Update on Cardiovascular Imaging

New Applications of Myocardial Perfusion Imaging

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A decade ago, most patients were evaluated for coronary artery disease with treadmill testing alone, but now there are a variety of complementary and competing diagnostic modalities—e.g., single photon myocardial perfusion imaging, positron emission tomography (PET), and stress echocardiography. The newly emerging technologies of cardiac magnetic resonance imaging (MRI) and fast computed tomography (CT) will soon provide additional competition. Moreover, within each of these individual fields there are complementary and competing methodologies. For perfusion imaging, planar and single photon emission computed tomography (SPECT) techniques are used. Radiopharmaceutical agents now commercially available include thallium-201, Tc-99m teboroxime, Tc-99m tetrofosmin, and Tc-99m sestamibi. Under investigation are at least 2 additional Tc-99m-labeled compounds, as well as fatty acid analogues. Regardless of the choice, the future of cardiac imaging certainly lies with the method or combination of methods that best affords the following advantages:

A) Provides optimal sensitivity and specificity in the diagnosis of coronary artery disease, including accurate information about the size, location, and severity of perfusion abnormalities.
B) Accurately differentiates viable (i.e., salvageable) from scarred myocardium.
C) Provides information helpful in determining the patient's prognosis and perioperative risk.
D) Maximizes the amount of information (e.g., perfusion, function, valvular disease, and myocardial mass) obtainable from a single examination, thereby minimizing the number of studies required.
E) Minimizes the patient's inconvenience and discomfort.
F) Maximizes the efficiency of the laboratory.
G) Provides diagnostic information not only for patients able to cooperate during imaging but also for acutely ill patients and for those undergoing interventions such as thrombolysis and percutaneous transluminal coronary angioplasty (PTCA).
H) Minimizes cost.

Although no single imaging modality and certainly no single radiopharmaceutical agent now satisfies all these criteria, this list at least provides us with a benchmark by which to judge many of the present and future methods. Currently, in my opinion, the diagnostic and prognostic goals listed above can best be achieved by myocardial perfusion imaging and functional assessment by gated SPECT or, alternatively, by 1st-pass radionuclide angiocardiography performed in conjunction with perfusion imaging using a Tc-99m-labeled agent.

Myocardial Perfusion with Gated SPECT

With gated Tc-99m sestamibi SPECT, myocardial perfusion and ventricular function can be evaluated simultaneously, after a single tracer injection.[1] Although perfusion images obtained after either a stress or rest injection can be gated, functional images are always acquired with the patient at rest, so only resting function can be evaluated. Generally, it is preferable to gate the sestamibi SPECT images with the higher count density: i.e., the stress images obtained in either a separate-day protocol or a single-day rest/stress protocol, or the resting images obtained in a single-day stress/rest protocol.

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With gated sestamibi SPECT, wall motion and wall thickening can be evaluated, in addition to perfusion distribution. Wall motion, assessed by observing inward excursion of the endocardial border during systole, is best evaluated with black and white images viewed in endless-loop cinematic format. Consequent to the partial volume effect, wall thickening is proportional to an increase in myocardial intensity during systole.[2] This intensity change is best evaluated by viewing color images, also in cinematic format.

It is possible to derive quantitative parameters of left ventricular function, including volumes and ejection fraction, for gated sestamibi SPECT.[3,4] In the horizontal and vertical long-axis mid-ventricular tomograms, both at end-diastole and end-systole, the endocardial border can be traced manually or by an automated edge-detection algorithm. From these tracings, the horizontal and vertical dimensions of the ventricular cavity can be determined at each point (pixel) from the apex to the base. After these dimensions have been corrected for scatter and for the inherent spatial resolution deficiencies of the camera and collimator system, left ventricular end-diastolic and end-systolic volumes and ejection fraction are calculated (Fig. 1). Ejection fractions determined by this method have corresponded closely with those obtained using gated blood pool and 1st-pass radionuclide angiocardiography techniques. Occasionally, in patients with severe perfusion defects, it is not possible to define the endocardial border entirely using this method, in which case the derivation of quantitative parameters is not possible.

