Abstract

Myocardial perfusion scintigraphy is an established method in cardiology for the diagnosis and evaluation of coronary artery disease (CAD). Thallium-201 and Tc-99m sestamibi myocardial perfusion imaging has been widely accepted as non-invasive diagnostic procedure for detection of CAD, risk stratification and myocardial viability assessment. But, standard TI-201 redistribution and same day or 2-day rest/stress Tc-99m sestamibi protocols are time-consuming. Hence, the dual isotope rest thallium-201/stress technetium-99m sestamibi gated single-photon emission tomography protocol has gained increasing popularity for these applications. Combining the use of thallium-201 with technetium-99m agents permits optimal image resolution and simultaneous assessment of viability. Dual-isotope imaging may be separate or simultaneous acquisition set-up. The more rapid completion of these studies is appreciated as an advantage by patients, technologists, interpreting and referring physicians, nurses and hospital management. Simultaneous imaging has the potential advantages of precise pixel registration and artifacts, if present, are identical in both thallium and sestamibi, and require only one set of imaging. Also, there are some disadvantages of spillover of activity from the Tc-99m to the Tl-201 window. Fortunately, despite this problem it can be overcome. Separate acquisition dual isotope also has some disadvantages. Difference in defect resolution in attenuation and scatter between T-201 and Tc-99m sestamibi potentially results in interpretation problems. But, studies about cost-effectiveness of dual isotope imaging showed that some selective elimination of the rest studies may decrease the cost of the nuclear procedures and should be considered in the current care health system. (Anadolu Kardiyol Derg 2004; 4: 161-8)

Key words: Dual isotope myocardial imaging-Ti-201-Tc-99m MIBI myocardial SPECT, Rest Ti-201/Stress Tc-99m MIBI

Introduction

Myocardial perfusion scintigraphy is an established method in cardiology for the diagnosis and evaluation of coronary artery disease (CAD). Since its introduction, myocardial perfusion imaging has advanced significantly. Significant advances in the interpretation of test results were resulted from the development of objective, quantitative methods for analysis and display of myocardial perfusion images. This article provides an overview of technical and clinical aspects of Ti-201 myocardial SPECT, Tc-99m sestamibi

Address for correspondence: Berna Okudan, MD, P.K 104, Isparta/Türkiye
Cell-phone: 90 532 364 9024, Fax: 90 246 237 02 40, E-mail: brokudan@hotmail.com
imaging and rest TI-201/sress Tc-99m sestamibi dual-isotope myocardial perfusion scintigraphy.

Myocardial perfusion scintigraphy with Thallium-201

Numerous clinical studies have validated the use of myocardial perfusion imaging with Tl-201 for detection and evaluation of coronary artery disease (CAD). In addition, TI-201 scintigraphy plays a valuable role in the risk stratification of patients with suspected or known CAD to determine prognosis.

Thallium is a metallic element in group IIIA of the periodic table, with biologic properties similar but not identical to those of potassium. Thallium 201 is a cyclotron product and decays by electron capture to mercury 201; emitting mercury x-rays of 69 to 83 keV (94.4 percent abundant) and thallium gamma rays of 167 keV (10 percent abundant) and 135 keV (3 percent abundant). To improve the sensitivity of TI-201 imaging, a 20 percent of energy window centered on the 70-71 keV peak is used to reduce the scatter associated with lower energy photons [1-3]. A second 20 percent of energy window centered on 167 keV is also used on cameras that can acquire images simultaneously at different energies. The physical half-life of TI-201 is 73 h. For TI-201, the usual intravenously administered activity for clinical imaging in adults is approximately 2.0 to 3.0 mCi (74 to 111 MBq). Estimated total body radiation exposure dose for TI-201 is 0.72 rad/ 3mCi (1, 2). Firstly, transport of thallium across the cellular membrane presumed to be the sodium-potassium ATPase pump and this theory has been confirmed (3).

Since its introduction into clinical use in 1970’s, TI-201 myocardial perfusion imaging has been widely accepted as non-invasive diagnostic procedure for detection of CAD, risk stratification and myocardial viability assessment (4-6). Conventionally, TI-201 imaging is performed in conjunction with physical exercise or pharmacological stress and redistribution. Following injection at peak stress, TI-201 is taken up by myocardium in proportion to regional blood flow. After the rapid initial uptake of TI-201 by the normal myocardium, there begins a slower washout component of thallium from the myocardial intracellular compartment back into the vascular compartment. At the same time, there is a representation of additional blood-borne thallium to the myocardial cells for reextraction provided by the large pool of the injected radioisotope that was initially held by other organs of the body.

