What is the Current Role of Nuclear Cardiology in Clinical Medicine?*

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The application of noninvasive nuclear medicine imaging techniques to the study of patients with suspected or known cardiovascular diseases offers important diagnostic, pathophysiologic and prognostic information that may directly affect patient management. The complementary nature of the functional and physiologic information obtained from nuclear cardiology examinations with the anatomic and structural information obtained from cardiac catheterization procedures has led to widespread application of these techniques. This report will provide a perspective on the current role of nuclear cardiology techniques in clinical medicine.

BACKGROUND

Three procedures comprise the majority of readily available nuclear cardiology examinations at this time.1 Myocardial perfusion imaging is currently performed with thallium 201 and provides information concerning relative regional myocardial perfusion. Perfusion imaging is usually coupled with exercise stress. Images are obtained immediately after exercise and are compared with redistribution images obtained 3 to 4 h later. As an alternative to exercise, intravenous or oral dipyridamole may be used to produce near maximal coronary vasodilatation in patients unable to exercise. The hallmark of myocardial ischemia is reversible relative hypoperfusion.2 Studies are acquired either as planar images or with rotating gamma cameras permitting the reconstruction of sectional images using the techniques of SPECT. Studies are analyzed either visually or, preferably, with the aid of computer quantitation of regional tracer distribution and kinetics. Myocardial perfusion imaging also may be performed at rest and with redistribution imaging to detect reversible myocardial ischemia.

The second procedure is RNV, also known as radionuclide angiocardiography; RNV is used in the assessment of ventricular performance. Two methods are currently available. The first-pass method measures right and left ventricular performance sequentially during the initial transit of a bolus of a radiotracer through the right and left heart. Technetium 99m-labeled radiopharmaceuticals are the most commonly used tracers, and cameras with high count rate capabilities are mandatory. Time activity curves are generated and right and left ventricular ejection fractions and volumes may be measured and a qualitative or semiquantitative analysis of regional wall motion obtained. Rest examinations may be followed by exercise stress to assess cardiac reserve. Equilibrium RNVs are obtained following the labeling of red blood cells with technetium 99m pertechnetate and equilibration of the tracer throughout the blood pool. Images are synchronized, or gated, to the electrocardiogram, permitting continuous viewing of cardiac emptying and filling. Imaging may be performed in multiple projections for as long as 6 h following injection and, thus, acquisitions may be performed at rest and during exercise stress. The hallmarks of exercise-induced myocardial ischemia include the inability to improve ventricular performance measured as the ejection fraction by at least 5 ejection fraction units over baseline, the inability to decrease end-systolic volume, and of the development of new or worsening regional wall motion abnormalities.3 Finally, infarct-avid imaging may be performed with either the administration of 99mTc-PPI or indium 111 antimyosin antibodies. Zones of acute myocardial necrosis, as small as 1 to 3 g using SPECT and planar techniques, respectively, are detected as areas of increased radiopharmaceutical uptake when 99mTc-PPI is used for myocardial infarct detection.4,5

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SPECT = single photon emission computed tomography; RNV = radionuclide ventriculography
DETECTION OF CORONARY ARTERY DISEASE

An important goal in clinical medicine is the accurate identification of patients with myocardial ischemia. Exercise stress testing with electrocardiography is widely used for this purpose. One or more millimeters of horizontal or downsloping ST-segment depression during exercise in men with chest pain has a reported sensitivity ranging in general from 60 to 70 percent and a specificity of 80 to 90 percent. The predictive value of exercise electrocardiography has been found to be reduced in women, patients with resting electrocardiographic abnormalities including hypertrophy, conduction defects, pre-excitation patterns and digitalis effects, patients with limited exercise capacity (<85 percent predicted maximal heart rate) and patients taking cardiac drugs, such as beta blockers.

Numerous reports document that combining exercise electrocardiography with either myocardial perfusion imaging or RNV provides superior diagnostic accuracy in the detection of coronary artery disease. Sensitivities and specificities of approximately 80 to 90 percent for the detection of coronary heart disease can be expected with thallium perfusion imaging. In particular, greater accuracy compared with standard stress electrocardiography has been demonstrated in women, patients with baseline electrocardiographic abnormalities, patients with limited exercise capacity and patients taking cardiac drugs. An important exception is the patient with LBBB. A recent investigation has demonstrated that either reversible or fixed perfusion defects of the left ventricular septum occur frequently in patients with LBBB unassociated with important coronary artery disease and should be anticipated in these patients. Exercise-induced myocardial hypoperfusion in regions other than the septum may still be a reliable marker of underlying coronary artery disease. Of particular clinical importance is the recent report that the sensitivity of thallium imaging for the detection of coronary artery disease is less affected by the heart rate or workload achieved during exercise than is exercise electrocardiography, and it is superior to ST segment depression at all exercise levels.

