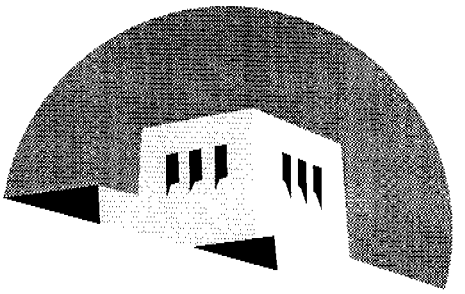

The University of New Mexico

THE UNIVERSITY OF NEW MEXICO
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Radiopharmaceuticals Used for Myocardial Imaging

by:

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RADIOPHARMACEUTICALS USED FOR MYOCARDIAL IMAGING

STATEMENT OF OBJECTIVES

The primary purpose of this lesson is to increase the reader's knowledge and understanding of myocardial perfusion imaging and the radiopharmaceuticals used for this purpose.

On completion of this continuing education lesson, the reader should be able to:

1. discuss the clinical utility of myocardial perfusion studies.
2. explain the relationship between myocardial blood flow and metabolism.
3. describe the physical properties and biodistribution of radiopharmaceuticals used for myocardial imaging.
4. explain the advantages and disadvantages of dual-isotope cardiac imaging.
5. describe the three planes utilized in myocardial SPECT imaging and their relationship to myocardial anatomy and physiology.
6. describe the preparation and quality control procedures for each radiopharmaceutical.
7. discuss the various aspects of radiopharmaceutical and imaging protocol selection.

COURSE OUTLINE

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II. INCIDENCE AND PREVALENCE OF CORONARY ARTERY DISEASE

III. ANATOMY AND PHYSIOLOGY OF THE HEART

IV. IMAGE AND ANATOMY CORRELATION

V. CLINICAL APPLICATIONS OF MYOCARDIAL PERFUSION IMAGING

VI. RADIOPHARMACEUTICALS FOR PERFUSION IMAGING
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- B. ^{99m}Technetium Myocardial Perfusion Imaging Agents
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VIII. CASE STUDY

IX. SUMMARY

RADIOPHARMACEUTICALS USED FOR MYOCARDIAL IMAGING

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INTRODUCTION

Coronary artery disease (CAD) is the single most common cause of death in the United States. The evaluation of myocardial perfusion is vital to the overall assessment of this disease process. Nuclear medicine diagnostic imaging plays an important role in the clinical assessment of myocardial perfusion. Nuclear cardiology procedures have steadily increased in number over the past several years, making myocardial perfusion imaging the most commonly ordered procedure in most nuclear medicine departments today. This lesson will review some important points concerning myocardial perfusion imaging and the radiopharmaceuticals used.

INCIDENCE AND PREVALENCE OF CORONARY ARTERY DISEASE

It is easy to understand why myocardial perfusion imaging (MPI) is the number one nuclear medicine procedure when one considers the prevalence of cardiovascular disease in the United States. According to 1995 estimates, 58,200,000 Americans have one or more forms of cardiovascular disease (heart disease and stroke). Heart disease alone killed 733,834 people in 1996, and ranks as the leading cause of death in the U.S. for both men and women. Over 13.9 million people alive today have a history of heart attack, angina pectoris (chest pain) or both. Typically a patient already has greater than a 50% occlusion in the coronary arteries before any symptoms of coronary artery disease appear. This year an estimated 1,100,000 Americans will have a new or recurrent coronary attack, and about one third of them will die.[1]

ANATOMY AND PHYSIOLOGY OF THE HEART

Understanding how blood is supplied to the heart through the coronary arteries is necessary to interpret myocardial perfusion images.

The heart muscles need their own oxygen-rich blood supply. Oxygen is delivered to the myocardium by the left and right coronary arteries. (Figure 1). The left main coronary artery (LCA) divides into two main branches. The left anterior descending artery (LAD) supplies oxygen and nutrition to the interventricular septum and

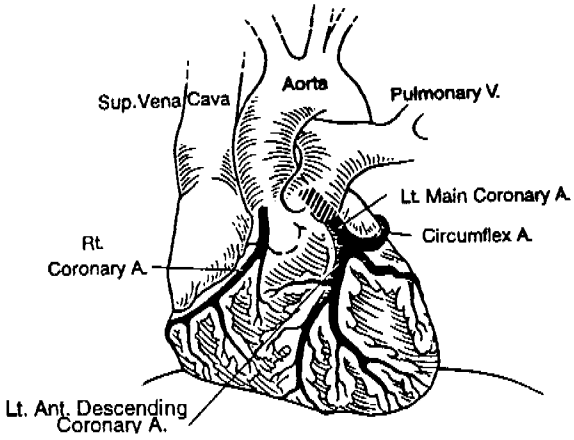


Figure 1: *From Clinical Electrocardiography: A Self-Study Course. Lea & Fe biger 1987*

anterior wall of the left ventricle, whereas the left circumflex artery (LCx) supplies the left atrium and the posterior and lateral walls of the left ventricle. The right coronary artery (RCA) supplies the inferior wall of the left ventricle, the free wall of the right ventricle, and the right atrium. Variations in the branching pattern of the coronary arteries are common. In about 67% of patients, the RCA is dominant, crosses the crux, and supplies part of the left ventricular wall and the ventricular septum. In 15% of patients, the LCA is dominant, in which case the Cx branch crosses the crux giving off the posterior interventricular branch and supplying all of the left ventricle, the ventricular septum, and part of the right ventricular wall. In 18% of patients, both coronary arteries reach the crux, which is called a balanced coronary arterial pattern. Blood flow is greater in the RCA than the LCA in about 50% of patients; equal in about 30%; and greater in the LCA in 20% of patients. Resting coronary blood flow (CBF) is about 225 mL/min or 5% of the cardiac output. A fivefold increase in CBF may occur during stress or exercise. The majority of CBF occurs during diastole when cardiac muscle relaxes and no longer obstructs flow through capillaries. Tachycardia is associated with a decrease in time for CBF to occur during diastole and further jeopardizes the adequacy of myocardial oxygen delivery, especially in arteries stenosed by atherosclerosis. Blood drains from the myocardium to the coronary veins, located alongside the coronary arteries, and terminate in the coronary sinus of the right atrium.

IMAGE AND ANATOMY CORRELATION

The standard SPECT views of the left ventricle are sometimes difficult to interpret. Because the location and orientation of the heart within the chest can vary greatly from person to person, standardization slices that use the left ventricle itself as a frame of reference have been created. Images are typically displayed in three planes (see figure 2): (a) vertical long axis (sagittal), (b) horizontal long axis (coronal), and (c) short axis (transverse). [For a pictorial comparison of nuclear images with human anatomy, the Fujisawa website is helpful at http://www.adenoscan.com/adenoscan/spectmonograph/imageinterfr.htm]. The cardiac short axis images of the left ventricle are the most clinically relevant for image interpretation. If perfusion defects are seen in the short axis view, a correlating defect should also be seen on the horizontal or vertical long axis view. Another method of displaying the images is in the form a tomographic "bull' s eye" plot. It is a functional map of the circumferential profiles of the short-axis slices from apex (center) to base (periphery), similar to flattening the short-axis segments down to the apex. A bull' s eye plot is seen in the case study that is presented later in this lesson.

