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COLLEGE OF PHARMACY



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## ***Clinical Applications of Myocardial Perfusion Spect and Myocardial Perfusion Spect Protocols***

Continuing Education for Nuclear Pharmacists  
and Nuclear Medicine Professionals

By

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# **CLINICAL APPLICATIONS OF MYOCARDIAL PERFUSION SPECT and MYOCARDIAL PERFUSION SPECT PROTOCOLS**

## **STATEMENT OF LEARNING OBJECTIVES:**

1. Select patients for whom Myocardial Perfusion Imaging (MPI) provides clinically relevant diagnostic and prognostic information
2. Risk stratify patients with CAD based upon MPI results
3. Use MPI to follow patients with CAD on medical management
4. Differentiate radiopharmaceuticals for MPI based upon convenience, radiation dose, image quality and diagnostic information provided
5. Select imaging protocols that optimize laboratory efficiency and patient convenience

## COURSE OUTLINE

<b>CLINICAL INDICATION FOR MYOCARDIAL PERFUSION SPECT</b> .....	<b>6</b>
DIAGNOSIS OF CORONARY ARTERY DISEASE.....	6
DETECTION OF JEOPARDIZED MYOCARDIUM IN PATIENTS WITH PRIOR MYOCARDIAL INFARCTION .....	7
<b>ASSESSMENT OF EVOLUTIONARY CHANGES IN PATIENTS WITH CORONARY DISEASE ASSIGNED TO MEDICAL THERAPY</b> .....	<b>7</b>
ASSESSMENT OF COMPLETENESS OF REVASCULARIZATION AND RECURRENCE OF CORONARY STENOSIS .....	8
PREOPERATIVE ASSESSMENT OF PATIENTS UNDERGOING PERIPHERAL VASCULAR SURGERY AND OTHER MAJOR SURGICAL PROCEDURES.....	8
SELECTION OF APPROPRIATE PATIENTS FOR MYOCARDIAL PERFUSION IMAGING.....	9
PATIENTS WITH ACUTE CORONARY ISCHEMIA SYNDROMES .....	10
<i>Myocardial Perfusion SPECT Protocols (14)</i> .....	13
<b>REFERENCES</b> .....	<b>17</b>
<b>ASSESSMENT QUESTIONS</b> .....	<b>20</b>

# **CLINICAL APPLICATIONS OF MYOCARDIAL PERFUSION SPECT and MYOCARDIAL PERFUSION SPECT PROTOCOLS**

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## **CLINICAL INDICATION FOR MYOCARDIAL PERFUSION SPECT**

### **Diagnosis of Coronary Artery Disease**

The primary application of myocardial perfusion SPECT is in the evaluation of patients presenting with signs and symptoms of coronary artery disease. Perfusion imaging has been demonstrated to be safe, accurate, and cost-effective in such patients (1-3). In addition, test results provide important information regarding patient risk stratification.

In order to provide referring physicians with the most valuable diagnostic and prognostic information, the following descriptors of myocardial perfusion defects should be included in the myocardial perfusion SPECT report:

- defect extent: typically defects are described as extensive, moderate, or small
- defect severity: marked, moderate, mild, or questionable
- defect reversibility (proportional to the amount of myocardial ischemia): fixed (non-reversible), partially reversible, nearly completely reversible, completely reversible
- the vascular territory or territories involved: left anterior descending, circumflex, right or posterior descending coronary arteries

Each of these descriptive parameters is of value in patient management and risk stratification. Extensive, marked, and multiple reversible defects are associated with a high risk of myocardial infarction and other cardiac events and justify aggressive patient management. In contrast, only mild defects that are not very extensive usually indicate conservative patient management. In such patient's medical therapy may be instituted, and cardiac catheterization may be postponed until the patients

symptoms worsen. Likewise, in patients with fixed defects due to myocardial scar, the incidence of congestive heart failure, arrhythmias, and cardiac death increase with the extent and severity of the fixed defect.

