Impact of Radionuclide Techniques on Evaluation of Patients With Ischemic Heart Disease

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Radiotracer studies of the heart have become clinically important in the last decade, especially for evaluation of patients with known or suspected ischemic heart disease. Radionuclide ventriculography provides quantitative measures of biventricular function and regional wall motion. Recent technical advances include the development of computer programs for analyzing diastolic function, parametric imaging methods such as “phase” analysis and methods for calculating absolute ventricular volumes.

Thallium-201 scans provide maps of regional myocardial perfusion. Recent advances include development of computer programs to quantitate regional thallium-201 uptake and to calculate thallium-201 turnover rates and the development of tomographic imaging systems.

Although radioisotopes were first introduced by Blumgart and Weiss (1) in 1927 to study circulation time, their wide application to clinical practice and clinical decision making has occurred only during the past decade. The techniques of myocardial imaging with thallium-201, infarct-avid imaging with technetium-99m pyrophosphate and radionuclide ventriculography with technetium-99m human serum albumin, red blood cells and, most recently, with short-acting radionuclides such as gold-195m are now well known and have been summarized in detail in previous reports (2,3). Rapid progress in radiopharmaceutical development and instrumentation continues. Techniques for single photon emission tomography are finding wide clinical application. Positron emission tomography, although still confined to clinical investigation, shows promise of providing new insight into the metabolism of the human myocardium. New radiopharmaceutical agents for single photon imaging are also being studied to provide insight into the metabolism of the heart and to study other variables such as adrenergic function (4).

In this article we will review some of the progress that has been made over the past decade in applying radioactive tracer techniques to the evaluation of patients with ischemic heart disease. We will concentrate on their use in patients with suspected rather than known ischemic disease, because this use is controversial and because it best illustrates the progress and current limitations of radionuclide techniques in the clinical evaluation of patients with ischemic heart disease. Progress has been and continues to be so rapid that we will not attempt to be comprehensive. The role of radioactive tracer techniques in the evaluation of patients with ischemic heart disease is undergoing constant investigation and must be viewed in the context of the rapid evolution and progress of other noninvasive techniques (Table 1), some of which have yet to be fully evaluated.

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Evaluation of the Patient With Suspected Ischemic Heart Disease

Despite the experience with radionuclide techniques and the proliferation of other noninvasive techniques, the evaluation of patients with suspected ischemic heart disease remains difficult. The clinician is increasingly asked to evaluate asymptomatic persons who have a risk factor associated with ischemic heart disease: executives and others undergoing routine stress testing as part of an “executive evaluation,” self-referred patients planning to start jogging or an exercise program, patients experiencing vague symptoms of dyspnea and fatigue as well as patients presenting with atypical or typical angina before diagnostic coronary angiography.

Sensitivity and Specificity

The sensitivity and specificity of thallium-201 myocardial imaging and radionuclide ventriculography for the detection of ischemic heart disease have been examined in many centers around the world. The sensitivity of exercise planar thallium-201 myocardial imaging is approximately 85% when visual interpretation is used (5, 6) and 90 to 95% when quantitative computer techniques (7) or tomographic imaging (8) is used. The sensitivity of radionuclide ventriculography is also in the range of 85 to 95% (6, 9). Both techniques appear to be more sensitive than exercise electrocardiography when large numbers of patients are included, many of whom may have baseline electrocardiographic abnormalities due to cardiovascular drugs, left ventricular hypertrophy or the presence of intraventricular conduction abnormalities.

The specificity of exercise thallium-201 myocardial imaging is also considerably better than that of exercise electrocardiography (approximately 85 to 90% versus 70 to 85% (6). However, the specificity for exercise radionuclide ventriculography may be considerably lower than that for exercise electrocardiography depending on the population studied (9–11).