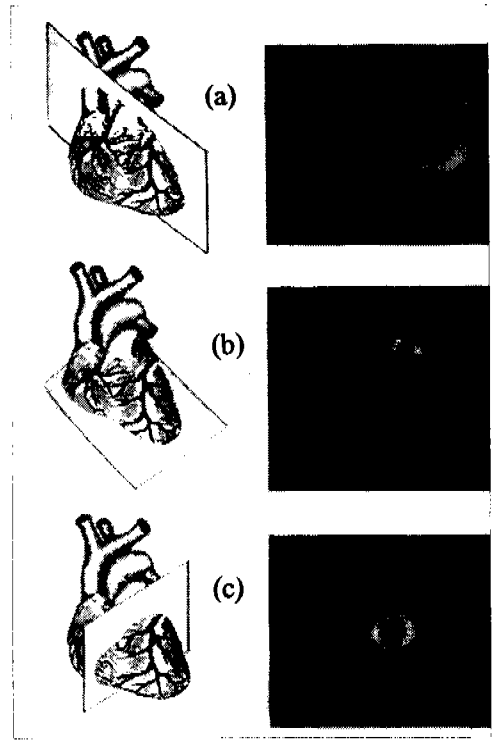


Figure 2 *Adapted from Cardiac Nuclear Medicine, McGraw Hill 1997.*

CLINICAL APPLICATIONS OF MYOCARDIAL PERFUSION IMAGING

Previously, all patients with chest pain or suspected coronary artery disease (CAD) were considered candidates for MPI. Currently, better criteria have evolved as accepted indications for MPI. One of these criteria is an uninterpretable EKG in a patient with symptoms suggestive of CAD. The ability to directly image myocardial perfusion is not affected by EKG changes. Patients with classic symptoms of CAD, EKG findings, or laboratory findings strongly suggestive of CAD will usually not undergo routine screening with MPI. Many of these patients will go directly to cardiac catheterization to assess the operability of the coronary lesions. It may also be noted that women are less likely to demonstrate the classic symptoms of CAD, and MPI may be an effective tool in diagnosing underlying disease.

Subsequent to cardiac catheterization, it is quite common to reevaluate the patient with MPI. Lesions that are technically correctable or well-collateralized lesions may prove somewhat deceptive at the time of catheterization. Differences in projection in the catheterization lab may cause lesions to appear to have greater or lesser diameter narrowing than the actual value. One of the difficulties of cardiac catheterization is the inability to image small vessels. It is essentially a larger vessel imaging system. When disease involves small vessels, the catheterization may underestimate the degree of disease present. MPI depicts small vessel disease as well as large vessel disease. In addition, when wall motion abnormalities are detected, catheterization may not determine whether the myocardium in that area is simply hypoperfused and viable, or infarcted. The MPI study is not subject to this problem since it directly measures the perfusion of the cardiac muscle. When MPI indicates a stress or drug-induced perfusion defect in the myocardium that reverses at rest, the case for revascularization is strong. Where the zone does not reverse between stress and rest, it is more difficult to advocate a surgical intervention. It should also be kept in mind that the cost of a cardiac catheterization may be six to ten times that of an MPI study. Catheterization is also more invasive, carrying a greater risk of morbidity, and possible mortality.

Table 1: Summary of Clinical Indications for Myocardial Perfusion Imaging

- Diagnosis of coronary artery disease
  - presence
  - location (coronary territory)
  - extent (number of vascular territories involved)
- Assessment of the degree of coronary stenosis and impact on regional perfusion
- Myocardial viability assessment
  - ischemia vs scar
  - prediction of improvement in function following revascularization
- Risk assessment (prognosis) in patients:
  - post myocardial infarction
  - pre-operative for major surgery who may be at risk for coronary events
- Monitoring treatment effect
  - after coronary revascularization (coronary artery bypass grafting, angioplasty, etc)
  - medical therapy for congestive failure or angina
  - lifestyle modification

from the SNM Procedure Guideline for Myocardial Perfusion Imaging

RADIOPHARMACEUTICALS FOR PERFUSION IMAGING

Currently there are five radiopharmaceuticals approved by the Food and Drug Administration (FDA) for the assessment of myocardial perfusion: (1) ^{201}Tl thallous chloride, (2) ^{99m} Tc-sestamibi, (3) ^{99m} Tc-teboroxime, (4) ^{99m} Tc-tetrofosmin, and (5) ^{82}Rb rubidium chloride. Rb-82 requires the expensive ^{82}Sr/^{82}Rb generator and the use of a PET camera or coincidence imaging, and ^{99m}Tc-teboroxime is no longer commercially available in the U.S. For these reasons this lesson will primarily focus on ^{201}Tl, ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin. The role of ^{18}F-fluorodeoxyglucose in the assessment of myocardial viability will also be considered.

We will begin by looking at the properties of an ideal myocardial perfusion tracer found in Table 2. It will become apparent that the ideal radiopharmaceutical for MPI does not exist.

Table 2. Properties of an Ideal Myocardial Perfusion Tracer

- Myocardial uptake in direct relationship to myocardial blood flow
- High extraction fraction (high % of tracer is extracted from the blood)
- Negligible interference with myocardial visualization from adjacent organs and tissues
- No significant attenuation of the agent by tissues between the heart and the camera
- Constant location and concentration of the tracer in the myocardium during image acquisition
- Lack of interference with tracer uptake into the myocardium by pharmacologic agents or impaired myocardial metabolism
- High photon yield detectable with standard imaging equipment
- Low cost
- High degree of patient safety
- Rapid availability for imaging patients with acute chest pain

^{201}Tl Thallous Chloride

Although ^{201}thallium was the principal myocardial imaging agent for twenty years, recently the ^{99m}technetium agents have passed ^{201}Tl in popularity as stress imaging agents. Thallium is still used in many nuclear medicine departments, especially for resting images in the dual-isotope protocol. Interest in thallium as a myocardial tracer stemmed from its biological similarities to potassium, the principal cation in the human myocyte. Potassium is concentrated in the myocyte by the adenosine triphosphate (ATP) - dependent sodium-potassium pump. It was observed that the sodium-potassium pump does not differentiate between potassium and thallium. It is currently believed that thallium enters into the myocardium by a combination of active (energy-dependent) and passive (chemical gradient) mechanisms.[4] The cellular uptake of thallium may be blocked by ouabain and digitalis because of inhibition of the sodium-potassium ATPase system. Furosemide may inhibit the co-transport system. The linear relationship between

^{201}Tl myocardial uptake and myocardial blood flow is maintained during conditions of increased myocardial oxygen demand. When coronary blood flow is increased without a corresponding increase in myocardial oxygen demand (e.g., during pharmacologic stress with dipyridamole or adenosine), myocardial uptake of ^{201}Tl increases substantially less than myocardial blood flow. Over a broad range of flows, the mean extraction fraction is approximately 73%.[4] The myocardial ^{201}Tl activity reaches 80% of peak activity within 1 minute following intravenous injection, and peak ^{201}Tl activity occurs approximately 24 minutes following injection in anesthetized dogs.[25] As myocardial blood flow is progressively reduced, the percentage of peak activity reached in 1 minute is reduced and the time-to-peak myocardial activity is prolonged.

One of the most important aspects of thallium kinetics is tracer redistribution. The myocardial concentration of ^{201}Tl at any point in time is determined by an equilibration process. This equilibration process has two components - washout of ^{201}Tl from the myocardium and new myocardial uptake of ^{201}Tl from the blood pool. In myocardium that is ischemic, the relative amount of thallium in the zone of diminished perfusion is lower than that of the normally perfused zone (in direct proportion to the difference in tissue blood flow to the two regions). If serial images are recorded over several hours, the relative loss of thallium from the normally perfused zone is greater than that of the ischemic zone. At about 3 to 4 hours, the relative concentration of thallium in the two areas may appear similar. This phenomenon is called redistribution and has made thallium very useful for identifying ischemic myocardium. Although a second injection before rest imaging is not required, diagnostic accuracy is improved with a "booster" dose of ^{201}thallium. Usually 1-2 mCi of ^{201}Tl is injected to increase the visualization of reversible ischemia, thus reducing the number of false positives studies and increasing the exam specificity.

In normal subjects, the lungs extract a small percentage of ^{201}Tl before it reaches the systemic circulation. Greater extraction signals left ventricular failure and occurs with high pulmonary capillary wedge pressure and increased pulmonary transit time due to increased lung water. Several studies have demonstrated the prognostic significance of increased lung uptake in patients with known or suspected CAD. Lung uptake is not indicative of CAD in ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin imaging.

