Radiopharmaceutical Agents for Myocardial Perfusion Imaging

Aaron L. Baggish, MD; Charles A. Boucher, MD

Myocardial perfusion imaging (MPI) is a well-established noninvasive method of assessing coronary blood flow.1–5 MPI is capable of identifying regional abnormalities in coronary artery blood flow and determining their physiological relevance to myocardial function and viability. MPI requires the intravenous injection of a radioactive blood flow marker followed by imaging of regional myocardial uptake.6–10 Imaging is most frequently performed by tomographic techniques (ie, SPECT [single-photon emission computed tomography]) with electrocardiographically synchronized image gating. Used frequently in conjunction with either physical exercise or pharmacological stress, MPI is useful in unmasking myocardial perfusion deficits not evident at rest. A thorough discussion of clinical indications for MPI is beyond the scope of this review, but the reader is referred to recently published consensus committee documents.11,12

Three radioactive blood flow markers (RBFMs) are clinically available and in widespread use: (1) thallium TI 201 chloride, (2) technetium Tc-99m sestamibi (Cardiolite; Lantheus Medical Imaging, North Billerica, Mass), and (3) technetium Tc-99m tetrofosmin (Myoview; GE Healthcare, Princeton, NJ). In the present review, these agents will be referred to by their nonproprietary names. The oldest of the 3 RBFMs, thallium 201, has been in use since approximately 1980, and the original experimental and clinical validation studies of MPI were performed with this agent.1,13–16 More recently, 99mTc-labeled sestamibi, approved in 1990, and tetrofosmin, approved in 1995, have been developed and validated clinically.6–8,17,18

In comparative imaging studies analyzed for accuracy (sensitivity, specificity, and normalcy rates), no obvious differences have been found among these 3 agents. Each RBFM has unique properties that determine the logistics of its use and its test performance characteristics. The purpose of the present review is to compare and contrast these 3 RBFMs. It is hoped this detailed overview will assist clinicians in choosing which agent(s) to use and in understanding how each specific RBFM contributes to the results of an imaging study.

Physical Properties

Physical properties of the 3 RBFMs are shown in the Table. Thallium 201 is supplied as thallous chloride in isotonic solution with a concentration of 1 mCi/mL.19 It is generated in a cyclotron and must be delivered from a radiopharmacy. This agent decays by electron capture to mercury Hg 201, and it is the lower-energy x-rays (75 to 80 keV) omitted from this decay product that are captured during imaging. Whole-body radiation exposure after a typical dose (2 to 4 mCi) is approximately 0.68 rad, and the kidneys are the organ exposed to the most radiation. The relatively long half-life (T1/2=73 hours) and low energy of 201Tl are important considerations during imaging. The long T1/2 contributes to its significant inpatient residence time and requires lower doses to minimize risk of radiation exposure. The low energy emission requires longer imaging times and leads to more image attenuation, especially in obese patients. As a result, 201Tl has important limitations when used in conjunction with SPECT and is better suited for planar imaging.

Technetium Tc 99m is eluted from molybdenum Mo 99m in a generator. It decays by isomeric transition with a physical T1/2 of 6.0 hours. The emissions are gamma rays at an energy level of 141 keV. The organ that receives the most radiation exposure after 99mTc RBFM injection is the gall bladder. Total whole-body radiation after a typical MPI dose (10 to 25 mCi) is roughly 0.50 rad. Free 99mTc diffuses in total body water and is not extracted selectively in the myocardium. As such, for 99mTc to be an indicator of coronary blood flow, it must be bound to another compound (ie, sestamibi or tetrofosmin) that selectively concentrates in the myocardium. The labeling process for both sestamibi and tetrofosmin is complex and requires a quality-control process after preparation that involves chromatography.

Sestamibi is a nonradioactive solid that comes in a lyophilized vial that contains tetrakis (2-methoxy isobutyl isonitrile) with stannous chloride (pH =5.5).20 Preparation for clinical use requires the addition of radioactive sodium pertechnetate Tc 99m. This mixture is shaken vigorously, boiled for 10 minutes, and then cooled at room temperature for 15 minutes. It must then be used within 6 hours of preparation.

Similarly, tetrofosmin is a nonradioactive solid that comes in a lyophilized vial containing tetrofosmin [6,9-bis(2-ethoxyethyl)-3,12-dioxo-6,9-diphasphatetradecane] with stannous chloride.21 Radioactive sodium pertechnetate Tc 99m is added, and the solution is mixed gently for 10 seconds and

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then incubated at room temperature for 15 minutes. Use of this lipophilic cationic complex should occur within 12 hours of this preparation process. The $^{99m}$Tc-labeling reaction involved in the preparation requires maintaining the tin in the divalent (reduced) state. Any oxidant present in the sodium pertechnetate may adversely affect the quality of the preparation.

