Nuclear Cardiology, Part III: Scintigraphic Evaluation of Cardiac Perfusion

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Objective: After reading Part III of this series of nuclear cardiology articles, the technologist should be able to: (a) compare and contrast radiopharmaceuticals used for myocardial perfusion imaging; (b) describe imaging protocols used for detecting coronary artery disease; and (c) describe imaging patterns seen following reconstruction of myocardial images.

Key Words: myocardial perfusion scintigraphy; thallium-201; technetium-99m-sestamibi; technetium-99m-tetrofosmin; coronary artery disease; imaging protocols

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Myocardial perfusion scintigraphy is a well established method in the evaluation of patients with coronary artery disease. In addition, perfusion scintigraphy also has a place in the assessment of myocardial viability. The issue of viability will be discussed in Part IV of this series.

Myocardial perfusion scintigraphy has advanced continuously since it's introduction more than 20 yr ago. Improvement in computer technology (SPECT and gated SPECT), the development of ^{99m}Tc-labeled tracers and the availability of different stress-testing protocols are responsible for the fact that myocardial perfusion scintigraphy today is the most commonly performed procedure in nuclear cardiology.

PHYSIOLOGICAL BASIS OF MYOCARDIAL PERFUSION IMAGING

Myocardial perfusion scintigraphy demonstrates coronary blood flow because the injected tracer distributes throughout the myocardium and is extracted by the myocardium in proportion to regional blood flow. The myocardium is dependent on oxygen delivery (aerobic metabolism). The ability to increase the blood flow through the coronary vessels as a response to the changing metabolic demands is essential. At rest the myocardial blood flow may be uniform even in the presence of significant stenoses of the coronary arteries. During stress the coronary blood flow increases three- to fivefold due to vasodilation (coronary flow reserve) (*1,2*). In the presence of a significant stenosis, the ability to increase coronary blood flow after stress is limited. Consequently most protocols that aim to demonstrate coronary artery lesions will use techniques that increase coronary blood flow and thus unmask focally diminished flow reserve.

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RADIOPHARMACEUTICALS

The introduction of ^{201}Tl in the 1970s (*3*) and, more recently, the development of ^{99m}Tc-labeled perfusion tracers (*4*), ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin, allowed a significant growth in the number of myocardial perfusion imaging examinations performed (Table 1). The myocardial uptake of these tracers is proportional to the regional blood flow. At high flow rates (> 2 ml/min/g), however, the extraction of these tracers relatively decreases and myocardial blood flow is underestimated (*5*). When selecting the tracer one has to be aware of the differences in biological as well as in physical characteristics. Clearance from the blood and cellular release are the most important factors that are responsible for myocardial retention and distribution of tracers. Peak as well as net levels of extraction have been calculated for most tracers (*6,7*).

Thallium-201

Thallium-201 uptake in the cytosol is presumed to be mediated by an active mechanism (the sodium-potassium ATPase pump) (*8*). After administration, ^{201}Tl initially distributes in the myocardium according to regional blood flow (*9*) and the ability of the myocardium to extract the tracer from the blood. The distribution pattern of ^{201}Tl in the myocardium is not stable but changes as a function of time (redistribution). The tracer is cleared at a slower rate from hypoperfused zones as compared to normally perfused zones (*10,11*). As a result of this, areas with stress-induced ischemia will be recognized by a lower tracer uptake on the initial images but will appear normal on delayed images (reversible defect) (Fig. 1).

TABLE 1
Comparison Between Thallium-201 and Technetium-99m-Labeled Flow Tracers

Property	Thallium-201	Technetium-99m-labeled tracers	
		Sestamibi	Tetrofosmin
Class	K+ analog	Isonitrile	—
Half-life (hr)	73	6	6
Mode of decay	100% electron capture	100% isomeric transition	100% isomeric transition
Energy of gamma (keV)	167 (60–80 keV x-rays)	140	140
Redistribution	Significant	Negligible	None

Technetium-99m-Labeled Perfusion Agents

Technetium-99m-Sestamibi. The transcellular transport mechanism of ^{99m}Tc-sestamibi is not mediated by the ATPase system but is suggested to be a passive mechanism, dependent on the concentration gradient and the electropotential gradient across the mitochondria and cellular membrane (*5,12*). The uptake of sestamibi is depressed when there is cellular hypoxia secondary to severe myocardial ischemia. The clearance from the myocardium is slow and the redistribution 3–4 hr after administration is negligible (*13*). Early after injection the liver uptake is high, but the clearance through the hepatobiliary system is more rapid than the myocardial clearance. Separate rest and stress studies are necessary to distinguish ischemia from myocardial scar because sestamibi does not redistribute.