The imaging properties of ^{201}Tl are not ideal. The physical and biological characteristics of ^{201}Tl pose problems for imaging. Thallium-201 (physical $t_{\frac{1}{2}}$ = 73 hours) is minimally excreted through the bowel and kidneys (only 10% is lost from the body over 10 days), resulting in a long biologic half-life. Approximately 10% of each dose of thallium localizes in each kidney with a radiation burden of 1.7 rad/mCi to the kidney.[27] Organs receiving a higher radiation dose include the thyroid (2.3 rads/mCi) and the testes (3.1 rads/mCi). The radiation dose to the patient limits the administered dose to 4 mCi, of which only about 3 -5% of the injected dose localizes in the myocardium (<200 uCi). Along with the low energy of the characteristic Hg X-rays at 68-80 keV, the attenuation artifacts may be particularly prominent and result in a poor quality image. Cyclotron production may also limit availability. All of these factors contributed to the development of the ^{99m}Tc-labeled radiopharmaceuticals for MPI.

^{99m}Technetium Myocardial Perfusion Imaging Agents

After roughly ten years of using thallium for perfusion imaging, the first technetium compounds were introduced. The potential advantages of a ^{99m}Tc myocardial perfusion agent in comparison to ^{201}Tl include the following:

- The 140 keV gamma emission of ^{99m}Tc is ideally suited for imaging on a standard gamma camera.
- The 140 keV photon of ^{99m}Tc is less attenuated by soft tissue compared to the 68 to 80 keV x-ray emissions of ^{201}Tl.
- The shorter half-life of ^{99m}Tc (6 hours) compared to the 73 hour half-life of ^{201}Tl permits greater administered activity because of the lower radiation dose, thus improving count statistics.
- There is an increased availability of ^{99m}Tc over the cyclotron-produced ^{201}Tl which is especially helpful for acute use situations.
- There are fewer scheduling conflicts in the nuclear medicine department due to the six hour time window for imaging stress patients. ^{201}Tl patients must be imaged directly after stress (i.e. if a cardiologist is late, the camera must be held open awaiting the stress imaging, which may disrupt the imaging schedule).
- Gated SPECT studies with wall motion information can be obtained with the ^{99m}Tc agents.

A comparison of ^{201}Tl thallous chloride and the ^{99m}Tc myocardial perfusion imaging agents is found in Tables 3-9.

^{99m}Tc-sestamibi versus ^{99m}Tc-tetrofosmin

Until recently, most clinical studies assessing the ^{99m}technetium agents were conducted as a comparison of these agents with ^{201}Tl or cardiac catheterization results. At this time, there are few studies that directly compare ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin for the detection coronary artery disease. Recent studies by Taillefer et al.[34] and Acampa et al.[35] indicate that the sensitivity of

these two radiopharmaceuticals is essentially equivalent. There is a need for studies with larger numbers of patients and with breakdowns for the sensitivity of the agents in single- and multi-vessel disease. Currently, the selection of technetium agents is principally based on physician preference and national account contracts rather than any significant differences in kinetic behavior or clinical utility. The sections immediately following explore ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin in more detail.

^{99m}Technetium Sestamibi

Sestamibi is a cationic complex comprised of six MIBI (2-Methoxy IsoButyl Isonitrile) molecules chelated to one technetium atom, hence the name sesta (six) mibi. This structure is associated with sufficient lipophilicity to enable it to partition across biological membranes. However, the entry of ^{99m}Tc-sestamibi into myocardial cells cannot be explained by passive diffusion across the myocyte cell membrane alone. The distribution of ^{99m}Tc-sestamibi in myocytes is strongly dependent on plasma membrane and mitochondrial membrane potential.[4] The accumulation depends on the maintenance of myocyte viability as well as blood flow. At one hour after injection, approximately 1.2% of the administered activity is localized in the heart, 5.6% is localized in the liver, and 0.9% is localized in the lung.[11] ^{99m}Tc-sestamibi does not undergo significant myocardial redistribution. The activity in the heart remains virtually fixed at the time of injection. Therefore, delayed imaging demonstrates the myocardial perfusion at the time of injection, which is useful for flexible camera time scheduling and acute use situations. It is also advantageous to allow the patient to wait following exercise stress, so that the patient's breathing (chest movement) returns to normal and the cardiac tilt that occurs during exertion returns to a resting position.

Sestamibi Preparation The package insert recommends that 25-150 mCi of ^{99m}Tc-sodium pertechnetate in a volume of 1-3 mL be added to the vial. The vial should then be heated in a boiling water bath or heating block at 100°C for 10 minutes. (The volume of the kit should be kept small to prevent the build up of excess pressure in the vial during heating, which may cause the vial to rupture). After cooling, the radiochemical purity determination is performed using a 7.5 cm Baker-Flex aluminum oxide-coated plastic plate and absolute ethanol. It is important to heat the plates to 100°C to drive off any moisture prior to use (then store in a desiccator) and to use high quality ethanol (>95% ethanol content) for accurate results.[24] The plate is pre-spotted with ethanol at the origin 1.5 cm from the bottom; before drying, a drop of the ^{99m}Tc-sestamibi preparation is placed at the origin line. The spotted plate is placed in the absolute ethanol solvent and allowed to develop until the solvent front has traveled 5 cm from the point of application. The plate is then cut 4 cm from the bottom and the activity is measured in each piece with an appropriate detector. Free pertechnetate and reduced hydrolyzed technetium remain at the origin while the labeled ^{99m}Tc-sestamibi travels with the solvent front.[15] The radiochemical purity must be at least 90% prior to patient administration. There are alternative quality control procedures being used in practice that utilize the Sep-Pak cartridge or solvent saturations pad and ethyl acetate.[21]

^{99m}Technetium Tetrofosmin

Similar to ^{99m}Tc-sestamibi, ^{99m}Tc tetrofosmin is a lipophilic cationic complex that is concentrated in myocardial mitochondria. At 5 minutes after resting injection, 1.2% to 1.8% of the ^{99m}Tc-tetrofosmin dose is localized in the myocardium. With the resting injection, heart-to-liver ^{99m}Tc-tetrofosmin activity ratios increase from 0.8 at 5 min to 1.3 at 60 min and 2.1 at 180 min, which is slightly higher than ^{99m}Tc-sestamibi.[4] The heart-to-liver ratios increase for both ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin at exercise, because blood is shifted to the peripheral muscles during exercise. Like ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin does not undergo significant redistribution. Potential advantages of ^{99m}Tc-tetrofosmin include (1) relatively rapid hepatic clearance,[36] which may permit earlier imaging following injection at rest and (2) room temperature kit preparation. Approximately 66% of the injected activity is excreted within 48 hours post-injection, with approximately 40% excreted in the urine and 26% in the feces.

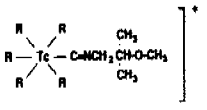
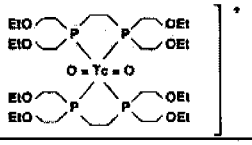
Tetrofosmin preparation: The package insert recommends the addition of 4-8 mL (up to 240 mCi) of ^{99m}Tc-sodium pertechnetate, in a concentration not to exceed 30 mCi/mL, to the vial. After the addition of pertechnetate, the labeling reaction should be allowed to incubate for 15 minutes at room temperature. The reconstituted vial should be stored at room temperature and used within 8 hours. Before patient administration, the radiochemical purity determination should be completed using a 2 x 20 cm Gelman ITLC/SG strip with a 35:65 v/v mixture of acetone/dichloromethane as the solvent. Alternative quality control procedures have also been developed for ^{99m}Tc-tetrofosmin.[22]

Other Approaches to Myocardial Imaging

In addition to standard perfusion imaging, other approaches have also been utilized to assess perfusion and viability, including determination of oxidative metabolism with [^{11}C] palmitate or [^{11}C] acetate, uptake and retention of ^{82}Rb or [^{13}N] ammonia, [^{18}F] fluorodeoxy-

Table 3: General Information			
General Information	***^{201}Tl***	***^{99m}Tc-Sestamibi***	***^{99m}Tc-Tetrofosmin***
generic name	^{201}Tl thallous chloride	technetium ^{99m}Tc-sestamibi	technetium ^{99m}Tc-tetrofosmin
trade name	---	Cardiolite®	Myoview™
other name	---	MIBI; hexamibi, RP-30	P53
Chemical name	TlCl	hexa-2-methoxyisobutyl isonitrile	1,2-bis[bis (2-ethoxyethyl) phosphino]ethane
Classification	Ionic element	Isonitrile	Diphosphine
Manufacturer	DuPont, Mallinckrodt, Nycomed Amersham	DuPont	Nycomed Amersham
Approval date	Dec. 1977	Dec. 1990	Feb. 1996
current cost (actual cost may vary greatly)	List: $195/2.2 mCi	List: $1666/5-vial kit	List: $2400/5-vial kit

* Courtesy of James A. Ponto, University of Iowa Hospitals and Clinics.

