Thallium-201 (Tl-201):
Diagnosis of CAD:

Tc-99m Radiology and Nuclear Medicine

Myocardial perfusion imaging (MPI) is useful

• Combined Pharmacological stress:
  • Physical stress or exercise stress:
    - Treadmill test: Most commonly used
    - Bicycle ergometer.
  • Pharmacological stress:
    - Inotropic stress (dobutamine, arbutamine)
    - Vasodilator (adenosine, dipyridamole, regadenoson).
  • Combined
    - Exercise with vasodilator stress.

Perfusion Imaging
Cardiac Stress Modalities for Myocardial imaging shows the relative distribution of coronary flow, which is increased metabolic demand or vasodilation. Thus, early detection of CAD to prevent myocardial infarction (MI) or cardiac death is the primary objective of noninvasive cardiac stress testing.

Exercise stress test is most widely used initial screening test for detection of CAD. The current accepted electrocardiogram (ECG) criteria for the detection of occlusive CAD is the development of 1 mm horizontal or down sloping ST-segment depression in at least two contiguous ECG leads. It has a sensitivity of 68% and specificity of 77% for detection of CAD. With adjustment for referral bias, sensitivity is 50% and specificity is 90%. Limitations of stress ECG changes are low sensitivity and also the changes in the ECG leads do not necessarily correlate with the vascular territories of the disease. Coronary angiography is limited in its ability in assessing the physiologic significance of a particular lesion, especially if the luminal narrowing is between 40% and 70%.

BASIS OF STRESS RADIONUCLIDE CARDIAC IMAGING
In CAD, up to 75% of the cross-section area (< 50% of luminal narrowing), coronary vessel narrowing does not affect resting coronary flow. Thus, the basis of stress imaging is the visualization of heterogeneity of regional myocardial blood flow through either increased metabolic demand or vasodilation. Myocardial perfusion imaging shows the relative distribution of coronary flow, which is normally uniform in the absence of ischemia or infarction.

Cardiac Stress Modalities for Myocardial Perfusion Imaging
• Physical stress or exercise stress:
  - Treadmill test: Most commonly used
  - Bicycle ergometer.
• Pharmacological stress:
  - Inotropic stress (dobutamine, arbutamine)
  - Vasodilator (adenosine, dipyridamole, regadenoson).
• Combined
  - Exercise with vasodilator stress.

Single-photon Emission Computed Tomography Tracers for MPI
• Thallium-201 (Tl-201): It is potassium analog and decays to Hg-201 with a half-life of 73 hours. The myocardial segments with reduced flow rates have relatively low uptake compared to the well-perfused segments. Washout of Tl-201 from the myocardium is faster from areas with higher initial uptake (and higher regional flow) and is slower from hyperperfused but viable areas supplied by arteries with inadequate flow during stress. This leads to “redistribution” of initial defects. The recommended time for delayed imaging is 3–4 hours after tracer injection. Tl-201 redistribution is consistent with presence of viable, but hyperperfused (or ischemic) myocardium.
• T99m-labeled sestamibi/Tetrofosmin/Teboroxime: The uptake is dependent on plasma membrane and mitochondrial membrane potentials. They have low first-pass extraction fraction compared to Tl-201, but because of higher gamma ray energy of T99m, they give higher counts. The yield in diagnostic and prognostic information is similar to that of Tl-201. However, they do not have significant redistribution of tracer.

Interpretation of Stress Myocardial Perfusion Imaging
• Normal perfusion + wall thickening = No stress induced ischemia
• Defect in stress images + improvement in rest images = Reversible stress induced ischemia
• Defect in stress images + corresponding defect in rest images = Fixed defect.

Identification of attenuation artifacts and other types of pathophysiological diagnoses identifiable on a gated single-photon emission computed tomography (SPECT) study:
• Fixed defect + wall thickening (no evidence of MI) = Attenuation
• Fixed defect + wall thickening (history of previous MI) = Viable tissue
• Fixed defect + no wall thickening = Infarction
• Normal perfusion + no wall thickening = Stunning.