Technetium-99m-Tetrofosmin. The myocardial uptake and retention of ^{99m}Tc-tetrofosmin is related to diffusion along an electropotential gradient (*14*) similar to ^{99m}Tc-sestamibi. Compared to sestamibi, tetrofosmin demonstrates less prominent liver uptake (*15,16*) and kit preparation requires no heating.

IMAGING PROTOCOLS FOR DETECTING CORONARY ARTERY DISEASE

A variety of imaging protocols has been proposed depending on tracer selection and clinical objective (*17*). The aim of these protocols is to accurately delineate the location, extent and severity of stress-induced perfusion defects and to define their reversibility. The choice of a particular protocol should be

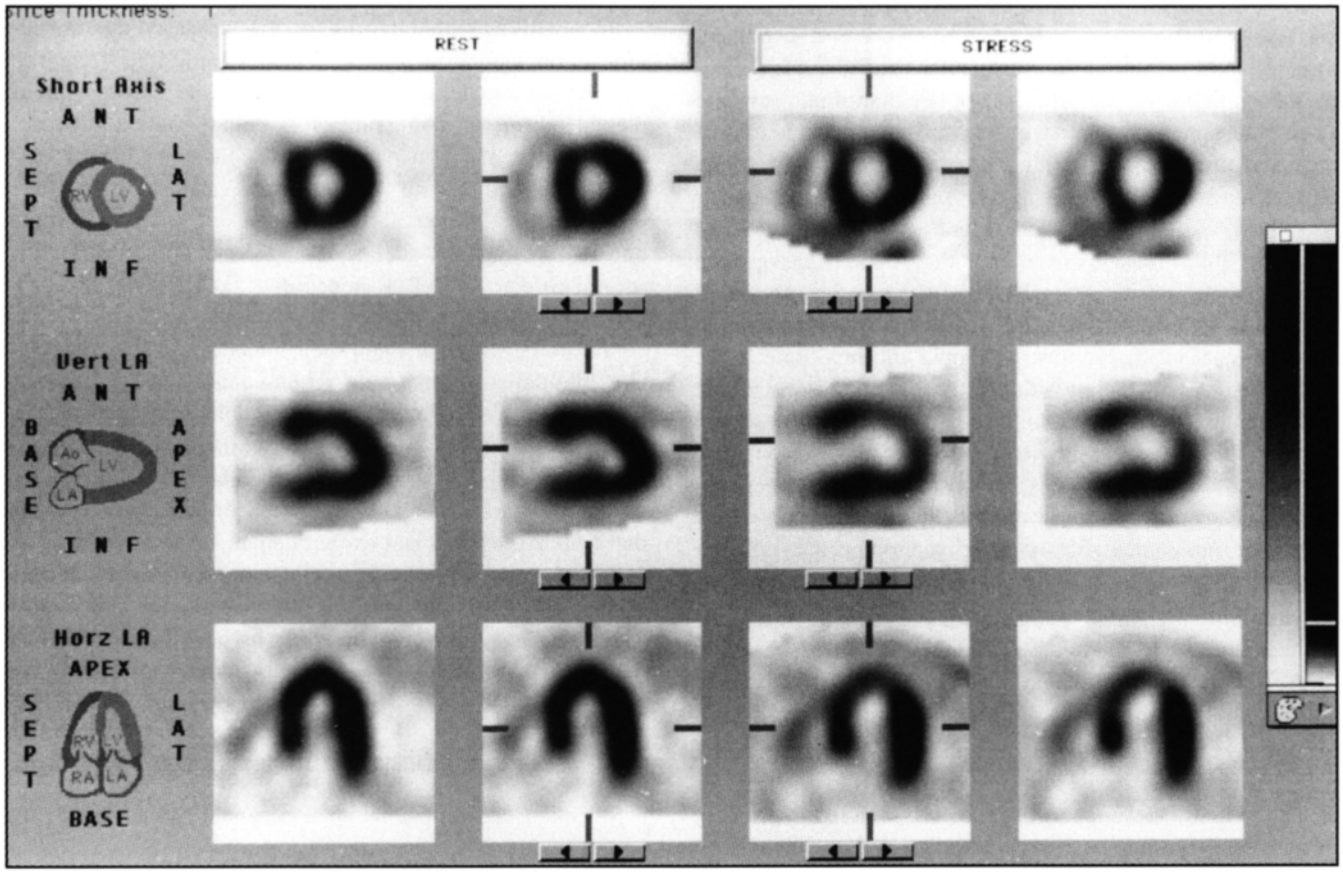

FIGURE 1. Short-axis (SA), vertical (VLA) and horizontal long-axis (HLA) ^{99m}Tc-sestamibi images obtained in rest and during stress. The stress images demonstrate perfusion defects in the apex and anterior wall, while a normal tracer distribution is seen in rest, indicating the presence of a significant stenosis and a limited capacity to increase coronary blood flow after stress.

based on the clinical question, laboratory logistics, patient convenience and cost-effectiveness. The advantages and disadvantages of the different imaging protocols and their modifications have been reviewed recently in detail (*18*).