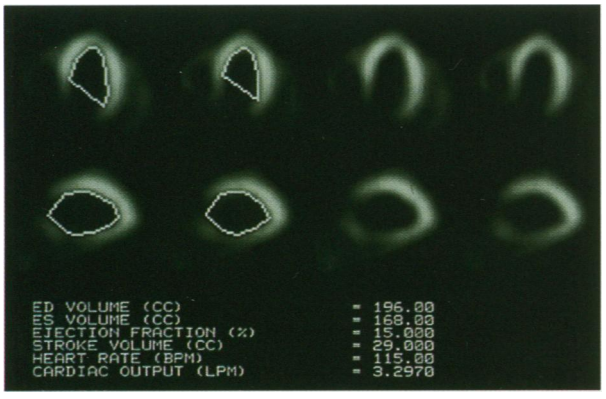

Fig. 1 *In a hypertensive patient with inferior myocardial infarction, horizontal long-axis (top row) and vertical long-axis (bottom row) mid-ventricular Tc-99m sestamibi tomograms at end-diastole and end-systole demonstrate a moderate decrease in count density in the inferior wall, consistent with prior myocardial infarction. In addition, quantitative analysis demonstrates that the left ventricle is dilated (end-diastolic volume = 196 cc, end-systolic volume = 168 cc) and that systolic function is markedly decreased (left ventricular ejection fraction = 15%). The disproportionate decrease in ventricular function is most likely due to a superimposed hypertensive cardiomyopathy.*

The combined assessment of myocardial perfusion and function is of particular value in a number of diseases in which ventricular functional abnormalities may coexist with, and often exceed, perfusion defects (Fig. 2). These include diffuse small-vessel disease, such as in patients with diabetes or connective tissue disorders, wherein epicardial coronary disease and associated regional perfusion defects may be less severe than small-vessel disease, causing a global decrease in ventricular function. Patients with chest pain who have been referred for perfusion imaging may have underlying cardiomyopathy, either in isolation (as the sole cause of symptoms) or in coexistence with coronary disease. Such

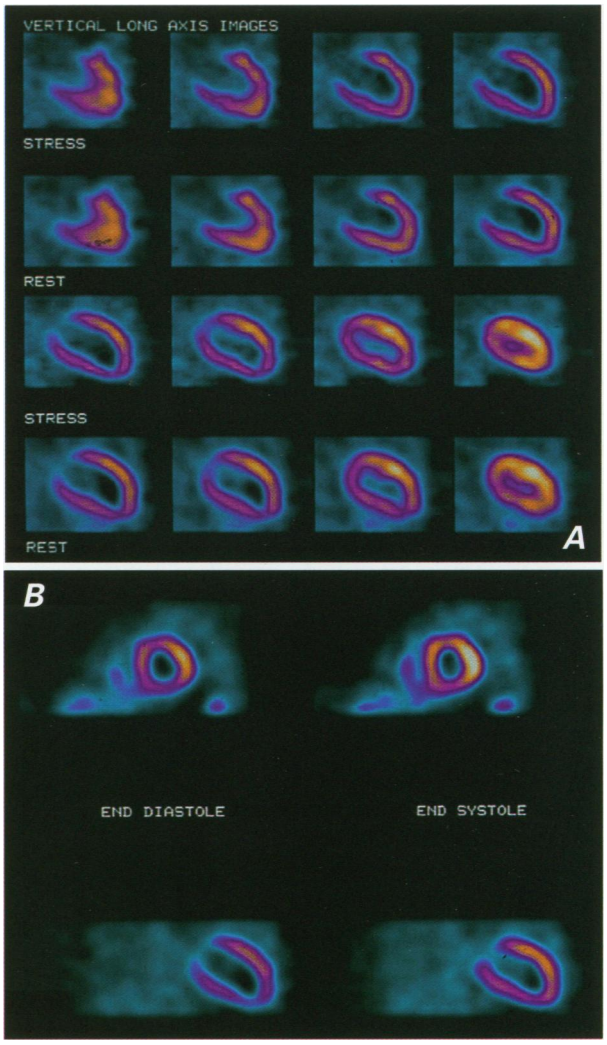

Fig. 2 *Drug-induced cardiomyopathy. Stress and rest vertical long-axis Tc-99m sestamibi tomograms (**A**) demonstrate homogeneous tracer distribution throughout the myocardium. There is no evidence of scar or stress-induced ischemia. However, end-diastolic and end-systolic short-axis (top) and vertical long-axis (bottom) tomograms (**B**) demonstrate diffusely and markedly reduced left ventricular wall motion and thickening. These abnormalities were attributed to a cocaine-induced cardiomyopathy in this 37-year-old man with atypical chest pain and dyspnea.*

patients include those with hypertension, renal failure, and drug-related cardiomyopathies.

