Nuclear Cardiology: Present and Future

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Abstract: Nuclear cardiology has made significant advances since the first reports of planar scintigraphy for the evaluation of left ventricular perfusion and function. While the current “state of the art” of gated myocardial perfusion single-photon emission computed tomographic (SPECT) imaging offers invaluable diagnostic and prognostic information for the evaluation of patients with suspected or known coronary artery disease (CAD), advances in the cellular and molecular biology of the cardiovascular system have helped to usher in a new modality in nuclear cardiology, namely, molecular imaging. In this review, we will discuss the current state of the art in nuclear cardiology, which includes SPECT and positron emission tomographic evaluation of myocardial perfusion, evaluation of left ventricular function by gated myocardial perfusion SPECT and gated blood pool SPECT, and the evaluation of myocardial viability with PET and SPECT methods. In addition, we will discuss the future of nuclear cardiology and the role that molecular imaging will play in the early detection of CAD at the level of the vulnerable plaque, the evaluation of cardiac remodeling, and monitoring of important new therapies including gene therapy and stem cell therapy. (Curr Probl Cardiol 2006;31:557-629.)

In the early 1970s, cardiology moved into the era of noninvasive nuclear assessment of myocardial perfusion and left ventricular function with the introduction of scintigraphic imaging with

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and gated blood pool imaging. At that time, the important role that nuclear cardiology would play in the management of patients with coronary artery disease (CAD) and the new technologies that would be developed could only be hypothesized. However, based on data from the Centers for Medicare and Medicaid Services, the use of nuclear myocardial perfusion imaging studies exceeds 500,000 studies per year. In the 35 years since those discoveries, the future of nuclear cardiology has included the wide acceptance of perfusion imaging as a substantive diagnostic tool with great prognostic value, the development of perfusion radiotracers and single-photon emission computed tomography (SPECT) and positron emission tomography (PET) that markedly improve image quality, and the application of electrocardiographic gating to SPECT and PET to allow for the simultaneous determination of perfusion and left ventricular function from a single study.

With the current investigative interest into new radiotracers to be used for molecular imaging, we are once again at an important juncture in which consideration must be given to what we are capable of doing with nuclear cardiac imaging techniques now and, more importantly, what the future holds for the field. Furthermore, while the recent release of criteria for the appropriateness for SPECT myocardial perfusion imaging by the American College of Cardiology Foundation and the American Society of Nuclear Cardiology appropriately emphasizes the state of the art of myocardial perfusion imaging and assessment of regional and global left ventricular function, it would be myopic not to also consider the future of nuclear cardiology and its promise with respect to targeted molecular imaging. Consequently, the future challenges those involved in nuclear cardiology will face will center not only on understanding of coronary and exercise physiology, radiotracer kinetics, and instrumentation but also on an understanding of cellular and molecular biology. However, meeting these challenges will likely provide the ability to gain not only diagnostic and prognostic insights but also mechanistic insights into the pathophysiologic processes responsible for cardiovascular disease.

Currently, clinical nuclear assessment of the cardiovascular system focuses on three main aspects: perfusion, left ventricular function, and viability. These each will be discussed in greater depth in this monograph in terms of the current state of the art for the evaluation of these important aspects of cardiovascular function. We will first discuss the current state of the art in evaluating myocardial perfusion using radiotracers. Specifically, we will address the diagnostic and prognostic value of cardiac SPECT perfusion imaging, with special emphasis on special potassium-43 and gated blood pool imaging.
populations, and the increasing role of positron emission tomography (PET) for detecting CAD. Next, we will discuss the current methods available for evaluating left ventricular function. Our final focus on the current state of the art centers on the assessment of myocardial viability.

Following this review of the current state of the art in nuclear imaging studies, we will turn our attention to what will likely be the future of nuclear cardiology: molecular imaging. In the discussion of molecular imaging, we will first review the application of quantitative metabolic imaging to the clinical setting. In addition, we will discuss imaging of sympathetic nervous system function and its clinical implications. We will then turn to the most exciting and challenging aspect of the future of nuclear cardiology, namely, molecular imaging of clinically relevant processes, including imaging of the vulnerable plaque, ventricular remodeling, and angiogenesis.

**Myocardial Perfusion Imaging: An Overview of the Diagnostic Value of SPECT Perfusion Imaging**

There are several aspects of a radiotracer that would be considered ideal for use in perfusion imaging. First, the imaging agent should accurately reflect myocardial blood flow over a wide range of values. This is determined in part by the degree of first-pass extraction of the agent and is reflected by the “roll-off” of the tracer, or the decrease in the ability of the radiotracer to reflect true blood flow accurately at higher rates of blood flow. Second, the imaging agent should not be affected by attenuation. The degree of attenuation is related to the energy spectrum of the tracer, with higher energy tracers being less affected by attenuation. Third, metabolism of the tracer should not affect quality by increasing uptake of the tracer in organs out of proportion to blood flow. This is reflected by increased uptake in organs such as the liver that may compromise the quality of the cardiac image through scatter. Fourth, the tracer should be irreversibly trapped in tissues following its initial uptake. This allows for the development of practical imaging protocols that are relatively time insensitive, although the “redistribution” of tracers may be used to assess myocardial viability, as discussed below. Fifth, the tracer should have a short enough half-life to allow for rapid serial imaging, but not so short that image acquisition cannot be practically performed. Currently, there are six agents in use in the United States for perfusion imaging: thallium-201 thallous chloride (Tl-201), technetium (Tc)-99m sestamibi, Tc-99m tetrofosmin, rubidium-81 (Rb-82) chloride, nitrogen-13 ammonia, and oxygen-15 water. The first three of these tracers are
single-photon-emitting agents and can therefore be used with planar gamma cameras and SPECT systems. In contrast, the latter three are positron-emitting tracers and require PET cameras for imaging as well as special equipment for tracer production (ie, the latter two agents require onsite cyclotron availability).

While planar imaging of myocardial perfusion imaging represented a significant improvement over exercise treadmill testing alone in the ability to detect myocardial ischemia, the introduction of cardiac SPECT offered an improvement in the sensitivity for detecting CAD compared to planar imaging\textsuperscript{11-13} and myocardial perfusion SPECT imaging is the most common nuclear cardiac study currently utilized. There are a variety of stress and imaging protocols that are currently in use in clinical practice (Fig 1) and several radiolabeled perfusion tracers that are available for detecting CAD. While we will discuss the growing incorporation of PET perfusion imaging using rubidium-82 (Rb-82) in clinical practice, we will first focus on the diagnostic value of the SPECT tracers currently in use in the United States: Tl-201, Tc-99m sestamibi, and Tc-99m tetrofosmin. The currently available perfusion tracers represent only approximations of an ideal imaging perfusion imaging agent.