Limitations. In relation to exercise electrocardiography, both exercise thallium-201 myocardial imaging and exercise radionuclide ventriculography have significantly greater sensitivity and exercise thallium imaging has greater specificity in detecting ischemic heart disease. Nevertheless, after a period of initial enthusiasm, these techniques are being critically reevaluated (12–14) and their use in detecting patients with suspected ischemic heart disease is diminishing in many centers. It has been argued that, although these techniques have advantages over exercise electrocardiography in detecting ischemic heart disease, they are not completely adequate, and it is more cost effective to proceed directly to invasive coronary angiography if there is any reason to suspect ischemic heart disease.

Bayes’ theorem has been used to show that the diagnostic value of these techniques will depend on the prevalence of disease in the population to be evaluated (12). Thus, in an asymptomatic group of 1,000 middle-aged executives with a disease prevalence rate of approximately 5% (that is, 950 without and 50 with coronary artery disease), a test such as exercise thallium-201 myocardial imaging with sensitivity and specificity values of approximately 90% would detect 45 of the 50 persons with significant arteriographic disease. Because the test has a 90% specificity, 95 of the 950 persons without significant disease would be diagnosed as having a positive exercise thallium image and, hence, disease. Thus, of 140 positive exercise thallium images, roughly two-thirds would be falsely positive. The post-test likelihood of ischemic heart disease in the subset with a positive thallium image would therefore be altered relatively little. Similarly, among 1,000 patients referred with a history of typical exertional angina pectoris a 90% prevalence rate of coronary artery disease can be anticipated (900 with and 100 without significant arteriographic disease). In this group, exercise thallium myocardial imaging would detect 810 of those with disease. Ten of those without disease also would be expected to have a positive image because of the imperfect sensitivity value of 90%. Thus of the 100 negative images in the population, 90 would be falsely negative. Again, the post-test likelihood of detecting significant disease in this population would be altered relatively little by the additional noninvasive test. Only in groups with an intermediate prevalence rate of disease, such as patients with atypical chest pain with an expected disease prevalence rate of 50%, would the post-test prediction of coronary artery disease be appreciably altered by the performance of exercise thallium-201 myocardial imaging or radionuclide ventriculography.

Although the reasoning inherent in the Bayesian approach is valid and the skepticism concerning the use of radioactive tracer techniques to evaluate patients with suspected ischemic heart disease is justified, additional information must be considered before assessing the role of these techniques for this indication. The imperfect sensitivity and specificity

Table 1. Noninvasive Techniques for the Evaluation of Patients With Ischemic Heart Disease

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<th>Technique</th>
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<td>Systolic time intervals</td>
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<td>Rest-stress digital radiography</td>
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<td>Rest-stress echocardiography</td>
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<td>Rest-stress thallium-201 myocardic imaging</td>
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<td>Rest-stress radionuclide ventriculography</td>
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<td>Infarct-avid imaging—technetium-99m pyrophosphate</td>
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<td>Single photon emission tomography</td>
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<td>Positron emission tomography (PET scan)</td>
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<td>Computed axial tomography (CAT scan)</td>
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<td>Nuclear magnetic resonance myocardal imaging (NMR)</td>
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of thallium-201 myocardial imaging and radionuclide ventriculography, and hence their limited applicability to evaluating groups with a low or high prevalence rate of disease, are due to several factors. These include inherent limitations in instrumentation, radiopharmaceutical agents and biologic factors, and the fact that these techniques are tests of function rather than anatomy. As tests of function, these techniques can never achieve 100% sensitivity or 100% specificity for the detection of anatomic coronary artery disease. The functional significance of a given lesion depends both on the degree and extent of coronary artery narrowing and on the degree of collateral flow, factors that are only partially assessed with the coronary angiogram.