Table 4: Chemical Properties			
Chemical Properties	***^{201}Tl***	***^{99m}Tc-Sestamibi***	***^{99m}Tc-Tetrofosmin***
Structure	Tl+ ion (thallous)		
Charge	+1	+1	+1
Philicity	hydrophilic	lipophilic	lipophilic

* Courtesy of James A. Ponto, University of Iowa Hospitals and Clinics.

Table 5: Radionuclide Properties			
Radionuclide Properties	***^{201}Tl***	***^{99m}Tc-Sestamibi***	***^{99m}Tc-Tetrofosmin***
half-life	73 hours	6 hours	6 hours
type of decay	electron capture	isomeric transition	isomeric transition
photon energy and abundance	135 keV γ rays (2.7%) 167 keV γ rays (10%) 68-80 keV x-rays (94%)	140 keV γ rays (89%)	140 keV γ rays (89%)
half value layer	0.25 - 0.4 mm Pb 3.6 - 4.8 cm water	0.17 mm Pb 4.5 cm water	0.17 mm Pb 4.5 cm water

* Courtesy of James A. Ponto, University of Iowa Hospitals and Clinics.

Table 6: Biodistribution Data

Biodistribution	*^{201}Tl*	*^{99m}Tc-Sestamibi*	*^{99m}Tc-Tetrofosmin*
uptake mechanism	Na^+/K^+ ATPase pump (active transport)	passive diffusion across myocardial membranes; electrostatic binding to mitrochondrial negative potentials	passive diffusion across myocardial membranes; electrostatic binding to mitrochondrial negative potentials
extraction fraction[4]	~ 82%	~ 66%	~ 60%
heart uptake of initial dose[19]	~ 4%	~ 1.2 %	~1.2 %
myocardial uptake vs. coronary flow[4]	Linear up to ~ 3 times normal and then gradual "roll-off"	linear up to ~ 2.5 times normal and then "roll-off"	linear up to ~ 2.5 times normal and then "roll-off"
myocardial washout[19]	~ 28%/hr	~ 10%/hr	~ 4%/hr
redistribution	Yes	Negligible	Negligible
blood clearance[19]	5-8% at 5 min.	8% at 5 min.	5% at 10 min.
heart:liver ratio[36]	Stress 2.1; delayed 1.4	t (min) / stress / rest: 5 / 1.3 / 0.5; 30 / 1.4 / 0.5; 60 / 1.8 / 0.6; 120 / 2.3 / 1.1; 180 / 2.4 / 1.4 [normal volunteers]	t (min) / stress / rest: 5 / 1.3 / 0.8; 30 / 1.4 / 1.0; 60 / 1.6 / 1.3; 120 / 1.8 / 1.7; 180 / 2.0 / 2.1 [clinical patients]
heart:lung ratio[36]	Stress 2.3; delayed 1.9	t (min) / stress / rest: 5 / 2.1 / 1.9; 30 / 2.3 / 2.2; 60 / 2.4 / 2.4; 120 / 2.5 / 2.5; 180 / 2.5 / 2.6 [normal volunteers]	t (min) / stress / rest: 5 / 1.9 / 1.8; 30 / 2.2 / 2.0; 60 / 2.1 / 2.1; 120 / 2.2 / 2.1; 180 / 2.1 / 2.1 [clinical patients]
excretion[19]	urine 4-8% in 24 hr. feces: 20% in 6 days Biologic half-life: 10 days	urine: 27% in 48 hrs. hepatobiliary/feces: 33%	urine: 40% in 48 hrs. hepatobiliary/feces: 34%
dosimetry[15, 16, 27]	rads/ 1 mCi	Rads/ 30 mCi: at rest / at stress	Rads/ 30 mCi: at rest / at stress
heart wall	1.0	0.5 / 0.5	0.5 / 0.5
gallbladder	0.3	2.0 / 2.8	3.9 / 3.0
small intestine	1.7	3.0 / 2.4	1.7 / 1.4
large intestine	1.3	5.4 / 4.5	3.0 / 2.3
kidney	1.7	2.0 / 1.7	0.5 / 0.5
bladder	0.2	4.2 / 3.0	1.9 / 1.6
liver	0.4	0.6 / 0.4	0.4 / 0.4
lungs	0.2	0.2 / 0.2	0.3 / 0.4
bone marrow	0.2	0.5 / 0.5	0.4 / 0.4
ovaries	0.4	1.6 / 1.3	1.0 / 0.9
testes	3.1	0.4 / 0.3	0.3 / 0.4
Effective Dose	1.3	1.7 / 1.4	0.9 / 0.8

* Courtesy of James A. Ponto, University of Iowa Hospitals and Clinics.

Table 7: Preparation [15, 16, 27]			
Preparation	***^{201}Tl***	***^{99m}Tc-Sestamibi***	***^{99m}Tc-Tetrofosmin***
radiolabeling procedure	Commercially available, ready to use	add ^{99m}Tc-pertechnetate, boil 10 minutes, cool for 15 min.	add ^{99m}Tc-pertechnetate, incubate for 15 min.
quality control	---	aluminum oxide TLC in ethanol	ITLC-SG in 35:65 acetone/ dichloromethane
shelf-life	6 days after calibration	6 hours	8 hours

* Courtesy of James A. Ponto, University of Iowa Hospitals and Clinics.

Table 8: Imaging Protocols			
Imaging Protocols	***^{201}Tl***	***^{99m}Tc-Sestamibi***	***^{99m}Tc-Tetrofosmin***
injection to imaging times	rest: ~15 minutes stress: ~5 minutes redistribution:3-4 hours; late redistribution: next day	rest: ~30-60 minutes or anytime thereafter stress: ~15 minutes or anytime thereafter vasodilator "stress": ~45-60 min. or later	rest: ~30 minutes or anytime thereafter stress: ~15 minutes or anytime thereafter vasodilator "stress": ~20-30 min. or later
duration of imaging time restrictions	Must complete stress imaging in ~45 minutes because redistribution may already be occurring	---	---
standard administered dosage(s)	2 mCi for planar 3-4 mCi for SPECT; 1-2 mCi for reinjection	Two day protocol: 20-30 mCi each One day protocol: 1st dose = ~ 8 mCi 2nd dose = ~25 mCi	Two day protocol: 20-30 mCi each One day protocol: 1st dose = ~ 8 mCi 2nd dose = ~25 mCi
Gated SPECT	No	Yes	Yes

* Courtesy of James A. Ponto, University of Iowa Hospitals and Clinics.

