ACC/AHA TASK FORCE REPORT

Guidelines for Clinical Use of Cardiac Radionuclide Imaging

Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), Developed in Collaboration With the American Society of Nuclear Cardiology

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Preamble

It is becoming more apparent each day that despite a strong national commitment to excellence in health care, the resources and personnel are finite. It is therefore appropriate that the medical profession examine the impact of developing technology and new therapeutic modalities on the practice of cardiology. Such analysis, carefully conducted, could potentially affect the cost of medical care without diminishing the effectiveness of that care.

To this end, the American College of Cardiology and the American Heart Association in 1980 established a Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures with the following charge:

The Task Force of the American College of Cardiology and the American Heart Association shall develop guidelines relative to the role of new therapeutic approaches and of specific noninvasive and invasive procedures in the diagnosis and management of cardiovascular disease.

The Task Force shall address, when appropriate, the contribution, uniqueness, sensitivity, specificity, indications, contraindications and cost-effectiveness of such diagnostic procedures and therapeutic modalities.

The Task Force shall emphasize the role and values of the developed guidelines as an educational resource.

The Task Force shall include a Chairman and six members, three representatives from the American Heart Association and three representatives from the American College of Cardiology. The Task Force may select ad hoc members as needed upon the approval of the Presidents of both organizations. Recommendations of the Task Force are forwarded to the President of each organization.

The members of the Task Force are Melvin D. Cheitlin, MD, Arthur Garson, Jr., MD, MPH, Richard P. Lewis, MD, Robert A. O'Rourke, MD, Thomas J. Ryan, MD, Robert C. Schlant, MD, William L. Winters, Jr., MD and James L. Ritchie, MD, Chairman.The Committee on Cardiac Radionuclide Imaging was chaired by James L. Ritchie, MD and included the following members: Timothy M. Bateman, MD, Robert O. Bonow, MD, Michael H. Crawford, MD, Raymond J. Gibbons, MD, Robert J. Hall, MD, Robert A. O'Rourke, MD, Alfred F. Parisi, MD and Mario S. Verani, MD.

This document was reviewed by the officers and other responsible individuals of the American College of Cardiology and American Heart Association and received final approval in October 1994. It is being published simultaneously in *Circulation* and *Journal of the American College of Cardiology*. The document also was reviewed and endorsed by the American Society of Nuclear Cardiology and will be published in the March/April issue of the *Journal of Nuclear Cardiology*.

Introduction

The American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures was formed to make recommendations regarding the appropriate utilization of technology in the diagnosis and treatment of patients with cardiovascular disease. One such important technology is cardiac radionuclide imaging (nuclear cardiology).

The current committee was given the task of reviewing and revising the Guidelines for Clinical Use of Cardiac Radionuclide Imaging, December 1986 (1). Since that report, many changes have taken place and are considered in the present report, including the development of pharmacologic stress testing, the development of new classes of isotopes (technetium- and rubidium-based perfusion agents) and refinements in single-photon emission computed tomography (SPECT) and positron emission tomography (PET).

Similar to the previous report, the usefulness of cardiovascular imaging techniques in specific disease states is indicated in the present report by means of the following classification:

class I = usually appropriate and considered useful;
class II = acceptable but usefulness less well established;
class IIa = weight of evidence in favor of usefulness;
class IIb = can be helpful but not well established by evidence;
class III = generally not appropriate.

Techniques considered investigational are not further classified.

In considering the use of a specific cardiovascular radionuclide technique in individual patients, the following factors are important:

1. the quality of the available laboratory and equipment used for performing the study and the quality, expertise and experience of the professional and technical staff performing and interpreting the study;
2. the sensitivity, specificity and accuracy of the technique;
3. the cost and accuracy of the technique as compared with other diagnostic procedures; and
4. the effect of positive or negative results on subsequent clinical decision making.

The format of the present report includes a brief description of nuclear cardiologic techniques, followed by a discussion of its usefulness in specific cardiovascular diseases. Utility is considered for 1) diagnosis, 2) severity of disease/risk assessment/prognosis, and 3) assessment of therapy. The tables that appear in each section summarize the recommendations for that particular disease entity.

The Committee reviewed and compiled all pertinent published reports (by computerized and hand search, excluding abstracts), and recommendations made are derived from these reports. When no or few data existed, this is identified in the text, and recommendations are based on committee consensus. A complete list of the multiple publications on cardiac imaging is beyond the scope of this communication, and only selected references are included. The Committee membership consisted of acknowledged experts in radionuclide testing, as well as general cardiologists and cardiologists with expertise in other imaging modalities; both the academic and private practice sectors were represented. This document will be reviewed 2 years after the date of publication and yearly thereafter by the Task Force to determine whether a revision is needed. The guidelines will be considered current, unless the Task Force publishes revisions or a withdrawal.

This report does not include a discussion of digital subtraction angiography, high speed (cine) computed tomography or nuclear magnetic resonance imaging, which are not radionuclide based per se but were included in the 1986 guidelines. This guideline applies to adults; indications for radionuclide testing in children are not included.

Description of Specific Procedures

Most current nuclear cardiology applications utilize a gamma camera of either 1) the single-crystal type, or 2) the multicrystal type. The single-crystal gamma camera (Anger camera) is the most widely available system. It is technically adequate for generating most of the clinically important nuclear cardiology information, that is, equilibrium (gated) blood pool angiography, myocardial perfusion imaging and myocardial infarct-avid imaging. The SPECT images are tomographic reconstructions derived from either a single- or multiple-head gamma camera that rotates around the patient. Tomographic imaging, by displaying data in the format of slices with discrete thickness, allows better separation of myocardial and other nonmyocardial structures and individual coronary artery beds and is inherently quantitative. A standardized nomenclature for tomographic views (short axis, vertical long axis and horizontal long axis) and displays has been developed for both SPECT and PET (2). The multicrystal camera has a somewhat lower resolution but is generally a more sensitive device; thus, it is best used for "first-pass" radiotracer studies.

The positron camera or PET scanner consists of multiple rings of stationary detectors that encircle the thorax, detect the high energy photons (511 keV) that are released from positron-emitting tracers and produce a series of multiple tomographic images encompassing the heart. Positron emission tomographic tracers have been developed for the evaluation of numerous physiologic processes, including regional myocardial blood flow, metabolic processes, oxygen consumption, receptor activity and membrane function. Improved quantitation of these processes is possible with PET. Positron emission tomographic scanners are more costly and less widely available than standard Anger cameras or SPECT systems.

Gamma Camera Imaging (Single-Photon Approaches)

Radionuclide angiography. "First-pass" approach (rest, stress). First-pass radionuclide angiography utilizes rapidly acquired image frames to observe a bolus of technetium-99m or another suitable radionuclide as it moves through the venous system into the right atrium, right ventricle, pulmonary artery, lungs, left atrium, left ventricle and aorta. Because the sampling rate is short relative to the RR interval, it is possible to sample continuously several cardiac cycles as the bolus passes through the right and then the left ventricle. By determining the change in radioactivity over time (i.e., by generating time–activity curves), it is possible to derive ejection fraction measurements from both the right and the left ventricles. It is also possible to measure ventricular and pulmonary blood volumes and to assess regional ventricular wall motion. The first-pass approach is uniquely well suited for shunt detection and quantitation and evaluation of right ventricular function because the right and left ventricles can be temporally isolated. Left-to-right shunts can be quantitated by application of a mathematical approach to a region of interest placed over the lung. The first-pass approach can be applied to patients both at rest and during exercise stress.

Gated equilibrium blood pool radionuclide angiography (rest, stress). Equilibrium or gated blood pool radionuclide angiography most commonly utilizes technetium-99m (Tc-99m) pertechnetate bound to red blood cells. Accordingly, technetium remains within the blood pool, and serial imaging studies to assess function can be acquired over several hours. Acquisition of the images is synchronized with the electrocardiographic (ECG) QRS complex. Every cardiac cycle is divided temporally into numerous frames, and all corresponding frames from all the cycles within a given RR interval range are added together for an acquisition time ranging from 2 to 10 min. The resultant study provides composite images of all cardiac cycles during this time period. The equilibrium blood pool approach generates reliable left and right ventricular ejection fraction values and a means for assessing regional wall motion. It can be applied both at rest and during exercise stress or pharmacologic stress. In addition, it can be used to measure ventricular volumes, changes in pulmonary blood volumes with stress and valvular regurgitant fractions. Equilibrium studies can be acquired by both planar and SPECT approaches.

Myocardial perfusion imaging. *Thallium-201.* A unique feature of nuclear cardiology is the ability to image regional myocardial blood flow distribution. Thallium-201 is very efficiently extracted by viable myocardial cells. After intravenous administration, thallium distributes in proportion to regional blood flow. Images of the heart shortly after thallium administration show deficits in regions where blood flow is relatively reduced and in zones of nonviable myocardium (e.g., previous myocardial infarction). Over time, "redistribution" of isotope generally occurs in previously ischemic zones, that is, defects related to ischemic myocardium normalize or "fill in." Defects related to infarcted or scarred myocardium typically do not "redistribute" over time and remain fixed. However, imaging at 24 h or after reinjection of thallium-201 may show viable but hypoperfused segments not otherwise identified by a standard redistribution study performed at 3 to 4 h after isotope injection. Assessment of lung thallium-201 activity on the initial unprocessed anterior view image provides a means to assess exercise-induced increases in pulmonary venous pressures. Thallium studies can be performed at rest, with exercise or dobutamine stress or after the myocardial hyperemia induced by intravenous administration of dipyridamole or adenosine. Myocardial perfusion imaging is most commonly

used in conjunction with exercise stress, with thallium-201 administered through an indwelling intravenous line at peak exercise. The patient then exercises for an additional 30 to 60 s, and images are generally acquired immediately after and again 3 to 4 h after thallium administration. In patients with stable angina who are unable to exercise, pharmacologic "stress" (i.e., dobutamine, adenosine or dipyridamole) has been used to induce myocardial hyperemia, with subsequent regional in- homogeneities in the perfusion pattern related to coronary stenoses. Finally, in patients with unstable angina or acute myocardial infarction, a perfusion study can be performed at rest. As with exercise, serial imaging can be performed after pharmacologic or rest thallium administration and demonstrate redistribution in regions of rest ischemia or underperfused but viable myocardium.

Technetium-99m – *based agents*. Recently, technetium-99m (Tc-99m) sestamibi and Tc-99m teboroxime were introduced for myocardial perfusion imaging. Other technetium-based agents, such as tetrofosmin and furifosmin, may be introduced in the near future and used in a similar manner. The shorter half-life of technetium-99m (6 h) compared with thallium-201 (73 h) allows administration of a larger dose, with resulting improved count statistics. The more favorable imaging characteristics of technetium-99m (higher emission energy, less scattered radiation) are additional benefits of using this agent. There is a good correlation between thallium-201 or sestamibi uptake and myocardial blood flow when the latter is normal, decreased or moderately increased (up to two times the baseline values). The uptake underestimates flow when the latter is increased >2.0 to 2.5 times the baseline values. Because sestamibi only undergoes a small amount of washout after initial myocardial uptake, the distinction between transient, stress-induced perfusion defects and fixed perfusion defects requires administration of two separate injections, one during stress and one at rest.

Technetium-99m teboroxime is another myocardial perfusion agent available in the United States. Because it undergoes rapid washout after initial accumulation in the myocardium, imaging with teboroxime is technically more difficult and must be completed within 2 to 8 min from the time of injection. This requirement is especially difficult to meet with single-head SPECT systems. Imaging may be optimized by using systems with two or three detectors. Fast, dynamic acquisition by planar imaging has also been used to minimize the problem of rapid washout. Teboroxime undergoes prominent liver uptake, which may render interpretation of the inferior wall of the heart difficult. Imaging with the patient sitting upright has been proposed to overcome the liver activity by displacing it inferiorly.