**Role of Coronary Angiography**

The coronary angiogram long used as the standard for detecting coronary artery disease, is itself imperfect. Its limitations in determining the extent of disease and the degree of collateral supply are well recognized. The coronary arteriogram is also limited in evaluating the degree of coronary artery narrowing. In most series in which the sensitivity and specificity of thallium-201 myocardial imaging or radionuclide ventriculography have been determined, arteriographic narrowings of 50 to 70% have been considered "significant." However, a vessel may be diffusely narrowed so that flow reserve is compromised without a focal lesion of 50 to 70%. There is also considerable inter- and intraobserver variation in the assessment of the degree of coronary artery narrowing even among experienced angiographers (15). Thus, a positive exercise thallium-201 myocardial imaging test result in a patient classified as having a 30% arteriographic lesion might be considered a false positive result. Because of observer variability, it is possible that another angiographer would classify this lesion as a 50% or greater narrowing and the thallium-201 image as a true positive result.

**Functional significance of coronary artery narrowing.** The discrepancy between the anatomic presence or absence of "significant" coronary artery narrowing and its functional significance can be seen in recent studies by Marcus et al. (16) in which a newly developed Doppler catheter flow transducer was used to measure coronary artery flow reserve in patients sent to the operating room for coronary artery bypass graft surgery. Coronary artery flow was measured under control conditions and during peak reactive hyperemia after a transient coronary artery occlusion. Peak reactive hyperemic flow was considered an index of maximal coronary artery flow reserve. In angiographically normal vessels, Marcus and co-workers found a four- to sixfold increase in flow during peak reactive hyperemia. Patients with severe coronary artery narrowing (>90%) had a reduced flow reserve, suggesting that these lesions are hemodynamically significant. In patients with lesions considered "significant" in most studies (70% but <90%), flow reserve was frequently reduced but occasionally normal. Patients with angiographically "insignificant" lesions (<50% narrowing) often had a pronounced reduction in flow reserve, suggesting functional impairment of flow delivery. These studies point to the hazard of using angiographically determined percent narrowing as the standard for judging the utility of a noninvasive technique. Further limitations in defining the presence or absence of ischemic heart disease by the extent of angiographically determined percent of coronary artery narrowing can be seen from the recent study of Opherk et al. (17). Their patients with typical angina pectoris but normal coronary arteriograms were found to have myocardial ischemia evidenced by a reduction in coronary flow reserve after administration of dipyridamole. Positive findings on thallium-201 imaging or radionuclide ventriculography in such patients might be interpreted as false positive if the flow reserve data are unavailable.

**Exercise radionuclide ventriculography in patients with normal coronary arteriogram.** Another example of the limitation of currently available information on the specificity of radioactive tracer techniques can be found in recent studies in which the results of exercise radionuclide ventriculography were compared in a group of volunteers with less than 1% likelihood of coronary artery disease and a group of patients referred for angiography because of chest pain but subsequently found to have normal coronary arteries (18). The patients had a relatively large incidence of regional myocardial wall motion abnormalities during exercise compared with the volunteers. The cause of the myocardial function abnormalities in patients with atypical chest pain and normal coronary arteries is not yet certain. The abnormalities of wall motion during exercise detected in such patients may be due in part to the functional significance of angiographically insignificant lesions, inadequate flow reserve despite normal coronary arteries, focal scarring from early cardiomyopathy, or undefined mechanisms of ischemia or regional dysfunction.

**New techniques to quantitate and assess functional significance of coronary narrowings.** The difficulties in determining the degree of coronary artery narrowing and the functional significance of a given coronary artery lesion at coronary angiography are being resolved by the application of new computer and digital radiographic techniques. Several groups including our own have developed semiautomatic computer techniques to quantitate the degree of coronary artery narrowing (19–21). Data obtained with these techniques have correlated with postmortem data on coronary narrowing. It is evident from our own and previous studies that absolute coronary artery diameter is a better predictor of the functional significance of a coronary lesion than is percent narrowing. These new quantitative techniques have a low inter- and intraobserver variability and,
hence, should increase the reliability of assessing the severity of coronary artery narrowing. However, even the most precise quantitative technique for measuring the degree of such narrowing will not definitively clarify whether a given lesion is functionally significant. As discussed previously, the functional significance of a lesion depends not only on the degree of coronary narrowing, but also on its extent, the effect of multiple occlusions in series, residual vasomotor tone and collateral function. In one approach to assessing the functional significance of a given anatomic lesion, digital radiographic techniques are used to determine the coronary flow reserve during contrast medium-induced hyperemia (22). Although still in the early stages of development, this technique and others currently being developed may allow us to determine during routine angiography the functional significance of a coronary lesion as well as the presence and degree of anatomic narrowing.