Table 9: Quality, Sensitivity & Other Issues

Other Issues	*^{201}Tl*	*^{99m}Tc-Sestamibi*	*^{99m}Tc-Tetrofosmin*
image quality	poor -- * low abundance of γ rays * low energy x-rays - attenuation, scattering * small injected dose because of dosimetry * restricted duration of imaging time at stress because of redistribution	good-- * abundant γ rays * less attenuation and scattering * larger injected dose * unrestricted duration of imaging time * optional EKG-gating * especially valuable for "large chested" patients	good -- * abundant γ rays * less attenuation and scattering * larger injected dose * unrestricted duration of imaging time * optional EKG-gating * especially valuable for "large chested" patients
sensitivity for CAD[32,33,37]	Planar:80-85% overall SPECT: 92% overall 1-vessel dx: 80% 2-vessel dx: 83% 3-vessel dx: 96%	SPECT: 89% overall 1-vessel disease: 84% 2-vessel disease: 91% 3-vessel disease: 96%	SPECT: 85% overall 1-vessel disease: 78% 2-vessel disease: 80% 3-vessel disease: 95%
viability	Compared to ^{18}FDG PET, 10-50% of fixed defects on rest, redistribution or reinjection ^{201}Tl scans are really viable "hibernating" myocardium	compared to ^{201}Tl, less likely to show uptake in resting ischemic, but still viable "hibernating" myocardium	compared to ^{201}Tl, less likely to show uptake in resting ischemic, but still viable "hibernating" myocardium
provision of additional data[4]	↑ lung activity is often correlated with 3-vessel disease	cardiac function - first pass ejection fraction, EKG-gated wall motion	cardiac function - first pass ejection fraction, EKG-gated wall motion
purposeful interventions		whole milk, fatty meal, etc. to promote liver clearance	whole milk, fatty meal, etc. to promote liver clearance
combination (dual isotope) studies	---	resting ^{201}Tl followed by stress ^{99m}Tc-sestamibi	resting ^{201}Tl followed by stress ^{99m}Tc-tetrofosmin
marketing restrictions	none	kits: not sold, rather have bailment/licensing fee which includes certain restrictions unit doses: only from Syncor and certain independent pharmacies	unit doses: only from Amersham/MediPhysics, Mallinckrodt, and certain independent pharmacies
additional indications	Parathyroid imaging [tumor imaging - brain, thyroid, mediastinal tumors, etc]	breast tumor imaging [parathyroid imaging; thyroid imaging]	---

*Courtesy of James A. Ponto, University of Iowa Hospitals and Clinics

glucose (^{18}FDG) and [^{18}F] fluoroisonidazole imaging, and the water perfusable tissue index. Table 10 lists some of the most commonly used PET radiopharmaceuticals. The two positron imaging agents that have seen the most clinical use are ^{82}Rb rubidium chloride and ^{18}FDG.

Table 10. Commonly Used PET Radionuclides

Radionuclide	Half-Life (min)
^{82}Rubidium	1.3
^{15}Oxygen	2.1
^{13}Nitrogen	10.0
^{11}Carbon	20.3
^{18}Fluorine	110.0

^{82}Rb Rubidium Chloride

Rubidium-82 is a generator-produced positron emitter approved by the FDA for myocardial perfusion imaging. Strontium-82 ($t_{\frac{1}{2}}$ = 25 days) decays by electron capture to ^{82}Rb, a potassium analog with a physical half-life of only 75 seconds, which allows for repeated blood flow measurements within short time intervals. Unfortunately, the short half-life has some negative effects as well. Following injection, imaging must be delayed for at least 1-2 minutes to permit clearance of blood pool activity and considerable decay of the tracer occurs during this time. Also, due to changing myocardial activity from decay, imaging times must be short to prevent backprojection reconstruction artifacts.[3] The typical dose for the perfusion exam is 40 to 50 mCi infused over 20 to 30 seconds. The critical organ is the kidney. Drawbacks to the use of ^{82}Rb rubidium chloride include the need to have equipment capable of imaging the 511 keV annihilation gamma emissions and the extremely high costs (~$25,000/generator/month). Rubidium-82 has the worst resolution of all the positron emitting agents, with most positrons traveling about 12.4 mm prior to undergoing annihilation.[3] For ^{82}Rb imaging in the evaluation of myocardial viability, there is unfortunately no association between the severity of a fixed defect and the likelihood of myocardial viability in that area. In defects containing less than 50% relative activity, 30% were shown to be viable by ^{18}FDG imaging.[7]

Metabolic Imaging with ^{18}FDG

Fludeoxyglucose F-18 (^{18}FDG) imaging is considered the "gold standard" for evaluation of myocardial viability.[8] With the increased use of PET and molecular coincidence detection (MCD) with SPECT cameras and more readily available distribution of ^{18}FDG, we will likely see an increased use of ^{18}FDG in the clinical setting.

Fluorine-18 has a physical half-life of 110 minutes a[illegible] the best resolution of all positron emitters. Fluorine-18 labeled to deoxyglucose is an effective means of measuring glucose metabolism of myocardial cells, thus providing viability data. At rest and in the fasting state, the primary substrates of myocardial energy production in the normal myocardium are fatty acids. Upon feeding, circulating levels of insulin increase, stimulating glucose metabolism and diminishing free fatty acid metabolism.

Breakdown of fatty acids occurs in the mitochondria via beta-oxidation. During hypoxia or myocardial ischemia, beta-oxidation of fatty acids in the mitochondria is reduced. Myocytes compensate for the loss of oxidative potential by shifting toward glucose utilization to generate high-energy phosphates. Although the amount of energy produced by glycolysis may be adequate to maintain myocyte viability and preserve the electrochemical gradient across the cell membrane, it may not be sufficient to sustain the mechanical work, and thus impaired contractile function results. This ischemic, but viable myocardium is termed "hibernating" myocardium.

Most studies are performed following glucose loading to stimulate the release of insulin, thus increasing glucose metabolism in the myocardium. Patients generall[illegible] present to the department in a fasting state, and either a[illegible] oral or intravenous administration of glucose is given. As might be expected, the intravenous administration provides a better predictability of serum glucose levels because the oral absorption variable is eliminated. Glucose levels are monitored and the ^{18}FDG is usually injected approximately 10 minutes following intravenous glucose administration or 60 minutes following oral glucose administration. In the diabetic patient, a combined insulin and glucose infusion is given. The diabetic patient is administered glucose to avoid hypoglycemia that may result from the administered insulin. The amount of glucose administered is dependent on several variables including patient weight, fasting blood glucose levels, and degree of insulin resistance. Images are usually acquired 45-60 minutes following injection of the radiotracer.

Only about 1% to 4% of the injected dose of ^{18}FDG is trapped in the myocardium, but the target-to-background ratios are favorable. The typical dose of ^{18}FDG is usually 5-10 mCi infused over a 60 second interval.

Determination of ischemic, but viable, myocardium can only be made in relationship to the perfusion study. Whe[illegible] regional myocardial ^{18}FDG uptake is disproportionate[illegible] enhanced as compared to regional myocardial blood flow,

the pattern is termed a perfusion-metabolic "mismatch." In the setting of chronic coronary artery disease, a perfusion-metabolic mismatch is highly predictive of myocardial viability and indicates a high likelihood of improved cardiac function following revascularization (82% of cases). PET studies have shown that cardiac morbidity and mortality are increased in patients with flow-metabolic mismatches. Up to 50% of patients that demonstrate a perfusion-metabolic mismatch will have a cardiac event in the subsequent 12 months in the absence of intervention. The incidence of cardiac events drops to 15% in these patients if revascularization is performed.[12]

Clinical drawbacks of ^{18}FDG imaging include limited data in diabetic patients and reports which suggest that ^{18}FDG can accumulate in infarcted tissue.[9] There are also financial considerations in using ^{18}FDG which include the cost and delivery of the short half-life cyclotron-produced radiopharmaceutical, equipment to image the 511 keV photon, and the lack of third party reimbursement. Currently, Medicare and Medicaid do not reimburse for cardiac PET studies, however some private insurance companies will reimburse this expense.