Myocardial infarct-avid imaging. Another unique aspect of radionuclide imaging involves the administration of T-99m (stannous) pyrophosphate or labeled antibody to cardiac myosin* for imaging myocardial infarction. These agents are localized in zones of recently infarcted myocardium. The most intense visualization of infarcted regions usually occurs 48 to 72 h after infarction for Tc-99m pyrophosphate.

Positron Emission Tomography

Instrumentation. Positron emission tomographic tracers simultaneously emit two high energy photons in opposite directions. The ability to detect these two simultaneously generated photons (by coincidence detection) allows the PET scanner to identify and localize true events and reject single (i.e., unpaired) photons as random, scattered photons. Such high energy photons and coincidence detection allow improved spatial resolution compared to SPECT. Coincidence detection provides a means of correcting for tissue photon attenuation, a capability not yet fully demonstrated with SPECT. Such attenuation correction results in improved measurement of regional tracer activity compared with SPECT methods and permits true quantification of this activity, which can be translated into quantification of physiologic and metabolic processes. Such quantitation is facilitated further by the high temporal resolution capability not available with SPECT.

Positron-emitting tracers. A number of tracers have been developed for clinical PET studies. These include oxygen-15 (half-life 2 min), nitrogen-13 (half-life 10 min), carbon-11 (half-life 20 min) and fluorine-18 (half-life 110 min), which may be coupled to a number of physiologically active molecules. These tracers require a local or on-site cyclotron for production, except for fluorine-18, which can be shipped for same-day use. Rubidium-82 (half-life 75 s) does not require a cyclotron and may be delivered directly to the patient from an on-site generator. The most frequently used agents to assess myocardial perfusion with PET are rubidium-82, nitrogen-13 (N-13) ammonia and oxygen-15 (O-15) water. Carbon-11 (C-11) Nlabeled fatty acids and fluorine-18 (F-18) fluorodeoxyglucose are common metabolic tracers, and C-11 acetate is used as an agent to assess oxidative metabolism and oxygen consumption.

Clinical applications. There are two specific clinical applications of PET that have been proposed for the evaluation of patients with coronary artery disease. The first is the noninvasive detection of coronary artery disease and estimation of the severity of the disease. This is performed using a PET perfusion agent at rest and during pharmacologic vasodilation. The short half-lives of these agents permit rapid sequential examinations, such as rest–dipyridamole studies, within a short time frame (1 to 2 h). A unique application of PET is the noninvasive calculation of absolute regional myocardial blood flow or absolute myocardial blood flow reserve in humans using O-15 water or N-13 ammonia. However, most centers rely on the qualitative or semiquantitative interpretation

*Not Food and Drug Administration (FDA) approved.

of rubidium-82 or N-13 ammonia images for both the diagnosis of coronary artery disease and the estimation of its severity. The second clinical application of PET is the assessment of myocardial viability in patients with coronary artery disease and left ventricular dysfunction. The most common approach is to determine whether metabolic activity is preserved in regions with reduced perfusion, using F-18 fluorodeoxyglucose as a marker of glucose utilization and thus tissue viability.

Clinical Uses of Radionuclide Imaging

Acute Myocardial Infarction

Diagnosis. The clinical use of radionuclide imaging for the diagnosis of acute myocardial infarction should be restricted to special limited situations where the triad of history, ECG changes and laboratory measurements is unavailable or less reliable. In patients who present late (>24 h and <7 days) without diagnostic ECG changes and in patients early after coronary artery bypass surgery, myocardial infarct-avid scintigraphy using Tc-99m pyrophosphate has moderate sensitivity and specificity in the diagnosis of acute myocardial infarction (3,4). Localized uptake of pyrophosphate usually indicates myocardial necrosis, although false-positive results can occur in the presence of intracardiac calcification, ventricular aneurysm and previous myocardial infarction. If the test is performed <24 h or >7 days after the onset of infarction, false negative results are frequent. A possible exception is the administration of pyrophosphate within 2 to 3 h after successful thrombolytic therapy (5). False-negative results may also occur after small infarctions when planar imaging is used (6); however, SPECT imaging allows the detection of a number of the smaller infarcts that may be missed by planar imaging. Pyrophosphate scintigraphy usually permits localization of the area of myocardial necrosis. More recently, infarct-avid scintigraphy with antimyosin antibody has been described as an alternative to pyrophosphate scintigraphy (7,8), but antimyosin antibody imaging remains investigational in the United States at this time. Sensitivity comparisons between pyrophosphate and antimyosin antibody imaging have generally provided similar results.

In selected patients with right ventricular infarction, radionuclide imaging may also have a role in diagnosis. Right ventricular infarction can often be diagnosed at the bedside. When these findings are not definitive, pulmonary artery catheter placement or right ventricular imaging may be indicated. In these circumstances, radionuclide angiography may support the diagnosis of right ventricular infarction by demonstrating a reduced right ventricular ejection fraction and right ventricular asynergy (9). In patients in whom right ventricular infarction is suspected to have occurred >24 h previously, the localization of myocardial necrosis to the right ventricle by pyrophosphate scintigraphy may also be useful.

Localized perfusion defects occur in a high percentage of patients with acute left ventricular infarction that is associated with coronary occlusion (10). However, such perfusion defects do not distinguish between acute ischemia, acute infarction or previous infarction. Serial changes on follow-up perfusion images with either thallium-201 or Tc-99m sestamibi suggest an acute process but still do not distinguish between ischemia or infarction.

Severity of disease/risk assessment/prognosis. The clinical severity of acute infarction is primarily a function of infarct size. The principal determinant of infarct size is the amount of myocardium at risk for infarction at the time of coronary occlusion, even if successful reperfusion occurs. Animal and clinical studies have documented the variability of myocardium at risk for a given coronary occlusion (11–13), which presumably reflects both the variation in the actual territories supplied by the native coronary arteries and the effect of coronary artery collateral vessels.

Technetium-99m sestamibi is uniquely suited to the accurate measurement of myocardium at risk in clinical infarction. Because there is minimal redistribution of the radiopharmaceutical over time, imaging can be delayed for several hours after injection and

still provide accurate information about myocardial perfusion at the time of injection. The validity and feasibility of this approach has been well established in animal and clinical studies (14–17).

As mentioned previously, myocardium at risk is a major determinant of final infarct size. However, final infarct size may be considerably smaller than the initial myocardium at risk, reflecting the effects of reperfusion therapy, spontaneous reperfusion and collateral blood flow (11). Clinical data have demonstrated the importance of final infarct size as a major determinant of subsequent patient survival. Radionuclide techniques are clearly useful for this purpose. In patients who have not received reperfusion therapy, measurement of rest ejection fraction and end-systolic volume index before hospital discharge by equilibrium-gated radionuclide angiography is highly associated with subsequent patient outcome (18,19). In patients who have received reperfusion therapy, the postdischarge rest ejection fraction by equilibrium radionuclide angiography after the resolution of myocardial stunning and compensatory hyperkinesia is highly associated with subsequent patient outcome (20–22).

Myocardial perfusion imaging with thallium-201 and Tc-99m sestamibi can also be used to assess infarct size (22–24). Most recently, Tc-99m sestamibi has been utilized with tomographic imaging for this purpose. Measurements of infarct size with Tc-99m sestamibi have been correlated closely with other measurements of infarct size, including ejection fraction (13), regional wall motion score (13), creatine kinase release (17), and thallium-201 defect size (24). However, no long-term studies are available to demonstrate an association with patient outcome.

Radionuclide techniques are useful for assessing the presence and extent of stress-induced ischemia. In patients who did not receive reperfusion therapy, both exercise radionuclide angiography (19) and exercise or pharmacologic stress thallium-201 perfusion imaging (25) have been carefully studied. Both are superior to the exercise ECG in the identification of patients who are likely to have subsequent cardiac events.

There are far fewer data available regarding risk stratification using predischarge exercise testing in patients who have received thrombolytic therapy. It is now recognized that patients enrolled in clinical trials of thrombolytic therapy are less likely to have severe three-vessel coronary artery disease (26). In addition, coronary angiography is often performed during the hospital period in patients with recurrent chest pain, thereby identifying many patients with severe disease who merit revascularization (27). Patients who receive thrombolytic therapy have a significantly smaller infarct size. As a consequence of all of these factors, the patient population that undergoes predischarge exercise testing in clinical trials of thrombolytic therapy is far different from less selected, historical populations (28). Preliminary data have suggested that the long-term event rates in such patients are far lower (29). Many studies are in progress that will reassess the validity of risk stratification using radionuclide techniques in patients who have received thrombolytic therapy. However, prospective natural history studies are difficult to undertake because clinicians now intervene with angiography and revascularization in patients with an ischemic response on predischarge stress perfusion imaging.

In patients who are unable to exercise after myocardial infarction due to orthopedic or other physical limitations, pharmacologic stress perfusion imaging is a useful alternative. Pharmacologic stress also appears useful in patients with left bundle branch block in whom exercise perfusion images are difficult to interpret (30,31). Dipyridamole (32) and adenosine thallium-201 studies (33) are clearly useful in the identification of patients who are at high risk for subsequent cardiac events. Such testing may be performed as early as 48 to 72 h after admission to try to identify high risk patients (34,35), although the safety of this approach remains to be established. Myocardial viability is another important prognostic issue after myocardial infarction.

Echocardiography is most commonly used when mechanical complications associated with acute myocardial infarction are suspected. Radionuclide techniques may be a useful alternative to assess mechanical complications when echocardiography is not available or definitive. The diagnosis of left ventricular aneurysm and pseudoaneurysm are feasible with radionuclide angiography. First-pass radionuclide angiography can be used to detect and quantitate shunting in the assessment of infarct-related ventricular septal defect.

Assessment of therapy. The assessment of the efficacy of acute reperfusion therapy with either thrombolysis or percutaneous transluminal coronary angioplasty is an important clinical issue in an increasing number of patients. There are two separate but clearly interrelated issues—the determination of early reperfusion after acute therapy and the measurement of myocardial salvage.

Serial tomographic imaging with Tc-99m sestamibi has been used at 18 to 48 h after therapy to assess coronary artery patency (36). In this time frame, it will clearly identify patients who have both coronary artery patency and early evidence of myocardial salvage, but it will be unable to distinguish patients with persistent occlusion from patients with patent arteries without early evidence of myocardial salvage. Technetium-99m sestamibi imaging has yet to be tested earlier after reperfusion therapy (perhaps 4 to 6 h) when additional revascularization might still be feasible. Teboroxime perfusion imaging is also potentially promising for the assessment of early coronary artery patency (37).

Serial imaging with Tc-99m sestamibi can be used to assess myocardial salvage (38). Because this radiopharmaceutical measures final infarct size, it can determine myocardial salvage. Tables 1 and 2 summarize and classify the indications for radionuclide testing in acute myocardial infarction.

