# Value of nuclear cardiology for the diagnosis and risk stratification of coronary artery disease

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**ABSTRACT** **Nuclear cardiology has developed into an extremely valuable tool for the diagnosis and prognostication of coronary artery disease. With the low sensitivity and specificity of clinical symptoms, baseline and stress ECG, physicians and cardiologists require non-invasive techniques to detect and risk stratify patients with ischemic heart disease. Myocardial perfusion imaging (MPI) achieves great accuracy in the diagnosis of the disease and in identifying the patients with higher risk for adverse events. Literature shows that it is not the coronary anatomy but the ischemic burden that determines prognosis in patients with ischemic heart disease. Patients with normal MPI, independently of age, gender, symptoms, history of coronary artery disease, presence of anatomic coronary artery disease (CAD) or isotope or imaging technique, have a <1% risk of adverse events (myocardial infarction or cardiac death) for a period of at least 12 months. Left ventricular function, regional wall motion abnormalities as well as myocardial viability can be evaluated with MPI.**
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## INTRODUCTION

Nuclear cardiology has undergone an outstanding growth during the last 25 years.

With technical improvements and new radiopharmaceuticals, higher sensitivity and specificity of myocardial perfusion imaging (MPI) scans has been achieved for detection and evaluation of ischemic heart disease.

MPI is performed with the administration of radiopharmaceuticals which are taken up by the myocardial cells. Different radiotracers can be used, such as: Thallium-201, $^{99m}$Tc-Sestamibi, $^{99m}$Tc-Tetrofosmin, etc. The investigation is performed at rest and stress, providing semi-quantitative information on areas of myocardial infarction and ischemia.

Beller et al. showed in the "anginal cascade"[1] that, with increasing stress time and myocardial oxygen demand, ischemic ST depression and anginal symptoms appear after flow heterogeneity, regional myocardial dysfunction, significant perfusion defects and global left ventricular dysfunction. This accounts for the increased sensitivity, specificity and accuracy of MPI over symptoms and stress ECG in the diagnosis and follow-up of coronary artery disease.

It has developed into one of the most contributory fields in clinical decision making for the detection and risk stratification in patients with suspected and known coronary artery disease.

## USE OF MYOCARDIAL PERFUSION SCINTIGRAPHY IN THE CLINICAL SETTING

Myocardial perfusion SPECT (single photon emission computed tomography) is a widely utilized noninvasive imaging modality for the diagnosis and management of ischemic heart disease. This modality allows a three-dimensional assessment and quantitation of the myocardium and functional assessment through ECG-gating of the perfusion images.[2]

**TABLE 1:** Use of myocardial perfusion SPECT in the clinical setting

| |
|---|
| Diagnosis of coronary artery disease |
| Identify the site and extent of ischemia |
| Quantification of the extent and severity of impaired coronary flow reserve |
| Acute ischemic syndromes |
| Pre-surgical evaluation |
| Prognostic assessment of CAD patients |
| Assessment of tissue viability |

There are several indications for the use of myocardial perfusion SPECT, whether it is for a patient who is not known to have coronary artery disease and the aim is confirm or rule out the diagnosis, or in the patient with known ischemic heart disease, whether symptomatic or not, for risk-stratification (Table 1).

## Indications for myocardial perfusion scintigraphy

### If the patient does not have diagnosis of CAD

To exclude or diagnose CAD in patients with suspected CAD

- As a screening test in those with intermediate or high risk of CAD, e.g. familial hyperlipidemia, type II diabetes mellitus, family history of CAD, and those with atypical symptoms of ischemic heart disease (IHD). In patients with high pretest likelihood for CAD, MPI is mainly useful for risk stratification purposes.

- In patients with non-diagnostic electrocardiography (ECG), at rest or post-stress. While there are many causes for an abnormal baseline ECG (Table 2), STRESS- ECG is frequently not conclusive.