IMAGING CONSIDERATIONS

Imaging Protocols

I. *Thallium*:

A. Standard ^{201}Tl Protocol
1. Inject 3-4 mCi ^{201}Tl at peak stress
2. Stress scan at 5-15 min post injection
3. Rest scan at 4 hours post injection
4. 24 hour scan if viability information is needed

B. ^{201}Tl Reinjection Protocol
1. Inject 3-4 mCi ^{201}Tl at peak stress
2. Image at 5-15 min post injection
3. Inject 1 mCi ^{201}Tl following 3-4 hour rest period
4. Rest/redistribution images obtained 15 min following injection
5. 24 hour scan if viability information is needed

II. *^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin*

A. Stress/Rest Two Day Protocol
1. Inject 25-30 mCi of ^{99m}Tc-sestamibi/^{99m}Tc-tetrofosmin at peak stress
2. Stress images obtained at 15 min post injection
3. If stress images are abnormal, inject 25-30 mCi ^{99m}Tc sestamibi/tetrofosmin at 24 hours
4. Rest images obtained 15-60 min post injection

B. Rest/Stress One Day Protocol
1. Inject 8 mCi ^{99m}Tc-sestamibi/ ^{99m}Tc-tetrofosmin at rest
2. Rest images obtained at 15-60 min post injection
3. Exercise or pharmacologic stress
4. Inject 22-25 mCi ^{99m}Tc-sestamibi/^{99m}Tc-tetrofosmin at peak stress
5. Stress images obtained 15-60 min post stress

C. Stress/Rest One Day Protocol
1. Inject 8 mCi ^{99m}Tc-sestamibi/^{99m}Tc-tetrofosmin at peak stress
2. Stress image obtained at 15-60 min
3. Inject 22 mCi ^{99m}Tc- sestamibi/ ^{99m}Tc-tetrofosmin following 3-4 hour rest period
4. Rest image obtained 15-60 min post injection

Notes:
The package insert for tetrofosmin recommends a one day stress/rest protocol and does not carry the indication of use with a pharmacologic stress agent (although commonly used in clinical practice)

Generally the wait following injection of ^{99m}Tc-sestamibi at rest is slightly longer than ^{99m}Tc-sestamibi stress imaging or ^{99m}Tc-tetrofosmin imaging to allow time for the liver to clear some of the radiotracer.

Patients may be given milk or a fatty meal following injection to aid in liver clearance.

III. *Dual Isotope*

A. ^{201}Tl Rest / ^{99m}Tc Agent Stress

1. Inject 3-4 mCi of ^{201}Tl at rest
2. Rest images obtained at 15 min post injection
3. Exercise or pharmacologic stress immediately following imaging
4. Inject 25 mCi of ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin at peak stress
5. Stress images obtained at 15 min post stress injection

Dual isotope rest/stress single-photon emission computed tomographic (SPECT) imaging is a time-saving imaging protocol. Thallium-201 is injected at rest; immediately following the rest image acquisition, the patient undergoes exercise or pharmacologic stress with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin injection. Dual isotope imaging shows a good agreement with rest/stress ^{99m}Tc-sestamibi SPECT for assessment of rest perfusion defects and reversibility, and ^{201}Tl is a better agent to evaluate myocardial viability. If the rest and stress data appear similarly abnormal, the patient can return for imaging at 24 hours for delayed rest images. This sequence of imaging is particularly helpful for the detection of viable myocardium, especially in patients with diminished ejection fraction. However, it is important to note that thallium and technetium agents have different physical properties and myocardial kinetics. In patients with abnormal resting myocardial perfusion, these differences may affect quantification of rest defect size and defect reversibility.[29] In patients with prior myocardial infarction, stress-induced defect reversibility is quantitatively larger with dual-isotope imaging than with single-isotope imaging. Quantitative processing of dual-isotope images requires radiotracer-specific normal databases. Because of different characteristics of ^{99m}Tc-sestamibi and ^{201}Tl, assessment of defect reversibility on dual-isotope images should be made with caution. Only relatively large defect reversibility can be assumed to represent true stress-induced myocardial ischemia.[10]

Rest and Stress Imaging

An optimal approach to imaging involves the performance of the rest and stress examinations on separate days, thereby eliminating the problem of any residual background activity. However, patients usually prefer to have their studies completed on a single day. There appears to be little difference in the sensitivity and specificity of perfusion imaging regardless of whether a 1-or 2-day protocol is used. Same-day studies typically use 8-10 mCi for the first examination and 22-30 mCi for the second. There has been great debate about whether the rest or stress study should be performed first. When the stress study is performed first with normal results, the patient is not required to complete the resting portion of the procedure, thus saving time anddd money. However, if the results are abnormal, the patient must wait for several hours for the heart to return to a "resting state" for the second part of the procedure. Many nuclear medicine departments employ the rest/stress protocol. One rationale for this method is that the stress images, which are most diagnostic, are acquired with the higher dose (activity), increasing the sensitivity of the study. The stress/rest versus rest/stress imaging protocol is usually decided by physician preference.

Patient Preparation

The patient history should be obtained and the procedure should be explained to the patient. Patients are usually required to sign a consent form stating that they have been informed and accept the risks associated with the stress portion of the exam. The patient should have little or nothing to eat in the previous four hours. Stomach contents may not only contribute to nausea during exercise or pharmacologic stress but may also change the availability of blood to the myocardium. A patient scheduled for a treadmill exercise stress or dobutamine or arbutamine pharmacologic stress should be screened for any interfering medications as listed in Table 11. If a patient is scheduled for a pharmacologic

Table 11. Drugs That Can Affect Exercise Response

Drug	Discontinue* Prior to Use
Nitroglycerin	1 hour
Long-acting nitrates	4-24 hours
Tranquilizers/Sedatives	1 day
Antiarrhythmic agents	2 days
Beta Blockers	1-2 days
Diuretics	4 days
Antihypertensives	4-7 days
Digitalis	1-2 weeks

modified from Steves AM, Review of Nuclear Medicine Technology, 2nd Edition

*Caution and professional judgement must be used before discontinuing medications.

stress with adenosine or dipyridamole, the technologist should confirm that the patient has not taken an interfering xanthine derivative (caffeine, theophylline, etc). Treadmill exercise patients are generally stressed until they reach a target heart rate which is frequently determined by using the equation (220- patient age) x 85%. If the patient is unable to reach a diagnostic stress level, then a pharmacologic stress agent may be employed.

Gated SPECT Imaging

In recent years there has been considerable effort to reduce the number of false positive studies. The most successful approach is the technique known as Gated SPECT. This process combines EKG and image data to depict the myocardium in motion in multiple planes. By viewing the pattern of myocardial contraction, the nuclear physician can determine whether a given area of decreased perfusion is secondary to CAD or results from overlying structures such as the breast or diaphragm.[23] Although Gated SPECT studies can be recorded with ^{201}Tl, they pale in comparison with the high-quality gated SPECT of the ^{99m}Tc-labeled tracers.

Acute Use Imaging

Every year, millions of patients present to the emergency room with symptoms of acute chest pain. More than half of the patients will be admitted to the hospital and worked up for acute myocardial infarction. It is estimated that $13 billion is spent annually in the U.S. on hospitalizing patients with chest pain who turn out not to have an acute myocardial infarction.[13] A number of hospitals are now utilizing acute use imaging with the ^{99m}Tc-labeled radiopharmaceuticals to differentiate those patients with an MI from the non-MI population. According to a study by Hilton,[30] when patients are injected during an episode of chest pain, there is a high sensitivity (100%) and specificity (92%) of detecting acute ischemia. A normal study predicts a benign outcome whereas an abnormal study puts these patients into a high risk category. Information gained from a positive study indicating the extent and location of the perfusion defect can help determine the need and type of interventional therapy. The diagnostic and prognostic information of acute use studies is valuable in patient management.