Table 1. Uses of Radionuclide Testing in Diagnosis of Acute Myocardial Infarction

Indication	Test	Class
1. Right ventricular infarction	Rest RNA	IIa
	Tc-99m pyrophosphate	IIa
2. Infarction not diagnosed by standard means--early presentation with successful reperfusion	Rest myocardial perfusion imaging	IIb
	Tc-99m pyrophosphate	IIb
3. Infarction not diagnosed by standard means-- late presentation	Tc-99m pyrophosphate	IIa
4. Routine diagnosis	Any technique	III

Class I = usually appropriate and considered useful; class II = acceptable but usefulness less well established; class IIa = weight of evidence in favor of usefulness; class IIb = can be helpful but not well established by evidence; class III = generally appropriate; RNA = radionuclide angiography; Tc = technetium

Table 2. Uses of Radionuclide Testing in Risk Assessment, Prognosis and Assessment of Therapy After Acute Myocardial Infarction

Indication	Test	Class
1. Rest RV/LV function	Rest RNA	I
2. Presence/extent of stress-induced ischemia	Stress myocardial perfusion imaging	I
	Stress RNA	IIa
3. Detection of viable myocardium	See Table 4: Uses of Radionuclide Testing in Diagnosis of Chronic Ischemic Heart Disease	
4. Detection of infarct size	Rest myocardial perfusion imaging	IIa
5. Acute measurement of myocardium at risk	Rest Tc-99m setamibi perfusion imaging	IIa
6. Measurement of myocardial salvage	Sequential rest myocardial imaging with Tc-99m sestamibi	IIa

LV(RV) = left(right) ventricular; other abbreviations as in Table 1.

Unstable Angina

Diagnosis. The clinical use of radionuclide imaging for the diagnosis of unstable angina should be restricted to limited situations where the combination of history and ECG changes are unavailable or less reliable. In these circumstances, radionuclide techniques may be useful adjuncts for the diagnosis of unstable angina. Their clinical applicability is primarily an issue of logistics. Planar thallium imaging is useful for the detection of reversible, segmental myocardial perfusion defects (39,40). Redistribution on such images provides an indication of regional myocardial viability that differentiates ischemia at rest from previous infarction. However, the detection of redistribution requires prompt initial imaging, generally within 30 min, before the myocardial distribution of thallium-201 has changed substantially. This limits its usefulness in acutely ill patients.

Technetium-99m sestamibi tomography is useful for the detection of rest perfusion abnormalities (41). Because of the lack of clinically significant redistribution of this agent, imaging can be delayed for 1 to 6 h and still allow determination of myocardial perfusion at the time of administration. Logistic barriers to the use of this agent are 1) the time required for preparation, which is ~5 to 20 min, and 2) the fact that an hour delay is required before imaging to allow liver clearance (42). Thus, chest pain must persist long enough to permit the preparation and administration of the agent.

Severity of disease/risk assessment/prognosis. In the acute setting, the clinical use of radionuclide imaging to assess the severity of disease and patient risk should be restricted to those situations where history and ECG assessment are not definitive. Myocardial perfusion imaging can provide accurate information about the extent and location of the decrease in blood flow (39,41). This information is generally more precise than that provided by the ECG. It may be helpful in patient management, particularly with respect to identification of the “culprit” angiographic lesion when revascularization with angioplasty or operation appears to be necessary. Although such information could conceivably be obtained with either thallium-201 or Tc-99m sestamibi perfusion

imaging, the latter radionuclide is generally preferable because imaging of the acutely ill patient can be delayed for a period of several hours if necessary.

Radionuclide techniques are potentially useful with respect to two specific issues concerning the prognosis in patients with unstable angina—assessment of myocardial viability and prediction of future cardiac events in patients whose angina is successfully stabilized with medical therapy.

Some patients with unstable angina will have normal regional and mechanical function between episodes of chest pain. In such patients, the myocardial segments that develop regional dysfunction during pain can be presumed to be viable. However, many patients will continue to have global and regional dysfunction between episodes of chest pain, which may represent ongoing subclinical ischemia or myocardial stunning. In patients with mechanical dysfunction, myocardial perfusion imaging with thallium-201 is valuable to distinguish myocardial stunning or ongoing ischemia from previous myocardial infarction, or both. Technetium-99m sestamibi is also potentially useful in this regard.

In patients with unstable angina that is satisfactorily stabilized with medical therapy, myocardial perfusion imaging can help determine future cardiac risk. The size and number of the perfusion defects are the best predictors of the extent of underlying coronary artery disease. The presence and extent of thallium-201 redistribution on stress testing (after stabilization) are predictive of subsequent cardiac death and nonfatal myocardial infarction (43,44). Myocardial perfusion imaging is therefore one option for the noninvasive risk stratification of patients whose angina is stabilized with medical therapy (45).

Assessment of therapy. Radionuclide angiography can assess improved left ventricular function in patients who have undergone revascularization and have evidence of dysfunction between episodes of unstable angina. Myocardial perfusion imaging can document the improvement in rest perfusion to areas with previous rest ischemia. Both exercise and pharmacologic stress with perfusion imaging are useful for assessing the completeness of revascularization and for determining the functional significance of any unrevascularized lesions. The utilization of these techniques in patients with previous unstable angina who have undergone revascularization is essentially similar to their application in patients with chronic ischemic heart disease. Table 3 summarizes the indications for radionuclide testing in unstable angina.

Table 3. Uses of Radionuclide Testing in Diagnosis, Prognosis and Assessment of Therapy in Patients With Unstable Angina

Indication	Test	Class
1. Identification of ischemia in the distribution of the "culprit" lesion or in remote areas	Stress myocardial perfusion imaging	I
2. Identification of the severity/extent of disease in patients with ongoing ischemia	Rest myocardial perfusion imaging	IIa
3. Identification of the severity/extent of disease in patients whose angina is satisfactorily stabilized with medical therapy	Stress myocardial perfusion imaging	IIa
4. Diagnosis of myocardial ischemia in patients where the combination of history and ECG changes are unreliable	Rest myocardial perfusion imaging	IIb
5. Measurement of baseline LV function	RNA	I

ECG = electrocardiographic; other abbreviations as in Tables 1 and 2.

Chronic Ischemic Heart Disease

Radionuclide imaging has played a pivotal role in the diagnosis and risk stratification of patients with coronary artery disease. The largest accumulated experience in myocardial perfusion imaging has been with the tracer thallium-201, but the available evidence suggests that the newer tracer Tc-99m sestamibi yields similar diagnostic accuracy (46–54). Thus, for the most part, thallium-201 or Tc-99m sestamibi can be used interchangeably, with similar diagnostic accuracy in coronary artery disease. Myocardial perfusion imaging may use either planar or tomographic (SPECT) techniques. Thallium-201 SPECT is generally more accurate than planar imaging for diagnosing coronary artery disease, localizing hypoperfused vascular territories, identifying left anterior descending and left circumflex coronary artery stenoses (55) and correctly predicting the presence of multivessel coronary artery disease (56). Thus, SPECT is generally preferable to planar imaging, although the latter remains useful if the more expensive and complex SPECT gamma cameras are not available, or if the patient cannot tolerate lying on the SPECT table because of musculoskeletal reasons, or for bedside imaging in an intensive care unit.

Diagnostic accuracy of myocardial perfusion imaging in chronic coronary artery disease.*Thallium-201 planar scintigraphy.* The utility of thallium-201 planar scintigraphy in the diagnosis of coronary artery disease was extensively documented in the late 1970s and early 1980s. The average values of sensitivity and specificity are 83% and 88%, respectively, by visual analysis (57–60). The less than perfect sensitivity and specificity may in part be explained by the fact that visually estimated angiographic severity of coronary stenoses does not closely correlate with functional severity as assessed by coronary flow reserve after maximal pharmacologic coronary vasodilation (61).

Quantitative techniques have been used in association with planar thallium-201 perfusion imaging. These techniques are based on the distribution of thallium-201 activity over the myocardium assessed by horizontal (62) or circumferential (63–65) profiles. Myocardial segments with abnormal thallium-201 uptake and washout are identified versus either normal segments in the same image (62) or relative to the values of a normal cohort (64–66).

Quantification of planar thallium-201 images may improve the test's sensitivity, especially in patients with single-vessel disease (60,65–69). The overall reported sensitivity for quantitative planar thallium scintigraphy is 90% (60). However, quantification techniques may at times result in lower specificity, particularly when they rely on isolated analysis of thallium-201 washout, which can be affected by such factors as intensity of exercise, peak heart rate achieved and diet consumed by the patient between the stress and redistribution images. Overall specificity of quantitative thallium scintigraphy is 80%.

Thallium-201 SPECT *scintigraphy*. Qualitative analysis of SPECT has resulte in a higher frequency of detection of coronary artery disease relative to planar scintigraphy (55). The average sensitivity and specificity of qualitative exercise thallium-201 SPECT are 89% and 76%, respectively (67,69,70).

Single-photon emission computed tomography has afforded diagnostic improvement over planar imaging for more precise localization of the vascular territories involved, particularly the identification of left circumflex coronary artery stenoses and prediction of multivessel coronary artery disease (67,69,70). Quantitative analysis of thallium-201 SPECT has further enhanced its accuracy. This has been achieved by generating perfusion maps of the three-dimensional myocardial thallium-201 activity on the basis of circumferential profiles of individual myocardial slices, which are then displayed on a “polar map” or “bull's-eye” plot. Computer coding of abnormally perfused myocardium, relative to a composite map from normal subjects, can then be obtained and expressed as a percentage of left ventricular volume (70–77). A recent review of studies using quantitative analysis of exercise thallium-201 SPECT has shown an overall sensitivity of 90% and specificity of 70% (70). The lower than expected specificity in these recent series has been ascribed to a “posttest referral bias” that postulates that patients with abnormal SPECT study results are preferentially referred for cardiac catheterization. This selection process would curtail the number of “true negative” results in the studies because most subjects with normal SPECT results would not undergo coronary angiography. The end result of such a selection bias would be to decrease the specificity of the test while at the same time increasing the test's sensitivity. In an attempt to circumvent this “posttest referral bias,” some investigators have proposed a “normalcy rate” as a surrogate for specificity. The normalcy rate is the fraction of negative studies in a cohort of “clinically normal” subjects, meaning subjects with a very low likelihood of having coronary artery disease on the basis of history, negative physical findings and normal exercise ECG test results but who have not had heart catheterization. The normalcy rate by quantitative thallium-201 SPECT averages 89% (70).

Although patient selection undoubtedly plays a role in decreasing the observed SPECT specificity, it is likely that other factors, such as photon attenuation and artifacts created by the tomographic reconstruction process, are also important. Clearly, SPECT requires more rigorous quality control for image acquisition and processing than planar imaging.

Technetium-99m perfusion tracers. Most of the studies comparing Tc-99m sestamibi with thallium-201 perfusion imaging or coronary angiography have used a 2-day sestamibi protocol. These studies have been recently summarized (53,54). By quantitative analysis of planar imaging, the average sensitivity and specificity were similar to those of thallium-201 scintigraphy. By quantitative analysis of SPECT, the corresponding values are similar to those of quantitative thallium-201 SPECT. On average, SPECT imaging yields better detection of individual coronary stenoses than planar imaging with Tc-99m sestamibi (54,78). Reports of several small series have documented the diagnostic sensitivity and specificity of exercise Tc-99m teboroxime imaging, and they appear to be comparable to those of exercise thallium-201 imaging (79–83).

Positron emission tomography. A number of studies, involving a total of several hundred patients, indicate that perfusion imaging with PET using dipyridamole and either rubidium-82 or N-13 ammonia demonstrates abnormal coronary perfusion patterns in the majority of patients with coronary artery disease. This experience indicates that PET may be a sensitive and specific clinical means to diagnose coronary artery disease (84–92). Sensitivities with either tracer range from 87% to 97%, with specificities from 78% to 100%. At the present time, rubidium-82 is the only PET perfusion tracer approved by the FDA for clinical use; N-13-ammonia is also used for assessment of myocardial perfusion, yet is still considered investigational by the FDA. The advantage of rubidium-82 is that it is obtained from a generator, obviating the need for a cyclotron; the disadvantage is the high cost of the generator.