**Role of coronary spasm.** Another cause of discrepancy between the presence or absence of anatomic coronary artery narrowing and functionally significant ischemic heart disease that may not be appreciated by angiography could be coronary artery spasm. It is well recognized that myocardial ischemia and occasionally infarction can occur in patients with angiographically normal coronary arteries. Exercise-induced coronary artery spasm is increasingly recognized (23,24). Positive findings on exercise thallium-201 myocardial imaging or radionuclide ventriculography in a patient with exercise-induced coronary artery spasm but angiographically normal coronary arteries could be interpreted as a false positive result if provocative testing with an agent such as ergonovine was not performed. Coronary spasm has been detected by both thallium-201 myocardial imaging and radionuclide ventriculography during spontaneous and ergonovine-provoked episodes. Although we have found thallium-201 myocardial imaging during ergonovine provocation useful in detecting coronary artery spasm in selected patients with angiographically normal coronary arteries in whom prior ergonovine testing was not carried out, the risk of this procedure suggests caution if it is performed outside of the catheterization laboratory.

**Myocardial disease in absence of coronary artery disease.** Patients with left ventricular hypertrophy due to valvular heart disease, such as aortic stenosis, idiopathic hypertrophic cardiomyopathy or hypertension may also manifest a discrepancy between the presence or absence of anatomic coronary artery narrowing and myocardial ischemia. In patients with aortic stenosis, exercise thallium-201 myocardial images may occasionally show focal defects in thallium uptake although the coronary arteries are angiographically normal (25). Small focal areas of myocardial scarring and occasionally gross areas of infarction may be found in patients with ventricular hypertrophy and normal coronary arteries. The myocardial scarring in such patients may be due to inadequate flow reserve and oxygen transport. Thus, although the thallium image may indicate ischemia, it does not necessarily indicate the presence of obstructive coronary artery disease in this situation.

In light of these considerations, it is likely that the specificity of thallium-201 myocardial imaging for the detection of ischemia is greater than currently reported. Nevertheless, positive thallium images may be obtained in patients without any evidence or cause for myocardial ischemia, abnormality of flow reserve or membrane dysfunction. These false positive images are partly due to technical errors in acquisition or interpretation, or both, as well as to biologic factors such as relative myocardial wall thinning. It is also likely that the specificity of radionuclide ventriculography for the detection of ischemic heart disease may be lower than currently appreciated. In exercise thallium-201 myocardial imaging, a positive image (one showing a defect in tracer uptake) is likely to be due to inadequate delivery of tracer or inadequate transport of the tracer across the cell membranes, both of which are usually related to myocardial ischemia. In contrast, a positive radionuclide ventriculogram (one showing an inadequate increase in left ventricular ejection fraction or development of a wall motion abnormality) may be due to a variety of causes not associated with myocardial ischemia.

**Any pathologic condition, such as previous scarring from myocarditis (26), granuloma formation (27) or cardiomyopathy (28), may cause an abnormality of cardiac function at rest and during stress.** Thus, if 1,000 middle-aged Brazilian patients, many of whom may have Chagas’ disease, were screened with these techniques, the specificity for ischemic heart disease might be relatively low but the specificity for heart disease would be high. In evaluating a patient with vague precordial chest discomfort, dyspnea on exertion, fatigue or an abnormality on a rest electrocardiogram, an abnormal exercise radionuclide ventriculogram would indicate the presence of some functional impairment due to a cardiac disorder rather than a nonspecific or noncardiac disorder. In many instances the etiology of the functional impairment will be evident from the history, physical examination or other noninvasive data. If these techniques are to be used to screen patients with atypical chest discomfort, dyspnea, palpitation or fatigue, it may be important that they be both highly sensitive and highly specific for heart disease of any origin. Additional noninvasive and invasive tests may be required to determine the specific cause of the heart disease.