This aforementioned simultaneous process of thallium washout and re-extraction across the cell membrane provide a mean for a dynamic equilibrium between intracellular and extracellular thallium, which defines the phenomenon known as “redistribution”. Unlike the re-extraction of TI-201 by the myocardium from the circulating blood pool, the washout component of redistribution is strongly dependent on coronary perfusion, with ischemic areas demonstrating much slower washout than normal regions. Also, heart rates and gender are another factors affecting on thallium washout (3, 7).

Protocols

A number of modifications in TI-201 imaging protocol have been suggested to overcome the TI-201 imaging shortcomings. These protocols are mainly Thallium stress-delayed, Thallium rest-redistribution and Thallium reinjection imaging protocols. Redistribution images are obtained at 3 to 4 hours after the initial study. Repeat imaging at 24 hours after rest injection and also reinjection may further enhance the detection of redistribution in severe defects (8, 9).

Patients should remain NPO (non peroral) for 4 to 6 hours before the exercise test. This allows to decrease splanchic blood flow and; therefore, diminish thallium uptake in the bowel and liver. Calcium channel blockers and β blockers should be discontinued, if possible, for a sufficient length of time before the examination to avoid any interference with obtaining an adequate stress by limiting heart rate response. Long-acting nitrates should also be withheld on the day of testing. The relatively low energy decay photons and the long half-life of TI-201 limit the use of TI-201 to assess functional myocardial parameters such as ejection fraction, wall motion, and wall thickness. Various modifications, such as increasing acquisition times or maximizing the administered dose have been used to improve TI-201 myocardial perfusion images. Though some investigators have used these modifications to acquire clinically useful gated SPECT images using TI-201, it has not been adopted widely because of long acquisition times and the continued perception of poor image quality (10-12).

Myocardial perfusion scintigraphy with Technetium-99m sestamibi

New myocardial perfusion agents labeled with Tc-99m have been developed to circumvent the radiophysical limitations of TI-201 (13, 14). Myocardial perfusion agents labeled with Tc-99m isonitriles, particularly Tc-99m sestamibi has some advantages over TI-201, including on-site availability and higher-quality images. Tc-99m methoxyisobutyl isonitrile (Tc-
99m sestamibi) is a member of Tc-99m isonitrile group that exhibited the best biological properties for clinical application (15). In comparison with other compounds in this group, Tc-99m sestamibi is positively charged particle and predominantly is bound to mitochondria. Its transport across the cell membrane is not dependent on ATP due to its high lipophilicity. The initial myocardial uptake is directly related to myocardial blood flow but with a "decrease" in uptake occurring at high flow rates (16). After IV injection, initial concentration of sestamibi is the highest in the heart and liver. Tc-99m labeled methoxyisobutyl isonitrile (Technetium-99m sestamibi) initially distributes in the myocardium proportional to flow, similar to thallium-201 (16, 17). This trace reportedly does not demonstrate significant delayed redistribution during low flow and shows minimal delayed redistribution after initial IV administration but the lack of substantial redistribution necessitates separate injections of the tracer during stress and at rest (16). But after transient ischemia, delayed redistribution clearly occurs (18, 19). Therefore, to assess stress defect reversibility with Tc-99m sestamibi, a two-injection protocol is required.

Protocols

Diagnostic evaluation using post-stress and subsequent delayed resting imaging requires two separate injections, one at peak stress and a later one at rest. Ideally stress and rest imaging with Tc-99m agents should be performed on two separate days (2-day imaging protocol). In this protocol, stress and rest injections, each with 15-30 mCi, may be performed on two separate days. However, because of logistical reasons, both stress and rest studies are often performed on the same day (1-day imaging protocol). One protocol employs a resting injection of 8-10 mCi, followed by an injection of 25-30- mCi of Tc-99m-sestamibi at peak exercise. There was exact concordance in the detection of reversible and fixed defects with these two same-day, split-dose protocols. A delay of 2 to 3 hours is required between the two injections to allow time for the adequate clearance of the firstly injected radiotracer from the hepatobiliary and gastrointestinal system. For the sestamibi, the minimum delay time of 60 to 90 minutes for rest, 15 to 20 minutes for exercise, 45 to 60 minutes for pharmacological stress following radiopharmaceutical injection are optimal (8, 9). A two-day protocol is optimal from the standpoint of defect contrast because it avoids contamination from one image acquisition to the next and it also provides optimal defect contrast with minimal background activity. An unequivocally normal stress Tc-99m sestamibi study on Day 1 may eliminate the need to perform the rest study on the second day. This circumstance can decrease effectively diagnostic costs.

