Cardiovascular Nuclear Medicine: The Next Step

The growth of cardiovascular nuclear medicine occurred in conjunction with a remarkable improvement in understanding of ischemic heart disease. Over the past three decades the pathophysiology of acute myocardial infarction was intensively studied, methods of reducing infarct size and techniques of revascularization were implemented (*1,2*) and the importance of recurrent ischemia and ventricular function on prognosis were appreciated (*3*). During this interval, a wide array of radionuclide procedures were described to aid in both the diagnosis and therapeutic decision making of patients with heart disease. To continue to thrive, radionuclide imaging must meet the evolving needs of cardiologic practice.

Four major areas: (a) detection of provocable or persistent ischemia, (b) identification of viable myocardium, (c) prediction of the onset of congestive heart failure, and (d) measurement of the progression of atheromatous disease remain major decision points in patient management. Perfusion imaging, determination of regional metabolism, measurements of ventricular function, and receptor imaging can help characterize these processes. To put the new procedures in perspective, it is helpful to take a critical look at one examination, myocardial perfusion imaging, to determine how well it meets our current clinical needs and define possible evolutionary changes in its performance.

Myocardial Perfusion Imaging

The initial approach in detecting ischemia with myocardial perfusion imaging utilized potassium-43 (^{43}K), with *separate* injections at exercise and rest (*4*) to measure the regional distribution of perfusion on each occasion. Comparing the two scans could help differentiate ischemia from scar. When the potassium analog thallium-201 (^{201}Tl) was introduced as a replacement for ^{43}K, it too, was used with a dual injection technique (*5*). When Pohost et al. (*6*) noted the phenomena of a "normalization" of activity in the ischemic myocardium over time, the concept of "redistribution" imaging - taking delayed images without the administration of additional tracer (*7*) was born.

Physiologically, the two image/one injection approach measures two different phenomena: Perfusion on the initial scan, and the relative "volume" of intracellular cation on the delayed scan. Since the initial concentration of intracellular thallium is higher in zones of normal perfusion, loss of thallium from normally perfused zones is greater than from zones of ischemia (*8,9*) and the "volume" distribution in areas of viable tissue that were ischemic at the time of injection become similar. Areas of fibrosis, however, lose ^{201}Tl at the same rate as normal tissue, maintaining their relative difference over time. These concepts produce a straightforward approach to differentiate normal, ischemic and scarred myocardium (Table 1).

Recent studies suggest that up to 30% of patients with fixed abnormalities on 3-hr redistribution ^{201}Tl scans have *viable* myocardium, not scar (*10–12*). The cause for this lack of redistribution is unclear, but may be related to the ingestion of glucose between initial and delayed imaging (*13,14*). Patients who eat between their initial and delayed scans have a higher incidence of fixed perfusion abnormalities, than patients who fast (*15*). Under the influence of insulin, intracellular potassium turnover is accelerated; since thallium is a

TABLE 1
Perfusion Scan Interpretation (Circa 1976)

Observation		
Initial	Delayed	Interpretation
Homogeneous	Unchanged	Normal
Focal decreased uptake	Improved	Ischemia
Focal decreased uptake	Unchanged	Scar

potassium analog, its clearance from the intracellular space is also accelerated (*12*). Other sugars, however, such as ribose, may have the opposite effect. Recent experimental studies (*16*) suggest that ribose infusion accelerates the process of redistribution, possible because of the role of this sugar in nucleoside biosynthesis and/or the pentose monophosphate shunt. The observation that redistribution may not occur in zones of ischemia on conventional 3-hr redistribution images leads to a new scheme for the interpretation of thallium scans (Table 2).

To identify ischemia in patients with fixed abnormalities at 3 hrs, some investigators suggested 24-hr delayed imaging (*11*) to permit "equilibration" to occur. This technique improves the detection of viable tissue, but the residual thallium content of the myocardium is low, and 24-hr delayed scans are difficult to interpret. An alternative approach is to re-inject ^{201}Tl at rest (*17*). Rather than wait for equilibration in the intracellular "volume", reinjection provides a second measurement of *perfusion.* Since most patients will lose 30–50% of their myocardial ^{201}Tl concentration between initial and delayed (3–4 hr) scans, it is possible to use a smaller dose of thallium for the reinjection study, while obtaining a count rate similar to the initial study. In addition, since it is helpful to have less residual thallium in the myocardium, it is advisable to have patients eat between their initial scan and their second injection. Our experience with reinjection in over 200 patients suggests 1 mCi (37 MBq) will suffice. One difficulty with the reinjection approach, is the loss of thallium clearance as a marker of diffuse ischemia. Since diffuse ischemia is relatively rare, the loss of this marker in exchange for a simplified approach to the detection of ischemia is probably warranted in most patients.