**Physiological Properties**

The use of MPI for the diagnosis of coronary artery disease relies on the ability of the RBFM to distinguish myocardial regions with normal flow from those with significant impediment to flow. Regions with significant blood supply limitation, either at rest or during a maneuver that increases myocardial oxygen needs, are identified by the presence of perfusion defects. Perfusion defects represent an area of reduced or absent RBFM concentration that reflects an absolute or relative reduction of blood volume in the affected muscle.

Thallium 201 is a potassium analog and is extracted actively by cell membrane Na/K pumps on the first pass through the coronary vasculature. It has the highest myocardial extraction coefficient (85%) of the 3 available RBFMs, with peak myocardial concentration at 10 minutes after injection. Thallium 201 is cleared rapidly from the blood, with a biexponential curve (92% within 5 minutes; intravascular T$^{1/2}$=40 hours for the remaining 8%). Thallium also localizes in parathyroid and thyroid adenomas and other areas of active neoplasia. It does not concentrate selectively within the hepatobiliary system.

Because $^{201}$Tl concentrates primarily in intracellular space, it has a long biological T$^{1/2}$ of 2.4 days and is excreted equally in urine and feces. Thallium 201 is not sequestered permanently in the tissue responsible for its initial uptake, and it is continually exchanged between the extracellular and intracellular spaces. The magnitude and rapidity of this exchange are variable and are dependent on the degree of blood flow to the region of interest, which can result in resolution of stress-related perfusion differences in as little as 20 or 30 minutes if some perfusion to the ischemic area is intact. For this reason, imaging should begin within 10 to 15 minutes after peak stress injection. A second imaging series is useful for the capture of $^{201}$Tl “redistribution,” really equilibration, which provides a reflection of rest perfusion and viability. This second imaging series is typically performed 2 to 4 hours after the initial injection. In some patients with severe ischemia, redistribution may be very slow and may take more than 4 hours. For such individuals, a second low-dose (1 to 2 mCi) injection at rest may improve sensitivity for the detection of viability, as can imaging the next day. This unique redistribution capability of $^{201}$Tl establishes it as the “gold standard” of tissue viability assessment.

Sestamibi is a cationic tracer that diffuses into cells with no active uptake. Its extraction coefficient (65%) is considerably lower than that of thallium. Sestamibi accumulates in myocardial cell mitochondria because of its lower (more negative) membrane potential by electrostatic interactions. It is cleared rapidly from the blood (T$^{1/2}$ is 4.3 minutes at rest and 1.6 minutes with exercise). The intracellular passage of sestamibi is permanent, and redistribution is negligible. As a result, separate rest and stress injections/images are required for the detection of stress-related (reversible) perfusion defects.

The major pathway for excretion of sestamibi is the hepatobiliary system, and substantial liver uptake occurs. At 5 minutes after injection in a patient at rest, 1.2% of the administered dose is in the heart, whereas 20% is in the liver.

### Table. Summary of Commonly Used Commercially Available Radiopharmaceutical Agents for MPI

<table>
<thead>
<tr>
<th>Physical properties</th>
<th>Thallium 201</th>
<th>Sestamibi Tc-99m</th>
<th>Tetrofosmin Tc-99m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>N/A</td>
<td>Cardiolite</td>
<td>Myoview</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>73.1</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>First-pass myocardial extraction coefficient, %</td>
<td>85</td>
<td>65</td>
<td>54</td>
</tr>
<tr>
<td>Whole-body radiation after typical MPI dose, rad</td>
<td>0.68</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Dominant clearance mechanism</td>
<td>Urinary/GI</td>
<td>Hepatobiliary</td>
<td>Hepatobiliary</td>
</tr>
<tr>
<td>Time to imaging after exercise/rest injection, min</td>
<td>10–15/120–240</td>
<td>10–20/45–60</td>
<td>10/30–45</td>
</tr>
<tr>
<td>Recommended dose for planar imaging, mCi</td>
<td>1–2</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Recommended dose for SPECT imaging, mCi</td>
<td>2–3</td>
<td>10–25</td>
<td>10–25</td>
</tr>
<tr>
<td>Diagnostic accuracy for CAD</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Viability assessment</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Assessment of LV function</td>
<td>+</td>
<td>+++</td>
<td>+ +</td>
</tr>
<tr>
<td>Prognostic assessment</td>
<td>++ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
</tbody>
</table>

N/A indicates not applicable; GI, gastrointestinal; CAD, coronary artery disease; LV, left ventricular; +, not recommended/few existing supporting data; ++, feasible but compares less favorably with alternative agent; and ++++, recommended use/copious existing supporting data.