Clinical Utility of Myocardial Perfusion Imaging
• Diagnosis of CAD: Myocardial perfusion imaging (MPI) is useful in the following conditions for diagnosis of CAD:
  - In patients with intermediate pretest probability of CAD based on age, gender and symptoms
  - In high-risk factors for CAD
  - In patients who are unable to exercise adequately and in those with nondiagnostic baseline ECG, such as left bundle branch
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block (LBBB), paced rhythm, left ventricular hypertrophy or users of digoxin.
However, it is inappropriate in patients with low pretest probability due to the high rate of false-positive results. Sensitivity and specificity for diagnosis of CAD is approximately 90% and 70%, respectively. Moreover, patients with negative results on MPI are rarely referred for coronary angiography. Thus, true sensitivity and specificity estimation is difficult due to referral bias. In triple vessel disease, MPI may underestimate true ischemic burden due to balanced ischemia. Gated MPI could be of help in such cases by demonstrating reduced ejection fraction and wall motion abnormalities.

In diabetic patients, silent ischemia is a common finding, making diagnosis difficult on routine exercise stress testing. Angina or silent ischemia appears to be more frequent in diabetics with normal angiographic coronary arteries. Due to high risk of cardiac and noncardiac complications, assessment of myocardial perfusion in all patients with Type-2 diabetes is appropriate. The time of diagnosis and thereafter would be appropriate. Sequential radionuclide imaging with positron emission tomography (PET) or SPECT would be helpful in follow-up of the disease development and progression in such a higher-risk population group.

Restenosis in postrevascularization patient and graft failure of aortocoronary bypass needs further investigations as most of them do not have reliable symptoms. Myocardial perfusion imaging (MPI) is a noninvasive means to determine the need for repeat invasive procedure.

- **Variant or Prinzmetal’s angina:** The diagnosis of recurrent transient attacks of coronary vasospasm is difficult as mostly the symptoms occur out of hospital. It may cause chest pain and ST-segment elevation on ECG. Gated myocardial perfusion SPECT can exhibit wall motion abnormalities (stunning), even hours after an episode has occurred. Abnormalities in fatty acid metabolism persist long after an ischemic episode or even reperfusion.

- **Prognosis and risk stratification:** The patients with a normal stress perfusion scan can have a favorable prognosis even in the presence of CAD. Various parameters of risk stratification on myocardial perfusion SPECT imaging are:
  - Number of reversible defects (extent of ischemia)
  - Degree of perfusion abnormality (severity of ischemia)
  - Involvement of multiple vascular territories
  - Left ventricular dilation
  - Increased lung thallium uptake
  - Left ventricular ejection fraction (LVEF).

The number of segments in relation to risk has been shown in Table 1:

### Table 1: Risk stratification of chronic stable CAD patients

<table>
<thead>
<tr>
<th>Number of segments involved</th>
<th>Risk</th>
<th>Expected cardiac event per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Very low</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>1–2</td>
<td>Low</td>
<td>1–5%</td>
</tr>
<tr>
<td>3–4</td>
<td>Moderate</td>
<td>5–15%</td>
</tr>
<tr>
<td>5–6</td>
<td>High</td>
<td>15–25%</td>
</tr>
<tr>
<td>&gt; 7</td>
<td>Very high</td>
<td>&gt; 25%</td>
</tr>
</tbody>
</table>

Myocardial Perfusion Positron Emission Tomography Imaging

Advantages of PET over SPECT imaging are better attenuation correction, superior resolution, high temporal resolution, in vivo noninvasive measurement of coronary flow, and tracers with higher extraction fraction and short half lives.

Cardiac Positron Emission Tomography Perfusion Tracers

- **N-13 ammonia:** This is probably the best PET tracer for imaging and quantification of myocardial blood flow. After passively diffusing into the myocardium, it is converted into glutamine and is retained in the myocardial cells. Extraction fraction is high even with high flow rate during pharmacological vasodilatation. Its half-life of 9.8 minutes allows high-quality image acquisition and gating.
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- **Rubidium-82**: It is a potassium analog. Its advantages are that it is a generator produced and half life of 75 seconds, which results in multiple sequential imaging. Disadvantages are its high cost, poorer resolution due to high positron energy, noisy images due to short half-life.
- **Oxygen-15 Water**: Its advantage is high extraction fraction even at high myocardial flow. It is considered as gold standard for absolute flow quantification. Its disadvantages are noisy images due to short half life and poorer quality images due to rapid equilibration between blood pool and the myocardium. However, its utility is restricted to only research area.

**Newer Positron Emission Tomography Perfusion Tracers**
- Cu-62 PTSM
- F-18 BMS 747158-02.

**Clinical Application of Positron Emission Tomography Myocardial Perfusion Imaging**
- Diagnosis and risk stratification of CAD patients with non-diagnostic or equivocal previous tests.
- Patients with LBBB or ventricular pacing rhythm.
- Obese patients.
- This can also be used as first test for detection of extent and location of ischemia.