  Gianrossi et al. performed a meta-analysis of 147 consecutive published reports involving 24 074 patients who underwent both coronary angiography and exercise testing.[3] Mean sensitivity was found to be 68% (range 23 to 100) while mean specificity was 77% (range 17 to 100).

- Patients who are at risk of developing peri or postoperative cardiovascular events, i.e. peripheral vascular disease, aortic aneurysm, and the elderly.

- Acute chest pain – diagnosis of CAD.

**TABLE 2:** Non-coronary causes of ST-segment depression

| | |
|---|---|
| Severe aortic stenosis | Left ventricular hypertrophy |
| Severe hypertension | Hyperventilation |
| Cardiomyopathy | Mitral valve prolapse |
| Anemia | IV conduction disturbances (RBBB, LBBB) |
| Hypokalemia | Preexcitation syndrome (i.e. WPW) |
| Severe hypoxia | Severe volume overload |
| Digitalis effect | Severe pressure overload |
| Sudden excessive exercise | Supraventricular arrhythmias |
| Glucose load | |

LBBB can induce perfusion defect in the basal anteroseptal myocardial segment not attributable to CAD. This can potentially give a false interpretation of the scan. Specificity is not affected when evaluating other myocardial segments. However, a pharmacological stress with MPI will still provide high sensitivity in patients with LBBB.

The sensitivity and specificity of MPI ranges between 81% and 91% and between 82% and 91% respectively[4-7] for the detection of coronary artery disease.

Myocardial perfusion imaging is both more sensitive and more specific than exercise ECG for the diagnosis of CAD.

### In patients with diagnosis of CAD

- To evaluate the "functional" significance of a coronary lesion (stenosis).

- For risk stratification and evaluation of prognosis. Myocardial perfusion scintigraphy is one of the most powerful non-invasive techniques for risk stratification.

- The "functional" significance of the extent and severity of stress perfusion defect is closely related to subsequent cardiac events.

- The important variables are, therefore, extent, severity and reversibility of a stress perfusion defect.

- Detection of patients with "high risk" CAD. The factors that represent "high risk" stress myocardial perfusion defects are:

  - Multiple defects in different vascular regions (multivessel disease).

  - Proximal left anterior descending (LAD) coronary artery disease, leading to reversible defects in the antero-septal and apical regions; reversible defects in the antero-septal and lateral wall may indicate left main disease or equivalent.

Perhaps the most consistent observation in the literature concerning the prognostic value of MPI is that the presence and extent of transient myocardial perfusion imaging defects, a marker of jeopardized viable myocardium, predict important future cardiac events.

In 1983, Brown et al. compared $^{201}$TI with clinical, exercise ECG, and angiographic data in patients without known previous MI who presented for evaluation of chest pain. The best predictor of cardiac death or non-fatal MI was the number of myocardial segments with transient defects on $^{201}$TI imaging.[8]

Although the presence of jeopardized viable myocardium identifies patients at increased risk for cardiac events, more importantly cardiac risk is directly related to the extent of jeopardized viable myocardium.

**Post-infarction risk stratification**

- Detection of ischemia at the site of injury or remotely.
- Evaluate for myocardial viability in the infarct region.
- Evaluate the flow-function relationship (from gated SPECT).
- Selection of patients for medical treatment versus revascularization in stable angina.

Major determinants of prognosis after myocardial infarction patients are infarct size, left ventricular ejection fraction and the presence or absence of distant residual ischemia. All these variables can be determined with $^{99m}$Tc-Sestamibi, Tetrofosmin, Thallium-201 (and other tracers) scintigraphy.

**After Percutaneous Transluminal Coronary Angioplasty (PTCA)**

Restenosis after PTCA occurs in 30-40%[9-12] of cases but may remain asymptomatic for long periods. However, since the advent of intracoronary stenting, this rate has significantly decreased.[13] Perfusion imaging is superior to clinical and other non-invasive tests for detecting restenosis. Serial imaging at 6 weeks, 3-6 months, and then according to the clinical situation may be necessary for optimal monitoring of PTCA.