CASE STUDY

JB is a 56 year-old white male who presented to the cardiologist with complaints of chest pain. The patient was referred to the nuclear medicine department for a myocardial perfusion stress/rest study. The patient is a non-smoker with no prior history of myocardial ischemia or infarction. The patient is currently taking amlodipine (Norvasc®; calcium channel blocker) 5mg qd and aspirin 81 mg qd. JB was treadmill stressed to a maximum heart rate of 155 and a blood pressure of 200/98 at which point he complained of pain in his left arm. The patient was injected with 12 mCi of ^{99m}Tc-sestamibi and allowed to rest. The pain quickly dissipated. The cardiologist in attendance noted rhythm disturbances, but no ST segment changes indicative of ischemia were seen. Due to a positive stress image, a rest study was also indicated. The patient was injected with 30 mCi of ^{99m}Tc-sestamibi and scanned one hour later.

Findings

JB's images provided the following information: The gated SPECT study revealed a calculated ejection fraction (EF) of 46%, end diastolic volume (EDV) of 92 mL and end systolic volume (ESV) of 49 mL. There is also some abnormal wall motion septally. The myocardial perfusion images (Figure 3) reveal perfusion defects of the anterio-septal wall at stress that reverse on the resting images. The bull's eye plot (Figure 4) suggests that the LAD artery and possibly the septal branches of the RCA are stenosed. JB is a likely candidate for revascularization of the stenosis through coronary by-pass surgery or angioplasty. In this case it is clear why the LAD artery is referred to as the "widow maker."

SUMMARY

Myocardial perfusion imaging (MPI) is an excellent diagnostic and prognostic tool in the evaluation of coronary artery disease. Not only can MPI studies diagnose the presence or absence of disease and its reversibility, they correlate with the outcome of the patient as well. A normal MPI study predicts a less than 1% chance of a significant cardiac event in the following year. The amount and severity of ischemia on an abnormal study also correlates with the increased likelihood of a serious cardiac event.

While the localization and imaging characteristics of ^{201}thallium and the ^{99m}technetium MPI radiopharmaceuticals are different, they provide essentially the same information with regard to the diagnosis and prognosis of coronary artery disease. It is hoped that the development of future tracers will not only provide an accurate assessment of myocardial perfusion, but can also accurately measure myocardial metabolism and viability.

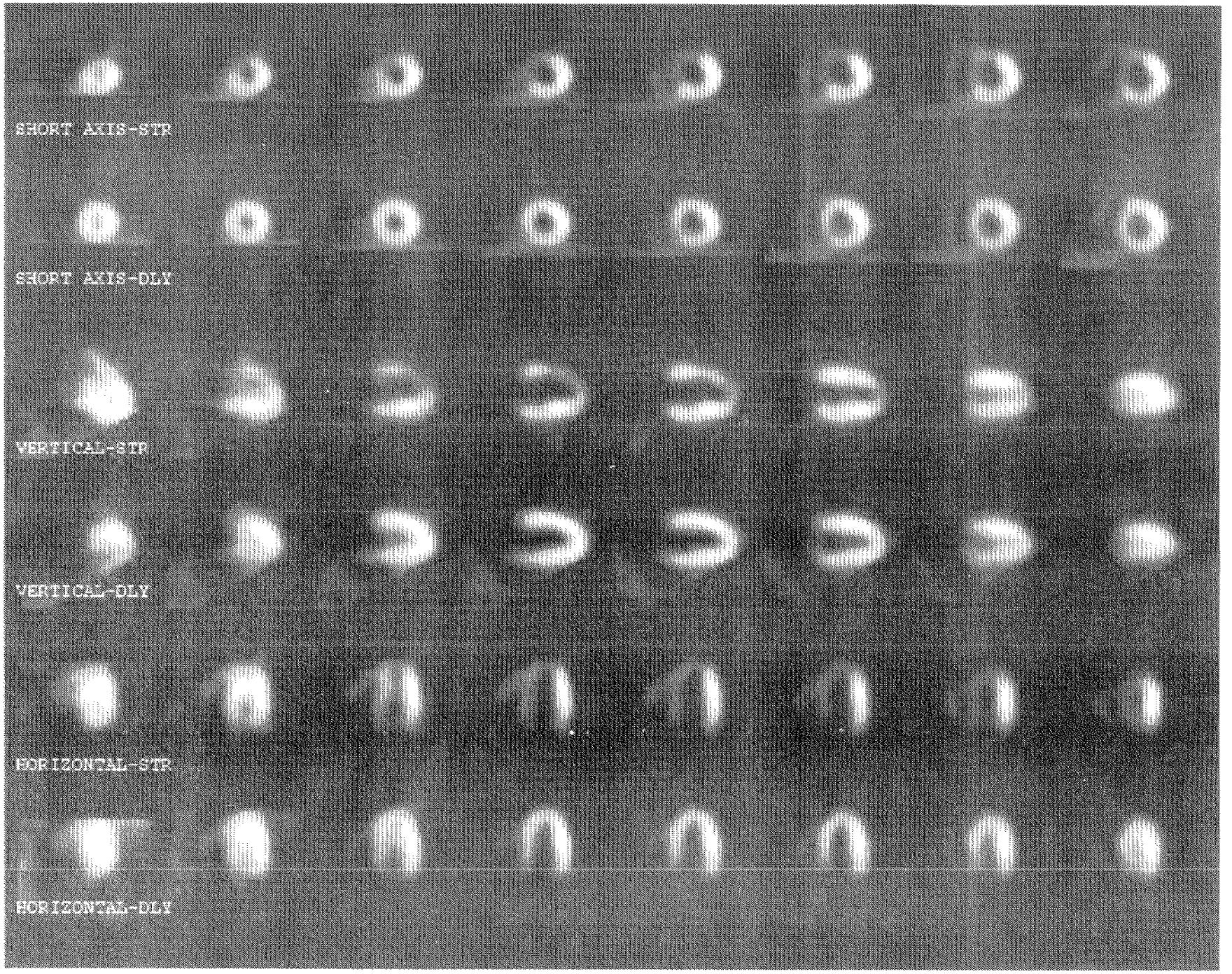


Figure 3. Myocardial perfusion images (refer to case study in text)