Because $^{201}$Tl concentrates primarily in intracellular space, it has a long biological T$^{1/2}$ of 2.4 days and is excreted equally in urine and feces. Thallium 201 is not sequestered permanently in the tissue responsible for its initial uptake, and it is continually exchanged between the extracellular and intracellular spaces. The magnitude and rapidity of this exchange are variable and are dependent on the degree of blood flow to the region of interest, which can result in resolution of stress-related perfusion differences in as little as 20 or 30 minutes if some perfusion to the ischemic area is intact. For this reason, imaging should begin within 10 to 15 minutes after peak stress injection. A second imaging series is useful for the capture of $^{201}$Tl “redistribution,” really equilibration, which provides a reflection of rest perfusion and viability. This second imaging series is typically performed 2 to 4 hours after the initial injection. In some patients with severe ischemia, redistribution may be very slow and may take more than 4 hours. For such individuals, a second low-dose (1 to 2 mCi) injection at rest may improve sensitivity for the detection of viability, as can imaging the next day. This unique redistribution capability of $^{201}$Tl establishes it as the “gold standard” of tissue viability assessment.

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The major pathway for excretion of sestamibi is the hepatobiliary system, and substantial liver uptake occurs. At 5 minutes after injection in a patient at rest, 1.2% of the administered dose is in the heart, whereas 20% is in the liver.
This high hepatic concentration may result in liver-dominant SPECT images with compromised cardiac resolution. A fatty meal or drink may be used to speed hepatobiliary clearance of the sestamibi, and additional fluids will help gastrointestinal mobility move activity away from the heart. However, there can be very intense activity in the colon many hours later, especially in patients with a high splenic flexure, which would also affect myocardial imaging. With exercise, splanchic blood flow lessens, resulting in less splanchic uptake than at rest. Therefore, imaging is best done after a brief waiting period to allow for some liver and biliary clearance but before significant accumulation can occur in the transverse colon. Typically, imaging is begun 10 to 20 minutes after peak exercise injection and 45 to 60 minutes after rest or pharmacological stress injection. Some laboratories prefer to begin imaging at an intermediate time point for combined pharmacological/exercise (ie, adenosine/walking) testing.

Tetrofosmin has a lower myocardial extraction coefficient (54%) than sestamibi. It accumulates in myocardium, with 1.2% of the injected dose appearing within 5 minutes. Background activity in blood, liver, and lung appears to be less than 5% of the administered activity at 10 minutes after injection. Some studies suggest that it has more rapid hepatobiliary clearance than sestamibi, which permits imaging sooner after injection and reduces the impact of unwanted liver uptake. During a typical 99mTc tetrofosmin study, imaging begins 10 minutes after exercise stress injection and 30 to 45 minutes after rest or pharmacological stress injection.

Logistical Considerations in Clinical Practice

Radiation Exposure/Safety Issues

Clinical preparations of these 3 RBFMs contain sufficiently small amounts of radioactive marker that toxicity from an excess dose is not an issue. No known contraindications exist, although rare hypersensitivity reactions have been reported.26 Although the amount of radiation contained in recommended preparations does not produce an appreciable hazard to the patient, their use should be avoided in pregnant or possibly pregnant patients. For at least several hours after 99mTc RBFM injection and for a number of days after 201Tl injection, patients may activate the alarms of the highly sensitive radiation detectors now commonly used in public places (eg, airports, government buildings, and tunnels) by the Department of Homeland Security. Consequently, all patients undergoing these tests should receive a card documenting that combined pharmacological/exercise (ie, adenosine/walking) testing

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No safety concern has been documented for healthcare workers or social contacts who come into close contact with patients after 201Tl-based testing. In contrast, the substantially higher doses of radiation that accompany 99mTc injection may be of importance to care providers, family, and friends who come in close proximity to the patient after testing. The importance of exposure is time dependent and cumulative.

Healthcare workers should minimize the time they spend within 3 feet of patients injected with 99mTc on the day of the test. Other tests that require healthcare workers to be in close proximity to the liver shortly after a 99mTc RBFM injection (such as a cardiac echocardiogram or coronary angiography) should be delayed to keep occupational exposures as low as possible.

