Nuclear Cardiology: Finally a One-Stop Shop for Diagnosis, Risk Stratification, and Management of Coronary Artery Disease

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Nuclear Cardiology Today

Since the introduction of myocardial perfusion imaging using planar thallium-201 (Tl-201) in 1975, myocardial perfusion imaging using single-photon emission computed tomography (SPECT) and technetium-99m (Tc-99m) perfusion tracers has established itself as the most widely used non-invasive test for the diagnosis, risk stratification, and management of patients with suspected or known coronary artery disease (CAD).^{1,2} Table I lists the diverse patient populations for which SPECT has accumulated large amounts of data over the years that show efficacy, efficiency, and cost-effectiveness for diagnosis and prognosis as recommended in recent guidelines.¹ Single-photon emission computed tomography not only measures perfusion; beginning in the mid 1990s it became possible to perform electrocardiogram (ECG) gating of the perfusion data to measure global and regional left ventricular function at rest and in the poststress images. The ability to acquire not only perfusion but also functional information increased the value of SPECT, and nearly all SPECT studies are performed with ECG gating.³ For these reasons, SPECT has been shown to have tremendous value at all steps of the diagnosis and management of patients with CAD.

Some of the reasons that there are over 8 million SPECT studies performed yearly in the United States is that the protocols have been standardized, the technique is widely available in both the hospital and outpatient setting, and there is a tremendous body of literature in large numbers of patients supporting the efficacy of SPECT. These studies are patient-friendly and cost-effective, and reimbursement is well established. Physician certification and nuclear cardiology laboratory accreditation are in place to promote a consistent and

high-quality test. Guidelines for clinical utilization are in their third version, and appropriateness criteria, that is, when it is appropriate to use myocardial perfusion imaging studies, were first written for nuclear cardiology.⁴ Despite the potential of contrast echocardiography, cardiac magnetic resonance imaging, and computerized tomographic (CT) angiography to measure myocardial perfusion, these modalities are technically demanding, not widely available, and lack evidence-based proof of efficacy and prognostic value. For these reasons, SPECT will continue to be used widely in the future.

Not content with its role as a superior, cost-effective, and proven standard of reference for myocardial perfusion imaging and assessment of function, nuclear cardiology continues to evolve and enhance its accuracy and value through the growing use of (1) new, safe, and effective pharmacologic stress agents, (2) attenuation correction using radionuclides and CT, (3) positron emission tomography (PET), (4) hybrid SPECT/CT and PET/CT systems, and (5) new smaller imaging systems with very short acquisition times. These new and innovative developments within nuclear cardiology will be introduced and their impact on CAD diagnosis and management explored.

Selective A_{2A} Agents for Pharmacologic Stress Testing

Due to the aging of the population and the existence of comorbid diseases that do not allow a growing number of patients to perform maximal dynamic exercise stress, as many as 50% of all SPECT studies are performed using some form of pharmacologic stress. Nearly all of these studies are performed using adenosine or dipyridamole, which are given as a continuous infusion and act by a final common pathway: stimulating adenosine A_{2A} receptors on arteriolar vascular smooth muscle cells that dilate and increase blood flow. Unfortunately, this effect of adenosine is non-selective, and there is activation of adenosine A₁, A_{2B}, and A₃ receptors that results in frequent undesirable side effects and less frequent but serious side effects such as bronchospasm and high-grade atrioventricular (AV) block.^{5,6} In

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TABLE I Single-photon emission computed tomography has shown efficacy and efficiency in diverse patient populations

1. Multiple racial groups
2. Women
3. Patients with LBBB/pacemakers
4. Patients with LV hypertrophy and nonspecific ST-T wave changes
5. Elderly patients
6. Asymptomatic/high-risk patients
7. Obese patients
8. Patients with diabetes
9. After myocardial infarction
10. After revascularization

Abbreviations: LBBB = left bundle-branch block, LV = left ventricular.