In a study done in Johannesburg, South Africa, 122 patients at least 3 months after PCI (percutaneous coronary interventions) underwent myocardial perfusion scintigraphy. Ischemia was found in 56% of asymptomatic patients,[14] which was in keeping with other reports which showed clinically silent restenosis in 60% of patients with ischemia on MPI.[15] Regardless of whether restenosis was silent or symptomatic, an abnormal MPI post PTCA was associated with increased risk for hospital admission or myocardial infarction.[15]

Normal MPI post coronary angioplasty indicates:

- That the procedure was successful.
- That there is low risk for recurrent cardiac events.[15,16]
- Low probability of late restenosis.[16]

**After Coronary Artery Bypass Graft (CABG)**

Nuclear cardiology techniques are extremely useful in patients post CABG. Besides helping in the selection of patients for surgical revascularization, they can be used to:

- Check for perioperative myocardial infarction.
- Document improvement in myocardial perfusion and function after surgery.
- Demonstrate graft occlusion and ischemia due to incomplete revascularization or progression of disease.
- Predict future cardiac events.

The risk of graft occlusion is approximately 12% to 20% after the first year.[17] Independently of the technique used for CABG, graft patency can be accurately assessed with MPI, with a high correlation between myocardial perfusion scintigraphic and angiographic findings,[18-20] with sensitivity and accuracy superior to those of Stress ECG findings.[21]

In a study done in Johannesburg, South Africa evaluating 142 patients post CABG for ischemia, 68% of those asymptomatic were found to have ischemia on MPI.[22]

Stress imaging may distinguish patients with noncoronary chest pain from those with significant myocardial ischemia. Regardless of symptoms, normal results on a post-CABG stress perfusion scan essentially exclude significant graft stenosis.[18-20]

**Assessment of myocardial viability**

While improvements are made to treat acute coronary syndromes, decreasing its initial mortality, there is an increased prevalence of

patients with left ventricular dysfunction. These patients are at risk for severe morbidities, recurrent hospitalizations, cardiac death and severe lifestyle limitations.

LV dysfunction as a result of ischemic heart disease is not always due to irreversible myocardial necrosis or scarring. Ischemic injury can lead to left ventricular dysfunction through different processes like LV remodeling, impairment of metabolism, myocyte dysfunction or cell death due to necrosis or apoptosis.[23]

Besides the case of cell death, these processes can be reversible, with various degrees improvement in left ventricular function. Appropriate medial therapy and often revascularization in properly selected patients can represent the best therapeutic approach.

**Stunned myocardium** is defined as myocardium dysfunctional due to a transient coronary occlusion, salvaged by coronary reperfusion but still exhibiting prolonged but transient post ischemic dysfunction. So even though the blood flow has been restored, contraction has still not improved; that means there is a flow-contraction mismatch.[24] This can happen as a result of an acute myocardial infarction followed by reperfusion, after ischemia (spontaneous or exercise induced), after cardioplegic arrest during heart surgery.

**Hibernating myocardium** is defined as a state of persistently impaired left ventricular function at rest due to reduced coronary blood flow. Therefore, hibernating myocardium has a flow-contraction match.[25]

Patients with depressed left ventricular function have a worse prognosis than patients whose left ventricular function is normal.[26] The importance of myocardial viability assessment is to identify those patients with hibernating or stunned myocardium because ventricular function as well as symptoms and natural history may improve after revascularization. Although PET metabolic imaging with $^{18}$F-FDG has been considered the "gold standard" for evaluating myocardial viability for years, other radiotracers have been proven to have a high accuracy.

