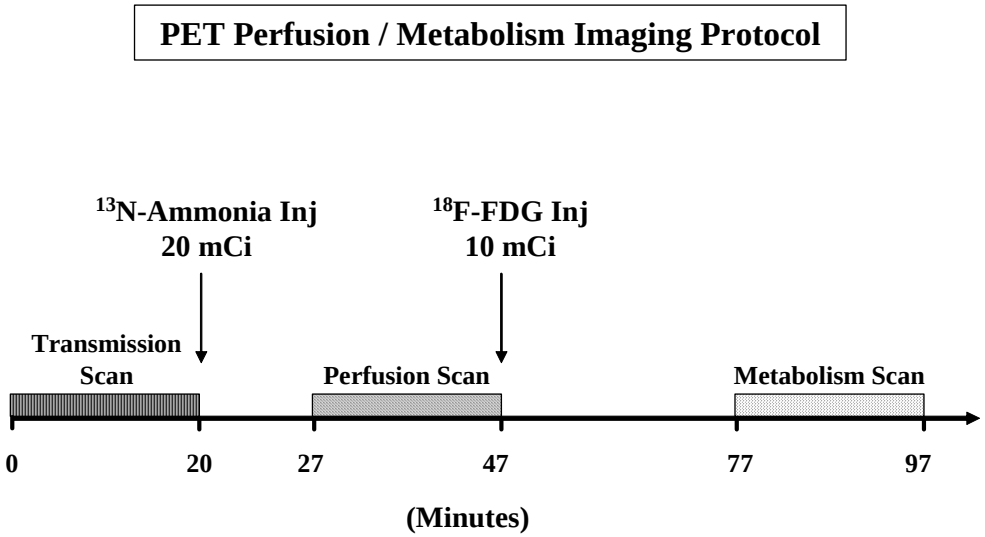


Figure 20. PET perfusion/metabolism imaging protocol to assess myocardial viability. (Reprinted by permission of the Society of Nuclear Medicine from: Maddahi J, et al. Role of thallium-201 and PET imaging in evaluation of myocardial viability and management of patients with coronary artery disease and left ventricular dysfunction. *J Nucl Med* 1994;35:707-715.)

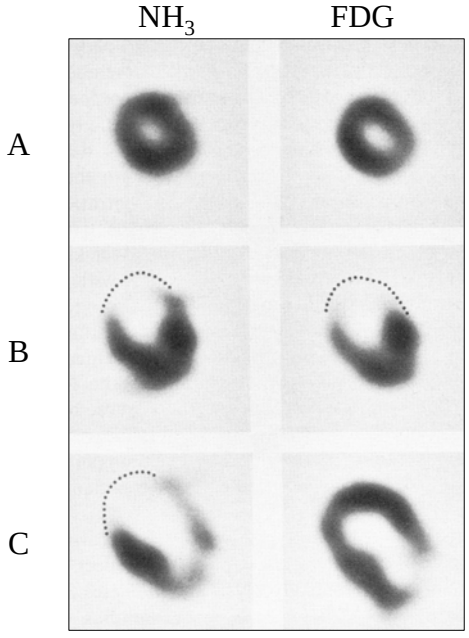


^{82}Rb or ^{15}O.[98] The metabolism phase of the study involves intravenous injection of ^{18}F-FDG (10 mCi [370 MBq]) following a loading dose of glucose to facilitate transport of ^{18}F-FDG into myocardial cells. The loading dose of glucose is important because in the fasting state, fatty acid is the principal substrate for myocyte energy requirements and ^{18}F-FDG is taken up very little under these conditions. Compared to 12-hr fasted subjects, subjects given 50 g of glucose orally prior to the ^{18}F-FDG study demonstrate heart-to-blood activity ratios 2.5 times higher.[99] The pattern of activity uptake between the perfusion and metabolism images is key to the diagnosis. If the ^{13}N-ammonia and ^{18}F-FDG activity distributions are identical in the region of a perfusion defect (a match), the defect is likely caused by lack of both perfusion and active metabolism and is due to scar. If there is increased uptake of ^{18}F-FDG in a region seen as a perfusion deficit with ammonia (a mismatch), the interpretation is that the region represents hibernating myocardium which is active metabolically and therefore viable (Figure 21).

Carbon C 11 Palmitate

Carbon C 11 palmitate (^{11}C-palmitate) is used to provide information about myocardial fatty acid metabolism (see Figure 19). The free fatty acid is largely distributed in the myocardium in proportion to blood flow whereupon it crosses the sarcolemmal membrane, presumably by passive diffusion or possibly facilitated transport.[41] Retention or trapping of ^{11}C-palmitate requires energy-dependent esterification to ^{11}C acyl-CoA, which can enter either of two routes. In one fraction it moves via the carnitine shuttle to the inner mitochondrial membrane where β-oxidation cleaves two carbon fragments off the long carbon chain, directing acetyl CoA to the tricarboxylic acid (TCA) cycle for complete oxidation to carbon dioxide and water. The other fraction of acyl-CoA is further esterified and deposited as triglyceride and phospholipid stores.

Figure 21. Regional myocardial blood flow and glucose utilization in a normal volunteer (A) and two patients with ischemic heart disease (B and C), evaluated with N-13 ammonia (NH_3) and F-18 2-deoxyglucose (FDG) and PET. Only one midventricular cross-sectional image of blood flow (left) and glucose utilization (right) is shown per subject. Note the homogeneous tracer uptake in the normal subject. In patient B, blood flow is decreased in the anterior wall (broken line) associated with a proportional decrease in FDG uptake. This pattern reflects scar tissue. By contrast, in patient C, blood flow is markedly decreased in the anterior wall and the anterior septum, while glucose utilization in the hypoperfused segment is markedly enhanced. Preservation of glucose utilization in hypoperfused and dysfunctional segments represents tissue viability. (Reprinted by permission of W.B. Saunders Co from: Schelbert HR. Current status and prospects of new radionuclides and radiopharmaceuticals for cardiovascular nuclear medicine. *Semin Nucl Med* 1987;17: 145-181.)