Dual-isotope imaging

Stress radionuclide myocardial imaging was used as modality to evaluate patients with known or suspected coronary artery disease. The dual isotope rest thallium-201/stress technetium-99m sestamibi gated single-photon emission tomography protocol has gained increasing popularity for these applications. By combining the use of thallium-201, the optimal radioisotope for assessment of viability, with technetium-99m labeled agents, maximization of clinical information can be achieved. These radionuclide agents permit optimal image resolution and simultaneous assessment of viability information (20). Dual-isotope imaging may be separate or simultaneous acquisition set-up.

Rest Thallium-201/ stress Technetium-99m sestamibi dual-isotope imaging

Protocol

In dual-isotope imaging, 1-day, rest imaging using TI-201 (2.5 to 3.5 mCi) [92.5 to 129.5 MBq] is first obtained within 10 minutes after injection of isotope, followed shortly by a stress study with Tc-99m sestamibi (25 mCi ) [925 MBq]. Tc-99m sestamibi SPECT is begun 15-30 minutes after isotope injection (21).

Potential advantages and disadvantages of separate acquisition rest TI-201/stress sestamibi dual-Isotope

As early of 1994, separate acquisition rest TI-201 and stress sestamibi dual-isotope SPECT is used (21). This approach is highly efficient. In comparison to rest/stress sestamibi same-day protocols, separate acquisition dual-isotope eliminates the 1-hour waiting period between rest-sestamibi injection and SPECT. It eliminates the delay between SPECT acquisitions required by stress redistribution TI-201 and suggested for same day rest/stress sestamibi studies. Therefore, an entire (rest and stress) study can be completed in approximately 2 hours (22). However, Weinman et al. demonstrated that the average duration of procedure was 194 ± 39 min (23). Also, patients can be brought back for late imaging the next day, or a rest-redistribution study can be completed before the sestamibi injection and provides the detection of an additional 8 percent to 15 percent of reversible segments, which would go undetected by...
rest scintigraphy alone (24). But, in the separate acquisition dual-isotope SPECT procedure is described to minimize contrast reduction. Due to the low abundance of high-energy Tl-201 photons, which scatter into the Tc-99m window, the contribution of TI-201 scatter on the Tc-99m sestamibi images at these dosages employed is only 2.9 percent (25). Loutfi et al. reported that for detecting myocardial ischemia or viability, the dual-tracer TI-MIBI acquisition technique appears superior to the single tracer Tc-99m sestamibi protocol (26). They also indicated that excessive liver uptake on the Tc-99m sestamibi was resolved by using liver shielding-electronic masking of liver uptake and scaling images to the highest count within the myocardium. Fukuoka et al. demonstrated that exercise TI-201/rest Tc-99m tetrofosmin dual-isotope SPECT with scatter correction could identify coronary artery disease with excellent diagnostic accuracy. Myocardial uptake of rest Tc-99m tetrofosmin image in dual-isotope SPECT is comparable with that of re-injection TI-201 imaging for assessing myocardial viability. Moreover, additional gated SPECT provides useful information about left ventricle function similar to that of left ventriculography (LVG) when therapeutic strategies are being considered for patients with ischemic heart disease. This sequential protocol for evaluating myocardial ischemia and function can be completed approximately in 2 hours (27). Groutars et al. suggested that TI-201 cross-talk in the Tc-99m window may be low and functionally and clinically unimportant (28). Hachamovitch et al. studied exercise dual isotope SPECT for risk stratification in patients with normal resting ECGs. Stress SPECT yields incremental prognostic value and enhanced risk stratification in patients with normal resting ECGs in a cost-effective manner (29). Paeng et al. studied an advantage of dual isotope SPECT. Paeng et al. examined to optimize the use of thallium-201 rest-redistribution study in TI-201/technetium 99m sestamibi dual-isotope SPECT, the predictability of TI-201 rest-redistribution for viable myocardium. They suggested that dysfunctional myocardium with persistent perfusion decrease should be assessed by TI-201 redistribution SPECT and it is possible to discriminate hibernating and stunned myocardium (30). The other advantages of dual isotope myocardial SPECT is that elimination of the rest study in patients with normal stress images. This application rarely alters interpretation. Rest studies are the most useful in images with abnormal or equivocal stress images. Such selective elimination of the rest studies may decrease the cost of the nuclear procedures and should be considered in the current managed care health system (31).