addition, there are concerns regarding the nonphysiologic hyperemia produced with adenosine and dipyridamole, as both agents produce a 4- to 4.5-fold increase in coronary blood flow.⁷ Since all the available radiotracers have non-linear uptake at higher flow rates (the so-called plateau or drop-off effect), less hyperemia may more closely approximate the response to dynamic exercise and take advantage of the uptake characteristic of the available radiotracers. Given the side effect profile, higher-than-needed flow rates, and complicated method of administration for adenosine and dipyridamole, there is also a need for a more selective agonist of the A2A receptor subtype that is easier to administer and is capable of producing controlled hyperemia in terms of magnitude and duration. Currently, three selective adenosine A2A receptor agonists have begun phase III studies as pharmacologic stress agents: regadenoson (CVT3146), binodenoson (MRE0470 or WRC0470), and apadenoson (BMS068645 or ATL146e).⁸

The desirable features of these agents include selective A2A adenosine receptor stimulation, resulting in selective coronary vasodilation; rapid onset and termination of action; and the potential for bolus administration.⁹ These properties should reduce the total occurrence of undesirable side effects and specifically reduce the more serious side effects such as AV block and bronchospasm in patients with reactive airway disease. Selective coronary vasodilation should produce minimal or no effect on blood pressure. As shown in Figure 1, rapid onset and offset would allow the vasodilatory effect to be available only when needed, that is, for 2 to 4 min to allow extraction of the radiotracer and increase blood flow two to three times above the baseline. Bolus administration, especially using a fixed dose, would obviate the need for an infusion pump and weight-based dose calculation.

The initial publications indicate that these tracers are capable of meeting many but not all of the desired features.^{10,11} It has been shown that changes in coronary blood flow can be regulated by the dose and time over which these selective agents are administered as a bolus or continuous infusion. Overall, in the published papers there was a reduction in side effects compared with adenosine, especially in the occur-

FIG. 1 Desirable features of A2A agonists for radiotracer single-photon emission computed tomography pharmacologic stress imaging. CBF = coronary blood flow.

rence of AV nodal block and bronchospasm. Tachycardia, flushing, and noncardiac chest pain still occurred, but to a reduced extent. Compared with adenosine, diagnostic efficacy, sensitivity, and specificity for two of these agents, binodenoson and regadenoson, have been shown to be similar in small studies.^{10,11} Phase III clinical trials comparing these agents with adenosine have been completed, and they found comparable diagnostic accuracy. The results are very promising as they show that these agents will allow greater ease of testing and be more selective in producing controlled changes in coronary blood flow for the desired time. In addition, the reduced side effects will make these agents more tolerable and allow them to be used with PET and cardiac magnetic resonance perfusion imaging.

PET and PET/CT Hybrid Systems

Limitations of Single-Photon Emission Computed Tomography

Despite the widespread utilization of SPECT, it has inherent limitations as an imaging modality with regard to spatial and contrast resolution, count density, attenuation and scatter correction, and resolution recovery. These important features of SPECT are compared with those of PET in Table II. Clearly, SPECT and PET cannot begin to compare with the spatial and contrast resolution that are attainable with cardiac magnetic resonance or even with a high-quality echocardiogram.

TABLE II. Single-photon emission computed tomography (SPECT) versus position emission tomography (PET) for myocardial perfusion imaging (MPI)

Variable	SPECT	PET
Spatial resolution	15–17 mm	3–4 mm
Contrast resolution	x	2x
Count density/unit time	x	4x
Attenuation correction	Optional	Routine
Scatter correction	Optional	5x
Resolution recovery	Optional	Routine

However, PET clearly does better than SPECT in all of these areas because of the superior imaging features of its camera systems and the use of higher-energy and shorter-lived radio-tracers.¹² Position emission tomography routinely performs attenuation and scatter correction as part of image acquisition and reconstruction, while with SPECT these corrections are optional and not widely performed in routine clinical practice or at recognized centers of excellence.¹³ Similarly, resolution recovery, which compensates for the loss of resolution the further a radioactive object is from the detector, is seldom performed with SPECT but is intrinsic to PET imaging.¹⁴ All of these features give a decided advantage to PET.