In a study done by Di Carli et al. with PET in patients with coronary artery disease and mean left ventricular ejection fraction of 25%, those with myocardial viability had a 50% annual survival when treated medically vs. 88% when treated with revascularization. Those patients that showed no viability on scan had 92% annual survival when treated medically vs. 50% when revascularized.[27]

In a meta-analysis by Allman KC et al. of 3 088 patients with decreased left ventricular ejection fraction that underwent viability study using different methods, those with viable myocardium showed an annual death rate of 3.2% when sent for revascularization and 16% when treated medically (p=0.0001), as opposed to those with no viable myocardium who had a 7.7% death rate when revascularized against 6.2% when medical treatment was chosen (p=0.23).[28]

Hass F et al. in a PET imaging study of patients with coronary artery disease and LV dysfunction considered for CABG concluded that the forgoing of a viability study resulted in too many high-risk patients without viability being sent for bypass surgery, resulting in a worse prognosis.[29]

Currently several radionuclide techniques are available to evaluate myocardial viability:

- Stress-delayed Tl-201
- Rest-delayed Tl-201
- Tc-99m Sestamibi
- Positron Emission Tomography (PET) metabolic imaging with 18F-FDG

In a meta-analysis of 33 studies with Tl-201 done by Bax JJ et al., sensitivity was found to be 86% and specificity 59%, while in 20 studies in which patients were evaluated using Tc-99m Sestamibi they were 81% and 86% respectively. The positive predictive value was 71% and negative predictive value 77%.[30] Collateral flow to the hypoperfused areas is improved by nitrates. When sestamibi imaging was nitrate-enhanced, sensitivity was 86% and specificity 83%.[30] In an analysis of 18 studies directly comparing 563 patients who underwent viability assessment with a nuclear technique (Tl-201 or F-18-FDG PET) versus dobutamine echocardiography, Bax and coworkers reported that pooled results indicate:

- Higher sensitivity and negative predictive value for the nuclear technique.
- Higher specificity and positive predictive value for dobutamine echocardiography.[31]

DiCarli et al. showed that the extent of the defect on PET imaging demonstrating hibernating myocardium can predict the functional recovery after revascularization.[31] PET is considered the "gold standard" for evaluation of viability using metabolic tracers.

Using metabolic tracers, both perfusion and regional function can be evaluated. It may be misleading to consider viability simply based on its presence or absence,[32] as it can exist in a range of situations, from necrosis due to infarction, which would represent non-recoverable myocardium, to transmural stunning or hibernation with prospective of full recovery .

DiCarli et al. established that the area of myocardial viability is related to the percentage of left ventricular function improvement post-revascularization. The larger the area, the greater the improvement.[31]

**Pharmacological Stress Testing**

As physical stress is not possible in many patients, either because they cannot achieve at least 85% of the target heart rate or because there are contraindications to the test (Table 3), pharmacological stress can be used as an appropriate alternative.

The pathophysiological basis for the use of coronary vasodilators is that in the presence of a narrowing in a coronary artery, the capacity to increase the myocardial blood flow with pharmacologic stimulation is decreased with inverse relation to the severity of the stenosis, causing a heterogeneous tracer uptake by the myocardium, with reduced uptake in the area supplied by the affected artery.

**TABLE 3:** Contraindications to exercise stress testing

| |
|---|
| Peripheral vascular disease |
| Arthritis |
| Cerebral-vascular disease |
| Orthopedic problems |
| Chronic pulmonary disease |
| Extremity amputation |
| Poor motivation to exercise |
| Poor exercise capacity |
| Beta-blocking drugs that limit heart rate response |
| Left bundle-branch block |
| Early after myocardial infarction (<5 days) |

*From Beller GA, Pharmacological stress imaging in clinical nuclear cardiology, Philadelphia, 1995, WB Saunders Company.*

Several coronary vasodilators can be used:

- Adenosine
- Dipyridamole
- Adenosine triphosphate
- Other agents, such as a selective A2 agonist.