A number of investigators have also demonstrated that combining RNV with exercise yields results superior to standard stress electrocardiography. Important coronary heart disease is excluded by normal global and regional left ventricular function at rest and maximal exercise. Compared with coronary arteriographic results, exercise RNV has a reported sensitivity of approximately 90 percent for the detection of coronary artery disease, but an overall specificity of only approximately 70 percent. Altered ventricular function in response to stress may also occur in some patients free of coronary heart disease, including some patients more than 60 years of age, patients with atrial fibrillation or LBBB and patients with hypertensive, valvular, or myocardial disease. Similar to exercise electrocardiography, the predictive accuracy of exercise RNV is lower in women and patients with limited exercise performance. Antianginal drugs may attenuate the ischemic response to exercise in patients with coronary heart disease, resulting in decreased detection of disease. Patients with LBBB may demonstrate septal wall motion abnormalities at rest and abnormal ventricular responses to stress in the absence of coronary heart disease.

Patients most suitable for study with stress nuclear imaging are those with an intermediate likelihood of coronary heart disease. In this population, the imaging studies appear to have a definite advantage over standard stress electrocardiography. The concepts of Bayes' theorem are important to consider when planning the evaluation of patients with suspected coronary heart disease. The indiscriminant use of nuclear cardiology examinations in patients with very low pretest probabilities of disease will result in lower diagnostic accuracy. Patients with classic symptoms of coronary heart disease will very likely have coronary heart disease, and a stress test of any kind will add very little to the differentiation of the presence or absence of coronary heart disease, although it may provide prognostic insight. Other candidates for stress imaging studies include the patient subgroups discussed above that demonstrate a decreased predictive accuracy with the standard stress electrocardiographic examination. For greatest accuracy, patients being evaluated for the presence of suspected coronary heart disease should be studied after discontinuation of antianginal therapy. The selection of a myocardial perfusion scintigram or RNV for a particular patient will depend in part on the availability of expertise in the performance and interpretation of these tests at a particular site. In addition, patients likely to have an abnormal ventricular response to stress from associated noncoronary conditions are usually better suited for thallium imaging. A recent comparative study of thallium imaging and RNV in unselected patients with chest pain referred for coronary arteriography demonstrated a higher predictive accuracy with exercise thallium imaging. Prudent use of cardiac nuclear imaging in the evaluation of patients with suspected coronary heart disease has been shown to reduce the need for cardiac catheterizations in selected patients.

CHRONIC CORONARY ARTERY DISEASE

Detection of Individual Coronary Stenoses

The ability of exercise electrocardiography to localize coronary artery obstructions and predict the
coronary anatomy is limited. Nuclear imaging techniques have superior accuracy for the detection of flow-limited coronary vascular distributions. Exercise RNVs are usually obtained in only one projection, and thus the detection and assignment of wall motion abnormalities to specific coronary distributions, especially those caused by right and circumflex coronary artery stenoses, are limited. Myocardial perfusion imaging with thallium 201 allows analysis of the location of hypoperfused myocardium in multiple projections, and permits improved estimates of the number and location of coronary stenoses. Thallium SPECT, in particular, provides improved spatial resolution and thus improved resolution of individual hypoperfused vascular beds. In studies comparing planar and SPECT thallium perfusion imaging, improved detection of stenoses in the circumflex distribution is observed with SPECT imaging. The ability to localize more accurately individual coronary stenoses permits improved detection of high-risk patients with multivessel disease. Using quantitative planar thallium imaging, more than two thirds of patients with left main disease have multivessel disease patterns and approximately 50 percent of patients with three-vessel disease without left main coronary stenosis have thallium-evidenced defects in two or more regions. Thus, SPECT thallium imaging appears to provide improved detection of three-vessel coronary disease compared with planar imaging. The ability to localize coronary stenoses producing hypoperfused myocardium has had an important role in the planning of revascularization procedures, particularly PTCA, in patients with multivessel disease.