For this review of the state of the art, we will restrict our discussion to SPECT imaging for the evaluation of CAD. Numerous studies have assessed the accuracy of SPECT imaging for the detection of CAD. Table 1 summarizes the ranges of sensitivities and specificities associated with the various protocols and agents used in SPECT. As is obvious from this table, there is a wide range of values reported for sensitivity and specificity that tend to overlap between different tests, although there have been studies comparing these different protocols in a head-to-head fashion. In studies directly comparing SPECT using Tl-201 and Tc-99m sestamibi, the sensitivity of Tc-99m sestamibi was significantly greater than that for Tl-201 (93% versus 80%), although the specificity was similar for the two agents.\textsuperscript{11} In the more recent ROBUST study of 2560 individuals randomized to undergo SPECT perfusion imaging with either Tl-201, Tc-99m sestamibi, or Tc-99m tetrofosmin, the sensitivities and specificities of the three agents were similar in the subset of 137 who underwent subsequent angiography.\textsuperscript{14} However, image quality was superior for the studies acquired with the Tc-99m-based agents, most likely due in part to the lower energy of Tl-201. In contrast, there is generally good agreement between Tc-99m sestamibi and Tc-99m tetrofosmin in identifying myocardial ischemia,\textsuperscript{15,16} although Tc-99m sestamibi may have better ability than Tc-99m tetrofosmin to detect mild-to-moderate ischemic defects.\textsuperscript{17}
FIG 1. Commonly used myocardial perfusion imaging protocols. *Note that for the 2-day protocol technetium-based perfusion imaging agents that although only about 160 minutes of time is needed for the actual study to be performed, more than 24 hours elapses from the beginning of the study to the completion. In contrast, the rubidium-82 PET protocol requires only about 30 minutes to complete both the resting and the stress imaging.
George A. Beller: Tetrofosmin has a lower first-pass extraction fraction compared to sestamibi and therefore with vasodilator stress it is more difficult to detect reversibility of defects in the distribution of mild to moderate stenoses. In a study we published some years ago, we found that dipyridamole thallium imaging detected more mild-to-moderate stenoses than tetrofosmin imaging in the same patients. However, high-grade stenoses were detected with equal sensitivity as were areas of scar. Tetrofosmin and sestamibi provide similar information for viability assessment when these tracers are injected at rest.

While there is important prognostic information that can be obtained from the level of exercise achieved during a stress test and the hemodynamic responses to exercise, not all patients can exercise adequately for a variety of reasons and therefore require a pharmacologic stress test. The currently available agents used for pharmacologic myocardial perfusion imaging include agents that cause vasodilation mediated through the adenosine receptor family (adenosine, adenosine triphosphate, and dipyridamole) and agents that increase the contractility of the heart and therefore myocardial oxygen demand and myocardial blood flow through β-adrenergic receptor stimulation (dobutamine and arbutamine). Studies comparing SPECT imaging following pharmacologic vasodilation with either dipyridamole or adenosine to exercise SPECT have shown similar sensitivities and specificities, although both modalities suffer from a decreased sensitivity for detecting single-vessel disease, especially in the right coronary artery.\(^{18-27}\) However, in patients with left bundle branch
block, SPECT following pharmacologic vasodilation may have greater specificity than exercise SPECT because of the presence of septal perfusion defects that can be exaggerated by exercise.\textsuperscript{28,29} Studies have suggested the combination of adenosine infusion and low-level exercise, when possible, may be preferable to adenosine infusion alone because of greater patient tolerance and decreased gastrointestinal radiotracer activity complicating interpretation of the myocardial images.\textsuperscript{30-32}

The problems associated with adenosine or dipyridamole infusion, including bronchospasm and hypotension, are due to activation of adenosine receptors other than the adenosine 2A (A2A) receptors found specifically in the coronary vasculature. To decrease the side effects of adenosine infusion, several A2A receptor agonists have been developed and are currently undergoing trials to assess their clinical usefulness. It has recently been reported that pharmacologic myocardial perfusion imaging using A2A receptor agonists results in similar image quality as adenosine, but with decreased symptoms and atrioventricular block.\textsuperscript{33,34} Another advantage of the A2A receptor agonists is that their half-life is longer than adenosine and can be given as a bolus rather than as an infusion.

Similar to adenosine and dipyridamole, pharmacologic myocardial perfusion imaging using dobutamine has been shown to be associated with a high sensitivity and specificity\textsuperscript{26,35-37} and a good concordance with exercise SPECT imaging.\textsuperscript{38,39} Furthermore, the presence of normal SPECT perfusion imaging following dobutamine infusion is associated with a low cardiac event rate, even in individuals with a high pretest likelihood of CAD.\textsuperscript{40} The \(\beta\)-adrenergic agonist arbutamine has also been used as a pharmacologic stress agent for myocardial perfusion imaging with a high sensitivity and specificity for detecting CAD\textsuperscript{41} and has demonstrated good agreement with adenosine and dobutamine for identifying ischemic myocardial segments.\textsuperscript{42-44} However, arbutamine infusion requires specialized infusion pumps that have decreased the general acceptance of this stress agent.

The visual assessment of SPECT images is inherently a subjective method of evaluation. An important aspect of the current state of the art in myocardial perfusion SPECT imaging is the quantitative evaluation of perfusion defects (Fig 2). There are several quantitative programs available for perfusion image analysis, including 4D MSPECT (University of Michigan), CEqual (Cedars-Sinai Medical Center and Emory University), and Wackers-Liu (Yale University). The quantitative methods for image analysis have been found to be reproducible,\textsuperscript{45-47} and
studies directly comparing qualitative and quantitative interpretation of SPECT studies using these programs have demonstrated an improved detection of CAD with the use of quantitative methods of image interpretation.15,48-50

FIG 2. (A) Exercise (Ex) and resting (Rest) Tc-99m sestamibi perfusion imaging in a 57-year-old man with hypertension, hypercholesterolemia, and exertional chest pain. The patient exercised for 6 minutes on a treadmill (Bruce protocol) but developed chest pain and ischemic ECG changes after only 3 minutes of exercise. The short-axis images show a reversible perfusion defect in the anteroseptal region (diagonal arrowheads). As shown on the vertical and horizontal long-axis images, this defect includes the left ventricular apex (arrowheads). In addition, there is an inferior reversible perfusion defect (upward arrowheads). In addition, there is transient ischemic dilation of the left ventricle. These findings are consistent with two-vessel ischemia.
Myocardial Perfusion Imaging: An Overview of the Prognostic Value of SPECT Perfusion Imaging

The prognostic power of SPECT myocardial perfusion imaging has been extensively evaluated in a variety of patient populations and in a variety of centers. To put this into perspective, a recent meta-analysis evaluated the previous studies that reported on the prognostic value of SPECT in patients with known or suspected CAD and included 53,762 individuals from 21 studies. This meta-analysis emphasized the findings of the previous work on which it was built, confirming the fact that information from myocardial perfusion SPECT imaging adds incremental...
prognostic value concerning cardiac mortality and myocardial infarction to the information gained from patient clinical variables, exercise treadmill testing, and angiographic findings.

One of the greatest strengths of myocardial perfusion SPECT imaging is the prognostic power associated with normal images (Fig 3). Specific-
cally, several studies have indicated that a negative SPECT study confers an excellent prognosis with an annual cardiac event rate of <1% for the general population.\textsuperscript{40,52-56} In the setting of a normal myocardial perfusion study in a low-risk patient, it takes 9 years for the risk of a cardiac event to reach 1%,\textsuperscript{57} suggesting that, in the absence of new symptoms, a repeat perfusion study may not be needed for 3 to 5 years. However, this “warranty period” does not appear to be absolute and is affected by clinical and technical factors, including the presence of diabetes or CAD, increasing age and male gender, and the need to perform a pharmacologic stress test rather than an exercise perfusion imaging test, which can increase the annual cardiac event rate in patients with a normal perfusion scan to as high as 1.8%.\textsuperscript{57} In these high-risk patients with normal myocardial perfusion studies, it may be prudent to perform repeat perfusion imaging on a more frequent basis.