Strengths of PET

These superior features of PET for myocardial perfusion imaging are well illustrated in the case shown in Figures 2 and 3. A 5-month-old baby girl with frequent crying after

eating was diagnosed as having the left main originate from the pulmonary artery, which caused myocardial ischemia. This was surgically corrected by reattaching the left main to the aorta. She did well for 3 months but her symptoms returned. At the time of the rubidium-82 (Rb-82) PET study shown in Figure 2, she weighed 11 pounds. The study clearly shows anterior and lateral wall ischemia with transient ischemic dilation of the cavity. Transient ischemic dilation is the appearance of the cavity being bigger on the stress than on the resting study due to the presence of severe subendocardial ischemia and failure to visualize the full thickness of the myocardium on stress. This makes the cavity appear larger than on the rest study, when subendocardial tracer uptake makes the walls appear thicker and the cavity smaller. This finding indicates extensive diffuse CAD or severe stenosis in a large vessel and is associated with a very high death and myocardial infarction rate. Diagnostic angiography following the PET study showed that the reattached left main was crimped and nearly occluded, and it was success-

FIG. 2 Serial dipyrindamole stress and rest Rb-82 PET imaging in an 8-month-old 3 months after surgical attachment of her left main coronary artery, which arose from the pulmonary artery, to her aorta. There is anterior and lateral ischemia (arrows) with transient ischemic dilation of the cavity on stress. Str = stress, rst = rest, post = posterior, ant = anterior, sep = septal, lat = lateral.

FIG. 3 Position emission tomography (PET) imaging of the same patient as in Figure 2 is shown, after balloon dilation of the kinked reattached left main. Now there is no ischemia, and the cavity became smaller on both the rest and stress images consistent with ischemic dilation of the left ventricle at rest on the prior PET study. Abbreviations as in Figure 2.

fully dilated with a balloon catheter. Figure 3 shows a PET study performed 3 months later, and the ischemia is no longer present on stress. In addition, the resting study shows a much smaller left ventricle, which had been dilated on the earlier study due to chronic ischemia. This change in cavity size with the improvement in blood flow was confirmed on echocardiography. Clearly, this small patient would not have received a diagnostic study with SPECT due to the limited resolution, but PET was able to provide diagnostic information on myocardial perfusion that made the diagnosis and determined management.

If PET is such a superior imaging modality for perfusion imaging, why is it not being used more widely? Part of the reason is the lack of availability and higher expense of PET imaging systems and the positron emitters that are required to perform perfusion studies. These factors will continue to be a limitation, but PET imaging cameras are becoming more widely available due to their widespread use in oncology for detection and monitoring of all types of tumors. With increasing availability of PET imaging systems, there will

be more opportunities to perform cardiac PET if the radio-tracers can become available.

Positron Emission Tomography Tracers

The available PET myocardial perfusion tracers are listed in Table III. The two most commonly used PET perfusion tracers are Rb-82 and N-13 ammonia; Rb-82 is generator produced, while all of the others require a cyclotron for pro-

TABLE III. Cyclotron-produced cardiac position emission tomography perfusion tracers and their half-lives

^{82}Rb	75 sec
^{15}O	2.0 min
^{38}K	7.6 min
^{13}N	10.0 min
^{11}C	20.4 min
$^{94\text{m}}\text{Tc}$	52 min

duction; N-13 ammonia is the better of the two tracers as it allows absolute measurement of blood flow, whereas at present, Rb-82, like the SPECT tracers, is interpreted using scaled or normalized data. However, the 10-min half-life of N-13 requires an on-site cyclotron, and the isotope needs to be produced using two separate cyclotron runs to complete a rest and stress study. These limitations restrict its use to a very limited number of research centers.

Rb-82 is a better alternative for cardiac PET. It is a potassium analog that has a nearly linear extract fraction over a wide range of flow rates. Perfusion defects can be visualized 2 to 7 min after injection, and image acquisition is performed close to the time of stress. By performing gated acquisition of the rest and stress studies, there is a higher chance of picking up regional wall motion abnormalities following stress, which adds to the information provided by the perfusion. Studies are performed using the same dose and isotope for the rest and stress study so that image quality is excellent and comparable for both studies. The very short half-life allows studies to be repeated if there is patient motion or other problems with the acquisition. Finally, the isotopes are available 24 h a day, 7 days a week, which is not possible with the SPECT perfusion tracers or the cyclotron-produced PET tracers. For these reasons, Rb-82 offers significant advantages, and with the establishment of adequate reimbursement by payers, it is anticipated that utilization will continue to increase in the future.