Prognosis

Both RNV and myocardial perfusion imaging provide important prognostic information in the patient with known coronary heart disease. Those patients with reduced ventricular function at rest, especially those with ejection fractions less than 40 percent, are known to have a poor prognosis. Patients with a decrease in their left ventricular ejection fraction during exercise have a significantly poorer prognosis than those who have an increase. The left ventricular ejection fraction at peak exercise has been reported to be the most important predictor of prognosis in patients with stable chronic angina. The prognostic implications of normal exercise thallium imaging have been examined by several investigators, and a normal maximal exercise thallium study is associated with a very low cardiac event rate (0.5 percent/year) in the subsequent one to four years. In patients with chronic coronary heart disease with abnormal scintigrams, the number of defects, the number of defects demonstrating redistribution and the presence of increased thallium uptake in the lungs following exercise, indicating exercise-induced left ventricular dysfunction and pulmonary venous hypertension, have all been shown to indicate a relatively poor prognosis.

Myocardial Revascularization

Myocardial perfusion imaging and RNV may provide relevant information for clinical decision-making related to revascularization procedures in patients with known coronary heart disease. The detection of myocardial viability in segments supplied by stenosed coronary arteries becomes the critical issue in predicting the response to revascularization procedures. The presence of reversible defects within 2 to 4 h of stress has been considered indicative of myocardial ischemia. Defects failing to demonstrate redistribution within this time frame have been considered to have a myocardial "scar." However, recent studies have demonstrated that some myocardial regions with persistent thallium defects may still demonstrate improved wall motion, indicating myocardial viability, following surgical revascularization or PTCA. This paradox has led to the recent realization that 4 h redistribution imaging may not be adequate in some patients for the demonstration of reversible hypoperfusion. Studies with redistribution imaging at 24 to 72 h have demonstrated in selected patients that up to 72 percent of thallium defects persistent at 4 h show late reversibility. Therefore, before a patient is excluded from revascularization procedures, late redistribution imaging should be performed. Alternatively, rest RNV or contrast ventriculography in conjunction with thallium perfusion imaging may be better than stress/redistribution imaging alone in assessing myocardial viability. Segments having persistent defects on thallium imaging that correspond to akinetic or dyskinetic segments would be unlikely to show improvement in regional contraction following revascularization. Alternatively, regions that demonstrate normal or hypokinetic wall motion are likely comprised of viable myocardium despite persistent thallium defects. Following PTCA, exercise thallium imaging has proven useful for the early detection of restenosis.

Acute Myocardial Infarction

Detection

The diagnosis of acute myocardial infarction can be made with certainty in most patients on clinical grounds. However, nuclear cardiology techniques play an important role in certain subsets. Patients with LBBB, those who delay their hospital admission by more than one day from the onset of symptoms, patients with suspected perioperative myocardial infarction following open-heart surgery, patients with non-Q wave infarcts and patients who have had several previous infarctions are particularly good candidates.
for infarct-avid imaging with either $^{99m}$Tc-PPI or indium-111 antimyosin antibodies. Following thrombolytic therapy, reperfusion may be documented by the presence of myocardial uptake of $^{99m}$Tc-PPI within the infarct within 1-3 h of successful reperfusion.

**Complications**

Radionuclide studies may assist in the management of patients with complicated infarcts by allowing their impact on global and regional ventricular function to be assessed. Studies comparing RNV measures of ventricular function with clinical and radiographic findings have shown some discrepancies, with substantial overlap between the range of ejection fractions found in the Killip classes 1 to 3. In particular, some patients in Killip classes 1 and 2 have severely reduced ventricular function. Right ventricular infarction may be detected by RNV or infarct-avid techniques and ventricular aneurysms can be reliably detected early after infarction with RNV.

**Pre-discharge Risk Stratification**

Radionuclide imaging techniques coupled with submaximal exercise have been shown to provide a safe and effective means for prognostic stratification of patients with minimally complicated infarcts, allowing the identification of patients at relatively high risk for future coronary events. Patients with left ventricular dysfunction at rest (ejection fraction $<$ 40 percent) are at risk for future ischemic events. In patients with better preserved function, the ejection fraction and end-systolic volume responses to exercise assessed with RNV add useful prognostic information. Similarly, exercise thallium imaging has been used in the uncomplicated infarct patient. The identification of thallium defects in more than one vascular territory, redistribution either within or remote from the zone of infarction, or increased lung thallium uptake identify postinfarction patients at increased risk for subsequent ischemic events.