Quantitative analysis of ^{201}Tl images has been proposed as a method of improving the detection and localization of myocardial ischemia (*18*). Unfortunately, computer programs for quantitation are in their infancy, using only regional distribution of relative activity and clearance as parameters for analysis. The programs cannot differentiate artifacts (breast attenuation, diaphragm, etc.) from real zones of decreased myocardial tracer content. As a result, the images must be evaluated subjectively by an *experienced* observer prior to integrating the quantitative data in the final report. Since relatively few practitioners perform a sufficient volume of ^{201}Tl imaging to maintain a high level of proficiency (the numbers of procedures required for competency is uncertain (*19*), but a minimum of two studies/day is probably required), the quantitative programs frequently serve the role of a "consultant". As image quality improves with high photon flux technetium-99- (^{99m}Tc) labeled perfusion agents, programs of increasing sophistication will emerge to permit more precise quantitation of regional perfusion. These programs could help differentiate attenuation artifacts from true perfusion abnormalities based on lesion shape, extension beyond the myocardium or by changes in wall thickening (based on gated acquisition); identify significant lung uptake and left ventricular cavity dilation; and determine the relative physiologic severity of the exercise stimulus based on splanchnic uptake. Preliminary studies integrating the outcome of exercise electrocardiography, clinical history and thallium imaging produce a more complete assessment of the patient (*20*) than any single parameter.

Single photon emission computed tomography (SPECT) has been advocated to enhance the contrast between lesions and normally perfused zones of myocardium, and thereby increase the sensitivity of ^{201}Tl imaging (*21,22*). Since tomography requires complete angular sampling and functions best with high count density images, the technique is prone to substantial artifact when applied to the thallium imaging where images are acquired over

TABLE 2
Perfusion Scan Interpretation (Circa 1988)

Observation Initial	Delayed (3 hr)	Interpretation
Homogeneous normal thickness	Unchanged	Normal perfusion
Focal decreased uptake	Improved	Ischemia
Focal decreased uptake	Unchanged	Cannot differentiate scar from ischemia*

* Ischemia may be differentiated from scar by 24-hr delayed images or reinjection.

180° and have a limited photon flux. Common difficulties in SPECT imaging include patient motion, and inappropriate correction for center of rotation and camera uniformity. Each of these problems can create an apparent abnormality in regional thallium distribution, which if not properly evaluated, will decrease the specificity of SPECT perfusion imaging. To maximize the accuracy of SPECT imaging the rotatogram or sinogram should be inspected for patient motion artifacts prior to interpreting the reconstructed data. Depending on the design and age of the SPECT device, a center of rotation and high count density flood should be performed at least once/month.

SPECT imaging can be enhanced with multidetector instruments. The newer three or four detector designs, or the collimated ring detector, offer improved sensitivity and improved spatial resolution (a result of better body contouring). The gantry design reduces the likelihood of center of rotation artifacts, while advanced electronics minimize detector nonuniformities. Although the instruments cost substantially more than single detector SPECT devices the increased patient throughput and improved image quality suggest these instruments will play an important role as the practice of cardiovascular nuclear medicine grows.

Ventricular Function

To enhance our ability to view specific areas of the left ventricle, data should be recorded with SPECT (*23,24*). Gated blood-pool tomography (GBPT) offers an opportunity to reconstruct the data in orientations that cannot be recorded with conventional planar images.

1. An apical four chamber view can be obtained, to provide simultaneous information about atrial and ventricular wall motion.
2. A true LV long axis view can be reconstructed, to provide information about LV wall motion without overlying RV activity.
3. The short axis of the ventricle can be sampled at multiple points, to permit independent assessment of motion at the base and apex of the left ventricle.

GBPT can be particularly useful in patients with apical aneurysms and left ventricular failure, to determine if retained function at the base is sufficient to warrant surgery (*25*).

Ambulatory Monitoring

Recently, a nonimaging probe has been developed to continuously record the beat by beat time-activity curve from the left ventricle and two channels of ECG while the patient performs activities of daily living. The instrument consists of radionuclide detectors, an ECG recorder and associated electronics placed in a garment which is worn like a vest (hence the name of the device-VEST). Normal subjects have a dynamic range of ejection fraction responses to daily activities. Standing, walking, micturition, mental arithmetic, and exercise (*26,27*) cause rapid changes in ventricular volumes, ejection fraction and relative cardiac output. In patients with coronary artery disease, transient decreases in ejection fraction, with or without ECG changes, have been observed during normal daily activity (*28*). These brief episodes of decreased ventricular function may offer important prognostic information. Kayden et al. (*29*) observed a transient, spontaneous, fall in ejection fraction during ambulatory monitoring in some patients recovering from acute infarction. During a 42-wk follow-up a significantly higher incidence of cardiac events was observed in these patients than those without decreases in ejection fraction. These preliminary studies suggest continuous monitoring of ventricular function may offer a new means of identifying patients at high risk of future cardiac events based on the frequency and degree of impairment of ventricular function.