### **Detection of Jeopardized Myocardium in Patients with Prior Myocardial Infarction**

In patients with prior myocardial infarction, the detection of coronary stenosis outside of the infarct territory is especially important. In patients with prior infarction and associated resting electrocardiographic abnormalities, the stress electrocardiogram may be both insensitive and non-specific in detecting additional stress-induced ischemia. Also, in the presence of regional functional abnormalities secondary to prior infarction, stress echocardiography may also be particularly insensitive and non-specific. Therefore, due to its ability to differentiate scar from ischemia and to visualize the entire left ventricular myocardium, stress myocardial perfusion SPECT is particularly valuable in the assessment of patient's with prior myocardial infarction (4-6). With regards to patient risk stratification, it has been demonstrated that in patients with prior myocardial infarction and ischemia involving less than 10% of the remaining left ventricular myocardium, patient prognosis is good, with an event-free survival rate of > 90% at 18 months. In contrast, in patients with greater degrees of ischemia outside of the infarct territory, prognosis is much poorer with nearly a 50% cardiac event rate at 18 months.

### **Assessment of Evolutionary Changes in Patients with Coronary Disease Assigned to Medical Therapy**

In patients with known coronary artery disease who are treated medically the assessment of disease progression (or resolution) may be difficult clinically. Exercise tolerance and symptomatology may be influenced by medications prescribed. It may be desirable to determine if patients are ischemic while on medical therapy, and to determine the progression of underlying coronary disease. However, beta-blocker therapy blunts the positive chronotropic response to exercise, so it is not possible to maximally exercise patients to assess disease progression. Under these circumstances, when it is desirable to assess progression while patients are on beta blocker therapy, coronary vasodilator pharmacologic stress can be substituted for exercise. The ability to quantify myocardial perfusion defects is particularly useful in following patients on medical therapy (7,8). An objective assessment of disease progression serves to justify catheterization and revascularization, if necessary.

## **Assessment of Completeness of Revascularization and Recurrence of Coronary Stenosis**

Following PTCA, the rate of coronary re-stenosis at 6 months approaches 50% without stenting. With stenting the rate is lower, but still significant. Nearly 50% of patients with restenosis may be asymptomatic. Therefore, patients may have “silent” myocardial ischemia following PTCA. After revascularization, with typical recurrent angina, a clinical diagnosis of restenosis is straightforward, so the patient should proceed directly to cardiac catheterization and subsequently to repeat revascularization, if necessary. On the other hand, in patients with symptoms that are not clear-cut and also possibly in those who are totally asymptomatic, evaluation with stress myocardial perfusion SPECT is of considerable value. Restenosis of the vessel(s) that was dilated can be detected, and progression of disease in other vascular territories can be determined (9,10).

In patients following coronary artery bypass surgery, myocardial perfusion SPECT is likewise of considerable value. Graft occlusion, of course, usually occurs much later than PTCA restenosis. However, stress myocardial perfusion SPECT can be of value in detecting graft occlusion in patients who become symptomatic and also in assessing progression of disease in vascular territories that have not undergone revascularization (11). Investigators have demonstrated that stress myocardial perfusion imaging is of value in determining long-term prognosis in patients following coronary artery bypass. Five years following bypass surgery, patients with evidence of only mild stress-induced ischemia demonstrated a cardiac event rate of less than 40%, whereas those with evidence of more marked and extensive ischemia demonstrated a cardiac event rate over 50%.

## **Preoperative Assessment of Patients Undergoing Peripheral Vascular Surgery and Other Major Surgical Procedures**

Patients with peripheral vascular disease often do not manifest symptoms of coronary ischemia because they are exercise-limited due to claudication. Similarly, patients who are scheduled for other major surgical procedures may be bedridden and do not manifest angina. Unfortunately, occult coronary artery disease in these patients results in a substantial incidence of perioperative myocardial infarction either during the induction of anesthesia or during the prolonged surgical procedure itself. . In a prospective study it was determined that over 90% of patients presenting for peripheral vascular surgery (carotid, aortic, or lower extremity) had coronary artery disease demonstrated by contrast angiography. In over 30% of these patients the degree of coronary stenosis was judged to be severe.