Advantages of PET/CT Hybrid Systems

The PET/CT hybrid systems offer several advantages over dedicated PET systems. The major advantage is the shortening of the time to perform a complete study by allowing the acquisition of a CT transmission attenuation map in a matter of seconds and using it in place of the slower germanium-68 maps that are used with conventional stand-alone PET cameras. For a simple attenuation map, a single-slice CT system is adequate. With a 6-slice CT detector, there is sufficient temporal resolution to freeze the motion of the heart and make it possible to perform calcium scoring, which has been shown to be an important variable in identifying the presence of CAD. Finally, with a 16-slice or higher PET/CT system, there is sufficient temporal resolution to image the coronary arteries using iodinated contrast agents, which can be precisely coregistered with the PET perfusion images to give a complete cardiac picture from a single study session.¹⁵

Disadvantages of PET/CT Hybrid Systems

Despite the advantages of PET/CT hybrid systems, a case can be made for having separate PET and CT systems for cardiac applications. If CT is required for the attenuation correction, this can be done using a single-slice CT system. One of the touted advantages of these hybrid sys-

tems with a 16- or 64-slice CT is the ability to perform calcium scoring and CT coronary angiograms on the same system. Although possible, in most situations this is not practical, and it is inefficient in terms of the separate PET and CT systems. Computed tomography angiography can be performed in 15 to 20 s, while PET rest and stress acquisition take an average of 45 min. Since the PET and CT studies are done sequentially and not simultaneously, the CT system cannot be used during the much longer PET study. It therefore sits idly, which does not allow maximal utilization of a very expensive system. In addition, it takes time to convert the room from performing the PET study to performing the CT angiogram portions of the study. For these reasons, having separate systems with image coregistration using software fusion is a more efficient way to utilize both systems.

Attenuation Correction Using Hybrid SPECT/CT Systems

Current Limitations of SPECT Nuclear Cardiology Imaging Systems

Current state-of-the-art SPECT systems represent a tremendous advance in imaging technology, but they are still limited by the items listed in Table IV. Foremost is the lack of adequate attenuation correction, which lowers the specificity. In women and obese patients, this makes image interpretation especially difficult.

In addition, when using Tc-99m radiotracers, the presence of activity in the liver and small bowel and reflux from the duodenum into the stomach creates problems at three separate steps in the acquisition, processing, and display process.¹⁶ During acquisition, scattered radioactivity originating below the diaphragm may erroneously increase the counts in the adjacent inferior wall. Since most cardiac SPECT studies are reconstructed using filtered back projection with a ramp filter, this may create a paradoxical decrease in counts in a normal wall adjacent to a very hot area of radioactivity. Thus, there are two ongoing and opposing processes in this situation: scatter increases the counts, and the ramp filter process decreases counts in the same area of myocardium. Finally, when the processed images are displayed for interpretation, they are scaled or normalized to the hottest pixel in the study. If the hottest pixel in the field is within the myocardium and not influenced by scatter, the images will be displayed correctly. However, if there is a piece of liver or loop of bowel within the field that is more intense, the myocardium may appear washed out due to incorrect normalization.

Finally, with all radiotracer imaging, there is a loss of spatial resolution as a function of distance between the organ of interest and the detector. This means that deep structures, such as the basal portion of the inferior wall, will have worse resolution than the apex, which is closer to the detector. Resolution recovery can be performed during the acquisition to minimize resolution loss.

TABLE IV Limitations of current single-photon emission computed tomography nuclear cardiology systems

- Attenuation: breast and diaphragm
- Scatter-liver and gut from Tc tracers
 - Adds counts to inferior wall
 - Ramp filter artifact
 - Display problems with normalization
- Loss of resolution as a function of distance

TABLE V Single-photon emission computed tomography (SPECT)/computed tomography (CT) attenuation correction

- Advantages
 - High-quality SPECT perfusion images with appropriate attenuation, scatter, and resolution corrections
 - Calcium scoring
- Disadvantages
 - Cost
 - Requires larger space
 - Shielding for CT

How SPECT/CT Systems Overcome the Limitations of SPECT

Computed tomography attenuation correction is the best form of attenuation correction, as it rapidly acquires an accurate tissue density map of the body that can be applied to correct for

loss of counts as a function of distance traveled and the various densities encountered. Transmission maps can be acquired within 15 to 20 s and applied to the radionuclide emission images. During acquisition, corrections for scatter as well as resolution recovery to compensate for structures further from the detector can be performed. Finally, during processing, iterative reconstruction methods can be used in place of filtered back projection to avoid the ramp filter artifact.