Imaging Protocol for Thallium-201

When ^{201}Tl is used, a stress-redistribution protocol is usually performed with or without rest reinjection. Stress imaging should not be started earlier than 10 min after tracer injection of 90–130 MBq ^{201}Tl to reduce the frequency of the upward creep artifact (*19*). If imaging is started too late, however, redistribution already may be present.

Fasting is recommended on the day of and for the interval between sequential ^{201}Tl imaging since it has been demonstrated that glucose loading results in decreased blood ^{201}Tl concentration and a slower redistribution (*20*). Resting imaging is started 3–4 hr after tracer administration.

Imaging Protocol for Technetium-99m-Labeled Tracers

For ^{99m}Tc-labeled tracers, separate rest and stress studies are necessary to distinguish myocardial scar from ischemia because redistribution with these tracers is negligible. Most data regarding the application of ^{99m}Tc-sestamibi in coronary artery disease have involved a ^{99m}Tc-sestamibi injection on two separate days to allow adequate decay of myocardial activity from the first image and to minimize interference of the first with the second image. Due to practical reasons, such as early availability of the results, patient convenience and scheduling logistics, most institutions perform both rest and stress studies on the same day (1-day protocol) rather than doing rest and stress studies on different days (2-day protocol). In the case of the 1-day protocol, the amount of tracer injected for the second study (3–4 hr later) has to be roughly three times higher (first study 370–400 MBq and second study 740-1110 MBq) than the initial dose to overcome the residual background activity of the initial dose. There are two 1-day protocols: rest-stress and stress-rest (*21,22*) which are comparable in assessing coronary artery disease. Small and mild defects are more frequently detected with the stress-rest protocol, while assessment of reversibility is better with the rest-stress protocol because the rest images represent true rest perfusion (*22*). Therefore, diagnostic studies are best begun with stress. In patients with known coronary disease, however, a resting study should be performed first to avoid superimposing exercise-induced defects on resting data, resulting in a potential underestimation of the degree of reversibility (*23*).

Dual-Isotope Imaging

In this approach the ability to collect data in different energy windows is used. Thallium-201 rest and ^{99m}Tc-sestamibi stress SPECT are usually registered seperately to avoid downscatter of ^{99m}Tc into the lower energy window of ^{201}Tl. In the protocol developed by Berman et al. (*24*) image acquisition is started 10 min after administering ^{201}Tl in rest. Immediately after the ^{201}Tl SPECT acquisition, stress testing is started and the ^{99m}Tc-sestamibi is injected at peak stress. Technetium-99m-sestamibi SPECT is started 15 min after injection (*24*) resulting in a total study time of less than 120 min.

STRESS TESTING

Physical Exercise

Exercise stress remains the technique of choice for evaluating the cardiovascular system because it provides additional information such as functional exercise capacity, occurrence of symptoms and electrocardiographic changes. The level of exercise achieved is closely related to the demand of oxygen and the increase in blood flow. Maximal exercise is necessary to achieve maximal coronary blood flow and to augment the imbalance between oxygen supply and demand. The patient should be instructed to exercise without using any specific pretest estimate of maximal predicted heart rate, since pretest estimations of maximal predicted heart rate are often misleading, related to the use of bradycardia-inducing drugs or common intrinsic dysrhythmias.

The tracer should be administered close to the end of a maximum symptom limited exercise. After administration the exercise should be continued for at least 1 min to allow tracer uptake by the myocardium. If the exercise has to be terminated prematurely, the reasons for stopping or limiting the effort (shortness of breath, hypotension, arrhythmias, chest pain, and/or other symptoms) should be noted.