**Positron emission tomography myocardial perfusion imaging in diagnosis of CAD**: It has sensitivity of 83-100% and specificity 73-100% for diagnosis of CAD. Rb-82 or N-13 ammonia PET MPI has superior diagnostic accuracy over thallium SPECT MPI. However, it is limited in its ability of accurately defining extent of disease in multi-vessel disease. This problem can be solved by estimation of left ventricular ejection fraction (LVEF) at baseline and during peak stress. An increase in LVEF of more than 5% during stress has NPV of 97% in ruling out triple-vessel disease (TVD).

**Positron emission tomography myocardial perfusion imaging in prognosis of CAD**: Studies have shown very low hard cardiac event rate (0.09% per year) in patients with normal Rb-82 PET-MPI. The (PET-MPI) also has incremental prognostic value in comparison with clinical and angiographic findings alone in CAD patients.

**Absolute Myocardial Blood Flow Quantification**
Positron emission tomography is the best noninvasive method for absolute quantification of myocardial blood flow (MBF) and quantification of coronary flow reserve (CFR). It is based on tracer kinetic models. O-15 water, N-13 ammonia and Rb-82 are commonly used tracers.

Clinical applications of absolute MBF quantification are preclinical diagnosis of CAD, i.e. endothelial dysfunction, accurate noninvasive diagnosis of multi-vessel disease, distinguishing the presence of collaterals and early hibernating myocardium in known CAD and assessing response to therapy or intervention for CAD.

**Hybrid SPECT-CT/PET-CT Technique**
With the introduction of fusion technology of diagnostic CT with SPECT or PET, simultaneously anatomy and physiology coronary arteries can be studied. Coronary CT angiography evaluates the burden of atherosclerosis and vulnerable plaque, while PET-MPI is highly specific and evaluates physiological consequence of atherosclerosis. Thus, this may prove as “one-stop shop” for noninvasive evaluation of coronary arteries.

**ASSESSMENT OF MYOCARDIAL VIABILITY**
- Hibernating myocardium in known CAD patients represent state of persistent LV dysfunction in chronically decreased blood flow but preserved viability.
- Approximately, 55-60% of the hibernating myocardium is expected to demonstrate functional improvement.
- Revascularization of viable myocardium may lead to reduction in the annual mortality rate, compared with medical treatment alone.

**Single Photon Emission Tomography**
- **Cell membrane integrity**: Retention of Thallium-201 reflects cellular membrane integrity, i.e. viable myocardium. Different protocols with this tracer are as follows:
  - **Stress—4 hours redistribution**: Can assess inducible ischemia.
  - **Stress—4 hours-24 hours redistribution**: More accurate than stress-4 hour protocol.
  - **Stress—4 hours redistribution (Reinjection)**: Most accurate protocol.
  - **Rest—redistribution**: When the clinical question is viability alone.

The criteria for the diagnosis of hibernating myocardium:
- Normal uptake at stress/rest imaging.
- Stress defects with redistribution on delayed images.
- Ten percent increase in activity in fixed defects on re-injection or delayed resting images.
- Uptake of 50% on redistribution—reinjection images.
- **Cellular metabolism** (Technetium-99m-labeled sestamibi and tetrofosmin): For uptake and retention of these tracers, perfusion and membrane integrity is essential, reflecting myocyte viability. Compared to thallium 201, these are inferior in assessment of viability. However, nitrate augmented rest imaging enhance collateral blood flow to severely hypoperfused regions, improving the accuracy of Tc-99m tracers for identification of viable myocardium.

**Positron Emission Tomography**
- In ischemic myocardium, normal free fatty acid metabolism switches to glucose as the main energy source.
- Increased 18F-fluorodeoxyglucose (FDG) uptake is therefore considered a marker of viability.
- F-18 FDG PET imaging is considered the “gold standard” for the detection of viable myocardium, with sensitivity of 93% and specificity of 58%.
- Interpretation criteria for evaluation of myocardial viability has been described in **Table 2**.

**TABLE 2** | Interpretation criteria for evaluation of myocardial viability

<table>
<thead>
<tr>
<th>Classification</th>
<th>Function</th>
<th>Perfusion</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Stunning</td>
<td>Decreased</td>
<td>Normal</td>
<td>Variable</td>
</tr>
<tr>
<td>Hibernating</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Preserved</td>
</tr>
<tr>
<td>Infarcted</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

**REFERENCES**
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