In patients who have sustained a myocardial infarction, the value of rest and exercise perfusion imaging in the evaluation of infarct size and in the detection of additional stress-induced ischemia is well recognized. The subsequent incidence of arrhythmias, heart failure, and other cardiac events is related to infarct size; and patients with additional stress-induced ischemia have a significantly greater incidence of death and future cardiac events than do those with normal scans or only fixed perfusion defects. Moreover, it is well known that the patient's prognosis is directly related to left ventricular ejection fraction. Therefore, with gated sestamibi SPECT, infarct size, the presence or absence of stress-induced ischemia, and left ventricular ejection fraction can all be evaluated using a single study. For many patients this "one-stop" assessment can obviate the necessity of a separate echocardiogram or gated blood pool study to measure ejection fraction, and thereby decrease hospitalization cost and (potentially) length of stay.

Attenuation artifacts are a significant cause of false-positive perfusion scans, resulting in decreased test specificity and ultimately in unnecessary and expensive cardiac catheterization. An advantage of gated sestamibi SPECT applicable to a broad spectrum of patients is its ability to differentiate scar from attenuation artifact as a cause of fixed perfusion defect. Transmural infarcts will demonstrate decreased wall thickening, whereas attenuation artifacts will move and thicken normally. In patients with marked breast or diaphragmatic attenuation, both end-diastolic and end-systolic count density may be reduced in the anterior and inferior walls, respectively; yet the increase in count density from diastole to systole will be equivalent to that in normal myocardium. Therefore, test specificity for coronary disease can be improved significantly by viewing gated tomograms routinely when sestamibi scans are interpreted.[5]

Finally, gated sestamibi SPECT has a potential role in the assessment of myocardial viability. If a fixed perfusion defect demonstrates relatively preserved wall thickening and motion, it should be viable. (An attenuation artifact will have a similar appearance, but should be easily differentiated on clinical grounds.) In contrast, an apparent defect that does not move or thicken probably represents scar tissue; the difficulty in this circumstance comes in distinguishing scar tissue from viable myocardium that has been severely stunned or is hibernating.

In sum, then, gated sestamibi SPECT is applicable to the majority of patients referred for myocardial perfusion imaging. Perfusion and functional data are complementary, providing a potentially cost-effective combination of diagnostic and prognostic information.

1st-Pass Radionuclide Angiocardiography

Myocardial perfusion and function can be measured using a single injection of 1 of the new Tc-99m perfusion agents. In the past, such an evaluation required the injection of 2 radiopharmaceutical doses and, for stress studies, the administration of 2 separate exercise tests. Therefore, the new Tc-99m agents make the simultaneous evaluation of perfusion and function less expensive, even as they increase laboratory efficiency and decrease the risk to the patient of repetitive stress testing. Because of the necessary interval between 1st-pass imaging and planar or SPECT perfusion imaging (i.e., time is needed to reposition the patient and change collimators or cameras), Tc-99m sestamibi has become the agent of choice when 1st-pass and perfusion studies are combined.