Pharmacological Intervention

In patients who, due to drug therapy, physical limitations or motivational impairment, cannot achieve a desired stress level with conventional exercise tests, stimulation with dipyridamole, adenosine or dobutamine is a valid alternative. An excellent overview of the mechanism of action, safety, appropriate patient population and procedure for each agent has been published by Blust et al. (*25*). When administered intravenously dipyridamole, adenosine and dobutamine can lead to several cardiac as well as noncardiac side effects (*26*). Only people qualified to conduct stress testing should be allowed to administer stress agents and their inhibitors. Table 2 summarizes the patient preparation requirements and contraindications for each stress agent. Dipyridamole and adenosine increase the levels of circulating adenosine and increase the coronary blood flow as a result of vasodilation. Dobutamine is a positive inotropic agent and induces an increase in myocardial contractile force and oxygen demand.

As for exercise, the tracer administration should be done at least 1 min before ending the pharmacological intervention when adenosine or dobutamine are used. With dipyridamole the radiopharmaceutical should be administered 2–5 min postinfusion.

DATA ACQUISITION AND PROCESSING

SPECT acquisition generally is accepted as the state of the art technique to assess myocardial perfusion. Several studies comparing planar with SPECT techniques clearly have demonstrated the superiority of tomographic imaging for diagnosing coronary artery disease (*27–29*). Tomographic imaging

TABLE 2
Patient Preparation and Contraindications for Pharmacological Stress

	Dipyridamole	Adenosine	Dobutamine
Preparation			
Withhold for at least 24–36 hr before the test	Xanthine derivatives	Xanthine derivatives and oral dipyridamole	Beta blockers (optional)
Withhold for at least 12 hr before the test	Caffeine	Caffeine	
Contraindications			
Unstable angina or resting ischemia	C	C	C
Very poor LV function	C	C	C
Severe systolic hypertension		C	C
Severe systolic hypotension	C	C	
Bronchospastic disease	C	C	
Severe aortic stenosis			C
History of tachyarrhythmias			C
Atrial fibrillation with rapid ventricular response			C
Second degree AV block		C	

C = Contraindication.

overcomes important limitations inherent in planar imaging because of its ability to separate overlapping myocardial regions and because of its higher contrast resolution. Optimal tomographic acquisition parameters for myocardial perfusion scintigraphy with ^{201}Tl and ^{99m}Tc-labeled tracers are given in Table 3.

Before reconstructing the tomographic images, a cine display of the projections should be performed to discover artifacts due to attenuation, patient motion during acquisition and upward creep (*19*). After reconstruction using the filtered backprojection technique, the images are reoriented with respect to the long axis of the heart. The reoriented images should be displayed together with the color scale used. Masking of noncardiac structures may be necessary to have the pixel with the maximal activity in the heart. Reviewing the images should be done on the computer screen, because reproduction methods may not be reliable and slice selection may not be ideal.

INTERPRETATION OF PERFUSION IMAGES

Normal myocardium is characterized by wide differences in appearance on perfusion scintigraphy due to the variation in size of the heart and the body and the quality of the acquisition. In women the most common site of variability is the anterior wall due to differences in breast size. In men variability in the inferobasal wall is due to attenuation caused by the left hemidiaphragm. In addition, respiratory motion may induce a blurring effect. Knowledge of these variants is mandatory to prevent the reporting of these variants as defects and not as normal variants. Attenuation correction and ECG gating have been proposed to assist in the decision process.

Defects on thallium scintigraphy are categorized based on the change from the stress to the rest or redistribution phase. Lesions are classified as: reversible; partially reversible; fixed or nonreversible; and reverse redistribution. Lesions are considered reversible if the net myocardial washout of ^{201}Tl is slower in the lesion than in normal myocardium resulting in an

TABLE 3
Optimal SPECT Imaging Protocols for Thallium-201 and Technetium-99m-Labeled Tracers

	Thallium-201	Technetium-99m-labeled tracers
Collimator	High resolution	High resolution
Matrix	64 × 64	64 × 64
Energy window (keV)	20% at 69–83 10% at 167	20% at 140
Views obtained over	180° for one- or two-head camera 360° for three-head camera	180° for one- or two-head camera 360° for three-head camera
Number of projections/head	32	32
Time per projection (sec)	60	40
Start after injection (min)	±6	±60
Gating	—	8 bins

equalization of tracer concentration in the late (redistribution) phase. Partially reversible lesions are those where the tracer concentration in the lesion and normal myocardium become closer to one another but not equalize during the redistribution phase. Lesions are classified as fixed or nonreversible if the ratio of ^{201}Tl concentration in the lesion and normal myocardium is similar in the initial phase and during the redistribution phase. Reverse redistribution lesions are where the ratio between ^{201}Tl in the lesion and the normal myocardium decreases over time because of a faster washout.