Preparation and Handling of Radioactive Agents

These agents have a variable shelf life, with thallium being the longest-lasting and most stable. Thallium comes as an inorganic molecule with no need for preparation or a quality-control step, and its use does not require a radiopharmacist. A dose of thallium could be used the following day, whereas sestamibi and tetrofosmin cannot.

In contrast, the 99mTc RBFMs need to be prepared by conjugating 99mTc with the carrier agent, which is a complex process that must be done in a radiopharmacy or by a dedicated radiopharmacist on site. These agents require a quality-control assessment of labeling before use. For laboratories that perform fewer than 5 to 10 studies per day, it may not be practical or cost-effective to hire a radiopharmacist and purchase/maintain a 99mTc/Mo generator. In this setting, precalibrated doses can be delivered from an outside commercial radiopharmacy. The number of doses must be ordered ahead of time, which leads to wasted doses in the case of cancellation and to an inability to add another patient for examination on short notice. The shelf life of the 99mTc-sestamibi and 99mTc-tetrafosmin is so short that more than 1 delivery may be needed each day, 1 for the morning doses and a second for the afternoon doses, if precalibrated syringes are used.

Until recently, the supply of RBFMs had consistently kept pace with demand; however, recent shortages in the supply of the 99mTc-based RBFMs have occurred. As discussed above, 99mTc has a short half-life and is made on site from the parent isotope, 99Mo. At the present time, commercial preparation of 99Mo for all of North America occurs in 1 location in Canada. A recent maintenance shutdown in this facility led to a widespread shortage in late 2007.27 This supply shortage required many nuclear cardiology laboratories to use 201Tl or to reduce MPI services. This situation has been rectified. To what degree 99mTc-based RBFM availability will be an issue in the future is uncertain at the present time.

Role of Computer Software Analysis in MPI

Computerized processing of MPI images is commonplace and has the potential to improve diagnostic accuracy. Attenuation, the decrease in photon signal intensity along its path to the detector, is caused by tissue located between the heart and the camera. Nonuniform attenuation due to subdiaphragmatic tissues, chest wall, and breasts can be a source of false-positive results during MPI interpretation.28 Although computer algorithms that correct for attenuation artifact have been developed, their contribution to overall diagnostic accuracy remains controversial.29–31 Second, computer software has been designed to quantify the extent of perfusion defects, and the diagnostic and prognostic merits of quantitative MPI have been shown.32,33 Finally, extracardiac or "background"
RBFM uptake is a well-recognized cause of both false-positive and false-negative MPI. This appears to be particularly true for 99mTc RBFM because of hepatobiliary excretion, with often higher splanchnic than cardiac uptake. Computer-based background subtraction algorithms may reduce diagnostic errors caused by this phenomenon. The fact that all imaging systems have different algorithms to handle defect quantification, background subtraction, and attenuation correction is an important source of procedural variability that complicates the problem of trying to uniformly standardized MPI from one laboratory to another.

Coordination of MPI

All 3 radioactive marker agents are given intravenously into a large antecubital vein either while the patient is resting or during stress testing. For 201Tl, a single injection is administered and followed almost immediately (within 10 to 15 minutes) by the initial imaging study. The administration of 201Tl must be performed in close proximity to the imaging equipment, because delays will reduce imaging accuracy. A second imaging series is performed 2 to 4 hours later. In aggregate, 201Tl-based testing requires at least 4 consecutive hours of patient time and cannot be segregated into multiple-day sessions.

In contrast, both 99mTc-labeled RBFM agents require 2 injections. Injections can be done on 2 separate days, but it tends to be impractical for the patient to have to travel to the laboratory on 2 days. For this reason, most laboratories perform a same-day protocol, with both the rest and stress injections and imaging completed on the same day. In general, the first injection is administered with the patient at rest, and imaging is performed 30 to 60 minutes later. A second injection at a 2- to 3-times higher dose is then administered during exercise or pharmacological stress, and repeat imaging is performed. The higher dose is necessary to overcome the background of the first injection to maximize image quality. As discussed previously, both 99mTc agents lack redistribution capacity, which results in long myocardial residence time. This permits slow, deliberate, or repeat image acquisition if needed and provides some time flexibility after injection, which allows for physical separation of stress and imaging equipment.