In addition to normal perfusion studies conferring an excellent prognosis, important prognostic information comes from the severity and extent of perfusion defects. In a variety of patient groups, there is an increasing annual cardiac event rate associated with increasing severity of both fixed or reversible perfusion defects in patients either with no prior history of CAD or with a history of prior myocardial infarction.\textsuperscript{54,58-62} While patients with mild perfusion defects have a low cardiac death rate, approaching that of patients with normal images, they are at higher risk than individuals with normal scans for nonfatal myocardial infarction.\textsuperscript{62} Furthermore, cardiac event rates are associated with the extent of perfusion defects in patients with a previous myocardial infarction.\textsuperscript{59} In a study of high-risk patients who underwent myocardial SPECT perfusion imaging and cardiac catheterization, a 1-unit increase in the summed stress score was associated with a 5% increase in the risk of death or nonfatal myocardial infarction and provided prognostic information independent of the information gained from angiography.\textsuperscript{63} The severity and extent of a perfusion defect can also be used to predict outcome following therapy, with patients with greater burden of CAD based on perfusion imaging benefiting from revascularization therapy compared to medical therapy, while patients with mild defects may be treated medically.\textsuperscript{62,64} Patients with an abnormal myocardial perfusion scan, showing evidence of either ischemia or infarction, are twice as likely to develop heart failure than individuals with normal perfusion scans.\textsuperscript{65}
George A. Beller: The prognostic value of stress myocardial perfusion imaging was comprehensively reviewed by Shaw LJ and Iskandrian AE. Prognostic Value of Gated Myocardial Perfusion SPECT. (J Nucl Cardiol 2004;11:171-85) who undertook a meta-analysis of all studies published in the literature. For 39,173 patients with normal or low-risk SPECT scans, the annual rate of cardiac death or nonfatal myocardial infarction was 0.6% per year with an average follow-up in these studies of 2.3 years. For the studies including low- and high-risk patients undergoing stress perfusion imaging, comprising 69,655 patients, the annual hard cardiac event rate was 0.85% per year for patients with normal scans and 5.9% per year for patients with moderately to severely abnormal scans. Patients with normal pharmacologic stress scans have a higher future cardiac event rate than patients with normal exercise scans, which may reflect the higher baseline clinical risk for patients who are deemed unable to exercise. Also, patients with abnormal pharmacologic stress studies have a higher subsequent cardiac event rate than patients with abnormal exercise scan results.

The prognostic value of myocardial SPECT perfusion imaging has also been demonstrated in elderly patients following exercise stress testing and shows that a normal perfusion study in patients ≥75 years of age is associated with an annual cardiac mortality of 0.8%. While exercise stress testing may be problematic in many elderly individuals, the prognostic value of myocardial SPECT perfusion imaging has also been demonstrated in elderly patients who could not exercise and required a dobutamine myocardial perfusion imaging study, with a ninefold higher risk of cardiac events in patients over 65 years of age and an abnormal perfusion study compared to patients over 65 years of age with a normal perfusion scan. As with younger individuals, patients over 65 years of age with a normal perfusion scan following pharmacologic stress had a very low annual event rate (0.7%).

In addition to identification and estimation of the severity of perfusion defects, myocardial SPECT perfusion imaging offers other important prognostic information associated with the presence of high-risk feature (Table 2). An elevated lung–heart ratio for either Tl-201 or Tc-99m sestamibi on SPECT imaging correlates with elevated left-sided filling pressures, as it does for Tl-201 planar perfusion imaging. Like planar imaging, an increased lung–heart ratio has been found to also be a marker of poor prognosis in SPECT imaging and to be a sensitive, but not necessarily specific, indicator of severe CAD. Furthermore, the presence of transient ischemic dilation (TID) of the left ventricle, due to decreased subendocardial perfusion making the left ventricular cavity appear larger, is associated with extensive CAD and poor prognosis, even in patients with no perfusion defects. While both an elevated lung
heart ratio and TID are associated with a high burden of CAD, it is believed that the two findings occur through different mechanisms and may therefore have incremental prognostic value.73-75

While this review focuses on the role of nuclear imaging in the detection of CAD, it is important to discuss the role that echocardiography plays in the detection of myocardial ischemia. In contrast to myocardial perfusion imaging using radiotracers, most of the echocardiographic methods of detection of myocardial ischemia are based on identifying transient regional left ventricular dysfunction. In early studies comparing dobutamine myocardial perfusion SPECT imaging and dobutamine stress echocardiography, there were similar sensitivities and specificities for the two modalities in the detection of CAD.26,76 However, the accuracy of stress echocardiography is limited in patients with preexisting wall motion abnormalities that make it difficult to detect new regional wall motion abnormalities.77,78 In addition, stress echocardiography may be less sensitive than myocardial perfusion SPECT imaging for the detection of single-vessel disease.79 In patients with a recent myocardial infarction, ischemia identified by dobutamine SPECT perfusion imaging was associated with an increased cardiac event rate, while the identification of ischemia by dobutamine stress echocardiography was not predictive of the risk of future cardiac events,80 indicating a greater prognostic value for myocardial perfusion SPECT imaging. Another study has demonstrated that TI-201 SPECT imaging is more accurate than

### TABLE 2. High-risk markers associated with stress testing and perfusion imaging

<table>
<thead>
<tr>
<th>Stress test markers</th>
<th>SPECT markers</th>
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<tbody>
<tr>
<td>● Ischemic ECG changes at a low (5 METS) workload</td>
<td>● Elevated lung heart ratio (&gt;0.50 for TI-201, &gt;0.43 for Tc99m-sestamibi)</td>
</tr>
<tr>
<td>● Typical angina occurring at a low (5 METS) workload</td>
<td>● Transient ischemic dilation of the left ventricle during stress</td>
</tr>
<tr>
<td>● Ischemic ECG changes or typical angina persisting late into the recovery phase</td>
<td>● Transient right ventricular visualization during stress</td>
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<tr>
<td>● Hypotensive blood pressure response to exercise</td>
<td>● Perfusion defects in multiple vascular territories</td>
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<tr>
<td>● Ischemic ECG changes during adenosine/dipyridamole infusion</td>
<td>● Large, severe perfusion defects</td>
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<tr>
<td>● Development of ventricular tachycardia/fibrillation</td>
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<td>● Development of pulmonary edema</td>
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dobutamine stress echocardiography in identifying ischemic myocardial regions with angiographically documented epicardial coronary stenoses.  

George A. Beller: One limitation of vasodilator stress perfusion imaging is the failure to detect defects in some patients with three-vessel disease because of what is referred to as "balanced ischemia." This occurs when there is a homogeneous diminution in flow reserve in the distribution of all three major coronary vessels that have obstructive lesions. Thus, during vasodilator stress, no areas show an increase in tracer uptake since flow is not increased segmentally in one area more than another. This results in what appears to be a normal perfusion scan. In contrast, PET imaging, which has the ability to quantitate flow in ml/min/g, might have identified this balanced ischemia by showing a failure of flow reserve in all three coronary territories. In some patients with diffuse diminution in flow reserve and three-vessel disease, regional systolic functional abnormalities observed on gated SPECT images may provide information that CAD is present and severe. This is due to postischemic stunning, where regional thickening abnormalities can be seen even 30 to 45 minutes poststress.