Myocardial perfusion SPECT, especially with pharmacologic stress substituted for exercise, serves as a valuable means to risk stratify patients prior to peripheral vascular surgery and other major surgical procedures (12). In patients with evidence of myocardial ischemia on myocardial perfusion SPECT performed with vasodilator pharmacologic stress it has been reported in several studies that the incidence of perioperative cardiac events, including myocardial infarction and death, is high, averaging 28%. In contrast, in patients with no evidence of stress-induced ischemia the cardiac event rate averages only 3%. Obviously, now that we have this knowledge base, patients with evidence of significant stress-induced ischemia do not proceed directly to major surgery. Instead, coronary angiography is recommended, and when feasible, coronary revascularization is performed prior to the major surgical procedure. In this way perioperative cardiac events may be averted.

Of note, more recent publications have documented that by treating patients with beta blockers, using a high enough dose to prevent tachycardia perioperatively, that patients may proceed directly to peripheral vascular surgery without increased risk of perioperative events. In this way surgery would not be delayed by non-invasive pre-operative testing (13).

### **Selection of Appropriate Patients for Myocardial Perfusion Imaging**

In these days of managed care and cost containment, it is essential that diagnostic tests be not only accurate but also cost-effective. Therefore, guidelines have been proposed for the most appropriate and cost-effective utilization of myocardial perfusion imaging. Patients who most greatly benefit from stress myocardial perfusion SPECT are those with an intermediate probability of coronary artery disease based upon age, gender, coronary artery disease risk factors (hypertension, hypercholesterolemia, smoking, family history, etc.) and treadmill test performance (when available). In this group of patients with an intermediate probability of coronary disease a negative scan renders the likelihood of coronary disease very low. In such patients and even in those patients with coronary disease and a negative scan (false-negative result) the likelihood of cardiac events in the subsequent two years is extremely low (<2%). Therefore, these patients can be followed and managed medically. On the other hand, if the perfusion scan demonstrates significant coronary ischemia, patients can be directed to cardiac catheterization, and subsequently to myocardial revascularization, if necessary. This approach has been demonstrated to be more cost-effective than performing coronary angiography in all such patients.

In contrast to those patients with an intermediate pre-test likelihood of coronary disease, those patients with a high likelihood of disease are usually most appropriately managed by direct referral to cardiac catheterization. Since the diagnosis of coronary ischemia is nearly certain based upon risk factors and clinical symptoms alone, coronary angiography rapidly confirms the diagnosis and directs the patient to the most appropriate type of coronary revascularization. However, in patients with such a high likelihood of coronary disease who are not candidates for revascularization due to medical contraindications or their own preferences, myocardial perfusion SPECT can be advantageous for purposes of risk stratification and prognostication.

Likewise, myocardial perfusion SPECT is frequently performed in patients who have already undergone coronary angiography and have known coronary artery stenosis. Whereas the coronary angiogram provides an anatomic road map of the distribution of coronary lesions, luminal diameter narrowing observed angiographically frequently correlates only poorly with coronary hemodynamics, particularly trans-stenotic pressure gradients and measurements of coronary flow reserve. For example, in a patient with a 50-70% coronary stenosis and atypical symptoms, a stress myocardial perfusion scan may be of great value in helping to determine the hemodynamic significance of the lesion. Also, sequential myocardial perfusion scans in such a patient may serve as a convenient, non-invasive way to determine anatomic and/or hemodynamic disease progression.

Lastly, in patients with a low likelihood of coronary disease based upon coronary risk factors, myocardial perfusion SPECT is usually not advised. Since the incidence of disease is quite low, the diagnostic yield from this relatively expensive technique is similarly low and generally not cost-justified. Moreover, since there is a finite incidence of false-positive scans, a significant proportion of these low-likelihood patients are inappropriately directed to cardiac catheterization.

### **Patients with Acute Coronary Ischemia Syndromes**

In patients admitted to the CCU with symptoms of unstable angina, a definitive diagnosis of coronary ischemia is often difficult, so patient management may be delayed and length of stay in the expensive CCU is prolonged. In order to establish a definitive diagnosis of resting myocardial ischemia as a cause of the patient's symptomatology, resting myocardial perfusion imaging may be employed. Patients can be injected during an episode of chest pain with either Tc-99m sestamibi or Tc-99m tetrofosmin. Since these tracers are distributed to the myocardium directly proportional to coronary blood flow and do not wash out or redistribute, once they are injected and localized to the

myocardium, the patient can be imaged at a later time when he/she is medically stable. By this means, resting perfusion abnormalities as a cause of the patient's symptoms can be identified. Of course, in patients with prior myocardial infarction, it is not possible to differentiate old scar from new resting ischemia. In selected patients it has been demonstrated that this method is far more sensitive and specific than electrocardiographic monitoring to identify resting ischemia. However, a dose of radiopharmaceutical must be made available in the CCU to be injected when the patient in question develops chest pain or when electrocardiographic abnormalities suggestive of ischemia occur. Appropriate personnel must be trained and certified to inject the radiopharmaceutical dose, and necessary radiation safety precautions must be taken.