Following intravenous administration of 15 to 20 mCi (555 to 740 MBq) of ^{11}C-palmitate and image acquisition, stored images of the ventricles are used to identifiy regions of interest from which time-activity curves are generated for analysis of uptake and clearance kinetics. The slopes of these curves can then be used to assess regional metabolism in the myocardium.[41]

Sodium Acetate C 11 Injection

Sodium acetate C 11 injection (^{11}C-acetate) is avidly extracted by the myocardium and activated to acetyl-CoA, which is oxidized in the mitochondria to ^{11}C-carbon dioxide and water (see Figure 19). ^{11}C-acetate permits an evaluation of flux through the TCA cycle and overall myocardial oxygen consumption because of its close link to oxidative phosphorylation.[41] A measure of myocardial oxidative capacity can be made by an analysis of uptake and clearance curves. These curves change with regional abnormalities in blood flow and metabolism. Thus, in ischemic regions, the initial uptake of ^{11}C-acetate decreases in proportion to myocardial blood flow and clearance curves are reduced significantly.[41]

Fluorine F-18 FDG and ^{11}C-palmitate are tracers that measure specific substrates in myocardial metabolism, whereas ^{11}C-acetate measures overall oxidative metabolism. Fluorine F-18 FDG measures the initial steps of exogenous glucose utilization, whereas ^{11}C-palmitate traces the entire metabolic pathway of fatty acid metabolism. In the fasted state, when fatty acid metabolism is highest in the myocardium, ^{18}F-FDG will demonstrate very little uptake in the heart, but ^{11}C-palmitate uptake and clearance curves will reflect rapid kinetics. The combination of ^{11}C-palmitate or ^{18}F-FDG with ^{11}C-acetate permits assessment of the contribution of fatty acid or glucose metabolism to overall oxidative metabolism or in the ischemic condition, an assessment of anaerobic versus oxidative glucose metabolism.[41]

VIABILITY ASSESSMENT

A principal reason for myocardial perfusion imaging is to predict whether ischemic dysfunctional myocardial segments are viable and therefore restorable to normal function following revascularization.

The four principal conditions that can cause left ventricular dysfunction are: (1) transmural myocardial infarction, which involves full-thickness myocardial necrosis, (2) non-transmural myocardial infarction, which is necrosis limited to the subendocardium or is scattered throughout the myocardium, (3) myocardial stunning, and (4) hibernating myocardium.[98] Revascularization is not expected to be beneficial for the first two conditions. Myocardial *stunning* results from severe acute ischemia followed by reperfusion, both of which cause myocardial injury and dysfunction.[100] Myocardial *hibernation* results in dysfunction being caused by chronic reduction in coronary blood flow. In stunning, reduced contraction is mismatched with increased perfusion, whereas in hibernation reduced contraction is matched by reduced perfusion.[100] In both situations the dysfunction is reversible and will resolve after restoration of myocardial blood flow to the affected region. Time is required in the case of stunning to restore muscle; improved blood flow is required in the case of hibernation.

Nuclear medicine studies have been shown to be valuable in predicting the viability of stunned and hibernating myocardium. Thallium viability studies have been reviewed by Maddahi.[98] The terms positive predictive accuracy and negative predictive accuracy are often used in viability assessment studies. *Positive predictive accuracy* (PPA) predicts the percentage of myocardial regions with reversible defects that will improve following revascularization, while *negative predictive accuracy* (NPA) predicts the percentage of myocardial regions without reversibility that will not improve following revascularization. In three independent studies reporting on rest-redistribution thallium imaging, the mean PPA was found to be 72% (range 57% to 92%) and the mean NPA was found to be 70% (range 62% to 77%).[101-103] In three additional studies, following exercise-redistribution-reinjection thallium imaging, negative predictive accuracies in studies conducted without ^{201}Tl reinjection were 43%, 53%, and 48%, but with reinjection these values improved to 100%, 75%, and 75%, respectively, demonstrating the value of thallium reinjection on improving diagnostic accuracy (see Figure 11).[65,67,104] For this reason, thallium reinjection is now a standard technique in SPECT imaging for assessing myocardial viability.

PET's ability to predict recovery of left ventricular function after revascularization procedures has been assessed with myocardial perfusion/metabolism studies using ^{15}O-water, ^{13}N-ammonia, ^{11}C-acetate, and ^{18}F-FDG. In seven studies reviewed by Maddahi the average reported positive predictive accuracy for a myocardial perfusion/FDG metabolism mismatch pattern was 83% (range 72% to 95%) and the average negative predictive accuracy for a matching pattern was 84% (range 75% to 100%).[98] Thus, while both ^{201}Tl and PET imaging methods have high accuracies, PET perfusion/metabolism imaging appears to have greater diagnostic power in predicting improvement of left ventricular function in patients with CAD compared to thallium SPECT.

Most institutions now use a ^{99m}Tc agent (sestamibi or tetrofosmin) for myocardial perfusion studies. The question remains, in the situation of chronic left ventricular dysfunction, whether ^{99m}Tc-sestamibi can distinguish between viable hibernating myocardium and fibrosis, as has been shown with the ^{201}Tl rest-reinjection technique.[11,62] Several studies indicate that ^{99m}Tc-sestamibi has limitations in identifying viability in hibernating myocardium. Cuocolo compared

^{99m}Tc-sestamibi and ^{201}Tl in chronic CAD, demonstrating that approximately 60% of myocardial regions identified as viable by thallium reinjection were categorized as "nonviable" by a resting ^{99m}Tc-sestamibi study.[105] In a comparison of ^{99m}Tc-sestamibi with ^{18}F-FDG-PET in patients with CAD, ^{99m}Tc-sestamibi was found to underestimate myocardial viability.[106] Five to 11% of severe defects with ^{99m}Tc-sestamibi uptake at rest ≤ 30% of peak activity were viable by ^{18}F-FDG-PET, whereas 13% to 61% of moderate to severe defects (31% to 70% of peak activity) were found to be viable by ^{18}F-FDG-PET. A case report, comparing ^{201}Tl exercise-redistribution with reinjection and exercise-rest ^{99m}Tc-sestamibi, in a patient with multivessel chronic CAD evaluated before and after revascularization, demonstrated that thallium could distinguish between viable and nonviable regions whereas sestamibi could not.[107] Thus, it appears that ^{99m}Tc-sestamibi, as a perfusion marker, may be able to assess viability in stunned myocardium where perfusion is adequate, such as following reperfusion therapy for acute myocardial infarction, but that it is not able to adequately identify viability in hibernating myocardium in chronic CAD where there is sustained reduction in blood flow.[100] Thus, in those clinics without ^{18}F-FDG-PET capability, the thallium rest /redistribution protocol or the thallium stress/redistribution/reinjection protocol would be the procedures of choice for assessing myocardial viability.