In South Africa dipyridamole and adenosine are the pharmacological agents of choice. In case of contraindication to dipyridamole or adenosine, inotropic/chronotropic agents like dobutamine can be selected (see Table 4).

## Adenosine

The mode of action is by activation of A2 receptors, which causes coronary vasodilatation through the production of adenylate cyclase and cyclic AMP stimulation of K+ channels. Reduction of intracellular calcium also occurs.

## Dipyridamole

Acts by blocking the transport of adenosine into the cells, its uptake across the cell membrane and its metabolism, raising endogenous adenosine levels.

**TABLE 4:** Contraindications to pharmacological agents

| |
|---|
| **To Adenosine or Dipyridamole** |
| Bronchospasm |
| Hypotension at baseline (systolic BP <90 mm Hg) |
| Acute myocardial infarction (within 24 hours) |
| Acute coronary syndromes |
| Second degree or higher A-V block (in the absence of a pacemaker) |
| Hypersensitivity reaction |
| **To Dobutamine** |
| Severe hypotension or hypertension |
| Uncontrolled atrial flutter or fibrillation |
| Recurrent ventricular tachycardia |
| Severe left ventricular outflow obstruction |
| Recent acute myocardial infarction |
| Acute coronary syndromes |
| Large aortic aneurysms |
| Decompensated heart failure |

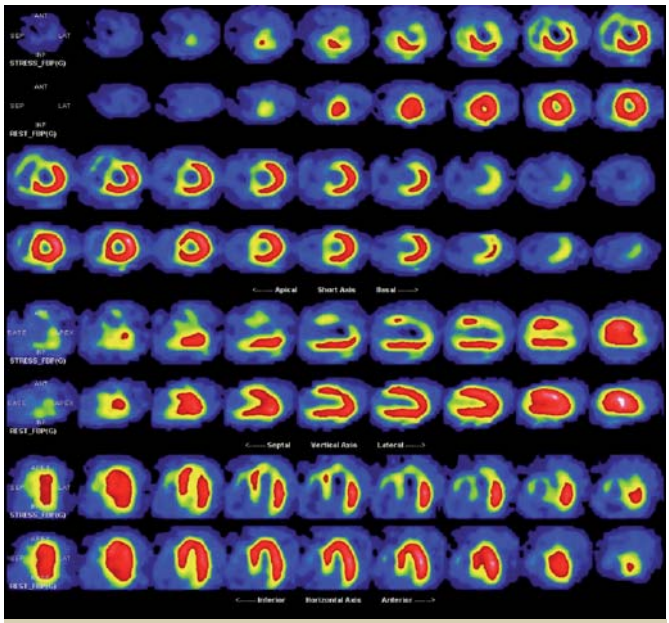

**FIGURE 1:** Stress-rest MPI studies showing severe apical, apical-anterior, mid-anterior, mid-anteroseptal and basal-anteroseptal segments, stress induced ischemia (Short axis, vertical long axis and horizontal long axis views. Upper row corresponds to stress study; lower row corresponds to rest study).

This causes coronary vasodilatation with minor decrease in peripheral vascular resistance. Its effects are reversed by aminophylline by competition for the receptor binding sites.

### Dobutamine

This is a powerful inotropic agent whose onset of action is at 1 – 2 minutes with the peak effect being achieved several minutes later.

Sensitivity and specificity for dipyridamole has been found to be 89% and 78%, for adenosine 90% and 91%, and for dubutamine 82% and 73%.[33-49]

It is better to do an appropriate pharmacological stress when indicated, rather than an insufficient exercise test (Figure 1).