Figure 4 shows an example of how CT attenuation correction can be used for improving imaging quality in even the most difficult of patients. This male patient weighing 385 pounds had a 1-day low-dose/high-dose protocol using 15/45 mCi of a Tc-99m agent. The second and fourth rows of images, stress and rest uncorrected, respectively, were acquired and processed using the conventional method of SPECT acquisition, using filtered back projection for reconstruction. The first and third rows, stress and rest CT corrected, respectively, were acquired using CT attenuation correction, scatter correction, resolution recovery, and filtered back projection. The difference is most noticeable on the 15-mCi dose rest uncorrected rows, where the inferior wall is heavily attenuated as shown by the arrows. With state-of-the-art SPECT, the corrections make the images more uniform (arrows), with the lost counts in the inferior wall, due to diaphragmatic attenuation, appropriately increased. Thus, an equivocal study with a possible inferior wall infarction can be correctly interpreted as normal. Instead of reporting "Decreased perfusion in the inferior wall possibly due to diaphragmatic attenuation, but an old myocardial infarction

FIG. 4 Comparison of SPECT/CT versus conventional SPECT in an obese patient. All images were acquired at the same time. The CT-corrected images have attenuation and scatter correction, resolution recovery, and iterative reconstruction, while the uncorrected images were reconstructed using filtered back projection without any other corrections. The arrows clearly show improvement in the extent of inferior wall attenuation with CT correction. CT = computed tomography, SPECT = single-photon emission computed tomography.

cannot be excluded. Clinical correlation is required," the report can be interpreted as "Normal study. No evidence of infarction or ischemia."

This ability to provide a definitive final interpretation without hesitation or equivocation is one of the greatest benefits of attenuation correction. This advantage is not without cost, as the SPECT/CT systems are more expensive and require a much larger space, and the shielding requirements for the CT system add to the cost. For these reasons, such systems may be more appropriate in hospital settings than in outpatient offices.

Small, Fast-Imaging SPECT Systems

The tremendous double-digit yearly growth rate of nuclear cardiology over the last 10 years has been due in part to the shifting of studies to the outpatient office setting. In such an environment, space and building restrictions have led to the development and purchase of small-footprint gamma camera systems. Such systems can be installed in small spaces without requiring extensive floor reinforcement. In addition, some of these camera systems provide innovative design features, including all digital detectors and collimation that allow studies to be acquired in a shorter acquisition time.

Two systems currently under development utilize ring detectors in a horseshoe configuration that surround the patient who sits upright in a chair, and tomographic images can be acquired without the camera having to rotate. Instead of studies taking 15 to 20 min to be acquired, high-count

studies can be acquired in 5 min with the patient sitting comfortably. Such rapid acquisition offers several advantages. First, studies are acquired in a much shorter time period so there is less opportunity for the patient to move. Second, the upright position is more comfortable and better tolerated, which will result in less motion.

An example of a 5-min acquisition using one of these systems is shown in Figure 5. The top series of short-axis images were acquired in 15 min using a conventional SPECT camera system, while the bottom images were acquired in 5 min using the CardiArc® ring detector system. Given the time difference for acquisition between the two systems, image quality is comparable.

Conclusion

Single-photon emission computed tomography perfusion imaging is the workhorse of diagnostic imaging in the United States due to its proven efficacy and efficiency for patient diagnosis and management. It is widely available and capable of producing excellent results in all patient populations. With the added feature of ECG gating, it provides functional assessment in addition to perfusion. For these reasons, it is truly a one-stop shop for diagnostic imaging. The continued development of new methods of pharmacologic stress, high-end PET, PET/CT, and SPECT/CT, and the development of rapid-acquisition, small-footprint systems, assure that the field will continue to be a vital part of cardiac patient care in the future.

FIG. 5 Matched stress and rest short-axis slices of conventional SPECT acquisition in 15 min versus rapid 5-min acquisition using a special collimation ring gantry system. SPECT = single-photon emission computed tomography.

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