Myocardial Perfusion Imaging with Gated SPECT and Attenuation Correction: The Current State of the Art for SPECT

One of the acknowledged weaknesses of cardiac SPECT studies is attenuation artifact, manifesting as specific defects associated with diaphragmatic attenuation or breast attenuation or through generalized poor image quality in obese patients. While the artifacts can be addressed to a certain extent through the use of prone imaging to evaluate diaphragmatic attenuation or gating of the SPECT images to evaluate regional wall motion, attenuation correction represents the optimum method of dealing with these artifacts. While attenuation correction can be performed using gamma-emitting external line sources, which has been shown to improve the diagnostic accuracy of SPECT imaging, the attenuation correction maps that are generated by these systems tend to have low count statistics and therefore relatively low resolution and therefore lead to the use of CT for attenuation correction. Furthermore, with the development of multislice CT systems with greater spatial and temporal resolution, there is increasing interest in the development of hybrid cameras that combine the ability to perform either SPECT or PET imaging and obtain CT scans that can be used for coronary artery calcium scoring and/or CT angiography as well attenuation correction (Fig 4).

In contrast to the numerous studies mentioned above that have evalu-
ated the ability of attenuation correction using line sources to improve image quality, there have been three studies to date that have demonstrated the improvement in SPECT perfusion imaging with low-dose CT attenuation correction when comparing these attenuation-corrected images to PET studies. The concordance between SPECT and N-13 ammonia PET perfusion studies was increased with the application of CT-generated attenuation maps are applied to the images (Rest-AC), the inferior perfusion defect improves.

**FIG 4.** Improvement in SPECT image quality with attenuation correction (AC). In a patient with evidence of diaphragmatic attenuation based on improvement in count recovery on planar imaging (lower panel), when the patient is moved from the supine to decubitus position, there is evidence of an inferior wall perfusion defect on both the stress and the rest SPECT perfusion images. However, when CT-generated attenuation maps are applied to the images (Rest-AC), the inferior perfusion defect improves.
studies to coronary angiographic findings, it was found that attenuation correction with multislice CT improves the sensitivity and specificity of the SPECT images.\textsuperscript{91,92} As with SPECT imaging without attenuation correction, quality control is important in obtaining meaningful images using CT attenuation correction. Misregistration of the CT and SPECT images degrades image quality in direct proportion to the degree of misregistration.\textsuperscript{93} Similarly, care must be taken with PET/CT studies to insure proper registration of the two image sets.\textsuperscript{94}

**Current State of the Art for Myocardial Perfusion Imaging: Myocardial Perfusion Imaging with PET**

As discussed above, SPECT imaging of myocardial perfusion for the detection of CAD is associated with a relatively high sensitivity and specificity. While SPECT imaging has benefited from the incorporation of attenuation correction, the method can still be affected by photon scatter. Other factors can also limit the usefulness of SPECT tracers for perfusion imaging. For example, because of the dosimetry of Tc-99m sestamibi and Tc-99m tetrofosmin, stress and rest imaging of obese patients must be performed on two separate days and, with Tl-201, the target organ exposure becomes prohibitive for its use in obese individuals. In contrast, PET tracers of blood flow offer several advantages. First, the high-energy 511-keV gamma photons produced by positron-emitting radionuclides, combined with the attenuation correction necessary with coincidence detection systems in PET cameras, makes assessment of myocardial perfusion with PET a good option in obese patients (Fig 5). Second, the

![FIG 5. Improvement in image quality with Rb-82 PET compared to Tc-99m sestamibi SPECT in an obese patient (weight: 109 kg, height: 1.68 cm, body mass index: 38.6 kg/m\textsuperscript{2}).](image-url)
very short half-lives of the commonly used PET radionuclides reduces
issues surrounding the dosimetry of the tracers. Finally, the short
half-lives of N-13 (10 minutes), O-15 (5 minutes), and especially Rb-82
(1.3 minute) also decrease the amount of time required to complete rest
and stress studies (Fig 1), improving study throughput. While N-13 and
O-15 production require an on-site cyclotron, Rb-82 is eluted from a
strontium-82 bench top generator, allowing its use for clinical imaging at
sites geographically remote from facilities that have a cyclotron.

In a head-to-head comparison, Rb-82 PET had a higher sensitivity (93% versus 76%) and accuracy (90% versus 77%) with a similar specificity (78% versus 80%) as TI-201 SPECT. In a follow-up of the patients in that study that had angiographically proven false-negative TI-201 SPECT studies but true-positive Rb-82 PET studies, 63% of the patients were subsequently referred for revascularization. In a study of 685 patients undergoing dipyridamole Rb-82 PET, there was a 90% event-free survival in patients with normal PET images, but 87, 75, and 76% event-free survival in patients with small, moderate, or large defects, respectively. Furthermore, the PET images provided incremental information to the clinical and angiographic findings with respect to event-free survival. Interestingly, in contrast to SPECT imaging, in which ischemic ECG responses in the absence of perfusion defects are associated with increased cardiac event rates, a normal Rb-82 PET image confers an excellent prognosis, even in the presence of ischemic ECG changes, suggesting that there may be a subset of patients with false-negative SPECT studies who might benefit from further risk stratification with PET imaging. While the majority of Rb-82 PET studies are performed using dipyridamole as a pharmacologic vasodilator, one recent study has demonstrated the feasibility of performing exercise treadmill testing with Rb-82, which would add the prognostic information gained from exercise. Rubidium-82 PET has also been used to identify patients at risk for restenosis following angioplasty prior to the development of symptoms.

SPECT imaging only provides information about relative flow heterogeneity but offers no information about absolute flow and therefore balanced ischemia in the setting of multivessel disease may be missed. For example, if there is a critical stenosis in the left anterior descending (LAD) coronary artery, but no stenoses in the left circumflex (LCx) or right coronary arteries (RCA), the absolute blood flow in response to maximal exercise could be reduced in the LAD by 50% compared to the LCx and the RCA (Fig 6). This would be reflected by a significant difference in tracer uptake in the LAD territory compared to the LCx and RCA territories. In contrast, if there are critical stenoses in all three
vessels, absolute maximal blood flow in response to exercise would be decreased in all three territories, but the relative difference in perfusion tracer uptake would be below the limits of discrimination. Because of the physical nature of the positron annihilation event in which a positron and an electron are annihilated, releasing two 511-keV gamma photons at almost 180° from each other, combined with the use of attenuation correction, dynamic PET imaging can be used to quantify the uptake and fate of positron-emitting tracers. This holds true not only for the determination of rates of substrate metabolism using carbon-11- and fluorine-18-labeled analogs of substrates (discussed below), but also for the measurement of absolute rates of myocardial perfusion using either N-13 ammonia, O-15 water, or Rb-82. While the longer half-lives of N-13 and O-15 make the kinetic analysis easier than the shorter lived Rb-82 because of increased signal-to-background activity ratios, several groups have developed kinetic models to estimate myocardial blood flow based on dynamic Rb-82 PET image analysis. A study of patients with
triple-vessel disease demonstrated that the perfusion defects were 57% larger using quantitative Rb-82 PET imaging when compared to a nonquantitative approach.102

**Myocardial Perfusion Imaging in Specific Groups: Diabetes Mellitus**

The incidence of diabetes is increasing worldwide and the leading cause of death in diabetic individuals is cardiovascular disease.104 Unfortunately, a large number of diabetic individuals with CAD are asymptomatic, and when diabetic patients with CAD are identified, the atherosclerosis is extensive and severe. Furthermore, diabetic patients have a poorer outcome following myocardial infarction treated either with thrombolysis or with percutaneous coronary intervention that may be related to a greater burden of CAD.105-108 Based on retrospective database analysis, patients with diabetes and abnormal myocardial perfusion studies have a poorer prognosis than nondiabetic patients with similar perfusion defects.61 Indeed, the mortality rate following myocardial infarction for diabetic patients with a first myocardial infarction is as high as the rate for nondiabetic patients with a prior myocardial infarction.109 In this setting, it is important to identify diabetic patients with CAD early.