Positron emission tomographic versus SPECT imaging. Two studies, involving a total of 281 patients, in which PET perfusion imaging with rubidium-82 and dipyridamole was compared directly with thallium SPECT in the same patients, demonstrated significantly higher diagnostic accuracy of PET for detecting angiographically documented coronary artery disease. The first study (90) compared thallium-201 SPECT to rubidium-82 PET, using a single dipyridamole–hand grip stress (see later) for both imaging agents and showed improved diagnostic accuracy with rubidium-82. These results stemmed primarily from lower sensitivity in detecting coronary artery disease with thallium (76%) compared with rubidium-82 (95%). Over 75% of the false negative thallium studies that were correctly diagnosed during the rubidium-82 studies involved the inferior and posterior wall, a region known to have greater interpretative errors with thallium-201 because of true or perceived photon attenuation. In the second study (91), similar sensitivities between thallium SPECT (using either exercise or dipyridamole) and rubidium-82 PET (using dipyridamole–hand grip stress) were obtained in identifying coronary artery disease (90% and 87%, respectively) and individual coronary artery stenoses (65% and 64%, respectively). However, PET achieved higher specificity than SPECT, both in the diagnosis of patients (82% vs. 57%, respectively) and in identifying individual coronary artery stenoses (92% vs. 84%, respectively). Although each of these studies reported promising results with PET versus SPECT imaging, the results may have been influenced by patient referral biases and timing of the PET versus SPECT acquisitions and differing stress protocols between PET and SPECT. The low sensitivity of SPECT in the first study (90) could reflect the later injection of thallium several minutes after administration of the same dose of dipyridamole that was used for the stress rubidium-82 image acquisition and the fact that both dipyridamole and hand grip exercise were used for PET, whereas only dipyridamole was used for SPECT. The low specificity of SPECT in the second study (91) may represent a referral bias because patients underwent thallium SPECT imaging before being selected for coronary arteriography and PET imaging. Larger, more definitive comparative studies with comparable expertise in both PET and SPECT imaging are required to determine the relative diagnostic efficacies of the two techniques.

It is clear that PET would provide valuable diagnostic information in certain individual clinical situations. For example, because of the ability to correct for photon attenuation with PET, PET would be valuable in patients with equivocal thallium results related to questions of photon attenuation or in patients whose body habitus is likely to raise issues of photon attenuation.

However, it is less certain that PET is unequivocally superior to SPECT imaging for routine diagnostic purposes, despite its potential for improvement in diagnostic accuracy. A recent report from the American Heart Association (93) reviewed the available data and did not find PET superior to SPECT in diagnostic accuracy. No new comparative studies have appeared since that report was published. The available data indicate that PET provides a diagnostic accuracy for the detection of coronary artery disease and for the estimation of disease severity that is similar to SPECT imaging. However, the number of patients studied by PET is relatively small. Also, PET is an expensive imaging modality, and whether the greater cost of PET is justified by a possible improvement in diagnostic accuracy requires further rigorous study. Thus, until data from large-scale, definitive studies are published, PET is considered an effective modality for the noninvasive diagnosis of coronary artery disease but should be considered for routine diagnostic purposes only if the costs of PET are equivalent to or less than the costs of SPECT imaging in the same community.

Special issues with regard to exercise perfusion imaging for diagnosis of coronary artery disease.

Concomitant use of drugs. Medications that decrease myocardial oxygen demands, such as beta-adrenergic or calcium channel blocking agents, may limit the development of ischemia during the exercise test. Beta-blockers tend to attenuate the exercise-induced increase in heart rate. Consequently, the sensitivity of the exercise perfusion study for the diagnosis of coronary artery disease appears to be lower in patients taking such agents (74,94–97). Whenever feasible, use of beta-blockers and long-acting calcium channel blockers should be tapered and discontinued at least 48 h before the exercise test. One study (98) shows that nitrates may also decrease the extent of perfusion defects or even convert abnormal exercise scan results to normal results. Therefore, when feasible, long-acting nitrates should be discontinued at least 12 h before the test, although sublingual nitroglycerin may be given as needed up to 2 h before the test. Nonetheless, in patients who exercise to a submaximal level because of the effect of drugs, perfusion imaging still affords higher sensitivity than the exercise ECG alone (99). Pharmacologic perfusion imaging using dipyridamole or adenosine appears to be less affected by antianginal drugs and thus provides an appropriate alternative to exercise (100).

Myocardial perfusion imaging in selected patient subsets (female, elderly or obese patients). The treadmill ECG test is less accurate for diagnosis in women, who have a generally lower pretest likelihood than men. Myocardial perfusion imaging could be a logical addition to treadmill testing in this circumstance. However, the sensitivity of thallium perfusion scans may be lower in women than in men (60,101). Artifacts due to breast attenuation, usually manifest in the anterior wall, can be an important caveat in the interpretation of women's scans, especially when thallium-201 is used as a tracer. Theoretically, Tc-99m sestamibi may be preferable to thallium-201 scintigraphy in women with large breasts and those with breast

implants, although conclusive data on this issue are lacking. Positron emission tomography may also be superior in women with large breasts or breast implants, although this has not been studied carefully either.

Although many elderly patients can perform an adequate exercise test, many are unable to do so because of physical impairment. Pharmacologic stress imaging is an appropriate option in such patients. Very obese patients constitute a special problem because most imaging tables used for SPECT have weight-bearing limits (often $\leq$300 lb [135 kg]) that preclude imaging very heavy subjects. These subjects can still be imaged by planar scintigraphy. Obese patients often have suboptimal perfusion images, especially with thallium-201, owing to the marked photon attenuation by soft tissue. In these patients, Tc-99m sestamibi is probably most appropriate and should yield images of better quality than thallium-201. Positron emission tomographic imaging is also likely to be superior in these subjects.

Bundle branch blocks. Several studies have observed an increased prevalence of myocardial perfusion defects during exercise imaging, in the absence of angiographic coronary disease, in patients with left bundle branch block (102–104). These defects often involve the interventricular septum, may be reversible or fixed and are often absent during pharmacologic stress. Thus, perfusion imaging with pharmacologic vasodilation appears to be more accurate for identifying coronary artery disease in patients with left bundle branch block (105–107). Right bundle branch block or left anterior hemiblock are not ordinarily associated with such perfusion defects.

Bayes' theorem applied to cardiac imaging. According to Bayes' theorem, the diagnostic value of perfusion imaging is greatest in patients with a moderate pretest likelihood (in the range 30% to 60%) of having clinical coronary artery disease. Among symptomatic patients, this may include middle-aged women with angina, patients with abnormal ECG findings at baseline and those with angina with atypical features. In patients with a very low pretest likelihood for coronary artery disease, positive perfusion scan results are often false positive, whereas with a very high pretest likelihood, negative scan results are often false negative. Thus, exercise myocardial perfusion should generally not be used for routine diagnostic purposes in patients with a very low or very high likelihood of disease. A caveat to these Bayes' theorem considerations is that negative stress scan results in a patient with coronary artery disease may still be prognostically important because it predicts a low risk for future cardiac events. Likewise, in patients with a high pretest likelihood for coronary artery disease, myocardial perfusion imaging affords useful information regarding the extent, severity and reversibility of myocardial hypoperfusion, which also have powerful prognostic value.

Pharmacologic myocardial perfusion imaging. Since the introduction of dipyridamole-induced coronary vasodilation as an adjunct to thallium-201 myocardial perfusing imaging (108–110), pharmacologic interventions have become an important tool in the noninvasive diagnosis of coronary artery disease. Three drugs are commonly used as substitutes for exercise stress testing: dipyridamole, adenosine and dobutamine. Dipyridamole and adenosine are specifically approved by the FDA for use in combination with myocardial perfusion scintigraphy.

Dipyridamole causes coronary vasodilation indirectly by inhibiting cellular uptake of adenosine, thereby increasing the blood and tissue levels of adenosine, which is a potent, direct coronary vasodilator and markedly increases the coronary blood flow. The flow increase with adenosine or dipyridamole is of lesser magnitude through stenotic arteries, creating heterogeneous myocardial perfusion, which can be observed with a perfusion tracer. Although this mechanism can exist independently of myocardial ischemia, in some patients true myocardial ischemia can occur with either dipyridamole or adenosine because of a coronary steal phenomenon. The technical aspects of pharmacologic perfusion imaging have been reviewed elsewhere (100,109–123).

Dipyridamole planar scintigraphy has a high sensitivity (90% average) and acceptable specificity (70% average) for detection of coronary artery disease (111). In studies comparing exercise and dipyridamole thallium-201 scintigraphy in the same patients, a similar sensitivity and specificity were found (111). Dipyridamole SPECT imaging with thallium-201 or Tc-99m sestamibi appears to be at least as accurate as planar imaging (124–126).

Intravenous adenosine combined with thallium-201 SPECT has provided high sensitivity (85% average) and specificity (90% average) for detection of coronary artery disease (100,112–116). Results of myocardial perfusion imaging during adenosine infusion are similar to those obtained with dipyridamole and exercise imaging (113–115,117). Both dipyridamole and adenosine are safe and well tolerated despite frequent mild side effects, which occur in 50% (111) and 80% (118) of patients, respectively. Severe side effects are rare, but both dipyridamole and adenosine may cause severe bronchospasm in patients with asthma or chronic obstructive lung disease; therefore, they should be used with extreme caution if at all in these patients. Dipyridamole and adenosine side effects are antagonized by theophylline, although this drug is ordinarily not needed after adenosine, because of the latter's ultrashort half-life (<10 s). No large studies have compared adenosine and dipyridamole in the same patients.

Dobutamine in high doses (20 to 40 μg/kg per min) increases the three main determinants of myocardial oxygen demand, namely, heart rate, systolic blood pressure and myocardial contractility, thereby eliciting a secondary increase in myocardial blood flow. The flow increase (two- to three-fold above baseline values) is less than that which is elicited by adenosine or dipyridamole but is sufficient to demonstrate heterogeneous perfusion by radionuclide imaging. Although the reported experience with dobutamine perfusion imaging is relatively recent, the overall sensitivity and specificity are in the same range as those with exercise, dipyridamole or adenosine tests (119–122). Although side effects are frequent during dobutamine infusion, the test appears to be relatively safe (119–122).

Radionuclide angiography. Exercise radionuclide angiography (either supine or upright) can be used to assess indirectly the presence of myocardial ischemia by demonstrating deterioration of wall motion or an abnormal left ventricular ejection fraction response to exercise, or both. However, this technique is limited by 1) acquisition of images in only one view during exercise (an anterior or shallow right anterior oblique view for first-pass studies or the "best septal" view, which allows visualization of only the interventricular septum and inferoapical and posterolateral walls); 2) degradation of images due to chest motion; and 3) the well known dependence of the "normal" left ventricular ejection fraction response on exercise intensity, drug effects, age and gender. Despite these limitations, the exercise left ventricular ejection fraction remains a powerful prognostic indicator (127,128). The ability to assess both ventricular function and myocardial perfusion by Tc-99m sestamibi imaging constitutes a definite advantage of this agent, in that it allows a more comprehensive evaluation (129).

Detection of coronary artery disease in asymptomatic patients. Because of the low positive predictive value of noninvasive testing in asymptomatic patients, radionuclide techniques are not ordinarily recommended as a screening strategy for coronary artery disease. However, a stress radionuclide test (either perfusion imaging or radionuclide angiography) is valuable in asymptomatic patients with positive exercise ECG stress test results, in that it may assist in determining the need for coronary angiography. Their use may also be justifiable in asymptomatic patients with *known* coronary artery disease to determine the presence and severity of inducible myocardial ischemia. Furthermore, in patients with documented coronary artery disease, SPECT myocardial perfusion imaging shows a similar frequency and extent of perfusion defects and reversible hypoperfusion in patients with or without chest pain during exercise testing (130,131). Because perfusion defects during exercise are strongly associated with a worse prognosis, the presence, extent, severity and reversibility of perfusion defects often influence therapeutic decisions in patients with coronary artery disease with or without symptoms.