To obtain high-quality 1st-pass studies, it is necessary to use a camera with a count rate capacity of at least 200,000 counts per second during the time of maximum bolus activity in the heart. Multicrystal cameras currently provide the highest count rate statistics, but they are not widely available, especially when one considers the routine use of myocardial perfusion imaging in virtually all nuclear medicine and nuclear cardiology laboratories. Alternatively, single-crystal Anger cameras can be used if their electronics are fast enough to provide adequate counting statistics. In general, a bolus dose of only 12 mCi of Tc-99m can be used for 1st-pass studies performed on a multicrystal camera, whereas a bolus dose of approximately 20 mCi is preferable for a single-crystal camera. For exercise Tc-99m sestamibi studies performed using either a single-day (28 mCi) or separate-day (22 mCi) protocol, 1st-pass imaging is practical with either a single-crystal or multicrystal camera. However, for resting studies, the count rate afforded by the 8 to 9 mCi dose used for the single-day protocol is usually inadequate for either type of camera. In contrast, the 22 mCi dose recommended for resting studies using the separate-day protocol is adequate for either system. Therefore, to perform separate stress and rest 1st-pass studies with either a single-crystal or multicrystal camera, the separate-day protocol is mandatory.

Recent advances in nuclear medicine instrumentation have increased the level of sophistication of 1st-pass studies. With the multicrystal camera and dual photopeak acquisition, it is possible to correct for patient motion during bicycle or even treadmill exercise studies using an Am-241 positioning source taped to the patient's chest. Some of the newer multiheaded single-crystal cameras can acquire simultaneous 1st-pass images in multiple projections (e.g.,

45° right anterior oblique and 45° left anterior oblique using 90°-opposed detectors), thereby enabling evaluation of all myocardial segments with a single study (Fig. 3). Moreover, with multiheaded cameras, the possibility of rapid tomographic 1st-pass acquisition exists.

To achieve a technically adequate 1st-pass study, a rapid, compact radioactive bolus is necessary. It is preferable to use either a medial antecubital or jugular vein. Anesthesia of the injection site with lidocaine is helpful to avoid any discomfort associated with venipuncture. A 20-gauge intravenous catheter is used, attached to a length of IV tubing large enough to accommodate the entire radioactive bolus. Inadequate capacity of this IV tubing will result in bolus fragmentation and inadequate studies. The bolus must be injected rapidly and flushed by means of a 3-way stopcock. Coordination between the individual injecting the dose and the technologist operating the camera at the initiation of the 1st-pass acquisition is essential.

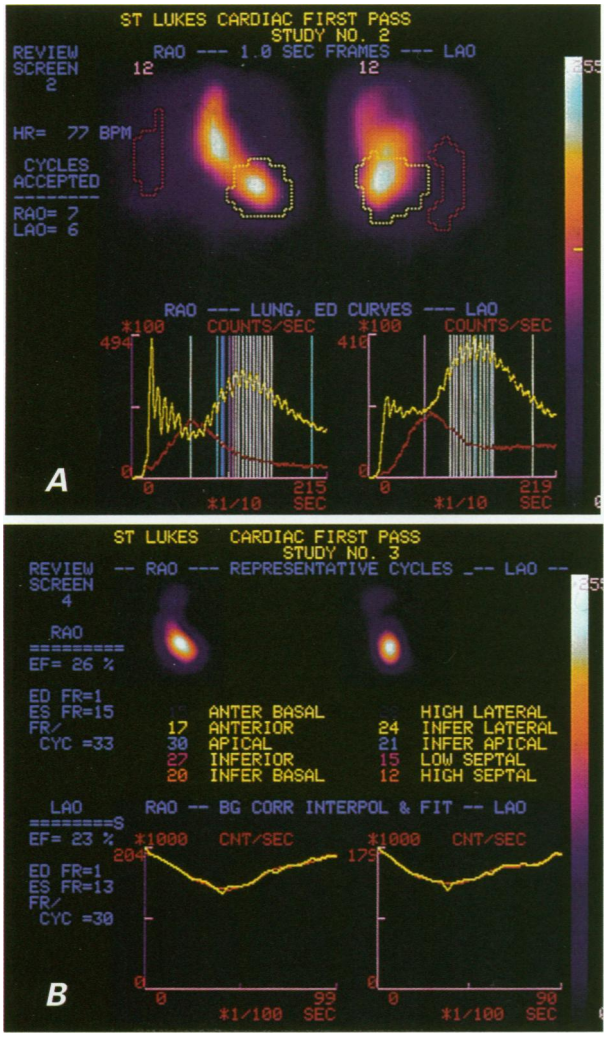

Fig. 3 *Simultaneous biplane 1st-pass radionuclide angiocardiography performed using a 90°-opposed 2-headed scintillation camera. Time-activity curves (**A**) from the left ventricle are obtained simultaneously in the 30° right anterior oblique (left) and 60° left anterior oblique (right) projection following the bolus intravenous injection of 22 mCi Tc-99m sestamibi. Left ventricular volume curves (**B**) in the right anterior oblique projection (left panel) and left anterior oblique projection (right panel) demonstrate diffusely decreased global and regional left ventricular function in this patient with cardiomyopathy.*