Likewise, the diagnosis of unstable angina and acute myocardial infarction in patients presenting to the Emergency Department with chest pain is often difficult. Symptoms of ischemia or infarction may be elusive and atypical, and musculoskeletal and gastrointestinal disorders may mimic angina pectoris. The electrocardiogram is relatively insensitive in the diagnosis of unstable angina because electrocardiographic abnormalities occur relatively late in the "cascade" of ischemic findings: perfusion abnormalities→ diastolic functional abnormalities→ systolic functional abnormalities→ decreased global ventricular function→ ECG changes→ symptoms. Moreover, pre-existing electrocardiographic abnormalities, electrical conduction abnormalities, and left ventricular hypertrophy can mask acute myocardial infarction. Laboratory tests for cardiac enzymes (CK-MB, SGOT, SGPT) usually take hours or even days to confirm or exclude the diagnosis of acute myocardial infarction.

Because these clinical, electrocardiographic, and enzymatic markers of unstable angina and acute myocardial infarction are notoriously unreliable, Emergency Department physicians and Cardiologists lack diagnostic confidence. Therefore, of the 3 million or more patients each year presenting to Emergency Departments in the United States, most are hospitalized. Often they are hospitalized in the CCU or Intermediate Care Unit for observation and ECG monitoring, which entails considerable expense.

To minimize unnecessary hospital admissions and to limit hospital length of stay of those patients admitted with acute chest pain, triage of patients in the Emergency Department with myocardial perfusion imaging has become increasingly popular. Patients with clear-cut symptoms and

electrocardiographic changes are, of course, admitted directly to the CCU. Those with extremely atypical symptoms and normal electrocardiograms are usually discharged to home without further testing. However, a significant percentage of patients fall into an intermediate likelihood category. In these patients triage with myocardial perfusion imaging has proven to be expeditious and cost-effective.

Patients are injected with the radiopharmaceutical during chest pain or as soon after the cessation of pain as possible. Nitrates and other coronary vasodilators should be withheld until after the tracer has been injected and has localized in the myocardium in a distribution proportional to resting coronary blood flow (approximately two minutes post-injection). Either of the Tc-99m labeled tracers, sestamibi or tetrofosmin, can be used since both are distributed to the myocardium according to resting coronary perfusion but do not wash out or redistribute. As for patients in the CCU, described above, it is consequently possible to image these patients at a later time when they are stable and when the personnel and instrumentation within the Nuclear Medicine laboratory are available.

If a myocardial perfusion defect is detected, the reduction in regional coronary perfusion may be due to unstable angina (resting ischemia) or acute myocardial infarction. Prior myocardial infarction will also result in a perfusion defect, so patients with historical evidence of prior myocardial infarction generally are not candidates for this technique unless a previous baseline myocardial perfusion scan is available for comparison. Any patient with a new perfusion abnormality is admitted to the CCU. The patient is managed appropriately until cardiac enzyme results are available. If enzymes are abnormal, a diagnosis of acute myocardial infarction is made. If enzymes are negative, a diagnosis of unstable angina can be established, and the patient can be directed to cardiac catheterization and revascularization, if appropriate.

It has been demonstrated that this triage approach indeed minimizes unnecessary hospitalization. Patients with chest pain and negative scans, of course, may have other serious or life-threatening abnormalities such as dissecting aortic aneurysms, acute cholecystitis, pericarditis, pulmonary embolization, etc. and may require hospitalization. However, admission to a regular medical floor might be considered. It has also been demonstrated that by decreasing hospital length of stay the myocardial perfusion scan triage approach is cost-effective.