FUTURE DIRECTIONS

Receptor Imaging

The aging population and high prevalence of hypertension make it desirable to assess the likelihood of developing heart failure. This may be possible by defining changes in the concentration of catecholamine receptors in the myocardium. The potential value of this approach was suggested in an experimental study with metaiodobenzylguanidine (MIBG), where dogs were subjected to chronic volume overload. The animals that developed failure had a marked reduction in the myocardial retention of MIBG (*30*). Attempts at imaging

myocardial beta adrenergic receptors have been reported, however the level of success has been extremely limited (*31*), primarily a result of uptake in the surrounding lung. The recent determination of the structure of the β_2 receptor (*32*) may solve this problem. Radiolabeled antibodies can be raised against portions of the receptor that are not involved with ligand binding, but are exposed at the myocyte surface.

Imaging of Atherosclerosis

The clinical use of drugs designed to lower cholesterol and thereby reduce the incidence of severe coronary artery disease, has increased the need to directly image atheromatous lesions for early lesion detection and to monitor therapy. Two approaches have been described to image atheromatous lesions with radiopharmaceuticals: lipoproteins and IgG. Lipoproteins interact with plaques to transport cholesterol in and out of the lesions. Radiolabeled low-density lipoproteins can localize these lesions in both experimental animals (*33,34*) and in human subjects (*35*). In addition, plaques contain foam cells (macrophages trapped beneath the endothelium that contain large quantities of cholesterol). The foam cells express large numbers of Fc receptors, and should be imageable with molecules that bind to these receptors. Human IgG binds to Fc receptors, and recently, IgG, radiolabeled with ^{111}In, was found to localize at sites of experimental arterial injury (*36*) and in human subjects at sites of severe arterial narrowings.

Positron Emission Tomography

Positron emission tomography (PET) imaging has several advantages over single photon techniques, including: (a) The short physical half-life of positron perfusion agents allow rest and exercise images to be acquired in rapid succession; (b) The high sensitivity and improved spatial resolution of PET allows precise definition of lesions; and (c) Both regional and absolute quantification of tracer distribution can be readily obtained. Since positron tomography can evaluate similar functions to those measured with single photon techniques and has the unique ability to identify focal zones of ischemic myocardium by their metabolic signature with fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) (*37*), clinical applications of PET for cardiac imaging are likely to grow.

The rationale for measuring myocardial metabolism stems from the heart's requirement for a constant source of high energy phosphate to provide fuel for contraction (*38*). In an aerobic environment, ATP for contraction is regenerated by the oxidation of long chain fatty acids (complete catabolism of one molecule of palmitate yields 129 ATPs, while one molecule of glucose yields 38), providing 80–90% of the energy requirement (*39*). A decrease in oxygen availability is accompanied by decreased catabolism of fatty acids and increased catabolism of sugar (*40*). During ischemia glucose undergoes catabolism to lactate with net production of only 2 ATP via the Embden Myerhof (anaerobic) pathway. This change in glucose catabolism markedly increases the uptake of glucose in ischemic zones. If the glucose analog [^{18}F]FDG is administered during, or immediately after ischemia, a focal increase in myocardial concentration at the ischemic site is seen. Some residual blood flow is critical for this process to take place. When flow is markedly impaired, increases in lactate and hydrogen ion in the cytosol inhibit residual glycolysis. This downward course of biochemical events may progress to complete cessation of energy production and thus, to irreversible cell injury.

In studies where images were recorded with both a perfusion agent and [^{18}F]FDG, zones of diminished perfusion associated with increased FDG uptake had a 50% likelihood of improved function following revascularization (*19*). In contrast, zones of diminished perfusion associated with decreased FDG uptake did not have improved function after surgery.

While PET is an expensive technology (both to acquire and maintain), the importance of definitively identifying viable ischemic myocardium with [^{18}F]FDG makes a compelling argument to apply this technology for clinical care.

CONCLUSION

The role of established radionuclide procedures for diagnosis and therapeutic planning in patients with coronary artery disease continues to grow. In addition to the continued acceptance and refinement of these procedures, the field is likely to have another period of

accelerated growth because of the push-pull of technical developments (new radiopharmaceuticals and improved instrumentation) and improved therapeutic regimens, which create demands for better characterization of the tissue under treatment. For example, when the mechanism of accelerated atherosclerosis following angioplasty in some patients is understood, it is likely to lead to a new radiopharmaceutical to characterize the process.

Overall, radionuclide studies of the cardiovascular system appear to have a scintillating future.

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