The clinical usefulness of the measurement of left and right ventricular function at rest is well recognized. Investigators at Duke University have also demonstrated that in patients who have sustained myocardial infarction, the exercise ejection fraction (EF) is of even greater prognostic importance.[6] Pryor and associates used multivariate analysis to identify radionuclide variables that related to subsequent myocardial infarction or cardiovascular death in 386 medically treated patients. The exercise EF was the most important radionuclide variable providing prognostic information in patients with coronary artery disease. This simple variable contained over 70% of the prognostic information provided by other important variables (such as the coronary anatomy on arteriogram) in combination. The relationship between cardiac events and exercise EF was not linear. Patients with an exercise EF above 0.50 had very few myocardial infarctions or cardiac deaths for 2 years after their studies.

Myocardial Viability Assessment

In patients with severe coronary artery disease, chronically reduced myocardial blood flow or repeated episodes of transient coronary occlusion may result in decreased regional ventricular function, termed "hibernating myocardium." Also, a transient state of asynergy termed "stunning" may exist in patients who have undergone acute coronary occlusion without myocardial necrosis. Although severely jeopardized, both hibernating and stunned myocardium can be salvaged by percutaneous transluminal coronary angioplasty or surgical revascularization. Because the delivery of most radiopharmaceutical agents to the myocardium is flow dependent, decreased flow to hibernating or stunned myocardium may produce a resting perfusion defect, which unfortunately is indistinguishable from the scintigraphic appearance of infarction.

Thallium-201, when first injected, is distributed to the myocardium in direct proportion to coronary blood flow. However, after tracer washout and redistribution, thallium-201 distribution is proportional to myocardial oxidative metabolism. It is this property that makes delayed thallium imaging a valuable test to assess myocardial viability.[7] There is approximately a 90% correlation between delayed thallium uptake and F-18 fluorodeoxyglucose (FDG) uptake determined by PET.[8] Therefore, when thallium is injected at rest, initial images may demonstrate de-

creased blood flow, i.e., resting ischemia, in the distribution of a severely stenotic (>90%) coronary artery, whereas delayed uptake within the defect is indicative of viable myocardium rather than scar. This technique of immediate and delayed imaging at rest has also proved valuable in detecting resting ischemia of viable, jeopardized myocardium in patients with unstable angina, particularly those in the cardiac care unit.

However, 4-hour delayed imaging following a *stress* injection of thallium is notoriously insensitive in detecting viable myocardium, for it significantly overestimates the degree of scar and underestimates the degree of ischemia. For this reason, a reinjection protocol was introduced, wherein a resting thallium "booster" injection (1 to 1.5 mCi) is given to patients who manifest a fixed defect both in stress and 4-hour delayed images. Viability assessed by this method agrees well with viability assessed by F-18 FDG uptake or by improvement in ventricular function following myocardial revascularization. In general practice, the 4-hour delayed thallium image is often omitted; patients are reinjected at 3 to 4 hours and imaged 15 to 30 minutes later. It has been demonstrated that defect reversibility apparent in 4-hour delayed images may no longer be apparent in the reinjection images.[9,10] This discrepancy is most likely caused by flow-dependent abnormalities in images acquired shortly after the resting booster injection.

Because sestamibi is also a flow-dependent radiopharmaceutical agent, resting sestamibi imaging also underestimates myocardial viability. However, resting sestamibi images are acquired after the tracer is injected at rest (unlike thallium delayed images, which require tracer redistribution after a stress injection). Therefore, myocardial viability is underestimated less by rest/stress sestamibi imaging than by stress/rest thallium imaging. In patients with fixed sestamibi defects but clinically suspected viability, some laboratories combine the favorable "delayed uptake" properties of thallium with the superior imaging characteristics of Tc-99m sestamibi: they inject thallium (3.5 mCi) at rest the morning after the sestamibi scan and image the patient at 3 to 4 hours to demonstrate rest/delayed thallium uptake within the fixed sestamibi defect, as a marker of myocardial viability.