## DISCUSSION

Literature has shown that it is not the coronary anatomy but the ischemic burden that determines risk.[50] The physician's goal at present time is not so much identifying the patients with anatomic CAD, but predicting which patients are at risk for adverse events, i.e. cardiac death or nonfatal MI, and deciding management strategies that might reduce the risk of these outcomes after MPI. This risk-based approach includes not only symptomatic but also asymptomatic patients with suspected ischemic heart disease.[51]

In South Africa myocardial perfusion imaging (MPI) is underused, probably due to the underexposure and undertraining of cardiologists in these extremely valuable techniques. Consequently, too many patients end up in the catheterization lab, whether for diagnostic purposes, or for follow-up of patients with known ischemic heart disease, for reevaluation when they present with new symptoms after myocardial infarction, percutaneous interventions or CABG.

According to a statement by the American Society of Nuclear Cardiology published in 1997, a normal perfusion scan predicts a <1% risk of adverse events (myocardial infarction or cardiac death) for a period of at least 12 months, independently of gender, age, symptoms, history of coronary artery disease, presence of anatomic CAD or isotope or imaging technique used.[52] Other publications state that event rates following a normal MPI can be influenced by age and comorbidity taking the hard event rates to between 1.3% and 2.7% in elderly patients stressed pharmacologically.[52-55]

Still, as a group, patients with a normal MPI study are at very low risk of hard event during the first year post-test.[56]

When an MPI is found to be abnormal, the risk for hard events is related to the severity of the abnormality; the greater the affected area, the higher the risk.[51,57-66]

Hachamovitch et al. found that patients with a mildly abnormal scan were at intermediate risk for myocardial infarction (2.7%) but low risk for cardiac death (0.8%).[60] If the patients had to undergo pharmacological testing for any reason, or are elderly, have previous history of CAD, diabetes mellitus or atrial fibrillation, even with a mildly abnormal scan, the risk is increased.[55,59,67,68,69]

In studies done by Albro PC et al., and Hachamovitch R et al., when the scan is found to be moderate and severely abnormal, the risk for myocardial infarction and cardiac death correlates with the degree of the coronary stenosis supplying those territories and depends on the severity and extent of the perfusion defects.[70,71]

Fixed and reversible stress perfusion defects predict hard events; still, patients with extensive stress-induced defects are the ones at higher risk.[57-60,62,63,65,71-73]

Perfusion defects are not the only determinants of risk. When MPI is performed with 201-Tl, abnormally increased tracer uptake of the

tracer by the lungs is considered to be secondary to elevated pulmonary capillary wedge pressure, caused by ischemia or left ventricular claudication from a nonischemic etiology. This finding has been shown to add prognostic information over the perfusion defects.[74] Independently of the pharmacological agent used to perform the MPI, left ventricular transient ischemic dilation (TID) is present when the cavity in the post-stress is found to be significantly larger than in the rest images. The finding is considered to be caused by diffuse subendocardial ischemia which causes apparent cavity dilation.[71]

TID is a marker of risk and it has been found to add incrementally over perfusion data.[66,75,76]

The approach suggested by R. Hachamovitch and D. Berman[67,71] based on published evidence, is to manage patients with normal scans medically, as revascularization has not been shown to provide potential benefit in mortality. Patients whose MPIs show reversible perfusion defects extending to <10% of the myocardium (mild to moderate ischemia) should be managed medically including risk factor modification too, as revascularization will not provide a mortality benefit. If however they are symptomatic and the symptoms impact negatively on their quality of life, or if they have additional markers of severity such as increased pulmonary accumulation of 201Tl or TID, they should be referred for catheterization with a view to intervention.[67,71]

When the extent of the ischemic myocardium is 10-20% or >20%, patients have been found to have improved prognosis with revascularization as compared to medical treatment. Due to their higher risk for adverse events, the authors recommend these groups of patients to undergo catheterization, to assess the need for revascularization.[67,71]

## CONCLUSION

Myocardial perfusion imaging constitutes a highly valuable technique in the diagnosis of coronary artery disease, especially in patients with intermediate pretest likelihood. As it has been shown that patients' prognosis is determined by the ischemic burden, the information provided by MPI is seminal in patients with known ischemic heart disease for risk stratification (decision making), to assess the best possible management, medical or revascularization.

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