**Current Status of Imaging Techniques**

**Exercise thallium-201 imaging.** The sensitivity of both thallium-201 myocardial imaging and radionuclide ventriculography for detecting ischemic heart disease and myocardial disease of any origin has improved considerably since these techniques were first introduced (5,10,29). The sensitivity of exercise thallium imaging has been improved with the addition of quantitative computer analysis and tom-
ographic imaging techniques (7,8). Sensitivities of 90 to 95% have been achieved by computer determination of the rate of thallium-201 loss and redistribution over time using both planar and tomographic imaging techniques. In patients unable to exercise, functionally significant coronary artery lesions may be detected by thallium-201 imaging after maximal effect of a vasodilator (30–32). Despite careful attention to detail and computer analysis, it is unlikely that with current instrumentation thallium imaging will achieve a sensitivity greater than 95%. However, new tomographic scintillation cameras currently being developed and evaluated have helped improve resolution (33). Equally important is the development of new technetium-99m-labeled radiopharmaceutical agents that have a rate of uptake by the myocardium proportional to blood flow (34). These agents are currently undergoing preclinical evaluation. Should these agents prove to be as efficacious in patients as they have in preliminary studies with animals, it is likely that with the new scintillation cameras currently under development, a sensitivity greater than 95% may be achieved. Small branch lesions not detected with current thallium imaging techniques (35) should be readily visualized by the combined use of these new radiopharmaceutical agents and instrumentation.

Radionuclide ventriculography. The most progress in improving the sensitivity for detection of patients with ischemic heart disease and myocardial disease of any origin with currently available radiopharmaceutical agents and instrumentation has been accomplished with radionuclide ventriculography. In addition to the determination of left ventricular ejection fraction and regional myocardial wall motion at rest and during exercise, several other variables of ventricular function (Table 2) and tests of ventricular function (Table 3) have been developed and applied to the detection of patients with suspected ischemic heart disease.

Left ventricular ejection fraction. Since the introduc-

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<tr>
<th>Table 2. Radionuclide Ventriculography—Indexes of Ventricular Function</th>
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<tr>
<td>1. Left and right ventricular ejection fraction</td>
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<tr>
<td>2. Regional myocardial wall motion</td>
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<tr>
<td>3. Ventricular volume</td>
</tr>
<tr>
<td>4. Cardiac output</td>
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<tr>
<td>5. Mean circumferential fiber shortening</td>
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<tr>
<td>6. Rate of systolic emptying (dV/dt)</td>
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<tr>
<td>7. Rate of diastolic filling (−dV/dt)</td>
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<td>8. Time to peak filling</td>
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<td>9. Site, sequence and uniformity (&quot;skewness&quot;) of ventricular activation—phase analysis</td>
</tr>
<tr>
<td>10. Pressure-volume loops</td>
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<tr>
<td>11. Flow-volume loops</td>
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<tr>
<td>12. Distribution of pulmonary blood volume, apex/base ratio</td>
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<td>13. Regurgitant fraction</td>
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<td>14. End-systolic pressure-volume relation</td>
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tion of both first pass and "gated" equilibrium radionuclide ventriculography, numerous reports have appeared correlating the left ventricular ejection fraction obtained with these techniques with that obtained during contrast left ventriculography. Both radionuclide approaches appear to be accurate and reproducible. The choice of technique that an individual center uses will depend on available instrumentation and experience. Because the radionuclide technique of determining left ventricular ejection fraction depends on changes in counts within the left ventricle and does not assume a given ventricular geometry, such as an ellipsoid configuration, it is currently believed that in certain circumstances the radionuclide values may be more accurate and reproducible than those obtained with contrast ventriculography.