Myocardial perfusion SPECT imaging in diabetic patients is known to have similar sensitivity, specificity, and normalcy rates when compared to the use of myocardial perfusion imaging in nondiabetic individuals.110 In the past 3 years, several studies have focused on the use of myocardial perfusion imaging in asymptomatic diabetic patients to identify those at increased risk for cardiac events. In a small study of diabetic patients undergoing dipyridamole Tl-201 perfusion imaging prior to vascular surgery, 58% of patients without clinical signs of CAD had abnormal perfusion scans, although they had no perioperative cardiac complications.111 Another small study demonstrated that 26% of asymptomatic diabetic patients had an abnormal myocardial perfusion study and that the rate of myocardial infarction, cardiac death, and late revascularization in those patients was seven times higher than in asymptomatic diabetic patients without perfusion defects.112 These studies have been supported by subsequent studies that have enrolled large numbers of patients from multiple sites. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study found that 22% of type 2 diabetic patients had abnormal adenosine technetium-99m sestamibi SPECT studies113 (Fig 7). This study, performed in 1123 patients, demonstrated that cardiac autonomic dysfunction, as assessed by an abnormal Valsalva ratio, is a strong predictor of myocardial ischemia.113 In a study of the factors that identify
asymptomatic diabetic patients with perfusion defects, poor glycemic control, as assessed by a high hemoglobin A1C level, and retinopathy were significant predictors of the presence of silent ischemia. In a study comparing diabetic patients with symptoms of CAD to asymptomatic diabetic patients, it was found that there was a high rate of positive SPECT myocardial perfusion scans in both groups (51 and 39%, respectively). Based on these studies of asymptomatic diabetic patients, the prevalence of silent ischemia is between 20 and 60% and those patients with poor glycemic control or evidence of autonomic neuropathy may be at greater risk for silent ischemia and may represent the patients that should be the focus of screening myocardial perfusion studies. The DIAD study is currently in its second phase to determine the long-term outcome of this cohort of asymptomatic diabetic patients.

In a recently reported study, Tl-201 SPECT perfusion defects were identified in 62% of high-risk asymptomatic diabetic patients compared to inducible wall motion abnormalities in 10% of patients using dobutamine.

FIG 7. Findings of the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. In asymptomatic diabetic patients without a previous history of coronary artery disease (n = 522), 22% of the patients had abnormal myocardial perfusion SPECT studies, with a significant number of patients having moderate-to-large perfusion defects.
echocardiography. Interestingly, in the same cohort of patients, angiographically confirmed stenoses were identified by SPECT in 26% of patients and by dobutamine echocardiography in 5% of patients. These data suggest that SPECT has greater sensitivity than dobutamine echocardiography for detecting CAD in asymptomatic diabetic patients. Furthermore, the difference in the frequency of ischemic SPECT perfusion defects and the frequency of angiographically significant stenoses support the role of microvascular disease in diabetes. Interestingly, diabetic patients without myocardial ischemia can have evidence of systolic and diastolic dysfunction, which may impair diastolic myocardial perfusion. Furthermore, the perfusion reserve of diabetic patients is decreased compared to nondiabetic individuals, and this blunting of the perfusion reserve is even greater in diabetic patients with hypertension.

George A. Beller: Women diabetics have a significantly higher cardiac event rate with either normal or abnormal perfusion scans compared to male diabetics and compared to nondiabetic females (Shaw LJ, Iskandrian AE. Prognostic Value of Gated Myocardial Perfusion SPECT. J Nucl Cardiol 2004;11:171-85). The annual death or nonfatal infarction rate for women diabetics with abnormal scans exceeds 10% per year compared to approximately 6% per year for diabetic men with normal scans. Interestingly, the combined death or infarction rate for diabetic women with normal perfusion scans is more than 3% per year, which is substantially higher than seen in diabetic men. Also, the Mayo Clinic group has reported that asymptomatic diabetics have the same prevalence of high-risk perfusion scans (20%) as do symptomatic diabetics (Miller TD, Rajaqopalan N, Hodge DO, et al. Yield of Stress Single-photon Emission Computed Tomography in Asymptomatic Patients with Diabetes. Am Heart J 2004;147:890-96). Similarly, diabetics presenting with dyspnea actually have a higher prevalence of abnormal stress scans than patients presenting with chest pain. Thus, the diabetic population is one which truly benefits from risk assessment by noninvasive stress imaging.

Myocardial Perfusion Imaging in Specific Groups: Renal Disease

Similar to the effects of diabetes, the presence of chronic renal failure is associated with increased cardiac morbidity and mortality. Studies of dipyridamole myocardial perfusion imaging using Tl-201 indicate a sensitivity and specificity in patients with end-stage renal disease on hemodialysis that is similar to the values reported for the general population. Pretransplant evaluation in patients with end-stage renal disease demonstrates that patients with abnormal myocardial perfusion...
scans have higher cardiac event rates following renal transplantation compared to patients with normal perfusion scans \cite{121,122}, although coronary angiography may still be a better predictor of cardiac events in patients who are being considered for renal transplantation \cite{123}. In patients who have undergone renal transplantation, inducible ischemia was identified in 10% of the patients and predicted cardiac events \cite{124}. Interestingly, there is an association between acute graft rejection and the presence of perfusion abnormalities. In a small, single-center study, almost 50% of patients with end-stage renal disease beginning hemodialysis had perfusion defects on pharmacologic myocardial perfusion studies using Tl-201 and a 1-year cardiac event rate that was 15 times higher than that for patients with normal perfusion scans \cite{125}.

**Myocardial Perfusion Imaging in Specific Groups: Patients with Heart Failure**

The evaluation of patients with newly diagnosed congestive heart failure demands determining if there is a reversible cause for the cardiomyopathy. Because ischemic heart disease is the leading cause of heart failure in the United States, assessment for myocardial ischemia is essential in guiding potential revascularization therapy. While an argument can be made for using coronary angiography as the first diagnostic modality to assess the adequacy of coronary blood flow in patients with congestive heart failure, the morbidity (albeit low) associated with cardiac catheterization supports the contention that perfusion imaging as a first step should be considered. It is not surprising that patients with large, severe, reversible defects are likely to have ischemic cardiomyopathy \cite{126}. In a study of 164 patients with depressed left ventricular function (LVEF <40%) and no previous history of CAD who underwent both gated SPECT and coronary angiography, the sensitivity and specificity of gated SPECT for diagnosing ischemic cardiomyopathy were 88 and 45%, respectively \cite{127}. The patients with the greatest gain following revascularization are those with the largest reversible defects. Interestingly, patients with depressed left ventricular function and severe resting Tc-99m sestamibi perfusion defects did not experience an increase in LVEF or a reduction in the left ventricular end-systolic and -diastolic volumes following 3 months of cardiac resynchronization therapy when compared to patients with no perfusion defects \cite{128}.