Simultaneous dual-isotope myocardial imaging protocols

Simultaneous dual-isotope imaging allows that rest TI-201/stress Tc-99m sestamibi imaging can be performed together. In the simultaneous dual-isotope study thallium 201 SPECT imaging is not performed immediately following TI-201 injection at rest; and, Tc-99m sestamibi was injected to the patient at the peak of stress. Approximately 15 minutes later, dual-isotope myocardial perfusion SPECT is performed. The entire procedure is completed in less than 1 hour, with a requirement of one SPECT acquisition of approximately 20 minutes duration. Generally, simultaneous acquisition would have many advantages in comparison with the conventional stress and rest protocols it halves camera utilization time (25, 32, 33).

Potential advantages and disadvantages of simultaneous acquisition rest TI-201/stress sestamibi dual-isotope

This protocol could improve patient throughput and scheduling since only one SPECT acquisition is employed. It would reduce the frequency of unrecognized artifacts associated with separate stress and rest image acquisitions (22). Unlu et al. found a good correlation and no significant difference between separate and simultaneous acquisition methods (34). However, Kiat et al. (25) and Kwok et al. (33) did a feasibility study of simultaneous dual-isotope rest/stress myocardial perfusion scintigraphy. They concluded that the current scintillation camera computer system did not provide the ability to eliminate cross-talk and without this adjustment they did not recommend a simultaneous dual-isotope method (25, 33). Nevertheless, because of higher energy of the Tc-99m photons and the higher dose of Tc-99m sestamibi used, compared with that of TI-201, Tc-99m sestamibi cross-talk into dual-rest TI-201 images has the potential to obscure TI-201 defects without correction. Kiat et al. reported that Tc-99m cross-talk into TI-201 window contributed 27 percent of the dual TI-201 counts (25). However, Lowe et al. reported a 10 percent reduction in defect contrast in dual TI-201 as a result of Tc-99m cross-talk and suggested that these changes were minimal (35). But, Yang et al. pointed out that by using the three window techniques; cross-talk interference could be significantly reduced (36). Also, Nakamura et al. indicated that simultaneous dual-isotope...
imaging with Moore's correction method is feasible, with acceptable accuracy for detection of coronary artery disease and a small amount of cross-talk into each window (37). Besides, Knesaurek et al. reported that a cross-talk correction method based on the assumption that the transformations, which modify the primary energy window images into the scatter images as viewed in the other energy windows. Knesaurek et al. also developed a novel transformation method for the correction of cross-talk in simultaneous dual-isotope SPECT imaging and concluded that the transformation three-window, dual radionuclide correction method with restoration improves the quality of simultaneous rest TI-201/stress Tc-99m sestamibi SPECT imaging (38). This method demonstrated that the sensitivities and specificities for CAD detection are similar to those in published studies with TI-201 or Tc-99m sestamibi alone. This method have several advantages compared with standard TI-201 or Tc-99m sestamibi protocol and is one of the current procedures of choice for performing same-day stress myocardial perfusion and myocardial viability SPECT studies (39). Moreover, Hannequin et al. reported the first clinical results obtained with the spectral deconvolution technique photon energy recovery (PER) for cross-talk stress technetium-99m sestamibi myocardial perfusion SPECT. Photon energy recovery (PER) is quantitatively efficient to correct for cross-talk in patients investigated with simultaneous rest TI-201/stress Tc-99m sestamibi myocardial SPECT (40).

Tc-99m Sestamibi gated acquisition

The other advantages of dual isotope imaging with TI-201/Tc-99m sestamibi SPECT are availability and suitability for gated acquisition and combined perfusion with functional assessment (motion, thickening, left ventricular ejection fraction (LVEF) using one injection and one imaging sequence) (10, 41-46). However, some studies reported that LVEF can be assessed by TI-201 ECG-gated SPECT (10, 11, 44). The results showed that TI-201 could provide clinically satisfactory LV functional information, whereas Tc-99m MIBI is more accurate and reliable for the assessment of LV function in a shorter acquisition time. Electrocardiogram-gated SPECT with TI-201 shows the poorer myocardial count rate and image quality in comparison with Tc-99m myocardial perfusion tracers (10, 11). Therefore, a long acquisition time was used in studies. Thus, ECG-gated TI-201 SPECT may not be feasible in busy laboratories. Patients discomfort and motion due to the long acquisition time may also cause problems (47). But, Wadhwa et al. concluded that application of energy window optimization (EWO) to TI-201 imaging allows good-quality gated SPECT myocardial perfusion images to be acquired without the need to increase the acquisition time or the dose of TI-201 as modifiers to improve image quality (48). Mazzanti et al. reported that TI-201/stress Tc-99m sestamibi dual isotope myocardial perfusion SPECT is also useful for the identification of patients with severe and extensive coronary artery disease. The automatic measurement of transient ischemic dilatation in dual-isotope myocardial perfusion SPECT is clinically useful marker for CAD (49). Germano et al. developed an automatic quantitative algorithm for the measurement of regional wall motion and wall thickening from three-dimensional gated Tc-99m sestamibi myocardial perfusion SPECT images (50).