Right ventricular ejection fraction. Right ventricular ejection fraction also can be readily determined with radionuclide ventriculography (36–38). For this determination "first pass" techniques may have some advantage over equilibrium techniques, because at equilibrium there is often overlap of right and left ventricular activity in the right anterior oblique or anterior projection and of atrial activity in the left anterior oblique projection. Although good correlations have been reported (37) between right ventricular ejection fraction obtained with first pass techniques and with equilibrium radionuclide ventriculography, technical difficulties remain with the latter approach.

Routine determination of right ventricular ejection fraction and regional myocardial wall motion in patients undergoing evaluation for suspected ischemic heart disease should improve the sensitivity of radionuclide techniques for detecting those with isolated lesions of the right coronary artery primarily supplying the right ventricle. The sensitivity of exercise radionuclide ventriculography or contrast ventriculography in which only left ventricular ejection fraction is assessed is obviously less for detecting single right coronary lesions than for detecting lesions of the left anterior descending or left circumflex artery, which primarily involve the left ventricle. With continued refinement of in-
strumentation and development of short-lived radiopharmaceutical agents, further improvement in determination of right ventricular ejection fraction and regional wall motion, and hence sensitivity for detecting patients with ischemic heart disease, can be expected.

**Regional wall motion and ejection fraction.** Regional myocardial wall motion was originally determined during radionuclide ventriculography by superimposing end-diastolic and end-systolic frames of the gated radionuclide ventriculogram and determining the percent change in long- and hemi-axes, similar to that determined with contrast left ventriculography (39). Subsequently, multiframe cardiac sequences from either first pass or equilibrium techniques were viewed as an endless loop on a computer oscilloscope or video display and regional myocardial wall motion was assessed visually, as is the current practice in most centers using contrast ventriculography. The lower spatial resolution of the radionuclide technique makes it difficult to detect minor degrees of hypokinesia that are easily appreciated with contrast ventriculography. More recent studies have used functional or “parametric” images and computer analysis to assess regional myocardial wall motion and regional ejection fraction. This approach permits evaluation of non-border-forming regions of the heart that are difficult to assess with either contrast or radionuclide two-dimensional analysis. Because the intensity of each pixel in the radionuclide image is proportional to the count rate, and hence blood volume at that point, nonborder-forming regions of the ventricle can be evaluated. In “stroke volume images,” obtained by subtracting the end-systolic image point by point from the end-diastolic image, the relative intensity at each pixel location in the image is proportional to the changes in volume occurring at that pixel. The “ejection fraction image” is obtained by dividing the stroke volume image point by point by a background-corrected end-diastolic image (40). The intensity at each point is proportional to the ejection fraction at that point. The “paradox” image (41) is the result of subtracting the end-diastolic frame from the end-systolic frame. In patients with ventricular dyskinesia, areas of increased activity can be seen to project outside of the end-diastolic outline, whereas with normal ventricular motion there is a void over the region of the left ventricle. Although all of these functional imaging techniques have been shown to be useful, their ability to increase sensitivity or specificity in detecting patients with ischemic heart disease over that obtained from visual inspection of the closed loop cinematic display has not been convincingly demonstrated in large series of patients.

**Phase analysis of the radionuclide ventriculogram has also been advocated to evaluate regional myocardial wall motion** (42). Each point in the phase image is coded to indicate its time course of contraction with respect to a reference point. Contraction in a normal ventricle is relatively uniform and thus the phase analysis of each of the pixels within the left ventricle is relatively uniform. In patients with ischemic heart disease and subtle abnormalities of regional myocardial wall motion, there is greater dispersion of the phase angles within the ventricles. Areas with a normal but delayed onset of ventricular ejection, “tardokinesia” can be detected with these images, and areas of dyskinesia are identified as being out of phase with the normal areas of the ventricle but similar in phase to the atria.