George A. Beller: Ischemic and nonischemic cardiomyopathy can often be distinguished by the heterogeneity of thickening abnormalities on gated
SPECT imaging. Patients with nonischemic cardiomyopathy have more uniform abnormal systolic myocardial thickening compared to patients with ischemic cardiomyopathies. The authors make an excellent point that patients presenting with heart failure and who have severe nonreversible defects have little chance of showing improved function after revascularization and will surely show continued left ventricular remodeling over time.

Myocardial Perfusion Imaging in Specific Groups: Women

It is well known that the presentation of women with CAD can be different from that of men. Women under 50 are twice as likely to die early after a myocardial infarction than are men in the same age group. Furthermore, issues of the effects of breast attenuation on image quality and the specificity of myocardial perfusion imaging indicate that special attention should be paid to whether myocardial perfusion imaging should be approached differently in women than in men. Although most of the early studies of the utility of myocardial perfusion imaging in establishing the diagnosis and prognosis of CAD included predominantly men, studies have established that SPECT myocardial perfusion imaging using either Tl-201 or technecium-99m sestamibi provides excellent diagnostic and prognostic information in women. While the specificity of planar or nongated SPECT imaging in women can be adversely affected by breast attenuation and a relatively smaller left ventricle, the use of gating improves the specificity of SPECT in distinguishing breast attenuation from scar based on regional wall motion. Supplementing gated SPECT with attenuation correction may also help to further minimize artifacts related to attenuation from breast tissue.

George A. Beller: The authors make an important point regarding the detection of CAD in women using stress SPECT imaging. The use of gating and attenuation correction can improve the specificity of CAD detection in women and allow distinguishing breast artifacts from true CAD defects. Some women will show perfusion defects that are ischemic but, when cardiac catheterization is performed, no high-grade stenoses are found. This is because the ischemia is due to endothelial dysfunction and microvascular abnormalities that produce stress-induced defects. In the past, such women were considered to have false-positive scans for ischemia. Also it has been shown that women with more than 20% of the ventricle rendered ischemic on stress perfusion imaging have a significantly worse outcome with medical management compared to revascularization (Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the Short-term Survival Benefit Associated with Revascularization Compared with Medical Therapy in Patients with no Prior Coronary Artery Disease Undergoing Stress Myocardial Perfusion Imaging Curr Probl Cardiol, September 2006 579)
Single Photon Emission Computed Tomography. Circulation 2003;107:2900-7). In this study from Cedars Sinai the event rate was 17% per year for women treated medically with more than 20% of the LV showing ischemic defects compared to 4.4% a year after revascularization. Surely, many of these women were probably diabetics.

Myocardial Perfusion Imaging in Specific Groups: Racial and Ethnic Groups

 Appropriately, greater attention is being placed on evaluating the application and prognostic power of diagnostic testing to specific racial and ethnic groups. African Americans have a higher mortality associated with CAD. However, there are little data concerning the ability to determine prognosis based on myocardial perfusion imaging in African Americans. Two studies have addressed the application of myocardial perfusion SPECT imaging to the African American population. In the first study from a single, urban institution, a normal exercise treadmill test in African Americans conferred a low annual cardiac event rate (1%), although a normal perfusion study in African Americans was associated with a slightly elevated cardiac event rate (1.2%) and the need to use pharmacologic stress testing in African Americans was associated with an intermediate risk of myocardial infarction or cardiac death (5%).

Unfortunately, that study was limited by the fact that approximately 20% of the patients were lost to follow-up and that there was no comparison to a non-black population evaluated at the same institution. A subsequent multicenter study compared the clinical characteristics and SPECT imaging results in a large population of African American, Hispanic, and non-Hispanic Caucasians. A higher proportion of both African-American and Hispanic patients had moderate to severely abnormal SPECT scans and had higher cardiac event rates compared to non-Hispanic Caucasians. While the patients in the three groups were not well matched with respect to baseline clinical characteristics, including age, gender, history of CAD, and myocardial infarction, presence of congestive heart failure and risk factor profile, the presence of depressed left ventricular function (LVEF <45%) was associated with threefold and fivefold higher annualized risk-adjusted death rates for African-American and Hispanic individuals, respectively, compared to non-Hispanic Caucasians. Similar to the prior study discussed above, a “low-risk” myocardial perfusion study in the African-American and Hispanic patients had an increased annual cardiac death rate of 2.4 to 3.5%, compared to a rate of 0.2% for the non-Hispanic Caucasian patients. While these studies demonstrate the ability of myocardial perfusion imaging to provide important prognostic
information concerning cardiac events in ethnic groups, it also emphasizes the greater risk of adverse cardiac events in these populations. While many factors most likely contribute to these differences in the cardiovascular outcomes of ethnic minorities, results of these and other studies remind us of the need to correct disparities in health care access for underserved groups.

One racial group of increasing clinical interest that has not been studied extensively is the population of Asians that present with metabolic syndrome and CAD but not with other traditional risk factors. In one study comparing the causes of left ventricular systolic dysfunction in different racial groups, there was a higher proportion of Asian patients with an ischemic cause of dysfunction compared to Caucasian patients. In individuals of Asian origin, presumably with specific genetic factors that increase the risk of CAD, the question becomes whether myocardial perfusion imaging will have the same diagnostic and prognostic power as in the other racial and ethnic groups that have been studied. It also supports the argument that further development of molecular imaging agents based on the elucidation of cellular mechanisms of disease is needed.

Assessment of Left Ventricular Function: The Current State of the Art

It is well known that left ventricular function is one of the major determinants of survival. For many years, the accurate quantitative assessment of left ventricular ejection fraction was required mostly for monitoring patients receiving anthracycline chemotherapy and remains an important tool for evaluating patients during and after chemotherapy, while qualitative assessment of left ventricular function was generally sufficient for most other clinical applications. However, with the confirmation of the important role of treating ventricular arrhythmias in patients with an ejection fraction below 30% based on the MADIT II trial, the need to accurately assess left ventricular function in a quantitative and reproducible manner has gained newfound importance.