To illustrate these principles, a hypothetical example with a 99mTc-labeled RBFM agent is as follows: A nuclear cardiologist might be requested to perform 8 MPI studies. These protocols use an injection of 2 different radioactively labeled agents, typically 201Tl and 1 of the 99mTc-based agents, to capitalize on their respective strengths. A standard dual-isotope test combines a resting 201Tl injection and immediate scan with the injection of a 99mTc RBFM during subsequent stress imaging. Such protocols have been reported to result in improved laboratory throughput and increased patient convenience. However, the comparison of rest scans obtained with 1 radioactive agent and stress images obtained with another radioactive agent may be problematic. Work done to further clarify the value of dual-isotope testing is warranted, and laboratories that routinely stock both 201Tl and 99mTc-based RBFMs may consider the use of such protocols.

Cost Considerations

Cost of the RBFMs differs widely depending on the number of studies performed and whether an outside or in-house radiopharmacy prepares the doses. In general, 201Tl is less expensive per patient than the 99mTc agents. The use of 201Tl results in a less expensive test for 2 other reasons: (1) It can be used with planar imaging without computer processing,
which is reimbursed at a substantially lower rate, and (2) it does not add ventricular function assessment, which is a separately reimbursed code. The $^{99m}$Tc agents are generally more expensive than thallium, which is off patent. When sestamibi goes off patent, its cost likely will be lower.

Clinical Performance Considerations

In addition to its lower cost, $^{201}$Tl has several functional properties that compare favorably with the $^{99m}$Tc RBFMs. Thallium 201 may be a better detector of ischemia, because it is not plagued by the intensive splanchnic activity and resultant imaging artifacts that are common with the $^{99m}$Tc agents. In addition, $^{201}$Tl redistribution permits assessment of myocardial viability in regions with a prior infarction or severe ischemia. Accurate viability assessment is not possible with the $^{99m}$Tc-labeled RBFMs.

Sestamibi and tetrofosmin are considered equivalent in terms of their clinical use.

Alternative MPI Strategies

Use of the 3 RBFMs discussed above accounts for the vast majority of MPI testing in current clinical practice; however, other noninvasive strategies to examine myocardial perfusion have been developed and deserve mention. Technetium Tc-99m has been used with myocardial blood flow markers other than sestamibi and tetrofosmin. Rubidium 82, a functional potassium analog, is an alternative radioactive tracer of myocardial perfusion that can be imaged with positron emission tomography. Its diagnostic and prognostic performances appear comparable to conventional RBFM/SPECT imaging. A major limitation with rubidium testing is its ultrashort half-life, which limits its use to pharmacological stress MPI.

Recognition of the process of myocardial uptake and metabolism of fatty acids has led to development of labeled fatty acid tracers such as $^{11}$I-labeled 15-(p-iodophenyl)3-R, S-methylpentadecanoic acid (BMIPP). Used in conjunction with SPECT, BMIPP has the ability to define regions of myocardial ischemia. In addition, BMIPP-based imaging reflects both regional blood flow and metabolic function and thus provides information regarding tissue viability in patients with prior myocardial infarction. Most recently, imaging techniques capable of examining cardiac both presynaptic (innervations) and postsynaptic (receptor density) autonomic system properties have been developed. Radiolabeled catecholamine/catecholamine analog imaging permits characterization of presynaptic neurotransmitter uptake, whereas selective receptor binding agents ($^{11}$C-CGP12177, $^{11}$C-CGP12388) are capable of defining sympathetic nervous system receptor density. Although this novel imaging field does not directly measure myocardial perfusion, it has shown promise in the characterization of coronary artery disease. The optimal use of these alternative imaging modalities and their values relative to conventional MPI are areas of ongoing study.

Conclusions

MPI varies greatly from laboratory to laboratory, in part because of the choice of the RBFM. The selection and subsequent use of a particular agent has implications as to how testing is performed and interpreted. The $^{99m}$Tc agents have a higher energy and shorter half-life and thereby have the best physical properties for imaging. In contrast, properties of $^{201}$Tl, including active myocardial cell uptake and redistribution potential, make it a more physiological myocardial perfusion agent. At the present time, no clear overall superiority has been found of one agent over the other. Physicians involved in nuclear cardiology should review the relative advantages and disadvantages of all 3 agents before choosing one for their laboratory or patient population. Familiarity with the similarities and differences between the 3 widely used, commercially available myocardial perfusion agents is essential for all care providers who order, interpret, or oversee stress MPI testing.

Disclosures

None.

References


**Key Words:** isotopes radioisotopes myocardial ischemia nuclear medicine radiopharmaceuticals
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