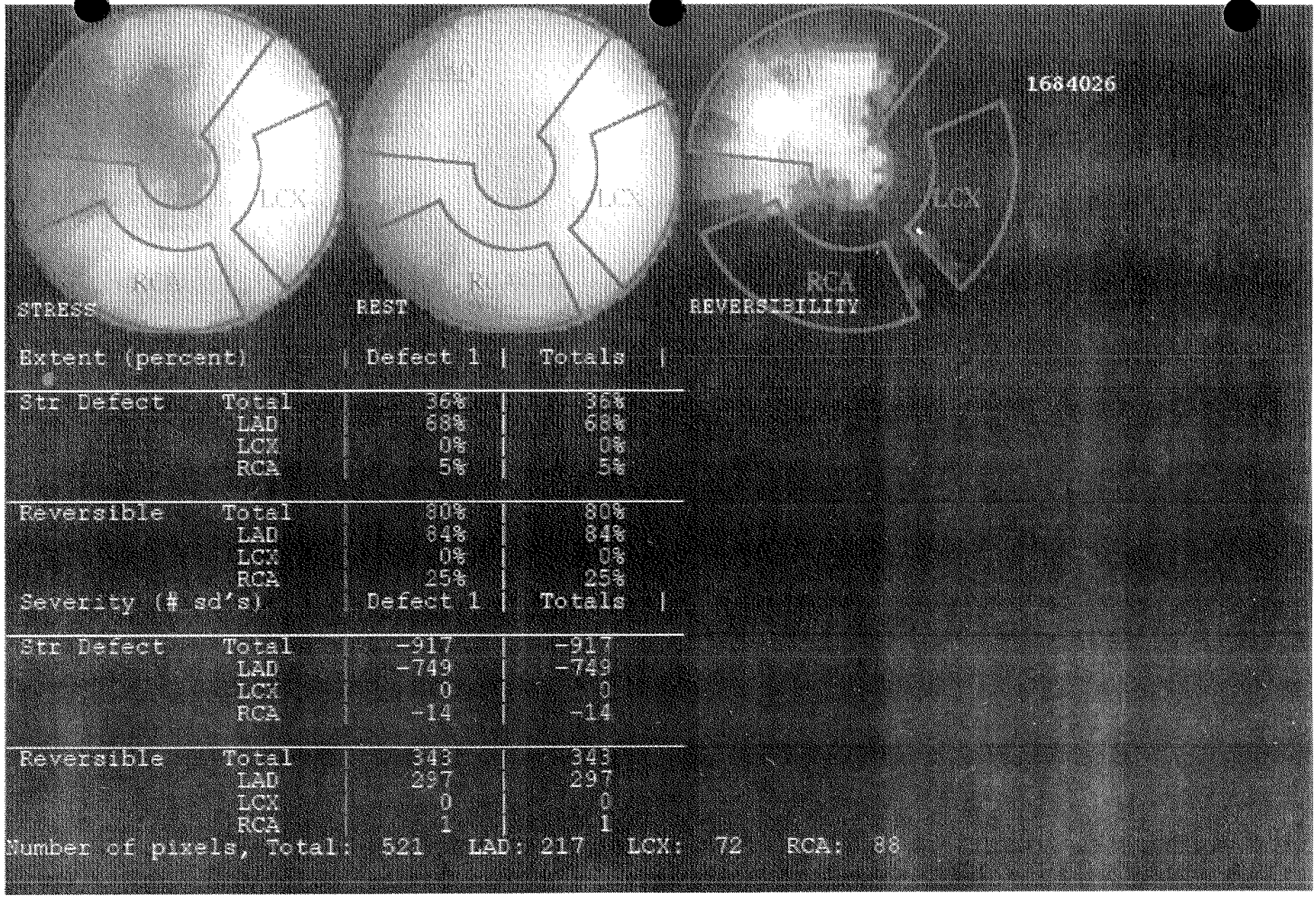


Figure 4. Bull's eye plot (refer to case study in text)

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QUESTIONS

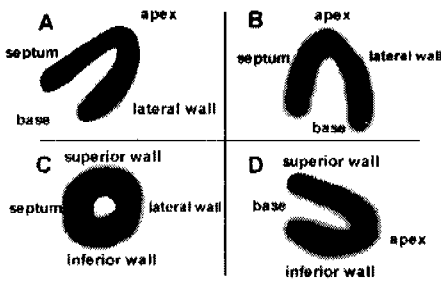
1. What is the leading cause of death for women in the U.S.?
   A. Breast Cancer
   B. Lung Cancer
   C. Heart Disease
   D. Pneumonia

2. Which radiopharmaceuticals are used for rest/stress dual-isotope MPI?
   A. ^{201}Thallium / ^{99m}Tc Sestamibi
   B. ^{99m}Tetrofosmin / ^{201}Thallium
   C. ^{201}Thallium / ^{82}Rubidium
   D. ^{82}Rubidium / ^{18}FDG

3. In the stress/rest thallium protocol, a 1-2 mCi dose of ^{201}Tl may be injected prior to the rest image to:
   A. make up for the thallium lost to decay
   B. visualize infarcted tissue more clearly
   C. visualize reversible ischemia more readily.
   D. minimize tissue attenuation artifact

4. Why is the imaging time 30-60 minutes post injection for a resting image of ^{99m}Tc-sestamibi?
   A. allows time for maximum uptake by myocardium
   B. waiting for blood pool clearance
   C. allows time for hepatic clearance
   D. in vivo rbc labeling occurring

5. Which of the following diagrams is a correctly labeled representative slice of a vertical long axis of the left ventricle?



6. Which of the following statements concerning imaging times is true?
   A. You can image tetrofosmin sooner than sestamibi in rest imaging.
   B. Thallium redistribution offers flexible imaging times.
   C. ^{99m}Tc tracer imaging times are the same post exercise as pharmacologic stress.
   D. Liver uptake of the ^{99m}Tc tracers is greater following exercise stress than rest injection.

7. An advantage of sestamibi over thallium would include all of the following except:
   A. Increased counting statistics for imaging
   B. Ability to use in acute-use risk stratification
   C. Ability to do gated SPECT
   D. More likely to detect hibernating myocardium

8. Patient preparation for a cardiac stress test would include:
   A. NPO for the previous 4 hours
   B. Discontinuation of all medications
   C. Mild laxative 24 hours preceding exam
   D. Use of bronchodilator inhalers

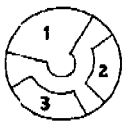
9 The bull's eye plot is a functional map for which of the following SPECT tomographic slices?
   A. Transverse
   B. Short Axis
   C. Horizontal Long Axis
   D. Vertical Long Axis

10. What intervention is often done to aid in clearing the hepatic uptake prior to a sestamibi or tetrofosmin image.
   A. Inject 0.02 mcg/kg CCK
   B. Inject 50 mg aminophylline
   C. Have the patient get up and walk around.
   D. Have the patient drink whole milk.

11. Which radiopharmaceutical is considered the "gold standard" for viability.
   A. Thallous Chloride Tl-201
   B. ^{99m}Tc Tetrofosmin
   C. Rubidium Rb-82
   D. Fludeoxyglucose F-18

12. MPI may follow cardiac catheterization because:
   A. MPI is the gold standard for assessing operability of coronary lesions.
   B. MPI is reserved until last because of the higher cost
   C. Catherization may underestimate small vessel disease
   D All patients should receive a MPI following revascularization

13. Identify arteries corresponding to the bull's eye areas labeled 1,2,3 respectively.



   A. LAD, RCA, LCX
   B. RCA, LAD, LCX
   C. LCX, RCA, LAD
   D. LAD, LCX, RCA

14. The critical organ for ^{99m}Tc Tetrofosmin is the:
   A. Kidney
   B. Bladder
   C. Gallbladder
   D. Large intestine

15. The left main coronary artery branches into the:
   A. Left Anterior Descending & Left Circumflex
   B. Left Anterior Descending & Right Coronary Artery
   C. Left Anterior Descending & Left Posterior Descending
   D. Left Posterior Descending & Left Circumflex

16. Which of the following radiopharmaceuticals are analogs of potassium?
A. Thallium
B. Sestamibi
C. Rubidium
D. A and C

17. Using the traditional target heart rate calculation, what was the target heart rate that they were initially hoping to achieve for J.B in the case study?
A. 115 beats/min
B. 122 beats/min
C. 139 beats/min
D. 155 beats/min

18. In J.B's images, uptake was visualized in his thyroid. This is most likely a result of:
A. presence of unbound pertechnetate
B. presence of hydrolyzed/reduced pertechnetate
C. normal physiologic uptake
D. thyroid adenoma carcinoma

19. Patients usually have coronary occlusion of >___% before symptoms or a positive test are seen.
A. 20%
B. 30%
C. 50%
D. 80%

20. Which of the following is/are classified an isonitrile compound?
A. Sestamibi
B. Tetrofosmin
C. Rubidium
D. A and B

21. Increased lung activity is indicative of multi-vessel disease in:
A. Thallium imaging
B. Technetium agents imaging
C. Delayed imaging
D. Gated SPECT

22. Which of the following positron emitting radionuclides does not require a cyclotron for production?
A. ^{11}Carbon
B. ^{18}Fluorine
C. ^{15}Oxygen
D. ^{82}Rubidium

23. The primary substrate of myocardial energy production in the normal myocardium is:
A. glucose
B. fatty acids
C. phosphates
D. troponin

24. The tetrofosmin package insert recommends that the sodium pertechnetate concentration for preparation should not exceed:
A. 15 mCi/mL
B. 20 mCi/mL
C. 30 mCi/mL
D. 50 mCi/mL

25. Which of the following drugs may inhibit the cellular uptake of thallium-201?
A. Propranolol
B. Verapamil
C. Lisinopril
D. Digoxin