Clinical studies have shown that ^{99m}Tc-tetrofosmin accurately detects coronary artery disease when compared with thallium [108-110] and ^{99m}Tc-sestamibi.[111] The heart-to-liver ratios at rest and after dipyridamole stress indicate higher ratios for ^{99m}Tc-tetrofosmin compared to ^{99m}Tc-sestamibi, but there is no significant difference in the quality of images or diagnostic interpretation of these two agents.[112] When compared qualitatively to thallium for viability assessment in CAD following exercise-rest studies, ^{99m}Tc-tetrofosmin imaging was found to underestimate myocardial viability compared to thallium reinjection and the difference correlated with severity of the persistent defect on rest images.[112]

Intact membrane function and metabolic processes are required for myocyte viability. Thus, markers of membrane integrity and metabolic function, theoretically, should be equally effective in assessing myocardial viability. The differences in the reported accuracies between SPECT and PET imaging agents for assessing viability may reside in the different abilities of these modalities to detect the physiologic processes that are occurring. Hence, PET would seem to have the advantage currently because of its better resolution, ability to correct for photon attenuation, and ability to assess metabolic function independent of perfusion.[113]

BLOOD POOL IMAGING AGENTS

The essential requirements for a blood pool imaging radiopharmaceutical for evaluating dynamic heart function include, (1) slow blood clearance to provide steady blood pool activity during the time of data acquisition, (2) minimal localization of radioactivity in nearby organs and extravascular space that would interfere with measurements of the heart blood pool, and (3) high photon flux, which is necessary for high-resolution and high-sensitivity measurements of dynamic heart function with the gamma camera. The latter requirement is most easily met by ^{99m}Tc, and the first two requirements are met by labeling ^{99m}Tc to red blood cells.

Technetium Tc 99m Red Blood Cells

Various methods of labeling red blood cells with technetium are possible. These include the in vitro method, the in vivo method, and the modified in vivo method.

In Vitro Method

The *in vitro method* for preparing ^{99m}Tc-labeled red blood cells (^{99m}Tc-RBCs) was perfected with a kit developed at the Brookhaven National Laboratory.[114,115] This technique was modified by Srivastava to permit labeling in whole blood without isolating the red cells.[116] A commercial kit is now available (Ultratag RBC - Mallinckrodt Inc) based on this method. The blood cells are usually autologous but may be donor cells if carefully typed and cross-matched and checked for viral contamination. The kit consists of three components:

1. 10-mL Reaction Vial: Lyophilized mixture of stannous chloride dihydrate 105 μg, sodium citrate dihydrate 3.67 mg, and dextrose anhydrous 5.5 mg at pH 7.1 to 7.2.
2. Syringe I: sodium hypochlorite 0.6 mg in 0.6 mL at pH 11 to 13.
3. Syringe II: citric acid monohydrate 8.7 mg, sodium citrate dihydrate 32.5 mg, and dextrose anhydrous 12 mg in total volume of l.0 mL at pH 4.5 to 5.5.

The cells are labeled as follows:

1. Collect 1 to 3 mL patient's blood. Use 0.15 mL ACD or 10 to15 units heparin per mL blood maximum. Do not use EDTA or oxalate as anticoagulants.
2. Transfer blood to the reaction vial to dissolve crystals. Incubate 5 minutes.
3. Add contents of syringe I. Mix by gentle inversion 5 times.
4. Add contents of syringe II. Mix by gently inversion 5 times.
5. Add 10 to 100 mCi (370 to 3,700 MBq) sodium pertechnetate in up to 3 mL.
6. Mix gently 5 times. Incubate 20 minutes to label cells.

The labeling mechanism is as follows: addition of RBCs to the reaction vial causes a portion of the stannous ion to cross the red cell membrane into the cell. Too much ACD impairs this diffusion process and is the reason for its limited amount. All of the stannous ion does not enter the cells, and sodium hypochlorite is added to oxidize this extracellular stannous ion. This is effective because hypochlorite cannot cross the red cell membrane to oxidize intracellular tin. The citrate solution in syringe II is added to sequester excess extracellular stannous ion to enhance its oxidation by hypochlorite. At this point ^{99m}Tc sodium pertechnetate is added which readily diffuses into the cells, encounters intracellular stannous ion, becomes reduced and bound in the cell. If extracellular stannous ion were present, it would reduce the pertechnetate extracellularly and prevent it from entering the cell. This would lower the labeling efficiency.

Radiochemical purity can be checked by mixing 0.2 mL of ^{99m}Tc-RBCs with 2 mL saline and centrifuging. Assay of the supernatant (unbound activity) and the red cell precipitate (bound activity) will provide a measure of labeling efficiency. The labeling efficiency must be ≥ 90% and is typically > 95%.[117]

^{99m}Tc-RBCs are a blood pool imaging agent indicated for cardiac imaging and for the detection of gastrointestinal bleeding with an IV dosage range of 10 to 20 mCi (370 to 740 MBq). The critical organ is the spleen with an absorbed radiation dose of 0.11 rad(cGy)/mCi.[117]

In Vivo Method

The *in vivo method* of labeling red cells was first suggested by Pavel[118] and Stokely[119] for use in cardiac blood pool studies. The method was based on the intravenous injection of stannous pyrophosphate (Sn-PPi) 20 minutes to 24 hours prior to IV administration of ^{99m}Tc sodium pertech-

netate which then labeled the "tinned" red cells. The Pavel technique involved reconstituting one vial of Mallinckrodt TechneScan PYP (which contained about 15.4 mg stannous pyrophosphate (Sn-PPi) and on average, about 2 mg Sn^{2+}) with 5 mL saline, and injecting the patient with 1.4 mg Sn-PPi per 1000 mL whole blood volume. Based on these parameters the average 70 kg adult male (~5400 mL whole blood) would receive about 7.5 mg Sn-PPi (one-half vial) per dose, equivalent to ~ 15 μg Sn (II)/kg. Within 20 to 30 minutes of injecting the Sn-PPi, 15 to 25 mCi (555 to 925 MBq) of ^{99m}Tc sodium pertechnetate is administered intravenously to label the red cells for blood pool imaging.

Hamilton investigated the amounts of stannous ion required to label red cells and reported that maximal in vivo labeling efficiency is obtained with an IV dose of 10 μg Sn (II)/kg or greater.[120] Although Pavel reported labeling efficiencies of ~ 96% with the in vivo technique, others reported only about 75% labeling efficiency.[121,122] Callahan noted that when the in vivo technique was used for gastrointestinal bleeding studies, variable amounts of gastric and urinary activity interfered with the study. Investigation into the possible causes of this extravascular activity led to the deduction that immediately following intravenous injection of free pertechnetate with the in vivo method there occurs a competition for pertechnetate between the red cells and the extracellular fluid space, gastric mucosa, thyroid and salivary glands. This led to the development of the modified in vivo method for labeling red cells.[123]

Modified In Vivo Method

The *modified in vivo method* was developed to increase the labeling efficiency of ^{99m}Tc-RBCs and to provide a firm label prior to intravenous injection.[123] With this technique the patient receives ~ 500 μg of stannous ion as Sn-PPi from a Pyrolite® kit intravenously. Equivalent amounts of stannous pyrophosphate from other marketed kits can also be used. Twenty minutes later, 3 mL of tinned red blood cells are withdrawn through a heparinized Butterfly infusion set into a shielded syringe containing 20 mCi (740 MBq) of pertechnetate. The mixture is incubated for 10 minutes with gentle agitation and then reinjected into the patient. Labeling yields > 90% are achieved with this method because the red cells compete for pertechnetate only with the plasma in the syringe.