Radionuclide imaging before noncardiac surgery. It is well known that patients undergoing noncardiac vascular procedures often have associated coronary artery disease that may or may not be clinically apparent. In these patients the perioperative mortality and morbidity are usually due to underlying coronary artery disease. Hence, there is a need to thoroughly assess the cardiac risk status in these patients.

Dipyridamole thallium-201 scintigraphy has been extensively used in the preoperative cardiac evaluation of patients undergoing noncardiac vascular procedures. Patients with normal thallium-201 scan results or those without reversible defects have a very low risk of developing perioperative cardiac events. Conversely, those with reversible perfusion defects have an increased risk of developing cardiac complications. However, because the positive predictive value of an abnormal dipyridamole thallium-201 scan is only between 15% and 30%, other clinical variables (such as the presence of a previous myocardial infarction and a history of diabetes mellitus, angina or congestive heart failure) need to be combined with the results of the perfusion scan to optimize risk stratification in these patients (132). Adenosine thallium-201 scintigraphy has recently been shown to be similarly useful in the preoperative risk stratification of patients undergoing vascular, orthopedic or general surgery (133).

Although only limited data are available (132) with respect to use of dipyridamole thallium-201 scintigraphy for risk stratification before major nonvascular procedures, dipyridamole scintigraphy may be useful in selected patients with documented or suspected coronary artery disease who are thought to be at high cardiac risk for other major operations. Such testing is not necessary in most patients undergoing nonvascular surgery because their cardiac risk is low (134). Evaluation of the patient undergoing noncardiac surgery will be the subject of a future detailed report by the ACC/AHA Task Force on Diagnostic and Therapeutic Procedures.

Diagnostic accuracy in assessment of myocardial viability in chronic coronary artery disease. In a large subset of patients with coronary artery disease and left ventricular dysfunction, left ventricular performance is reduced on the basis of regionally ischemic or hibernating or stunned myocardium rather than irreversibly infarcted myocardium (135). The detection of reversibly dysfunctional myocardium is clinically relevant because regional and global left ventricular function in such patients will improve after revascularization.

The requirements for cellular viability include intact sarcolemmal function to maintain electrochemical gradients across the cell membrane, as well as preserved metabolic activity to generate high energy phosphates. These processes require adequate myocardial blood flow to deliver substrates and to wash out metabolites. Nuclear cardiology methods are ideally suited for this assessment. Thallium-201 SPECT and perfusion and metabolic PET imaging in particular have emerged as useful methods for demonstrating viable myocardium in patients with compromised left ventricular function. Approaches using radionuclide angiography, including imaging immediately after exercise or nitroglycerin, have been reported but have not achieved wide acceptance (136–138).

Thallium-201. The retention of thallium-201 is an active process that is a function of cell viability and cell membrane integrity. Although initial thallium uptake reflects regional perfusion, the ability of the myocardium to retain thallium or extract additional thallium over the subsequent 3 to 4 h, or both, is a marker of myocardial viability. Thus, a thallium defect on an immediate post-stress study that redistributes at 3 to 4 h represents ischemic but viable myocardium. However, many regions of severely ischemic or hibernating myocardium appear to have irreversible thallium defects on standard or conventional exercise–redistribution imaging protocols. It has been shown that up to 50% of regions with "irreversible" thallium defects will improve after revascularization (139). However, such irreversible defects are usually mild, with no more than a 25% to 50% reduction in thallium activity. The quantitative severity of the defect itself is thus one index of viability (139). However, exercise–redistribution thallium scintigraphy, analyzed qualitatively, may not provide satisfactory precision in differentiating between infarcted and viable myocardium.

An alternative approach uses other imaging protocols. Many apparently irreversible thallium defects at 3 to 4 h manifest substantial redistribution on late (24 to 72 h) redistribution imaging; in fact, perfusion improves after revascularization in >90% of myocardial regions with this finding (140). Despite this excellent positive predictive accuracy, the negative predictive accuracy is less optimal because nearly 40% of defects that do not show early or late redistribution also improve after revascularization (140). These results have been improved substantially by the development of thallium reinjection protocols. Up to 50% of apparently irreversible thallium defects on redistribution images show uptake when thallium is reinjected at rest. The two published series using this method (141,142), involving a total of only 45 patients, reported excellent positive (80% and 87%, respectively) and negative (82% and 100%, respectively) predictive accuracies for improvement in regional ventricular function after revascularization. Recent data (also involving small numbers of patients) (143,144) indicate that a rest–redistribution protocol in which thallium is injected at rest with immediate and 3 to 4-h redistribution imaging, with quantitative analysis of regional thallium activity, is another effective means for assessing viability, as determined by preserved metabolic activity by PET and improved wall motion after revascularization.

Technetium-99m sestamibi. Technetium-99m sestamibi, like thallium-201, requires intact cell membrane processes for retention and has been shown to be an excellent marker of cellular viability when perfusion is adequate (145). However, unlike thallium-201, Tc-99m sestamibi does not redistribute appreciably after its initial uptake. Thus, sestamibi may have inherent disadvantages compared with thallium for assessment of viability in clinical situations in which blood flow is severely impaired (and sestamibi delivery is reduced). This concept is supported by three recent studies (146–148) suggesting that rest–exercise sestamibi imaging underestimates viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction compared with exercise–redistribution–reinjection thallium imaging or PET metabolic imaging. However, more recent studies (149,150) indicate that sestamibi may provide useful information about viability, and more information is needed in this area before definitive conclusions can be reached.

Positron emission tomographic imaging. Four PET methods have shown promise in providing accurate information regarding myocardial viability. The method that has achieved the greatest attention, and the one with the greatest patient validation, is the identification of intact metabolic activity in regions of severely underperfused and dysfunctional myocardium. For this purpose, F-18 fluorodeoxyglucose has been used as a marker of regional exogenous glucose utilization in such hypoperfused regions (151). A pattern of enhanced F-18 fluorodeoxyglucose uptake in regions with reduced perfusion (termed the F-18 fluorodeoxyglucose/blood flow "mismatch") indicates ischemic or hibernating myocardium that has preferentially shifted its metabolic substrate toward glucose rather than fatty acids or lactate. The criteria to define F-18 fluorodeoxyglucose/blood flow mismatch have not been standardized. The finding of preserved metabolic activity in myocardial regions with reduced blood flow has been shown in several studies (151–154), involving a total of >100 patients, to be an accurate clinical marker with which to distinguish viable myocardium from myocardial fibrosis, with positive and negative predictive accuracies in the range of 85% in identifying regions that will manifest improved function after revascularization. Some of these studies (151,153) also suggest that the extent of myocardial mismatch may predict the magnitude of improvement

in left ventricular function after revascularization. Finally, the pattern of F-18 fluorodeoxyglucose/blood flow mismatch may have prognostic importance in patients with left ventricular dysfunction because patients with extensive mismatch have a high mortality rate during medical therapy but an excellent outcome after myocardial revascularization procedures (154,155). Although these studies suggest a poor outcome in patients with F-18 fluorodeoxyglucose/blood flow mismatch who do not undergo revascularization, these studies are limited by small patient numbers (total of 87 patients), retrospective analysis and lack of randomization.

Alternative approaches that have been proposed for viability assessment with PET include assessment of oxidative metabolism in dysfunctional segments using C-11 acetate (156), estimation of the extent of transmural perfusable tissue within a dysfunctional segment using O-15 water (157) and analysis of the washout kinetics of rubidium-82 within a dysfunctional segment (158). Each of these methods has thus far been studied in only small numbers of patients and awaits confirmation in larger series. F-18 fluorodeoxyglucose, C-11 acetate and O-15 water have not yet been approved by the FDA for clinical use. These three agents also require a nearby cyclotron for their production, which is likely to increase the cost of performing studies of viability.

Positron emission tomographic versus thallium imaging. In keeping with the finding that as many as 50% of irreversible thallium defects on standard exercise–redistribution imaging will improve after revascularization (139), a similar percent of apparently irreversible defects have been shown to be metabolically active by PET (159,160). The improved accuracy of reinjection protocols in predicting recovery of function after revascularization (141,142) is paralleled by a high degree of concordance between thallium reinjection imaging with PET imaging when both techniques are studied in the same patients (161,162). In a recent series, the results of rest–redistribution thallium imaging also approached those of PET imaging (144). Finally, as noted previously, the severity of thallium defects also provides important information regarding viability. Even in defects that remain irreversible on exercise–redistribution, exercise–reinjection or rest–redistribution protocols, measurement of the level of thallium activity within the redistribution or reinjection defect (relative to normal territories) corresponds very well to F-18 fluorodeoxyglucose activity (144,161,163).

Although thallium uptake provides important information about viability, all SPECT protocols share the limiting feature of increased photon attenuation of a lower energy radioisotope, in which apparently irreversible thallium defects suggesting fibrosis could be attenuation artifacts in viable tissue. This is likely to be of greatest concern in patients with severe left ventricular dysfunction and dilated ventricular chambers. In contrast, correction for photon attenuation is a routine procedure in PET imaging. Thus, it is anticipated that imaging with thallium or with technetium-99m–based agents will not achieve the accuracy of PET imaging for assessment of viability until methods to correct for photon attenuation are perfected for SPECT imaging.

In summary, positron emission tomographic imaging with a perfusion agent and F-18 fluorodeoxyglucose provides a reliable approach for identification of viable myocardium and is considered effective and acceptable. However, a number of thallium imaging protocols appear to approach the accuracy of metabolic PET techniques, and thallium imaging can be performed at lower cost. Thus, PET might be used to assess myocardial viability after a thallium test fails to provide definitive evidence of viability or nonviability or if a PET study with a perfusion agent and F-18 fluorodeoxyglucose can be performed at a cost equivalent to or less than a SPECT study. It is recognized that greater experience involving larger patient groups is necessary to assess the relative efficacies of these two modalities. The use of technetium-based perfusion agents for SPECT imaging for myocardial viability assessment, as well as the use of PET imaging with C-11 acetate, O-15 water or rubidium-82, is considered investigational at the present time.

Assessment of disease severity/risk stratification/prognosis in chronic coronary artery disease. Radionuclide techniques can be applied to the planning and monitoring of medical and interventional therapies, prognostication and advice about activity levels and occupation in patients with documented coronary artery disease.

Radionuclide angiography. One index of coronary artery disease severity is left ventricular function. Rest left ventricular ejection fraction is one of the most important determinants of long-term prognosis in patients with chronic stable coronary artery disease (164,165). Mortality rates increase progressively as left ventricular ejection fraction decreases (165). Knowledge of the rest LVEF is useful for determining appropriate medical therapies and for decision making about some surgical interventions. Recommendations about reasonable levels of activity, rehabilitation and work status also are influenced by knowing the degree of ventricular function impairment.

In patients with chronic coronary artery disease, radionuclide angiography can be helpful in evaluating dyspnea by establishing right and left ventricular performance. In those patients with clinical congestive heart failure, knowledge of left ventricular ejection fraction can distinguish that subset with systolic dysfunction. The decision to institute angiotensin-converting enzyme inhibitor

therapy in asymptomatic patients with chronic coronary artery disease depends on documenting a reduced left ventricular ejection fraction (166).