Planar gated blood pool imaging was the standard scintigraphic method for many years and remains the most accurate of the nuclear-based methods for determining left ventricular systolic and diastolic function. However, the assessment of left ventricular perfusion and function prior to the development of gated SPECT required the use of two different procedures and strategic planning of dual radioisotope injection. Beginning more than 25 years ago, methods were developed to assess regional and global left ventricular function based on acquisition of
electrocardiographically gated SPECT perfusion images based on left ventricular edge detection and/or changes in count density.\textsuperscript{151-160} The development of gated myocardial perfusion SPECT represents a significant advance in nuclear cardiology that allows for the simultaneous determination of perfusion, global left ventricular function, and regional wall motion. Multiple studies have demonstrated the ability of gated myocardial perfusion SPECT to provide an acceptable estimate LVEF compared to equilibrium gated blood pool imaging, first pass gated blood pool imaging, echocardiography, and contrast ventriculography.\textsuperscript{161-166} However, the presence of factors such as large perfusion defects, intense extracardiac activity, and small ventricular volumes, as well as technical factors including radioisotope energy and dose and number of gating frames, can affect the ability of gated SPECT to assess left ventricular function accurately.\textsuperscript{159,166-170}

The assessment of left ventricular function is an essential part of risk stratification in the cardiovascular evaluation of a patient. As mentioned above, left ventricular function plays an important role in determining survival. In addition, detection of transient ischemic left ventricular dysfunction during exercise has important prognostic value. Therefore, it would follow that the ability to evaluate left ventricular function as part of a myocardial perfusion study would add incremental prognostic information. In low-risk patients, the additional information provided by gated SPECT decreased the number of “borderline” interpretations of the perfusion scans and increased the number of normal studies from 74 to 93%.\textsuperscript{171} Conversely, in patients with a previous history of myocardial infarction or angiographically confirmed coronary stenosis, the percentage of patients with abnormal scans increased from 78 to 92%.\textsuperscript{171} Furthermore, the addition of attenuation correction to gated SPECT adds further incremental information, improving the sensitivity and normalcy rate for perfusion studies, with the greatest benefit coming from improved sensitivity for detecting abnormalities in the right coronary artery distribution.\textsuperscript{172}

In one study of patients with reversible perfusion defects, approximately one-third of the patients had a poststress gated SPECT LVEF that was more than 5% lower than the resting gated SPECT LVEF, suggesting that transient left ventricular systolic dysfunction can be identified by gated SPECT.\textsuperscript{173} Using a modified quantitative gated SPECT program that would allow evaluation of both systolic and diastolic function, investigators have been able to identify decreases in postexercise LVEF and peak filling rate in patients with known myocardial ischemia or infarction.\textsuperscript{174} The importance of evaluating left ventricular function was emphasized in
a study of high-risk patients in whom myocardial SPECT perfusion imaging and first-pass equilibrium radionuclide angiography (ERNA) were both performed. In that study, the stronger predictor of cardiac death was the LVEF, determined by first-pass ERNA, while an abnormal exercise perfusion study was the stronger predictor of nonfatal myocardial infarction.

In patients with large and dense perfusion defects, the accuracy of measurements of LVEF and regional wall motion by gated myocardial perfusion SPECT decreases because of the low count density in the region of the perfusion defect. Great interest has focused in recent years on the use of gated blood pool SPECT (GBPS) imaging for the assessment of both right and left ventricular function and anatomy (Fig 8). Several studies have demonstrated a good correlation between the LVEF determined by GBPS and planar ERNA as well as a good correlation with LVEF measured by cardiac magnetic resonance imaging. GBPS evaluation of LVEF appears to be robust in a variety of patient subgroups, including those with known myocardial infarction and congestive heart failure.

One of the benefits of gated blood pool SPECT is the ability to assess right ventricular function. Assessment of right ventricular function provides important information in assessing patients with signs of isolated right heart failure, valvular heart disease, and pulmonary hypertension.
and is also an independent predictor of survival in patients with left heart failure. With planar gated blood pool studies it is possible to assess right ventricular function based on the initial transit of tagged blood cells through the right ventricle (first-pass radionuclide angiography, FPRNA), although during the equilibrium phase of the gated blood pool studies, the geometry of the right and left ventricles does not allow adequate separation to determine right ventricular function. Furthermore, acceptable first-pass image acquisition is dependent on a variety of factors, the chief factors being a rapid and compact bolus injection of the tagged red blood cells and optimum gamma camera orientation. In fact, in one study comparing first-pass radionuclide angiography with gated blood pool SPECT, 25% of patients recruited for the study were excluded because of the inability to acquire acceptable FPRNA studies. With gated myocardial perfusion SPECT studies, partial volume effects caused by the relatively thin nature of the right ventricular free wall and the shape of the right ventricle make evaluation of right ventricular function virtually impossible. In contrast, gated blood pool SPECT imaging allows for the differentiation of right and left heart structures during the equilibrium phase of a gated blood pool study, during which adequate counts can be achieved for assessing right and left ventricular function. Furthermore, there is much less concern about partial volume for the right ventricular cavity when compared to the right ventricular free wall. Groups have demonstrated correlations between the RVEF derived from FPRNA and GBPS between 0.70 and 0.87, although differences in the model assumptions used in the programs to assess RVEF result in differences in the calculated value. Two studies that included a small number of patients have demonstrated superiority over contrast and planar radionuclide ventriculography in identifying regional wall motion abnormalities in patients with critical coronary stenoses. Further studies are necessary to determine whether the identification of regional wall motion abnormalities by GBPS will add incremental information over SPECT myocardial perfusion imaging.

The application of GBPS to the assessment of right ventricular disorder extends past the simple evaluation of LVEF and RVEF to use in determining response to therapy. In patients with arrhythmogenic right ventricular dysplasia, GBPS can be used to assess right ventricular enlargement, asynchronous right ventricular contraction, and increased contraction dispersion in addition to RVEF. GBPS has been used to evaluate the functional response to accessory pathway radiofrequency ablation. In a study of 44 patients with Wolff–Parkinson–White syndrome, patients with left-sided accessory pathways were more likely to
experience an increase in LVEF, as determined by GBPS, compared to those with right-sided pathways, and interestingly, based on phase analysis of the GBPS studies, persistent local preexcitation can be demonstrated despite ablation of the accessory pathway.189

The application of GBPS to patients with congestive heart failure to guide management may be useful in several ways. First, with the increasing interest in the use of cardiac resynchronization therapy in patients with depressed left ventricular function and intraventricular conduction delays, it is important to identify patients who will benefit from this therapy. Phase analysis of ventricular contraction has been advanced as a method to aid in the identification of patients who are appropriate for cardiac resynchronization therapy. Phase analysis has been applied to planar ERNA studies to identify dyssynchronous ventricular contraction. Evaluation of patients with idiopathic dilated cardiomyopathy with planar ERNA has demonstrated that patients with evidence of left intraventricular dyssynchrony are at greater risk for the development of ventricular tachyarrhythmias.190 However, when the reproducibility of planar ERNA and GBPS for determining right and left ventricular dyssynchrony were compared, GBPS was superior to the planar method,191 indicating that it would be the preferred method of assessing ventricular synchrony. Second, β-blocker therapy has been shown to be beneficial in treating patients with left ventricular dysfunction, although not all patients will respond to therapy. In one study, augmentation of the LVEF by ≥15% in response to up to 15 μg/kg/min of dobutamine was associated with a sensitivity of 91% and a specificity of 82% for predicting a >5% improvement in LVEF following 1 year of β-blocker therapy.192

Assessment of Myocardial Viability: The Current State of the Art

The assessment of myocardial viability in patients with depressed resting left ventricular function remains an important issue in light of several facts. First, patients with evidence of viability that undergo revascularization have better survival compared to those who receive medical management.193-196 Second, a significant proportion of patients with depressed left ventricular function have evidence of viability and can have improvement in left ventricular function following revascularization.197,198 While there are several methods that can be used to assess myocardial viability, which will be discussed below, the method that is considered the “gold standard” because of its correlation with improvement of left ventricular function following revascularization is [18F]-2-fluoro-2-deoxy-D-glucose (FDG)-PET. The basis for this method is that FDG is taken up by cells and phosphorylated by hexokinase in a manner
similar to glucose, but because of its chemical structure it does not undergo further metabolism. It is this phosphorylation of FDG to FDG-6-phosphate by hexokinase, which requires ATP, that is the foundation of viability assessment. In the setting of persistent low-flow ischemia, in which perfusion defects may show little evidence of reversibility, the ischemic cardiac myocytes will utilize glycolysis to generate ATP and will therefore take up FDG, producing the classic mismatch pattern between blood flow, determined by PET blood flow tracers such as N-13 ammonia, O-15 water, or Rb-82, and metabolism.