Is technetium-99m sestamibi adequate for detection of myocardial viability?

Irreversible defects identified by rest/stress Tc-99m sestamibi imaging might erroneously be identified as reversible by rest TI-201 / stress Tc-99m sestamibi dual-isotope imaging. As two radioisotopes emitting photons with different energies are used in the dual-isotope approach, differences in defect resolution may occur (21). Also, there are differences in attenuation and scatter between TI-201 and Tc-99m sestamibi, potentially resulting in the appearance of reverse redistribution of defects that are mildly reversible. Another consideration for dual-isotope imaging is the remarkable variation of tracer distribution concentration to the extracardiac organs. For the TI-201 liver activity is minimal in stress images but greater in resting studies, the amount of the liver activity varies depending on the injection to imaging interval. Bowel tracer concentration may be considerable and may be two or three times greater than that in the myocardium. If Tc-99m sestamibi bowel activity scatters into the TI-201 photo peak, an inferior Tc-99m sestamibi stress defect might appear reversible in the TI-201 rest study (37). Although TI-201 scintigraphy has been valuable for the assessment of myocardial perfusion and viability this radiotracer has significant limitations related to the physical properties; therefore, Tc-99m-labelled agents are being used increasingly in evaluation of viability. On the other hand, from the viability point of view, the role of Tc-99m based myocardial perfusion agents is deferred, and the value of Tc-99m sestamibi remained controversial and some studies sho-
wed that Tc-99m agents, particularly Tc-99m sestamibi, significantly underestimated the extent of hypoperfused myocardium, whereas other studies suggest that Tc-99m is valuable and comparable to TI-201 for viability assessment. Earlier studies suggested that Tc-99m sestamibi was not a good viability agent (51). Because in most previous publications, myocardial viability has been defined on the basis of an improvement in wall motion after coronary artery bypass surgery (CABG).

However, nowadays, later studies indicate that Tc-99m sestamibi may also be a good viability marker (52-54). Kauffman et al. reported similar Tc-99m sestamibi and delayed TI-201 activities in defects (53). Dilsizian et al. also compared results of stress-redistribution-reinjection TI-201 SPECT with Tc-99m sestamibi SPECT and found 93 percent concordance rate when the regional activities of the two tracers quantified (55). Maes et al. reported that sestamibi uptake was significantly higher in areas considered viable by 18F-fluorodeoxyglucose and in regions with improved regional contraction after CABG (54). Also, Dakik et al. demonstrated a close relationship between Tc-99m sestamibi activity and the extent of histologically documented myocardial viability in patients referred for CABG and their results lend support to the use of Tc-99m sestamibi as a viability marker (56). Kiser et al. in their series, the ability of TI-201, sestamibi and teboroxime to establish the existence of viable myocardium was compared with that of F-18 FDG concluded that there was no significant difference in the prediction of viable myocardium between TI-201, sestamibi and teboroxime (57). In addition, Takehana et al. concluded that resting perfusion imaging with Tc-99m sestamibi accurately determined viability of the infarct zone despite reperfusion through a residual stenosis. Tc-99m sestamibi imaging was proved to be useful in the clinical setting for the prediction of the amount of salvaged myocardium (58). Finally, the present data reported in the studies yield further evidence that sestamibi may be a valid viability agent when administered at an appropriate time.

**Conclusions**

Standard TI-201 redistribution and same day or 2-day rest/stress Tc-99m sestamibi protocols are time-consuming. However, coordination of stress testing and imaging is more flexible. The separate or simultaneous acquisition dual-isotope protocol is shorter than standard TI-201 or Tc-99m sestamibi protocols. Thus the more rapid completion of studies is appreciated as an advantage by patients, technologists, interpreting and referring physicians, nurses and hospital management. Simultaneous imaging has the potential advantages of precise pixel registration and artifacts, if present, which are identical in both thallium and sestamibi, and requires only one set of imaging. But, there are some disadvantages of spillover of activity from the Tc-99m to the TI-201 window. Separate dual isotope acquisition also have some disadvantages. Difference in defect resolution in attenuation and scatter between T-201 and Tc-99m sestamibi potentially results in interpretation problems. Also, studies about cost-effectivity of dual isotope imaging showed that in patients with normal stress images elimination of the rest study rarely alters interpretation. Rest studies are most useful in images with abnormal or equivocal stress images. Such selective elimination of the rest studies may decrease the cost of the nuclear procedures and should be considered in the current managed care health system.

**References**