An alternate approach to patients presenting to the Emergency Department with acute chest pain syndromes is to admit patients to the CCU, Intermediate Care Unit, or medical floor based upon the physician's initial clinical impression and electrocardiographic findings. Once the first set of cardiac enzymes is available, usually 4-6 hours after admission, a decision is made regarding patient management. In those patients with negative enzymes, a resting myocardial perfusion scan is performed using a separate-day rest/stress Tc-99m labeled tracer imaging protocol. If the resting study is normal, a stress study with intravenous dipyridamole is obtained. Ideally, both the rest and stress images are completed within 24 hours of hospital admission. This technique is attractive to many institutions since not only resting ischemia (unstable angina) and acute myocardial infarction can be evaluated, but stress-induced ischemia can also be detected. In addition, this 24-hour hospitalization provides the attending physician with a "safety net" whereby other serious non-cardiac medical conditions can be diagnosed.

### ***Myocardial Perfusion SPECT Protocols (14)***

The most important scintigraphic variables in identifying risk of cardiac events and mortality that should be considered when selecting a myocardial perfusion SPECT protocol are the following:

- Extent and severity of perfusion defects
- Multi-vessel disease pattern
- Extent of defect reversibility
- Transient ischemic dilatation
- Left ventricular ejection fraction
- End diastolic and end systolic volumes
- Lung uptake (Tl-201)

When choosing a protocol it is important to consider the physical and physiologic differences between radiopharmaceuticals, particularly between Tl-201 and Tc-99m:

Tl-201 is characterized by the following:

- A low (2-4 mCi) dose must be injected due to the long physical half-life, resulting in low count density/high noise
- Lower energy (60-90 keV Hg x-ray) than Tc-99m, resulting in poorer spatial resolution
- Greater soft tissue attenuation than Tc-99m due to the lower energy

- Wider energy window is necessary for Tl-201 (60-90 keV Hg x-ray), resulting in more scatter and poorer spatial resolution

Tc-99m is characterized by the following:

- A higher (25-40 mCi) dose, resulting in high count density/low noise
- Higher energy, resulting in better spatial resolution
- Less attenuation than Tl-201
- A 140 keV photon, for which a narrow (15-20%) energy window is used, resulting in little scatter and better spatial resolution

#### Rest/Delayed/Re-injection Tl-201 Protocol

- 2-4 mCi Tl-201 injected at peak stress
- Stress SPECT imaging 10 min. post-stress
- Delayed/redistribution SPECT at 3-4 hrs
- To enhance detection of viable myocardium, a booster dose of 1 mCi Tl-201 may be injected 1 hr prior to the delayed image acquisition. Alternately 24 hr. delayed images may be acquired.

#### Single-Day Rest/Stress Tc-99m sestamibi or Tc-99m tetrofosmin Protocol:

- 9 mCi Tc-99m labeled tracer injected at rest
- SPECT at 40 min.
- Stress immediately thereafter; inject 30 mCi Tc-99m labeled tracer
- Gated SPECT at 20 min. post-exercise or 30-40 min post-pharmacologic stress
- Increase dose in large patients
- 16 oz. water 15 min. prior to imaging to minimize/prevent stomach activity

The advantages of the Single-Day Rest/Stress Tc-99m sestamibi or Tc-99m tetrofosmin Protocol are the following:

- Short (105-125 min) protocol
- Tc-99m/Tc-99m images

The disadvantages are:

- Delay in stressing 1st patient on the laboratory schedule
- Low count density resting images in obese patients

Two-Day Stress/Rest Tc-99m sestamibi or Tc-99m tetrofosmin Protocol:

DAY #1

- 22-25 mCi Tc-99m labeled tracer at peak stress
- Gated SPECT at 20 min. post-exercise or 30-40 min post pharmacologic stress

DAY#2

- 22-25 mCi Tc-99m labeled tracer injected at rest
- Gated (optional) SPECT at 40 min

Some advantages of the Two-Day Stress/Rest Tc-99m sestamibi or Tc-99m tetrofosmin Protocol are the following:

- No delay in stressing 1st patient
- If stress SPECT is normal, eliminate rest SPECT (50-60 min. protocol), increasing laboratory efficiency
- Tc-99m/Tc-99m images
- High count density for both stress and rest images
- High count density for both gated stress and rest images
- The protocol is ideal for obese patients, patients in whom attenuation artifacts are anticipated (women with large breasts or implants, patients with diaphragmatic elevation, etc.), and low –likelihood patients

The disadvantages are:

- Two days required if stress images are not entirely normal

Single-Day Stress/Rest Tc-99m sestamibi or Tc-99m tetrofosmin Protocol:

- 9 mCi Tc-99m labeled tracer injected at stress
- SPECT at 20 min. post-exercise or 30-40 min post-pharmacologic stress
- 3-hr. delay (Tc-99m decay)
- 30 mCi Tc-99m at rest
- Gated SPECT at 40 min

The only advantages of the Single-Day Stress/Rest Tc-99m sestamibi or Tc-99m tetrofosmin Protocol are:

- No delay in stressing 1st patient (particularly advantageous to a busy Cardiologist)
- Tc-99m/Tc-99m images

- Eliminate resting study if stress is entirely normal

Significant disadvantages are the following:

- Very long (255-265 min.) protocol
- Relatively low count density stress images, prone to “reversible” artifacts; outright normal stress images are uncommon
- Low count density resting gated SPECT

Dual Isotope Rest Tl-201/ Stress Tc-99m sestamibi or Tc-99m tetrofosmin Protocol:

- 3.0 mCi Tl-201 injected at rest
- Resting SPECT at 10 min
- Stress physiologic protocol (exercise or pharmacologic vasodilatation)
- Post-stress SPECT acquisition 20 min post-exercise or 45 min post pharmacologic stress

The two advantages of the Dual Isotope Rest Tl-201/ Stress Tc-99m sestamibi or Tc-99m tetrofosmin Protocol are the following:

- The interval between the resting radiopharmaceutical injection and resting SPECT acquisition with Tl-201 is less than that with Tc-99m sestamibi or Tc-99m tetrofosmin (10 min vs. 40 or 25 minutes, respectively), thereby decreasing the time a patient is in the laboratory and potentially increasing lab efficiency.
- There is no possibility of “shine-through” of the resting counts into the stress image.

The principal, significant disadvantage of the Dual Isotope Protocol is the following:

- Low count-density, low-resolution Tl-201 resting images are compared to high count-density, high-resolution Tc-99m images, allowing the possibility for:
  - Over-reading defect reversibility (i.e. ischemia)
  - Over-reading transient ischemic dilatation (TID), a marker of diffuse subendocardial ischemia, often associated with multivessel and/or severe CAD



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## ASSESSMENT QUESTIONS

1. Myocardial SPECT imaging is particularly valuable in the assessment of patients
  - a. receiving beta blocker therapy.
  - b. with recurrent angina after revascularization.
  - c. with a low likelihood of coronary disease.
  - d. presenting for peripheral vascular surgery.
  
2. Myocardial perfusion SPECT imaging is particularly valuable in the risk stratification of patients with a prior myocardial infarct. This is due to the ability of SPECT imaging to
  - a. evaluate re-stenosis after coronary stent.
  - b. distinguish scar from ischemia and visualize the entire left ventricle.
  - c. predict coronary bypass surgery success.
  - d. predict the incidence of perioperative cardiac events.
  
3. Patients who most benefit from stress myocardial perfusion SPECT are those with a/an \_\_\_\_\_ probability of coronary artery disease based on patient history and treadmill test performance.
  - a. high
  - b. intermediate
  - c. low
  - d. very low
  
4. Emergency Department triage of patients using myocardial perfusion imaging has become increasingly popular since
  - a. SPECT imaging eliminates the need for patient hospitalization.
  - b. SPECT imaging is quick, reliable and cost effective.
  - c. SPECT is equal in reliability to clinical, ECG and enzymatic markers.
  - d. SPECT imaging is less time-consuming to perform than traditional tests.
  
5. A clinical advantage of a Two-Day Stress/Rest protocol over a Single-Day Rest/Stress protocol is that the two-day protocol
  - a. delays stressing the first patient of the day.
  - b. eliminates the rest protocol if the stress test is normal.
  - c. reduces patient radiation exposure.
  - d. delays the rest redistribution imaging several hours.