Labeling Mechanism of Tc Red Blood Cells

Following incubation of stannous pyrophosphate with red blood cells some of the stannous ion crosses the cell membrane, apparently transported inside the cell by a specific transport system[121] where it is believed to be associated with an intracellular protein.[124] The pertechnetate anion can readily diffuse into the cell, become reduced by the stannous ion, and subsequently bind to hemoglobin, which prevents it from diffusing back out of the cell.[124] In vitro studies have shown that within the hemoglobin molecule approximately 20% of ^{99m}Tc and 90% of tin are associated with heme and 80% of ^{99m}Tc and 10% of tin are associated with globin.[125] Transport studies in human erythrocytes have demonstrated that the pertechnetate anion is transported across the membrane via the band-3 protein transport system in exchange for chloride or bicarbonate ion.[126] It is worth noting that this transport can be inhibited by dipyridamole and may play a factor in decreasing the labeling efficiency of red cells in patients who receive therapeutic or diagnostic doses of this drug.[126]

In humans the biologic half-life in blood of ^{99m}Tc-RBCs prepared by the in vitro technique is biexponential, with 5% of the activity having a 20-minute half-life and 95%, a 29-hour half-life.[127] Cells labeled in

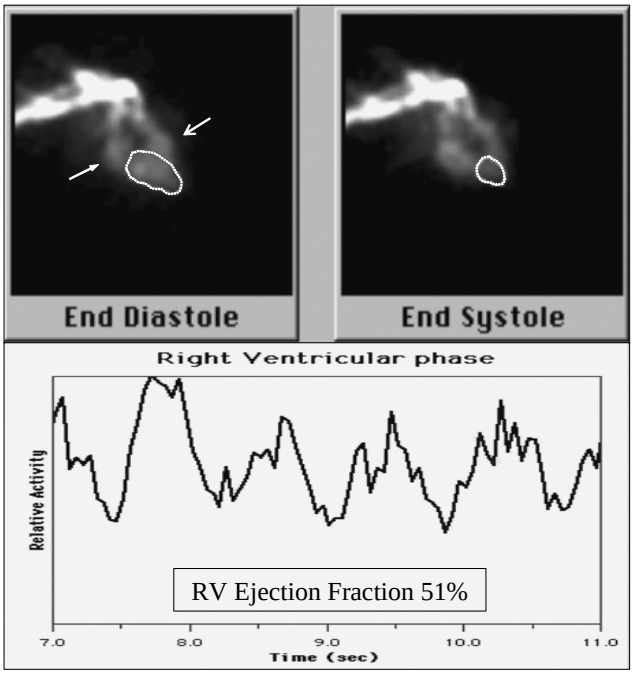
vivo are assumed to behave with a normal biologic half-life of red cells, i.e., about 80 days.

GATED EQUILIBRIUM RADIONUCLIDE VENTRICULOGRAPHY

A principal application of blood pool imaging agents is myocardial ventriculography for the assessment of wall motion abnormalities and measurement of ventricular ejection fraction and volume. The assessment is made with a two-part study: the first-pass study and the equilibrium study. A *first-pass study* permits assessment of right and left chamber function following administration of a bolus of ^{99m}Tc-pertechnetate activity (20 to 30 mCi [740 to 1110 MBq]). During the first couple of beats following initial injection of the pertechnetate bolus of activity, the right ventricle can be isolated on the images (Figure 22). Regions of interest can be drawn around the right ventricle during diastole and systole and a right ventricular ejection fraction can be estimated using the formula:

$$RVEF \text{ or } LVEF = \frac{(End-Diastolic\ Counts)-(End-Systolic\ Counts)}{(End-Diastolic\ Counts)-(Background\ Counts)}$$

Figure 22. Normal first-pass study to evaluate right ventricular performance. Shortly after a 30 mCi (1110 MBq) bolus of ^{99m}Tc sodium pertechnetate was administered in a right arm vein, radiotracer can be seen in the superior vena cava, right atrium (solid arrow), right ventricle (dotted region) and pulmonary outflow tract (open arrow). The right ventricle can be isolated because radiotracer has not yet advanced to the lungs or left ventricle. A time activity curve for the right ventricle was used to determine right ventricular end-diastole and end-systole. Regions of interest drawn around the right ventricle during end-diastole and end-systole gave a normal estimated right ventricular ejection fraction of 51%. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).



Once the pertechnetate is injected it labels red cells in vivo permitting an ECG-gated equilibrium study, which typically follows the first-pass study. The *equilibrium study* is conducted to assess left ventricular function. The equilibrium study is also known as the multigated acquisition or MUGA study because the activity labeled to the red cell blood pool is monitored as it passes through the heart by acquiring images triggered or gated on the R-wave of the electrocardiogram. The total activity passing through the heart during one cardiac cycle is divided into frames of activity which are stored in a computer (Figure 23). Typically 32 or more frames are acquired during each cycle so that incremental changes in left ventricular activity can be stored from end-diastole to end-systole. Many cardiac cycles (and frames) of data are stored over a long image acquisition time so that a statistically significant amount of activity is accumulated in each frame. The total amount of activity stored in the frames at each gated time point are then plotted versus total cycle time to obtain a time-activity curve of blood flowing through the left ventricle. From this plot, and the equation given above, the left ventricular ejection fraction (LVEF) can be determined from end-diastolic and end-systolic activities in the chamber. Figure 24 illustrates two patient studies for the determination of LVEF; one normal (LVEF = 73%) and one abnormal (LVEF = 30%). Normal LVEF is 55% or greater.

Gated SPECT also allows one to further evaluate fixed perfusion defects seen in a myocardial perfusion study by examining myocardial wall motion and thickening. Fixed perfusion defects with associated normal wall motion and thickening are indicative of viable functional myocardium and are likely related to attenuation artifacts usually caused by the diaphragm or breast. Fixed defects with abnormal focal wall motion abnormalities and decreased thickening are generally associated with scar.

INFARCT-AVID IMAGING AGENTS

Infarct-avid agents, otherwise known as "hot spot" markers, demonstrate an increased accumulation of radiotracer activity in regions of infarcted myocardium. Several types of radiolabeled agents have been developed for infarct imaging based on the pathophysiologic changes that occur in the infarct region. While these agents have provided useful diagnostic information in the past, presently, faster, more sensitive, specific, and less costly serum markers have replaced infarct-avid imaging agents as the standard of care. However, new radiotracers for imaging myocardial infarction are being investigated.