Left ventricular function during exercise also reflects disease severity and provides prognostic information. In patients with coronary artery disease, a decline in left ventricular ejection fraction during exercise compared with its rest value is an important indicator of coronary artery disease severity and is associated with a poorer 3-year survival than if left ventricular ejection fraction increases during exercise (167). However, the absolute value of left ventricular ejection fraction at the peak of exercise appears to be an even stronger correlate of survival over the subsequent 2 to 5 years (168,169). In patients with mild symptoms, rest left ventricular dysfunction and one-, two- or three-vessel coronary artery disease, an abnormal peak exercise left ventricular ejection fraction or a decrease in left ventricular ejection fraction during exercise identify patients with a poorer prognosis (169–171). Hence, inducible myocardial ischemia sufficient to reduce ejection fraction during exercise when it is superimposed on previous myocardial damage is important in determining prognosis. Patients with preserved left ventricular function at rest, but with enough inducible ischemia to severely reduce left ventricular ejection fraction during exercise, also appear to be at greater risk of death (172). However, the event rates in those with a normal rest LVEF are low, and one study indicates that exercise data do not confer independent prognostic information in such patients (173).

Myocardial perfusion imaging. The number, size and location of abnormalities on stress myocardial perfusion studies reflect the location and extent of functionally significant coronary stenoses. Lung uptake of thallium-201 on postexercise or pharmacologic stress images is a marker of stress-induced global left ventricular dysfunction and multivessel coronary disease (174,175). Transient post-stress ischemic left ventricular dilation also correlates with multivessel disease (176). These studies have suggested that SPECT may be more accurate than planar imaging for determining the size of defects, detecting coronary and left circumflex coronary artery disease and localizing abnormalities to the distribution of individual coronary arteries (177–179).

The number, size and location of perfusion abnormalities; amount of lung uptake of thallium-201 on post-stress images; and presence or absence of transient post-stress ischemic left ventricular dilatation can be used together to facilitate identification of important patient subsets, such as those with multivessel disease, left main coronary artery disease and disease of the proximal segment of the left anterior descending coronary artery. A most important objective is the detection of left main or multivessel coronary artery disease because patients with surgical intervention have improved survival compared those receiving medical therapy. Almost all patients with left main or multivessel coronary disease have abnormal thallium scan results (180–184). A left main pattern, characterized by reduced thallium uptake in the septum and anterior and lateral walls is uncommon; rather, ~60% of patients have multiple thallium defects, and almost 50% have abnormal lung uptake of thallium. Using planar thallium imaging, quantitative analysis of perfusion defects and thallium washout, consideration of lung uptake of thallium and other clinical and ECG indicators of high risk disease, ~86% of patients with left main coronary artery disease will have one or more of these high risk indicators (180). Within a specific coronary distribution, the size and severity of a perfusion defect is related generally to the site and severity of a coronary stenosis. Larger and more severe defects correlate with proximal and more severe stenoses (185–188).

Stress perfusion imaging may be performed to assess changes in the magnitude of ischemic myocardium. The presence and extent of altered perfusion may be similar regardless of the presence or absence of symptoms (131,132). There are no data documenting the value of serial testing in asymptomatic patients or patients with chronic stable angina. However, sequential testing, generally no more frequently than yearly, may be useful in some patients. Such studies are also frequently performed *after* angiography to better assess the functional significance of an anatomic stenosis (189,190). In patients with symptomatic angina, worsening of symptoms or a change in symptom character may provoke concern about disease progression. Stress perfusion scintigraphy, especially when compared with previous studies, can provide an objective basis for the change in symptoms and guide subsequent therapies.

Prediction of important cardiac events can be inferred from the results of stress myocardial perfusion imaging. The most consistent predictor of cardiac death or nonfatal myocardial infarction appears to be the number of transient perfusion defects, whether provoked by exercise or pharmacologic stress (191–198). The number of coronary vessels with angiographic disease may be less indicative of subsequent prognosis while providing important supplemental information (191,199). The size of the perfusion abnormality was the single most important prognosticator in a study establishing independent and incremental prognostic information from SPECT thallium-201 scintigraphy over that obtained from clinical, exercise treadmill and catheterization data (200). Three studies (174,175,201) have shown that increased lung uptake of thallium induced by exercise or pharmacologic stress is associated with an increased risk of cardiac events. Increased lung uptake is related to multivessel coronary artery disease and stress-induced elevation of left ventricular filling pressures and, as such, is an indirect index of jeopardized myocardium that reflects extensive myocardial infarction or ischemia, or both.

Normal post-stress thallium scan results are highly predictive of a benign prognosis, even in patients with known coronary disease (191–208). A collation of 16 studies involving 3,594 patients followed up for a mean of 29 months revealed that the rate per year of cardiac death or myocardial infarction was 0.9% (209), nearly as low as that of the general population (210).

Combined assessment of function and perfusion. A combination of perfusion and functional information during stress and at rest may be helpful in categorizing disease extent and severity (211–213). This combined information can be provided by performance of two separate exercise tests (e.g., stress perfusion scintigraphy and stress radionuclide angiography) or by combining the studies after a single exercise test (e.g., first-pass radionuclide angiography with technetium-99m–based agents followed by perfusion imaging). However, the incremental benefit of the added information provided by combined perfusion and ventricular function exercise testing has not been demonstrated in clinical outcome or prognostic studies, and in general a single measurement of rest left ventricular function and a measure of exercise/pharmacologic stress-induced perfusion or exercise ventricular function, but not both, are appropriate.

Radionuclide imaging before and after revascularization interventions. Myocardial perfusion imaging is a useful adjunct in the planning of revascularization procedures by virtue of its ability to demonstrate whether a given coronary stenosis is or is not associated with a stress-induced perfusion abnormality (214–216). Although less critical in coronary bypass graft surgery, where typically all suitable vessels with significant angiographic stenoses ($\geq$50%) are bypassed, perfusion imaging is particularly useful in determining the functional impact of single or multiple stenoses before percutaneous transluminal coronary angioplasty. This is especially important when coronary angioplasty is targeted to the "culprit lesion," that is, the ischemia-provoking stenosis. Similarly, because restenosis is a frequent problem after successful coronary angioplasty, stress SPECT perfusion imaging is particularly well suited for the functional evaluation of patients after coronary angioplasty and as a means of assessing the occurrence of restenosis. The ideal time for patients to undergo imaging after coronary angioplasty is controversial, but ~4 weeks after coronary angioplasty appears to be a good time to assess the functional results of angioplasty (217–220). Perfusion imaging in these patients may be performed in conjunction with exercise or pharmacologic vasodilation (221–223).
Exercise radionuclide angiography is also useful in selected patients for assessing the results of coronary angioplasty (224,225). Rest left ventricular ejection fraction does not usually improve after successful angioplasty but may improve in those patients with ventricular dysfunction caused by acute ischemia or more chronic hibernation. In the presence of widespread ischemia before angioplasty, exercise left ventricular ejection fraction would be expected to decrease and should improve after angioplasty. Regional wall motion at peak exercise would also be expected to improve after angioplasty and may be a more specific indicator of successful angioplasty than improvement in left ventricular ejection fraction.

When coronary angioplasty has been performed largely for symptom relief, follow-up testing is not generally recommended unless symptoms recur. In the absence of symptoms, the task force does not endorse routine testing, given the lack of data that outcomes are affected by this approach.

Myocardial perfusion scintigraphy can be useful in several situations after coronary bypass surgery. Patients with ST-T wave abnormalities at rest can be better evaluated for recurrent myocardial ischemia by scintigraphy than by ECG treadmill testing. In addition, ~30% of patients have an abnormal ECG response on treadmill testing (226) early after bypass surgery, and these patients can be assessed for possible incomplete revascularization and extent of myocardium affected. Patients with initial negative postoperative treadmill test results that later become positive usually have progressive ischemia due either to graft closure or progression of disease in the native circulation (227). Myocardial perfusion scintigraphy can be useful in determining the location, extent and severity of such ischemia.

With knowledge of anatomy before bypass surgery and the territories that have been bypassed, the scintigraphic data can help to determine whether the ischemia is most likely caused by pathologic results of bypass graft surgery, incomplete revascularization or new disease (228,229). However, in general radionuclide testing should be performed after bypass surgery only if symptoms recur, except as noted earlier. Tables 4 to 6 summarize radionuclide testing in chronic coronary artery disease.

Table 4. Uses of Radionuclide Testing in Diagnosis of Chronic Ischemic Heart Disease

Indication	Test	Class
1. Diagnosis of symptomatic and selected patients with asymptomatic myocardial ischemia	Exercise or pharmacologic myocardial perfusion imaging, including PET*	I
	Exercise RNA	IIa
2. Assessment of ventricular performance (rest or exercise)	RNA†	I
	Gated sestamibi imaging	IIb

3. Assessment of myocardial viability in patients with left ventricular dysfunction in planning revascularization	Rest-redistribution Tl-201 imaging	I
	Stress-redistribution-reinjection Tl-201 imaging	I
	PET imaging with F-18 flourodeoxyglucose	I
	Dobutamine RNA	IIb
	Postexercise RNA	IIb
	Post-NTG RNA	IIb
4. Planning PTCA--identifying lesions causing myocardial ischemia, if not otherwise known	Exercise or pharmacologic myocardial perfusion imaging	I
	Exercise RNA	IIa
5. Risk stratification before noncardiac surgery	Pharmacologic or exercise perfusion imaging	I
6. Screening of asymptomatic patients with low likelihood of disease	All tests	III

*The relative cost of positron emission computed tomography (PET), thallium (Tl)-201 or technetium (Tc)-99m agents and lesser availability of PET must be considered when selecting this technique. †Rest radionuclide angiography (RNA) can be accomplished by first-pass imaging of a technetium-based myocardial perfusion agent. F-18 = flourine-18; NTG = nitroglycerin; other abbreviations as in Table 1.

Table 5. Uses of Radionuclide Testing in Assessment of Severity/Prognosis/Risk Stratification of Chronic Ischemic Heart Disease

Indication	Test	Class
1. Assessment of LV performance	Rest or exercise RNA	I
	Gated or sestamibi perfusion imaging	IIb
2. Identification of extent and severity of ischemia and localization of ischemia	Exercise or pharmacologic myocardial perfusion imaging	I

Abbreviations as in Tables 1 and 2.

Table 6. Uses of Radionuclide Testing in Assessment of Interventions in Chronic Ischemic Heart Disease

Indication	Test	Class
1. Assessment of drug therapy		
a. Ventricular performance	Rest or exercise RNA	IIa
b. Myocardial perfusion	Exercise perfusion imaging	IIb
2. Assessment for restenosis after PTCA (symptomatic)	Exercise or pharmacologic perfusion imaging	I
	Exercise RNA	IIa
3. Assessment of ischemia in symptomatic patients after CABG	Exercise or pharmacologic perfusion imaging	I
	Exercise RNA	IIa
4. Assessment of selected asymptomatic patients after PTCA or CABG, such as patients with an abnormal ECG response to exercise or those with rest ECG changes precluding identification of ischemia during exercise	Exercise or pharmacologic perfusion imaging	I
	Exercise RNA	IIa
5. Routine assessment of asymptomatic patients after PTCA or CABG	All tests	III

CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Tables 1 and 3.

Myocarditis

Diagnosis. The diagnosis of myocarditis generally can be established on the basis of a careful history, physical examination and ECG and chest X-ray studies. Endomyocardial biopsy is useful in selected patients to confirm the diagnosis. The presence of myocardial inflammation can be assessed using radiotracers that are taken up by involved myocardium (Table 7). Both gallium-67 citrate (230) and Tc-99m pyrophosphate have been used for this purpose, but both false positive and false negative results are common. Pyrophosphate would be used to detect myocardial necrosis in this setting. More recently, indium-111–labeled antimyosin antibody imaging has been found to have a high specificity for making this diagnosis, although with a limited sensitivity (231); this agent remains investigational at the present time.