There is a newly reported method—somewhat akin to the rest/delayed thallium technique—to demonstrate resting ischemia of viable myocardium with sestamibi. First, one performs a resting sestamibi injection and scan. If a perfusion defect is present, the injection is repeated following the administration of nitroglycerine, a coronary vasodilator.[11] Defect reversibility with nitroglycerine is indicative of resting ischemia of viable myocardium. Moreover, it has correlated well with improvement in regional ventricular function following revascularization of the jeopardized regions.

Another approach to assessing myocardial viability with sestamibi is to compare the perfusion defect's uptake of tracer to that of normal myocardium. This method is based upon the knowledge that in animal hearts, and also in human hearts excised during heart transplantation, myocardial cellular uptake of sestamibi is directly proportional to cell viability. However, this approach does not fully account for the flow-dependence of tracer uptake. It has been reported that perfusion defects with ≥60% of maximal myocardial uptake are very likely to recover function after revascularization.[12]

Yet another approach to assessing viability with sestamibi incorporates gated SPECT. Perfusion defects that demonstrate preserved wall motion and wall thickening (an increase in count density during systole) have been demonstrated to be viable. However, since hibernating or stunned myocardium may be akinetic and may thicken only minimally or not at all, the lack of motion or thickening cannot exclude the presence of viable myocardium.

A new, unique approach to the assessment of myocardial viability is F-18 FDG SPECT.[13-15] Early scintillation cameras were modified with increased shielding and ultra-high energy collimators to image the 511 keV annihilation radiation of positron emitting isotopes. However, the technique was abandoned when a pharmacopoeia of Tc-99m agents

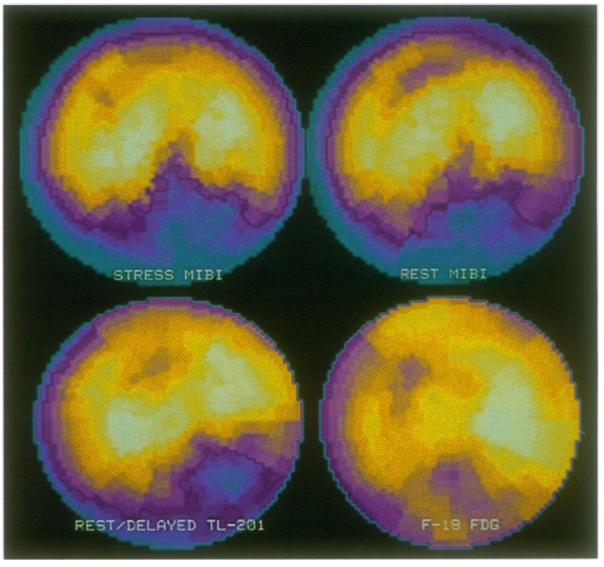

Fig. 4 *Viable hibernating myocardium. Stress and rest Tc-99m sestamibi polar plots (top row) demonstrate a moderate, fixed inferior defect. A subsequent Tl-201 SPECT study (lower left), performed 4 hours after a resting injection of 3.5 mCi Tl-201, demonstrates only slight reversibility of the inferior defect. However, a resting F-18 FDG SPECT study (lower right), performed on a dual-headed scintillation camera equipped with ultra-high energy collimators, demonstrates complete reversibility of the inferior defect, indicating viability.*

became available. Now, because myocardial viability has become an important clinical concern and because most laboratories (and patients) cannot afford PET scanning, FDG SPECT has been developed again by modifying commercially available 180°-opposed dual-headed SPECT cameras. Fluorodeoxyglucose SPECT may be performed as an adjunct to thallium or sestamibi imaging (Fig. 4). Moreover, simultaneous Tc-99m and F-18 dual isotope windowing enables the evaluation of a flow-dependent perfusion defect with myocardial viability in a single data acquisition.

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