Technetium Tc 99m Pyrophosphate

Technetium-labeled bone agents were first used for infarct localization following the serendipitous finding of heart uptake on bone scans in patients who had recent infarcts. In the 1970's these agents proved useful in the diagnosis of myocardial infarction because at that time there was a lack of sensitive enzyme assays for early diagnosis of MI. Investigations led to the discovery that, physiologically, ischemic damage to the myocardial cell membrane produces an imbalance in the myocyte's intracellular-extracellular Ca^{++} concentration. Under normal conditions the calcium ion concentration intracellularly is about 10^{-7} M and in extracellular fluid it is about 10^{-3} M (Figure 1). Following infarction with disruption of the myocyte membrane, calcium ions diffuse into the infarcted cells providing a focus for the uptake and binding of technetium-labeled agents.

In 1974, Bonte introduced the use of ^{99m}Tc-pyrophosphate for imaging myocardial infarction.[128] Its mechanism of localization was shown to be related to residual blood flow to the infarcted region, calcium

Figure 23. Gating mechanism to obtain serial single-frame images of left ventricle contraction through one cardiac cycle. See text for explanation. (Reprinted by permission of Bristol-Meyers Squibb Medical Imaging).

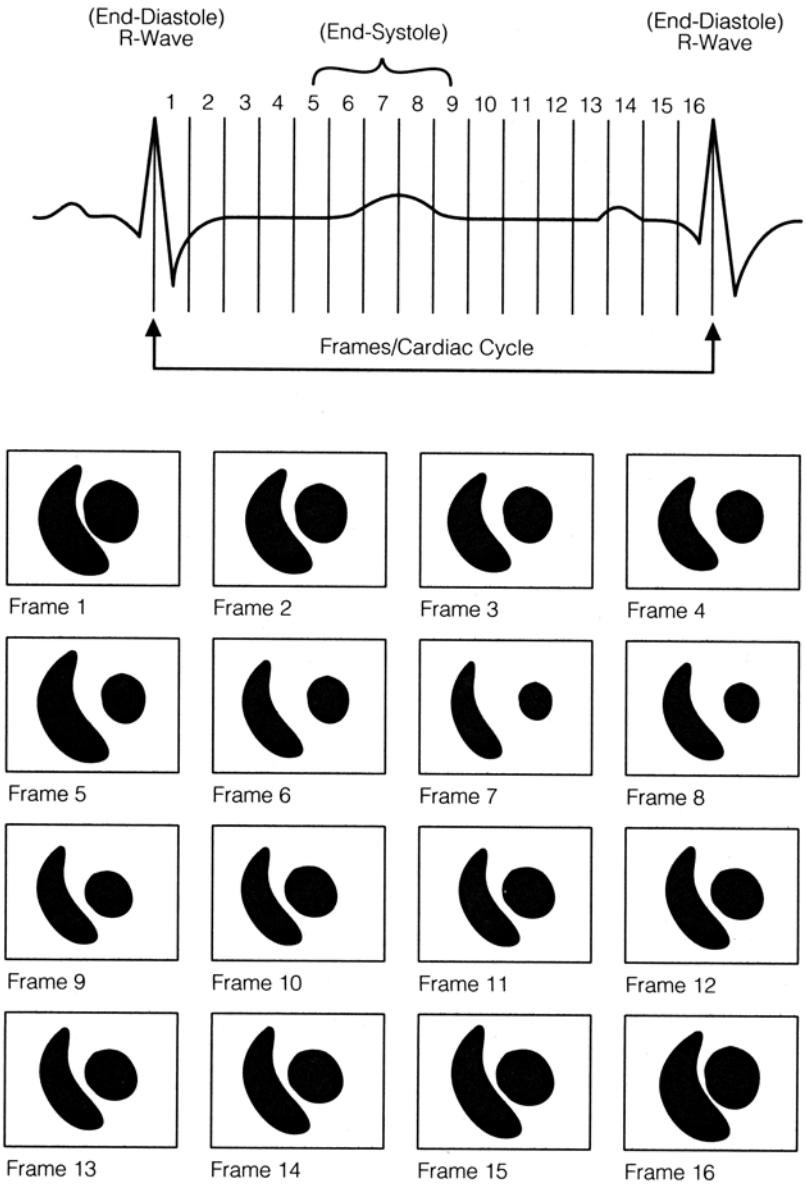
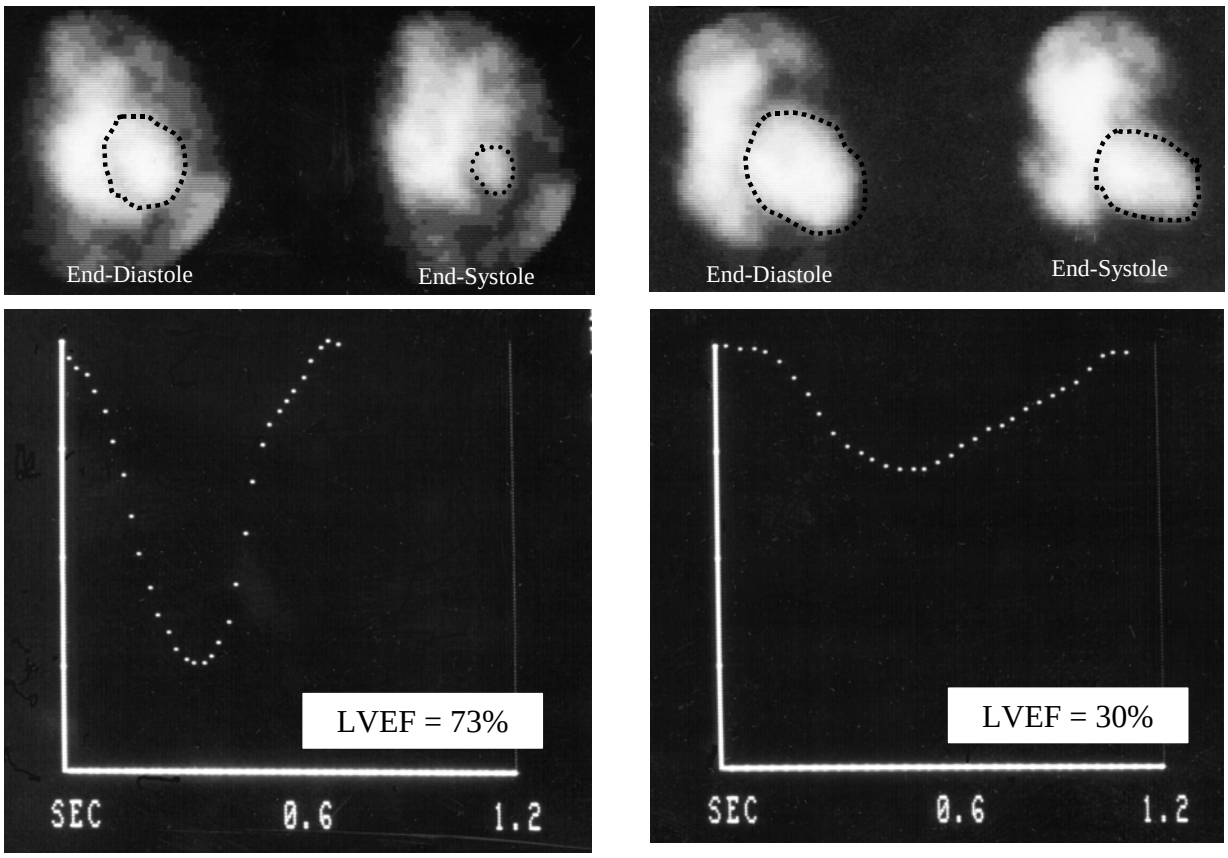