In patients with suspected myocarditis, radionuclide angiography often provides useful information by detecting left and right ventricular dysfunction. Although ventricular dysfunction in acute myocarditis is generally diffuse and results in generalized hypokinesia, isolated left or right ventricular dysfunction may exist, and regional wall motion abnormalities may occur. With thallium imaging, fixed focal defects are occasionally found in patients with active myocarditis, but there is usually homogenous distribution of thallium.

Table 7. Uses of Radionuclide Imaging in Myocarditis and Cardiomyopathies

Indication	Test	Class
1. Demonstration of myocardial inflammation and response to therapy	Gallium-67 imaging or Tc-99m pyrophosphate imaging	IIb
2. Determination of initial and serial LV and RV performance in myocarditis or dilated, hypertrophic and restrictive cardiomyopathy	Rest RNA	I
	Exercise RNA	III
3. Initial and serial evaluation of LV function in patients after recieving chemotherapy with doxorubicin	Rest RNA	I
	Exercise RNA	III
4. Differentiation of ischemic and dilated cardiomyopathy	Tl-201 imaging	IIa
	PET	IIb
5. Establishment of diagnosis of hypertrophic cardiomyopathy	RNA	IIb
	Rest Tl-201 imaging	IIb
6. Diagnosis of concomitant coronary artery disease in hypertrophic cardiomyopathy	Tl-201 or Tc-99m sestamibi imaging	III
7. Assessment of myocardial ischemia in hypertrophic cardiomyopathy	Tl-201 imaging	IIa
		IIb
8. Cardiac involvement in systemic diseases	RNA	IIb
	Myocardial imaging with Tc-99m pyrophosphate or gallium	
	Myocardial imaging with Tl-201	IIb

Abbreviations as in Tables 1, 2 and 4.

Assessment of disease severity/risk stratification/prognosis. Because the three prognostic factors—ventricular dysfunction, ventricular arrhythmias and exercise tolerance—are interrelated, severe ventricular dysfunction, as measured by radionuclide angiography, is a marker of patients with a poorer prognosis who may require a limited work and activity prescription.

Assessment of therapy. The utility of serial gallium or Tc-99m pyrophosphate scans in the management of patients with myocarditis has not been established; however, in some cases clinical improvement with immunosuppressive therapy has correlated with a resolution of gallium uptake by the myocardium. Indium-111 antimyosin antibody imaging might be useful for assessing the response of the left ventricle to immunosuppressive therapy, but this application requires further confirmation. Because the morbidity and mortality of myocarditis are largely related to the extent of ventricular dysfunction, radionuclide angiographic determinations of right and left ventricular size and performance are valuable for assessing the effects of management in such patients. Myocardial perfusion imaging is of little value in this regard. Radionuclide testing in myocarditis is summarized in Table 7.

Dilated Cardiomyopathies

Diagnosis. Determination of ventricular size and function using radionuclide angiography is a useful technique in establishing the diagnosis of dilated cardiomyopathy (232,233). Although global biventricular dysfunction is common, left ventricular dysfunction is usually more advanced. Thallium imaging most often reveals left ventricular dilation and homogenous or diffusely inhomogeneous uptake. Large defects (i.e., 40% of the circumference of the left ventricle) strongly favor left ventricular dysfunction due to ischemic heart disease, and a reversible defect usually indicates ischemia rather than scar. However, large, fixed (particularly apical) defects have been reported in patients with dilated cardiomyopathy. Metabolic imaging with positron emission tomography may be helpful in making this distinction (234).

Gallium-67 citrate and technetium-99m pyrophosphate imaging have been used to detect active myocarditis in patients with apparent dilated cardiomyopathy, but positive scans also occur in patients with various forms of infiltrative or degenerative heart disease. Greater specificity may be achieved using indium-111 antimyosin antibodies, but scans may be negative in patients with "myocarditis" on endomyocardial biopsy (see preceding section on myocarditis).

Risk stratification and prognosis. Determination of ventricular performance by radionuclide angiography provides an excellent means of assessing prognosis and activity guidelines in patients with dilated cardiomyopathy. Exercise radionuclide

angiography is of no proven value. Gallium-67 citrate, Tc-99m pyrophosphate and thallium imaging are of little value for risk stratification.

Assessment of therapy. Assessment of ventricular performance by radionuclide angiography is useful for guiding the management of patients with dilated cardiomyopathy. Radionuclide testing in cardiomyopathies is summarized in Table 7.

Doxorubicin Cardiotoxicity

Diagnosis. Chemotherapy with doxorubicin produces a dose-dependent impairment of left ventricular function because of toxic effects on cardiac myocytes. The dilated cardiomyopathy that results from doxorubicin usually produces severe, irreversible left ventricular dysfunction before the onset of symptoms of congestive heart failure. Ventricular dysfunction is progressive if doxorubicin therapy is continued after objective evidence of reduced systolic function (235). Radionuclide angiography is ideally suited as a noninvasive tool to provide quantitative measures of left ventricular dysfunction in patients who have received or are continuing to receive doxorubicin therapy (235–237).

Risk stratification and prognosis. Left ventricular dysfunction, as measured by reduced ejection fraction and serial reduction in ejection fraction, is an important determinant of prognosis in patients who have received or are currently receiving doxorubicin. In addition, patients with left ventricular dysfunction from preexisting cardiac conditions are at greater risk of congestive heart failure if doxorubicin therapy is to be initiated. In such patients, measurement of ejection fraction before beginning doxorubicin treatment is valuable and may determine whether doxorubicin should be administered or whether alternative chemotherapeutic strategies should be entertained.

Assessment of therapy. Serial evaluation of left ventricular ejection fraction at rest by radionuclide angiography has been shown to be an effective means of following up patients during the course of doxorubicin therapy. Data from several studies indicate that it is safe to continue doxorubicin therapy if rest ejection fraction remains above the lower limit of normal, even if serial studies indicate a consistent decline in ejection fraction compared with baseline values. If doxorubicin therapy is discontinued when ejection fraction becomes subnormal, ventricular function usually stabilizes at that point without the development of clinically overt heart failure in the future (235–237). In contrast, further doxorubicin administration once rest ejection fraction decreases below normal runs the risk of precipitous impairment in ventricular function associated with serious, life-threatening heart failure (235). Serial evaluation of exercise ejection fraction does not appear to be helpful in determining when to discontinue doxorubicin therapy (236).

In addition to the slow, indolent reduction in ventricular performance that is measurable during serial administration of doxorubicin, doxorubicin also commonly produces immediate deterioration in ventricular function with a single administration that is rapidly reversible over the course of several days. Because of the possibility of such immediate changes in ventricular function, radionuclide angiographic studies to follow the long-term progression of cardiotoxicity should be timed at least 10 to 14 days after the last dose of doxorubicin. The use of radionuclide testing during doxorubicin therapy is summarized in Table 7.

Hypertrophic Cardiomyopathy

Diagnosis. The diagnosis of hypertrophic cardiomyopathy can generally be established on the basis of the clinical examination and ECG and echocardiographic studies. Radionuclide studies are usually not indicated but may be of value in selected patients. Radionuclide angiography frequently demonstrates hyperdynamic left ventricular systolic function and disproportionate upper septal thickening in patients with hypertrophic cardiomyopathy (238,239). In addition, impaired left ventricular diastolic filling can be detected in the majority of patients (239).

Asymmetric septal hypertrophy may also be detected by thallium imaging by comparing septal thickness with that of the posterior left ventricular free wall (240). Typically, thallium images demonstrate a small left ventricular cavity with marked thallium uptake by the hypertrophied myocardium. The detection of concomitant coronary artery disease by thallium imaging is not possible in the presence of hypertrophic cardiomyopathy because reversible, exercise-induced thallium defects occur commonly in patients with hypertrophic cardiomyopathy in the absence of epicardial coronary artery stenoses (241).

Risk stratification/prognosis. There are no definitive data to recommend radionuclide imaging techniques for risk stratification. However, the demonstration of depressed left ventricular systolic function identifies a patient subgroup with a relatively poor prognosis. In addition, recent data (242) suggest that young patients with hypertrophic cardiomyopathy who have reversible perfusion defects on exercise thallium imaging may also be at high risk.

Assessment of therapy. The demonstration of normal or supranormal left ventricular systolic function despite symptoms of congestive heart failure is useful in determining that therapy with beta-blockers or calcium channel blockers is appropriate. Serial assessment of left ventricular function or myocardial perfusion may be helpful in selected patients who develop progressive symptoms during the course of
medical therapy by identifying those patients who have developed myocardial scarring and depressed left ventricular systolic function in the course of the natural history of their disease. Such patients usually manifest irreversible thallium defects (241). Thallium imaging may also be useful in assessing the effects of therapy in reducing myocardial ischemia (243), although there are limited data supporting this approach. Radionuclide testing in hypertrophic cardiomyopathy is summarized in Table 7.

Restrictive Cardiomyopathies

Diagnosis. A variety of diagnostic procedures, including cardiac catheterization, are usually necessary to establish the diagnosis. Characteristically, radionuclide angiography demonstrates normal or decreased left ventricular end-diastolic volume, normal or mildly depressed left ventricular ejection fraction and dilated atria. Myocardial uptake of Tc-99m pyrophosphate or gallium, or both, is common but can be due to various conditions, including amyloidosis, sarcoidosis, progressive systemic sclerosis and cardiac tumors. Fixed defects in myocardial thallium-201 images often occur in patients with sarcoidosis, progressive systemic sclerosis or cardiac tumors (244,245).

Risk stratification/prognosis. There are no current data to support the use of radionuclide imaging techniques for this purpose.

Assessment of therapy. Under special circumstances, serial measurements of ventricular performance by radionuclide angiography may be useful to follow the course of patients with those disorders and to document the effects of specific therapy (i.e., therapy for hemochromatosis). The uses of radionuclide testing in myocarditis and cardiomyopathies are summarized in Table 7.

Congenital Heart Disease in the Adult

Diagnosis. Echocardiography, properly applied, is the imaging method of choice for evaluating patients with known or suspected congenital heart disease because this modality is useful in identifying structural abnormalities and intracardiac shunting. However, in selected patients there are potentially important applications of nuclear cardiology techniques (Table 8).

In left-to-right shunting, first-pass radionuclide angiography demonstrates persistent high levels of activity in the lungs or right ventricle, or both, as a result of early recirculation (246). Resultant time–activity curves derived from different chambers can be used to distinguish an intracardiac from an extracardiac (patent ductus arteriosus) shunt. Right-to-left shunts can be detected from inspection of the tracer bolus as it traverses the heart, with early visualization of either the left heart chambers or the aorta. Left-to-right shunts can be quantitated using the pulmonary/systemic flow ratio from the time–activity curve over the right lung. Quantitation also appears possible using C-15 oxygen inhalation with positron emission tomography.

Radionuclide angiography provides useful information about the influence of the shunt on left and right ventricular performance. Lung perfusion scanning using intravenous injection of macroaggregates of albumin may be used for identifying right-to-left shunting. Appearance of technetium activity in brain and splanchnic viscera suggests right-to-left shunting. Rest and exercise thallium-201 imaging can define abnormal perfusion patterns in patients with anomalous coronary arteries or other types of congenital heart disease in which coronary blood flow may be regionally diminished.

Risk stratification/prognosis. The usefulness of radionuclide imaging, including rest and exercise studies, for decision making related to limitation of activity and work status remains to be defined.