**Ventricular volume determination.** Ventricular volumes have been measured using either a geometric approach similar to that used in assessing contrast angiograms or a count-based method (29,43–45). Both approaches have been found to correlate with data obtained from contrast angiography. The geometric approach is limited by overlap of the right and left ventricles if the equilibrium (gated) technique is used. The count-based methods are based on the principle that the net ventricular activity at any point in the cardiac cycle is proportional to ventricular blood volume. Left ventricular volume, for example, at end-systole can be computed from the ratio of net ventricular counts/s at end-systole divided by blood counts/s per ml obtained from a reference blood sample. Correction for attenuation from activity by the soft tissues in the thorax has been obtained by several different approaches (43–45). Volumes obtained with currently available methods have been shown to correlate with volumes determined with contrast angiography but have a considerable error in a given person. Determination of changes in end-systolic and end-diastolic volume from rest to exercise have been shown by both contrast and radionuclide angiographic studies to increase the sensitivity for detection of ischemic heart disease.

**Diastolic filling abnormalities.** Determination of the rate of ventricular emptying (46–48) and, more recently, of the rate of ventricular filling and time to peak filling (49) have also been suggested as possible means to improve sensitivity of radionuclide techniques for detecting patients with ischemic heart disease. Bonow et al. (49) in a study of 231 patients found an abnormality of diastolic filling at rest in more than 80% of patients with ischemic heart disease without any abnormality of systolic function at rest. Determination of an abnormality of diastolic function at rest or an abnormality of systolic function during exercise, or both, allowed a sensitivity of 99% to be obtained. If a sensitivity of 99% for the detection of ischemic heart disease could be achieved prospectively in a large number of patients by the calculation of diastolic function at rest in combination with variables of systolic function, ventricular volume, regional myocardial wall motion during exercise or other stress, we would have accomplished our goal of detecting patients with suspected ischemic heart disease or other forms of myocardial dysfunction. In an asymptomatic group with a low prevalence rate of disease (for example, 5%), a negative test result would virtually exclude significant ischemia or
other forms of myocardial disease. However, given the imperfect specificity of both thallium-201 myocardial imaging and radionuclide ventriculography, the value of a positive test in groups with a low prevalence rate of obstructive coronary artery disease would be questionable. Nevertheless, several groups (14,50,51) have shown that radionuclide techniques can be useful in determining the presence or absence of obstructive coronary artery disease in asymptomatic patients with a positive exercise electrocardiogram.

Future Prospects and Developments

In view of the limitations of current radionuclide techniques, which are tests of function, in determining the presence or absence of anatomic coronary artery disease, what are the prospects for the future? Based on the considerations discussed here, it is unlikely that any other noninvasive techniques listed in Table I will achieve a higher sensitivity than that suggested by current radionuclide techniques. The discrepancy between the anatomic presence of disease and its functional significance precludes perfection for any technique that does not define anatomic presence of disease. Although future developments in radiopharmaceutical agents or other noninvasive technologies may allow detection of early atherosclerotic plaques within the coronary artery, progress in this area has been slow and the rate of future success is uncertain. However, improved specificity for the detection of ischemic versus other forms of myocardial disease is likely to be achieved with some of the other noninvasive techniques. For example, it is likely that monitoring of metabolic function by positron emission tomography or flow by nuclear magnetic resonance techniques, or both, will allow separation of ischemic and nonischemic causes of impairment in ventricular function during stress. Progress in digital radiography and digital echocardiography is also occurring rapidly. The resolution of digital radiographic techniques for evaluating regional myocardial wall motion is inherently superior to that of radionuclide ventriculography. Although one might expect digital radiography to have increased sensitivity for detecting patients with suspected ischemic heart disease, other limitations, such as difficulty in analyzing images during exercise with current approaches and relative difficulty in obtaining the rate of ventricular emptying, make it unlikely that the overall sensitivity for detection of disease will be significantly improved.