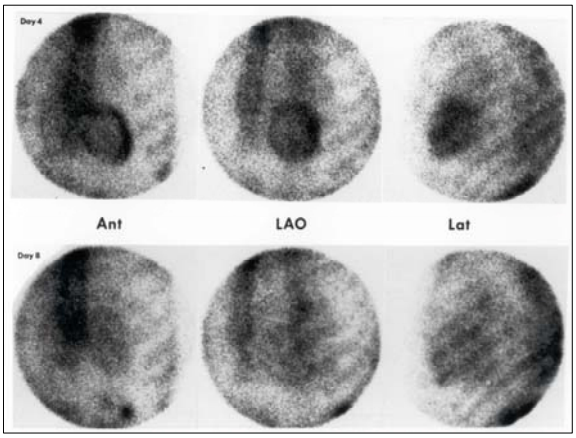
Figure 24. Left ventricular ejection fraction (LVEF) assessment. Images of the heart at end-diastole and end-systole with time-activity curves demonstrating, (A) normal LVEF of 73% and, (B) abnormal LVEF of 30%. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).



ion influx, and deposition of intracellular hydroxyapatite in infarcted cells.[129,130]

Following myocardial infarction membrane damage occurs which permits an influx of plasma proteins and calcium ions, some of which deposit in mitochondria where hydroxyapatite crystals form. The proposed mechanism of ^{99m}Tc-pyrophosphate localization is sorption to various forms of tissue calcium stores, including amorphous calcium phosphate, crystalline hydroxyapatite, and calcium complexed with various macromolecules at the infarction site. Maximal concentrations occur in peripheral zones of the infarct where there is adequate blood flow, with considerably less uptake in central zones of the infarct where blood flow is reduced.[130] Temporally, after fixed coronary occlusion, ^{99m}Tc-pyrophosphate begins to localize in the infarcted tissue within 12 to 24 hours. Scintigrams become more positive during 24 to 72 hours and remain abnormal for 6 days after infarction, fading thereafter and becoming negative by day 14 (Figure 25). The standard dose for myocardial infarct imaging was 15 mCi (555 MBq) with imaging in 3 to 4 hours.

Figure 25. Infarct avid scans obtained 4 and 8 days following extensive acute left ventricle infarction. Images are obtained 2 hours after intravenous injection of 15 mCi (555 MBq) of ^{99m}Tc-pyrophosphate. (Reprinted by permission, from *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine.* © 2004 by the American Pharmacists Association).



The sensitivity of ^{99m}Tc-pyrophosphate for detecting transmural infarcts was reported to be about 90%, but only about 40% for subendocardial infarcts.[131] The overall specificity has been found to be 64% in a multicenter study. Its lack of specificity is due in part to myocardial uptake in patients with stable angina without infarct and in regions of old infarcts several months after the acute episode. Additionally, the long time required before for ^{99m}Tc-pyrophosphate uptake is positive post infarct (24 to 48 hrs) precludes its use for early diagnosis.

Indium In 111 Imciromab Pentetate

Indium-111 imciromab pentetate (Myoscint™ - Centocor), otherwise known as ^{111}In-antimyosin, is a monoclonal antibody Fab fragment with specificity for myosin. Its localization is based on the disruption of the sarcolemmal membrane of dying myocytes exposing myosin filaments which are normally segregated from the extracellular fluid. Once exposed, the myosin may then bind the radiolabeled antimyosin antibody. Following dosing of ^{111}In-antimyosin, imaging is performed 24 hr or later to allow for background activity to clear. Although this agent has demonstrated high sensitivity and specificity for localizing myocardial infarcts, it is no longer on the market.[132,133]

Technetium Tc 99m Glucaric Acid

Technetium Tc 99m glucaric acid is a six-carbon sugar which was seridipitously found to localize in myocardial infarctions during the development of a technetium label for the antimyosin antibody.[134] Technetium-99m glucarate is taken up into irreparably damaged myocytes where it is associated with highly basic histones.[134] In one investigational study it was found to be taken up rapidly into infarcted myocardium early after the event with best identification occurring if the radiotracer is administered within 9 hours of the infarction.[135] Because it is taken up soon after infarction, ^{99m}Tc-glucarate has a potentially significant advantage over ^{99m}Tc-pyrophosphate and ^{111}In-antimyosin. Further investigational studies will better define is future usefulness.

Technetium Tc 99m Annexin V

Technetium Tc 99m annexin V is a radiolabeled form of annexin V, an endogenous protein that has a high affinity for exposed phosphatidylserine on apoptotic cells.[136] Apoptotic cells have been identified in areas of severe ischemia and infarction. During natural apoptosis (programmed cell death) in the body an enzymatic process is initiated that causes the phospholipid phosphatidylserine to become expressed on the outer membrane surface of dying cells, where it is able to bind the annexin V ligand. The purpose of this interaction is unknown but the binding affinity between annexin V and phosphatidylserine is high. This gives radiolabeled annexin V the potential to become a cardiac imaging agent.[127] Further investigational studies with this agent are

needed to define its diagnostic roll in cardiac imaging.[128]

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QUESTIONS

Begin Lesson 2 here.

1. Which one of the following statements is false?
   a. Approximately 30 to 60% of all nuclear medicine procedures involve heart studies.
   b. Radionuclide ventriculography is the most widely performed heart imaging study for assessing myocardial viability.
   c. Currently, infarct-avid imaging plays a lesser role in heart imaging than in the past.
   d. Approximately 84% of heart studies involve the assessment of myocardial perfusion.

2. The detection of restricted coronary blood flow in the heart is most sensitive when:
   a. coronary blood flow is at maximum levels.
   b. the stenotic vessel-to-normal vessel blood flow ratio is 2.4 or greater.
   c. coronary flow reserve is at a minimum.
   d. coronary blood flow is at resting levels.