Reversible and partially reversible lesions are believed to contain ischemic myocardium. Fixed lesions generally are regarded as myocardial scar although some viable tissue can be present. (Detection of viability will be discussed in Part IV of this series.) The reverse redistribution pattern observed for ^{201}Tl may been observed in the setting of a nontransmural infarction associated with a patent infarct-related coronary artery (*30*).

A certain amount of ^{201}Tl is extracted by the lungs before it reaches the systemic circulation. In pathological conditions associated with left ventricular failure and increased pulmonary wedge pressure a greater amount of ^{201}Tl is extracted by the lungs. The lung uptake is usually expressed as a ratio between uptake in the lungs and the heart, which is measured from an initial anterior planar image or from the tomographic acquisition. Usually the regions of interest are drawn over the entire right lung field and the whole heart. The upper limit of normal in patients without coronary artery disease varies between 0.78 and 0.86 (*31*).

For ^{99m}Tc-labeled perfusion agents, images obtained after tracer injection in stress are compared with images obtained after tracer injection in rest. The perfusion defects are categorized in a similar way into reversible, partially reversible, fixed and nonreversible lesions.

Several methods for quantification of myocardial perfusion images are available (*32–34*). SPECT images are quantified most frequently using circumferential profiles and displayed as polar maps. These polar maps provide a quantitative analysis of the myocardial tracer uptake in terms of percentage of the reference zone. In addition, the polar map of an individual patient can be compared to a normal database to determine the extent and severity of the perfusion defects (*33,35*).

Different investigators have demonstrated a similar sensitivity and specificity for ^{201}Tl and ^{99m}Tc-sestamibi with respect to detecting CAD (*36–38*) [sensitivity: ^{201}Tl = 83%; ^{99m}Tc-sestamibi = 90%; specificity: ^{201}Tl = 80%; ^{99m}Tc-sestamibi = 93% (*37*)].

SIMULTANEOUS ASSESSMENT OF MYOCARDIAL PERFUSION AND FUNCTION

First-Pass Radionuclide Angiography

Due to the favorable dosimetry of ^{99m}Tc-labeled tracers, larger amounts can be injected compared to ^{201}Tl. As a result, the counting rate is much higher and first-pass radionuclide angiography can be performed to assess the myocardial function at the time of injection (*39*) either at rest or during maximal exercise. In addition, the technique allows the study of right and left ventricular functions.

ECG Gating

Improvement in counting statistics with ^{99m}Tc radiopharmaceuticals makes gated data acquisition possible. There are two benefits of gated myocardial perfusion imaging. The first benefit is the spatial resolution increases by removing the blurring effect of the contracting myocardium. Analysis of end diastolic images improves the ability to detect small myocardial perfusion abnormalities. Second, left ventricular function, regional wall motion and wall thickening can be assessed. Wall motion can be observed as the perceived displacement of the endocardium from diastole to systole. Wall thickening can be assessed using the apparent increase in counts during the cardiac cycle (partial volume effect). The approach of assessing wall thickening using the partial volume effect has been validated by several groups (*40–42*). Analysis of wall motion and wall thickening may allow differentiation between viable tissue that is supposed to have a preserved wall thickening and scar where no motion and thickening can be demonstrated. In addition, wall motion and wall thickening can be used to identify artifacts due to attenuation. In areas with mildly reduced tracer uptake and normal motion and wall thickening, the likelihood that the reduction represents an artifactual attenuation of counts considerably increases (*43*). The various algorithms available to determine left ventricular ejection fraction from gated SPECT myocardial perfusion studies were discussed in Part II of this series.

ATTENUATION AND SCATTER CORRECTION

A recent important advance in cardiac SPECT is the introduction of attenuation correction. Attenuation artifacts caused by the varying distance of the different parts of the myocardium from the camera and the variable thickness of the interposed tissues are a frequent source of false-positive studies. Various algorithms are being developed to compensate for photon attenuation and scatter. Attenuation correction usually is accomplished from transmission data obtained with an external radiation source. The regional attenuation factors are than calculated by iterative reconstruction and a correction matrix is generated and applied to the raw data before reconstruction takes place.

CONCLUSION

Thallium-201 and ^{99m}Tc-labeled perfusion tracers provide similar information in the detection of coronary artery disease. Because of the higher photon flux when ^{99m}Tc-labeled tracers are used, simultaneous assessment of myocardial perfusion and function is possible. Gated studies provide valuable information concerning global (ventricular ejection fraction) and regional (wall motion and wall thickening) left ventricular function and should be considered the state of the art in myocardial perfusion SPECT imaging.

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