**Congestive Heart Failure**

**Etiology**

Nuclear cardiology techniques have an important role in the evaluation of the patient with symptoms of congestive heart failure and ventricular dysfunction. A significant percentage of patients referred for RNV because of symptoms of congestive heart failure prove to have normal or even supranormal ventricular function. Recognition of these patients may allow appropriate therapy aimed at the probable underlying abnormalities of diastolic ventricular dysfunction; RNV can distinguish biventricular from isolated left or right ventricular dysfunction. A specific etiology may be suggested by attention to other useful diagnostic clues RNV may provide, such as atrial dilatation, ventricular hypertrophy, rotation of the ventricular septum, and dilatation of the proximal aorta and pulmonary artery. However, differentiation of ischemic from idiopathic cardiomyopathies in patients with dilated ventricles is not always possible. Generally, patients with idiopathic cardiomyopathies demonstrate four-chamber dilatation and moderate to severe global biventricular dysfunction. The patient with coronary heart disease generally demonstrates relatively well preserved right ventricular function and localized segmental abnormalities of left ventricular function which may include an obvious ventricular aneurysm. Unfortunately, it is often not possible to distinguish one type of cardiomyopathy from another simply on the basis of focal or diffuse wall motion abnormalities. Thallium imaging has been used to distinguish idiopathic from ischemic ventricular dysfunction. Patients with idiopathic dysfunction usually demonstrate normal thallium scans or patchy defects involving less than 20 percent of the left ventricular circumference, whereas ischemic cardiac dysfunction is characterized by large thallium defects involving greater than 40 percent of the ventricular circumference.

**Doxorubicin Cardiotoxicity**

Doxorubicin hydrochloride is an extremely useful chemotherapeutic agent for a variety of neoplastic diseases. A cumulative dose-related cardiotoxicity is well known. Congestive heart failure may be of sudden onset, irreversible and associated with a high mortality. Serial RNV assessments of resting left ventricular ejection fractions have been used to monitor the cardiotoxic effect. Suggested guidelines include the assessment of ventricular performance before the initiation of therapy. If the baseline study is normal, a second study is performed after 250 to 300 mg/m$^2$. A repeat study is performed after 400 to 450 mg/m$^2$. Therapy is discontinued if there is an absolute decrease in ejection fraction to less than 0.50. In patients with abnormal baseline ventricular function, more frequent evaluations with RNV are recommended. Following these guidelines, the incidence of congestive heart failure was only 2.9 percent in one recent study.

**Valvular Heart Disease**

Radionuclide techniques have proven useful in the evaluation and management of patients with valvular heart disease. Characteristic abnormalities of chamber and great vessel size and function are demonstrated. The detection and severity of valvular regurgitation may be estimated from the ratio of left-to-right ventricular stroke volumes obtained from RNV. Since ventricular counts are proportional to volume, the left-to-right ventricular stroke count ratio in normal subjects should approximate unity. Regurgitation increases the stroke counts on the affected side of the
heart. A sensitivity of approximately 60 percent for the detection of ≥1+ regurgitation by contrast ventriculography may be expected.

Aortic regurgitation has been studied most extensively using RNV, and RNV has been used to help guide the selection of patients for valve replacement. Ventricular volumes and ejection fractions can be measured, and the RNV may be used as a simple noninvasive means of obtaining the same information found to have prognostic importance by contrast ventriculography. Symptomatic patients are generally referred for valve replacement. Some patients with aortic regurgitation develop left ventricular dysfunction at rest before symptoms develop. In order to identify these patients before severe ventricular dysfunction occurs, serial RNV has been suggested as a noninvasive means of monitoring for silent progressive ventricular dilatation and dysfunction. The left ventricular response to exercise has been studied in asymptomatic patients with aortic regurgitation. A decrease in exercise ejection fraction often precedes the development of angiographic and echocardiographic indices of ventricular dysfunction. Although an abnormal exercise response in these patients may serve to identify high-risk patients who require closer observation, referral for valve replacement in otherwise asymptomatic patients with preserved rest function is generally not warranted. However, the development of a resting ejection fraction below 50 percent with increased left ventricular end-systolic volume attributable to valvular aortic insufficiency is an indication to correct the aortic insufficiency.

REFERENCES
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