3. The amount of coronary artery stenosis that will likely cause chest pain (angina) during myocardial stress from insufficient oxygenation to the myocardium is:
   a. 25%
   b. 45%
   c. 70%
   d. 85%

4. An endogenous substance that is involved in the autoregulation of coronary artery blood flow is:
   a. dipyridamole
   b. adenosine
   c. dobutamine
   d. caffeine

5. Each of the following agents can be used to assess myocardial perfusion except:
   a. Tc-99m sestamibi
   b. Tc-99m red blood cells
   c. Tc-99m tetrofosmin
   d. Tl-201 thallous chloride

6. All of the following are myocardial metabolic imaging agents except:
   a. F-18 fludeoxyglucose
   b. C-11 acetate
   c. Rb-82 rubidium chloride
   d. C-11 palmitate

7. Which one of the following agents is best suited for assessing myocardial viability in hypoxic myocardium?
   a. C-11 acetate
   b. C-11 palmitate
   c. Tl-201 thallous chloride
   d. F-18 fludeoxyglucose

8. The most effective way to relieve the symptoms of adverse effects from adenosine administration is to:
   a. immediately administer 100 mg of aminophylline.
   b. give the patient a caffeinated beverage.
   c. administer esmolol as an antidote.
   d. discontinue the adenosine infusion.

9. The dosage of intravenous dipyridamole for a myocardial perfusion study for a 110-pound patient is:
   a. 7 mg
   b. 24 mg
   c. 28 mg
   d. 42 mg

10. Which one of the following statements is true?
    a. Adenosine and dipyridamole are effective coronary vasodilators with

similar plasma half-lives but are contraindicated in patients with heart block.
   b. Dobutamine is a beta-1 agonist that produces effects on the heart similar to exercise but is contraindicated in patients who have ingested food containing caffeine.
   c. A patient who has asthma and cannot exercise is a good candidate for receiving dobutamine for cardiac stress.
   d. When compared with pharmacologic stress, exercise stress produces a greater accumulation of perfusion imaging tracers in the splanchnic viscera, which may interfere with heart imaging.

11. Heart uptake and retention of which one of the following myocardial imaging agents is associated with intact myocyte plasma and mitochondrial membrane potentials?
   a. Tl-201 thallous chloride.
   b. Tc-99m sestamibi.
   c. N-13 ammonia.
   d. Rb-81 rubidium chloride.

12. Which one of the following myocardial imaging agents has the fastest clearance from the heart following intravenous administration?
   a. Tc-99m sestamibi.
   b. Tl-201 thallous chloride.
   c. Tc-99m teboroxime.
   d. Tc-99m tetrofosmin.

13. Which one of the following statements about dipyridamole is true?
   a. Maximal coronary vasodilatation is achieved about 3 minutes following cessation of the intravenous infusion of dipyridamole.
   b. Maximal coronary vasodilatation is achieved with a 6-minute infusion at a dosage of 0.14 mg/kg/min.
   c. Patients who complain of shortness of breath or wheezing should be given 50 to 100 mg of esmalol intravenously.
   d. Radiotracer injection is administered immediately following dipyridamole infusion.

14. During myocardial perfusion imaging with pharmacologic stress, which one of the following does not reflect the correct timing of radiopharmaceutical injection?
   a. Radiopharmaceutical should be administered immediately following a 6-minute adenosine infusion.
   b. Radiopharmaceutical should be administered 3 to 5 minutes following completion of dipyridamole infusion.
   c. Radiopharmaceutical should be administered 2 minutes before the end of dobutamine infusion.
   d. Radiopharmaceutical should be administered 7 to 9 minutes from the start of dipyridamole infusion.

15. Which one of the following statements about Tl-201 thallous chloride is true?
   a. Thallium's myocardial extraction is proportional to myocardial blood flow up to 4 mL/min/g of myocardium.
   b. Approximately 1% of the injected dose localizes in the heart.
   c. The critical organ is the heart.
   d. Thallium is a myocardial perfusion-viability agent.

16. Increased specificity in the diagnosis of ischemia versus infarction can be achieved if:
   a. 4 mCi of Tl-201 is injected instead of 2 mCi in a thallium exercise/rest study.
   b. a thallium exercise/redistribution/reinjection protocol is used.
   c. a sestamibi exercise/rest protocol is used.

d. adenosine is used instead of exercise for the stress study.

17. The SPECT procedure of choice for assessment of myocardial viability in a patient with known coronary artery disease and ventricular dysfunction is a:
    a. thallium rest/redistribution study.
    b. sestamibi rest/exercise study.
    c. tetrofosmin rest/exercise study.
    d. sestamibi adenosine/rest study.

18. In pharmacologic coronary vasodilator stress procedures the patient should abstain from caffeinated food and beverages prior to the procedure for at least:
    a. 1 hour.
    b. 12 hours.
    c. 24 hours.
    d. 48 hours.

19. Which one of the following best describes heart uptake as a percent of the injected dose?
    a. Sestamibi > Thallium > Tetrofosmin
    b. Tetrofosmin > Thallium > Sestamibi
    c. Thallium > Sestamibi > Tetrofosmin
    d. Thallium > Tetrofosmin > Sestamibi

20. Which one of the following best describes the effective dose (rad/mCi administered) for myocardial perfusion tracers?
    a. Sestamibi > Thallium > Tetrofosmin
    b. Tetrofosmin > Thallium > Sestamibi
    c. Thallium > Sestamibi > Tetrofosmin
    d. Thallium > Tetrofosmin > Sestamibi

21. Which one of the following best describes the myocardial extraction of heart imaging agents?
    a. Sestamibi > Thallium > Tetrofosmin
    b. Tetrofosmin > Thallium > Sestamibi
    c. Thallium > Sestamibi > Tetrofosmin
    d. Thallium > Tetrofosmin > Sestamibi

22. Which one of the following statements about Tl-201 thallous chloride myocardial exercise stress-redistribution study is true?
    a. Three to 4 hours following the stress study, regions of normal myocardium demonstrate a decrease in thallium activity while regions of ischemic myocardium demonstrate an increase in activity.
    b. Regions of myocardial scar demonstrate more rapid washout of activity during thallium redistribution than do ischemic regions.
    c. Regions of myocardial ischemia demonstrate perfusion defects on the stress study which persist on the redistribution study.
    d. Perfusion defects on the stress study that fail to fill-in on the 4-hr redistribution study is strong evidence for the presence of scar.

23. Which one of the following is the agent of choice for assessing myocardial viability with SPECT imaging?
    a. Tc-99m pyrophosphate
    b. Tc-99m tetrofosmin
    c. Tc-99m sestamibi
    d. Tl-201 thallous chloride

24. All of the following are advantages of Tc-99m sestamibi when compared to Tl-201 thallous chloride for myocardial imaging, except:
    a. Higher detection sensitivity and image resolution
    b. Ability to perform first-pass ventriculography
    c. Ability to repeat image acquisition
    d. Better sensitivity for detecting hibernating myocardium

25. Which one of the following statements about the biological properties of Tc-99m sestamibi is correct?
    a. Tc-99m sestamibi washes out of the heart quickly following intravenous injection.
    b. Tc-99m sestamibi has an affinity for myocyte mitochondria.
    c. Tc-99m sestamibi is taken up as a monvalent cation via the myocyte Na/K membrane pump.
    d. Heart uptake of Tc-99m sestamibi is readily blocked by oubain.