Similarly, the inherent resolution and ability to detect regional myocardial wall thickening with echocardiographic techniques are greater than those of radionuclide techniques, but the difficulties in obtaining adequate images during stress pose a severe limitation for significant improvement in sensitivity. Nevertheless, the rapid progress in digital echocardiographic techniques and tissue characterization by echocardiography suggests that echocardiographic techniques may have a more important role in evaluating patients with suspected ischemic heart disease in the near future. Even with currently available techniques and their limitations, important progress has been made in detecting patients with left main coronary artery disease (52).

Evaluation of the Patient With Known Ischemic Heart Disease

Evaluating patients for coronary bypass surgery. The clinical impact of radionuclide techniques on the evaluation of patients with known ischemic heart disease is in many respects greater than that for the evaluation of patients with suspected ischemic heart disease, and these techniques are finding increased use in assessing candidates for coronary artery bypass graft surgery. In patients with coronary artery lesions of less than 50%, the finding of an exercise thallium-201 tracer defect or exercise wall motion abnormality suggests functional significance and consideration for bypass grafting if clinically indicated. Conversely, areas of akinesia, often thought unsuitable for bypass graft surgery, can be predicted to be viable and to benefit from surgery on the basis of rest-redistribution thallium myocardial imaging and analysis of regional wall motion during exercise radionuclide ventriculography (53,54).

Evaluating therapy. The results of bypass graft surgery (55), percutaneous transluminal angioplasty (56) and, most recently, intracoronary administration of streptokinase (57) have been evaluated with thallium myocardial imaging and radionuclide ventriculography. The incidence of perioperative infarction in patients undergoing bypass graft surgery has been accurately determined by pre- and postoperative infarct-avid imaging. Patients with angina pectoris and a high risk of subsequent cardiac events have been identified by the finding of a positive infarct-avid scan (58). Radiouclide techniques also have been shown to be sensitive in detecting both acute and remote myocardial infarction (59,60), and a valuable aid in evaluating the extent of left ventricular dysfunction, the effect of therapeutic interventions, and prognosis (61–67).

Determination of prognosis. One important application of radionuclide techniques is the determination of prognosis in patients with ischemic heart disease. High risk subsets of patients with angina pectoris and myocardial infarction have been identified by these techniques (58,68). Submaximal exercise thallium-201 myocardial imaging and radionuclide ventriculography before hospital discharge have been found to be more sensitive than the electrocardiogram in detecting areas of jeopardized myocardium and subsequent risk of cardiac events (69,70). Evaluation of patients with suspected left ventricular aneurysms (71–73), detection of left ventricular thrombi (74), differentiation between ischemic and nonischemic causes of diffuse hypokinesia (28)
and evaluation of patients after resuscitation from an episode of sudden death (75) have been greatly facilitated by myocardial imaging with radionuclide techniques.

**Future progress.** The clinical impact of radionuclide techniques on the evaluation of patients with suspected and known ischemic heart disease has been and will continue to be great. However, experience with these techniques encompasses barely a decade compared with the relatively long experience with electrocardiography, echocardiography and invasive contrast angiography. It is possible that advances in digital left ventriculography, quantitative echocardiography, nuclear magnetic resonance imaging and other noninvasive techniques will make radionuclide techniques obsolete for evaluating patients with ischemic heart disease. But it is undeniable that the ability of the clinician within the early hours of myocardial infarction to determine the site, extent and effect of the infarcted area on ventricular function, assess the effect of therapeutic interventions and determine prognosis with use of radionuclide techniques has been gratifying. Many problems remain with currently available radionuclide techniques, some of which we have described. The lessons learned from these techniques—their insight into pathophysiology, diagnosis, therapy and prognosis—are an important impetus for further progress with radionuclide techniques, other noninvasive techniques and invasive techniques.

**References**


29. Strauss HW, Zaret BL, Hurley P, Natarajan TK, Pitt B. A scintipho-