Assessment of therapy. Serial assessment of shunt flow by first-pass radionuclide angiography may reveal spontaneous closure, successful surgical closure or residual left-to-right shunting. Relative lung perfusion also can be quantitated by measurement of count data over the right and left lung fields. Patency of palliative shunts can be demonstrated by careful assessment of pulmonary dilution curves or by
pulmonary perfusion imaging. Evaluation of left and right ventricular ejection fractions by radionuclide angiography may be useful in determining the optimal time for surgical correction in patients with left or right ventricular pressure or volume overload states and in relating any postoperative symptoms to residual ventricular dysfunction. The uses of radionuclide testing in congenital heart disease are summarized in Table 8.

Table 8. Uses of Radionuclide Imaging in Congenital Heart Disease In Adults

Indication	Test	Class
1. Detection and localization of shunts	First-pass RNA for left-to-right shunts	IIa
	Lung perfusion scanning for right-to-left shunts	IIb
2. Quantitation of left-to-right shunting	First-pass RNA	IIa
	Carbon-15 oxygen inhalation	IIb
3. Initial and serial assessment of ventricular function	RNA	I
4. Diagnosis of anomalies of coronary circulation	Exercise myocardial perfusion imaging	IIa

Abbreviations as in Table 1.

Hypertensive Heart Disease

Diagnosis. Radionuclide angiography at rest is useful for the accurate assessment of left ventricular systolic function in patients with hypertension (class I). Assessment of left ventricular peak diastolic filling rates by radionuclide angiography (247,248) may identify impaired diastolic function when systolic function is normal (class IIa).

Exercise radionuclide angiography is unreliable in identifying patients with coexistent coronary artery disease because an abnormal ejection fraction response to exercise occurs commonly in patients with hypertension (249). However, the abnormal exercise response occurs chiefly in patients with left ventricular hypertrophy (248,250); most patients without hypertrophy manifest normal ventricular function with exercise.

In patients without left ventricular hypertrophy, stress myocardial perfusion imaging can be useful for detecting reversible defects among those who have coexistent ischemic heart disease (class I). Perfusion imaging appears to be more reliable than radionuclide angiography in identifying coexistent coronary artery disease in patients with left ventricular hypertrophy.

Risk stratification/prognosis. Determination of left ventricular performance by radionuclide angiography may influence decisions concerning work status and extent of activity (class IIb).

Assessment of therapy. Radionuclide angiography is useful for evaluating the effect of blood pressure reduction and other medical therapy on left ventricular systolic function in patients with hypertension who have left ventricular dysfunction (class I).

Posttransplant Cardiac Disease

The major clinical problems of heart transplant recipients that can be evaluated with radionuclide testing relate to early postoperative left and right ventricular performance, rejection and coronary arteriopathy. Ventricular dysfunction in the perioperative period and allograft rejection account for most deaths (251). Coronary arteriopathy is a major cause of morbidity and mortality in the late phase after heart transplantation (252).

Anatomic differences of the transplanted heart are important with respect to both radionuclide angiography and perfusion imaging. The donor heart manifests increased cardiac mobility, paradoxic septal motion and leftward rotation with posterior displacement of the apex. As a result, the optimal left anterior oblique acquisition position is >50 ◦ in >60% of patients (253). The quality of planar thallium-201 images can be affected by this rotation such that the ventricular cavity may appear small or nonexistent. Thus, SPECT imaging may offer advantages over planar acquisition of both radionuclide angiography and perfusion scintigraphy by minimizing the effects of abnormal rotation and attenuation from overlapping structures.

Diagnosis and monitoring of transplant rejection. *Radionuclide angiography.* Abnormal left or right ventricular function, or both, during the first few days after transplantation is most likely not due to rejection, but beyond the first week depressed left ventricular function in the absence of another clinical etiology will most likely be secondary to rejection. Mild episodes are accompanied by myocardial inflammation that resolves with treatment, whereas more severe episodes result in myocardial necrosis. Although definitive diagnosis depends on myocardial biopsy results, several radionuclide techniques may be helpful for detecting and tracking rejection. Radionuclide angiocardiography has been the most studied technique. Although some patients with rejection may have marked left ventricular dysfunction, the majority with mild rejection and some with moderate or severe rejection have normal left ventricular function (253). Serial evaluation may be necessary for detecting rejection because the changes are often subtle: One study (254) showed that left ventricular ejection fraction decreased from 63% to 57% in patients whose biopsy results changed from no to moderate rejection and from 63% to 59% in those whose biopsy findings changed from no to mild rejection (254). Ejection fraction improved in successfully treated patients whose biopsy findings showed histologic resolution.

Reproducibility of radionuclide angiographic measurements may be enhanced by denervation and hence more regular heart rates. To detect the small changes that may occur during rejection, meticulous attention to technique is essential, including precise reproduction of the same acquisition angles from study to study. With severe rejection and reduced left ventricular ejection fraction, sequential radionuclide angiography can be helpful in monitoring therapy.

Other radionuclide imaging techniques for diagnosis and management of rejection. Indium-111 labeled lymphocyte imaging has been shown in animal models to detect rejection before overt myocardial necrosis occurs. However, in humans the degree of lymphocyte infiltration is variable and may not be severe in cyclosporine-treated patients despite significant rejection (255). Furthermore, uptake of labeled lymphocytes is not specific for rejection and also occurs with toxoplasmosis and cytomegalovirus myocarditis.

Antimyosin antibody uptake correlated with biopsy findings of rejection in 80% of scans in one study (256). The intensity of its uptake correlates with histopathologic rejection score. A persistent increased heart/lung ratio during the first year after transplantation is associated with rejection-related complications, and a decreasing ratio correlates with a favorable clinical outcome. Beyond the first year after transplantation, elevated heart/lung ratios of antimyosin correlate with a higher number of rejection episodes and a greater probability of developing rejection (255,257–259). Antimyosin antibody remains investigational at the present time. Gallium-67 imaging is useful for detecting acute and chronic inflammatory lesions in the body, but its preliminary application in transplant rejection has been disappointing (260).

Radionuclide techniques in diagnosis and management of allograft vasculopathy. Posttransplant arteriopathy is a unique, diffuse process preferentially involving the mid and distal coronary vessels and causing branch vessel pruning and occlusions. Because the heart is denervated, chest pain does not occur, and presentation with sudden cardiac death, myocardial infarction, congestive heart failure and arrhythmias is more likely. Detection of disease is important because percutaneous transluminal coronary angioplasty, coronary bypass and retransplantation are therapeutic options for some patients found to have transplant coronary arteriopathy.

There is insufficient information to evaluate perfusion imaging for the routine assessment of transplant recipients. The available data (261,262), in small numbers of patients, suggest that planar and SPECT thallium-201 after oral dipyridamole are poorly sensitive and specific for coronary artery disease. A more recent study (263) using exercise stress and SPECT thallium-201 or sestamibi reported a sensitivity of 77% and specificity of 100%. There are no specific data about the usefulness of radionuclide techniques in prognosis, rehabilitation and risk stratification or after intervention in transplant recipients. Table 9 summarizes the uses of radionuclide testing in transplant recipients.

Table 9. Uses of Radionuclide Testing After Cardiac Transplantation

Indication	Test	Class
1. Assessment of ventricular performance	RNA	I
2. Detection and monitoring of rejection	RNA	IIb
3. Assessment of coronary arteriopathy		
a. Detection	Exercise or pharmacologic myocardial perfusion imaging	IIb
b. Assessment of severity	Exercise or pharmacologic myocardial perfusion imaging	IIb

Abbreviations as in Table 1.

Valvular Heart Disease

Diagnosis. The major use of radionuclide angiography in regurgitant lesions is to reliably and serially evaluate left and right ventricular ejection fraction. Also, left and right ventricular volume can be estimated by radioactive count-based methods using equilibrium techniques (264,265). Ventricular enlargement suggests that regurgitation is at least moderate in severity. In addition, larger end-systolic and end-diastolic volumes imply a worse prognosis (266). Radionuclide imaging is not useful in diagnosing aortic valve regurgitation secondary to aortic dissection.

Both first-pass and equilibrium radionuclide angiography have been used to assess the severity of aortic or mitral regurgitation, or both. The difference in stroke counts between the right and left ventricles provides an index of the extent of volume overload in the absence of tricuspid regurgitation. The regurgitation fraction in a patient with left ventricular volume overload can be approximated using the stroke counts of the left ventricle minus the stroke counts of the right ventricle divided by the stroke count of the left ventricle (267,268). Difficulty in separating the counts from enlarged ventricles and atria and the frequent occurrence of multivalvular regurgitation limit the accuracy of this method.

Assessment of disease severity/risk stratification/prognosis. Myocardial perfusion imaging provides little information concerning risk stratification of valvular heart disease. Radionuclide angiographic assessment of right and left ventricular ejection fractions and volumes is useful in making decisions concerning prognosis, posttreatment rehabilitation and work status, whereas the value of radionuclide angiography with exercise continues to be investigated.

Assessment of interventions. Decisions about the timing of valve repair or replacement for aortic or mitral regurgitation or aortic stenosis are often based on assessing the effect of the valve lesion or lesions on ventricular performance at rest. Thus, radionuclide angiography is very useful for determining ventricular ejection fractions in the initial and serial evaluation of symptomatic and asymptomatic patients with severe valvular stenosis or regurgitation, or both, and in assessing the effects of valve replacement or repair on left ventricular function (269–273). In addition, assessment of right ventricular function is clinically useful in patients with chronic mitral regurgitation (270). The significance of a reduction, rather than an increase, in left ventricular ejection fraction during exercise in patients with aortic or mitral regurgitation remains controversial (272,273).

There are few indications for thallium imaging in patients with valvular heart disease, although it is sometimes used to diagnose and assess concomitant coronary artery disease. Exercise perfusion imaging in patients with valvular heart disease may be helpful in certain situations. Negative results in patients with mitral valve prolapse or in those with other forms of valvular heart disease generally indicate the absence of coronary disease. However, specificity is reduced in patients with mitral valve prolapse or left ventricular hypertrophy. In patients who are candidates for valvular surgery, coronary arteriography remains the most appropriate method for the definitive diagnosis of concomitant coronary artery disease. In patients with known coronary artery disease, especially those with lesions of borderline significance (50% to 70% diameter stenosis), stress perfusion imaging may be useful in evaluating the significance of symptoms and in planning medical or surgical therapy. In patients who have been treated surgically for valvular heart disease and who have undergone concomitant coronary artery bypass graft surgery, myocardial perfusion imaging can be performed to assess postoperative ischemia, as described previously in the section on evaluation of bypass surgery. Exercise radionuclide angiography is also of little value in detecting coronary disease in patients with valve disease because of the nonspecific nature of regional wall motion abnormalities at rest or during exercise. Rest radionuclide angiography is of some value in assessing the results of medical therapy on the severity of aortic or mitral regurgitation (274). Also, the changes in left and right ventricular ejection fractions and volume after valve repair or replacement can be evaluated accurately by radionuclide angiography.

Risk stratification for rehabilitation, occupation and prognosis. Myocardial perfusion imaging provides little information concerning risk stratification of valvular heart disease. Radionuclide angiographic assessment of right and left ventricular ejection fractions and volumes is useful in making decisions concerning prognosis, posttreatment rehabilitation and work status, whereas the value of radionuclide angiography with exercise continues to be investigated. Table 10 summarizes the uses of radionuclide testing in patients with valvular heart disease.

Table 10. Uses of Radionuclide Testing in Valvular Heart Disease

Indication	Test	Class
1. Initial and serial assessment of LV and RV volume and ejection fraction	Rest RNA	I

2. Quantitation of aortic or mitral regurgitation	Rest RNA	IIb
	Exercise RNA	III
3. Detection and assessment of functional significance of concomitant coronary artery disease	Stress myocardial perfusion imaging	IIa
	Exercise RNA	IIb
4. Detection of aortic dissection and its complications	RNA	III

Abbreviations as in Tables 1 and 2.

Appendix

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