Begin Lesson 3 here.

26. Which one of the following statements comparing Tc-99m tetrofosmin and Tl-201 thallous chloride is correct?
    a. The myocardial extraction of both agents is similar.
    b. The redistribution properties of both agents are similar.
    c. Both agents are monovalent cations.
    d. Both agents are equivalent in assessing myocardial viability.

27. Which one of the following pairs of myocardial imaging agents are most similar regarding their biologic properties?
    a. Thallium and sestamibi
    b. Sestamibi and tetrofosmin
    c. Tetrofosmin and thallium
    d. Thallium and fludeoxyglucose

28. Which one of the following agents is taken up into the heart by facilitated diffusion?
    a. F-18 fludeoxyglucose
    b. Tl-201 thallous chloride
    c. Tc-99m sestamibi
    d. Rb-82 rubidium chloride

29. Which one of the following statements about Tc-99m tetrofosmin is false?
    a. It localizes in the heart by passive diffusion.
    b. It is retained principally bound in the myocyte cytosol.
    c. It has a shelf life of 8 hours following preparation.
    d. It's radiochemical purity must be ≥ 90 percent.

30. Which one of the following PET radiotracer combinations is typically used to evaluate myocardial viability?
    a. Rb-82 rubidium chloride/C-11 palmitate
    b. O-15 water/F-18 FDG
    c. N-13 ammonia/C-11 acetate
    d. N-13 ammonia/F-18 FDG

31. Which one of the following PET agents is used for assessing overall oxidative metabolism in the heart?
    a. F-18 fludeoxyglucose
    b. C-11 acetate
    c. C-11 palmitate
    d. O-15 water

32. Which one of the following PET nuclides has the shortest physical half-life?
    a. O-15
    b. Rb-82
    c. N-13
    d. C-11

33. All of the following PET agents are markers of coronary blood flow except:
    a. N-13 ammonia
    b. O-15 water
    c. Rb-82 chloride
    d. F-18 FDG

34. The PET blood flow marker of choice is:
    a. Rb-82 chloride
    b. O-15 water
    c. N-13 ammonia
    d. F-18 FDG

35. All of the following are associated with the uptake of FDG into heart muscle except:
    a. lipophilicity
    b. anaerobic glycolysis
    c. facilitated diffusion
    d. phosphorylation

36. Positive predictive and negative predictive accuracies for assessing myocardial viability and restoration of ventricular function are highest with which one of the following studies?
    a. A thallium rest/redistribution study
    b. A thallium exercise/redistribution/reinjection study
    c. A PET perfusion/metabolism study
    d. A sestamibi rest/stress study

37. Which one of the following agents is able to assess myocardial perfusion abnormalities with a single dose injection?
    a. Tc-99m sestamibi
    b. Tc-99m tetrofosmin
    c. F-18 fludeoxyglucose
    d. Tl-201 thallous chloride

38. A revascularization procedure will likely improve ventricular function in which one of the following conditions?
    a. Hibernating myocardium
    b. Stunned myocardium
    c. Transmural infarction
    d. Non-transmural infarction

39. All of the following are desirable properties of a radiopharmaceutical for blood pool imaging except:
    a. Slow blood clearance over time
    b. Minimum accumulation of activity in the extravascular space
    c. High photon flux
    d. Long physical half-life

40. The labeling efficiency of Tc-99m red blood cells employing the in vivo labeling method is about:
    a. 60 percent
    b. 75 percent
    c. 85 percent
    d. 98 percent

41. Which one of the following statements regarding myocardial ventriculography is false?
    a. A first-pass study allows assessment of right ventricular function.
    b. An ECG multigated acquisition (MUGA) study allows assessment of left ventricular function only.
    c. Ventricular volumes and ejection fractions can be assessed.
    d. First-pass and MUGA studies can be done with Tl-201 thallous chloride or Tc-99m sestamibi or Tc-99m labeled red blood cells.

42. A normal left ventricular ejection fraction is equal to or greater than:
    a. 35 percent
    b. 45 percent
    c. 55 percent
    d. 65 percent

43. The purpose of the Tl-201 thallous chloride/Tc-99m sestamibi dual-isotope imaging protocol is to:
    a. Shorten the study time
    b. Improve study specificity
    c. Increase study sensitivity
    d. Reduce radiation dose

44. A patient in an emergency situation with unstable angina requiring immediate medical care for the condition could best be evaluated for possible myocardial ischemia at a later time by which one of the following studies?
    a. Tl-201 rest/redistribution study
    b. Tl-201 rest/Tc-99m sestamibi stress study

c. Tc-99m sestamibi rest study
d. Tc-99m sestamibi stress study

45. The radiochemical purity requirement of Tc-99m sestamibi or Tc-99m tetrofosmin must be greater than or equal to:
    a. 85 percent
    b. 90 percent
    c. 95 percent
    d. 98 percent

46. Which one of the following package insert instructions for labeling and use of Tc-99m sestamibi is false?
    a. Up to 150 mCi of Tc-99m sodium pertechnetate can be added to the kit.
    b. Heating time in a boiling water bath is 10 minutes.
    c. Two milliters of air must be introduced into the vial before heating.
    d. The radiolabeled product is stable for 6 hours.

47. Which one of the following agents is a neutral lipophilic species?
    a. Tc-99m sestamibi
    b. Tc-99m tetrofosmin
    c. Tc-99m $(NOEt)_2$
    d. F-18 fludeoxyglucose

48. Each of the following study findings would support a diagnosis of viable myocardium except:
    a. a fixed defect on a Tc-99m sestamibi rest/stress study with abnormal myocardial wall motion and decreased thickening on a gated SPECT study.
    b. a fixed defect on a Tc-99m sestamibi rest/stress study with normal myocardial wall motion and myocardial thickening on a gated SPECT study.
    c. a reversible defect on a Tc-99m tetrofosmin rest/stress study.
    d. a reversible defect on a Tl-201 rest/redistribution study.

49. Which one of the following is not associated with the mechanism of localization of Tc-99m pyrophosphate in a myocardial infarct?
    a. Residual blood flow to the infarct region
    b. Influx of calcium ions into the infarcted cells
    c. Membrane-associated phosphatidylserine on dying myocytes
    d. Mitochondrial deposits of hydroxyapatite crystals

50. The mechanism of localization of which one of the following infarct-avid agents is involved with binding to basic histones in damaged myocytes?
    a. Tc-99m pyrophosphate
    b. Tc-99m glucarate
    c. Tc-99m annexin V
    d. In-111 imciromab pentetate