Multiple early studies have demonstrated the ability of FDG-PET to predict improvement in left ventricular function following revascularization. While these studies utilized a variety of protocols for both perfusion imaging as well as metabolic imaging, they all demonstrate the ability to predict improvement in left ventricular function following revascularization. In a meta-analysis of these early studies, it was demonstrated that the sensitivity, specificity, positive-predictive value, and negative-predictive value of FDG-PET in predicting an improvement in left ventricular function are 88, 73, 76, and 86%, respectively. Because LVEF is such a powerful predictor of survival, it would be logical to conclude that FDG-PET viability testing would identify patients that would have an improvement in survival following revascularization. In comparing patients with viability who underwent revascularization to those with viability treated medically or patients without evidence of viability who underwent revascularization or patients without evidence of viability treated medically, revascularization decreased cardiac event rates only in patients with evidence of viability by FDG-PET, while there was no difference in event rates between medical treatment and revascularization in patients with no evidence of mismatch on FDG-PET. Furthermore, the demonstration of viability by FDG-PET also identifies patients that will have improvement in exercise capacity and congestive heart failure symptoms following revascularization. Interestingly, a recent retrospective study of patients with an LVEF <30% undergoing coronary artery bypass surgery has demonstrated that there is no difference in cardiac death between patients who had an increase in LVEF >5% following revascularization and those who did not have a significant increase in LVEF. While viability based on FDG or TI-201 imaging was not evaluated in this study, it suggests that factors other than improved left ventricular function following revascularization determines survival. This finding has been confirmed by a subsequent study.

The drawback to widespread use of PET for viability assessment centers on the need for a cyclotron for the production of FDG and the need for a
PET camera, which is a more expensive system than a SPECT camera. While distribution networks allow for efficient delivery of FDG to geographically defined areas, not all centers may be able to justify the addition of a PET system. To overcome this obstacle to viability assessment with FDG, SPECT systems have been developed that allow single photon imaging of FDG. These systems rely on the use of special ultrahigh energy collimators for image acquisition from the 511-keV photons that are produced by the positron/electron annihilation event.\textsuperscript{218,219} Single-photon FDG studies were initially performed using planar imaging and demonstrated the ability to identify areas with preserved FDG uptake following myocardial infarction as well as good agreement with PET-FDG/flow studies.\textsuperscript{220-222} Subsequently, SPECT methods were applied to single-photon FDG imaging, using typical SPECT perfusion tracers such as Tl-201 or Tc-99m sestamibi to assess flow. In small patient series, there is good agreement (76 to 100\%) between FDG-SPECT and FDG-PET for identifying viable myocardium in dysfunctional regions.\textsuperscript{223-227} However, it must be emphasized that an ultrahigh energy 511-keV collimator must be used to achieve adequate image quality.\textsuperscript{226} As with FDG-PET, FDG SPECT can be used to identify patients with cardiomyopathy who will have an improvement in regional left ventricular function and global LVEF following revascularization.\textsuperscript{228,229}

In addition to FDG-SPECT as an alternative to FDG-PET for assessment of viability, there are a variety of other noninvasive methods available to assess viability including Tl-201 imaging, Tc-99m sestamibi, dobutamine augmentation of left ventricular function, and late enhancement on cardiac magnetic resonance imaging. Viability assessment using Tl-201 is based on the fact that the uptake of thallium occurs via the sarcolemmal Na\(^+\)/K\(^+\) ATPase and therefore requires the presence of cytosolic ATP, as does FDG uptake and retention. A variety of imaging protocols, including rest/redistribution, rest/redistribution/reinjection, and stress/redistribution/reinjection have been employed for Tl-201 viability imaging. Studies comparing Tl-201 SPECT to FDG-PET have demonstrated good agreement between the two agents,\textsuperscript{225,230-232} although Tl-201 imaging appears to underestimate viability, especially in the inferior wall. As a result of this difference, the positive- and negative-predictive values of Tl-201 imaging are lower than those of FDG-PET.\textsuperscript{223,233,234}

In contrast to Tl-201, the uptake and retention of Tc-99m sestamibi is not directly based on ATP, but rather is based on the distribution of this lipophilic cation across biological membranes based on membrane
potentials, which is primarily driven by intact, functional mitochondria. Furthermore, because there is minimal redistribution of Tc-99m sestamibi, changes in a Tc-99m sestamibi perfusion defect with late imaging may not be relied on for the assessment of viability. Studies have demonstrated a linear relationship between Tc-99m sestamibi uptake and the degree of myocardial fibrosis, revealing that a Tc-99m sestamibi perfusion defect with <50% of the maximal counts is unlikely to have a significant improvement in regional function following revascularization. Furthermore, the sensitivity of detecting viable myocardium with Tc-99m sestamibi is increased by the administration of nitroglycerine, which is thought to increase perfusion to the region through the recruitment of collateral vessels. Viability assessment with Tl-201 or Tc-99m sestamibi gated SPECT imaging have been shown to provide similar results in several studies. In comparing Tc-99m sestamibi to the gold standard of FDG-PET for the evaluation of myocardial viability, there is a concordance of about 70%. However, Tc-99m sestamibi, like Tl-201, tends to underestimate viability and the majority of the segments with viability underestimated by Tc-99m sestamibi are present in the inferior wall, suggesting that diaphragmatic attenuation may have a significant impact on viability assessment with Tc-99m sestamibi.

George A. Beller: It has been acknowledged that resting sestamibi or tetrofosmin imaging for viability detection, particularly when nitroglycerine is given prior to tracer injection, provides similar information to rest thallium-201 redistribution imaging. This is because these Tc-99m-labeled tracers have a high cellular extraction in low-flow regions where myocytes have preserved mitochondrial integrity. These tracers are also very valuable in quantitating infarct size, which has prognostic value. The ability to gate the resting SPECT images allows for simultaneous assessment of LV ejection fraction and resting perfusion/viability. More recently, cardiac MRI imaging for detection of delayed hyperenhancement with gadolinium administration had proven perhaps more sensitive for detection of scar than use of SPECT imaging. This is because of the better spatial resolution of MRI permitting the detection of subendocardial scar.

Metabolic and Receptor Imaging: The Beginning of Molecular Imaging

While perfusion imaging will remain an important tool for determining diagnosis and prognosis in patients with suspected CAD, a paradigm shift is occurring in which we are attempting to identify patients with vulnerable plaques based on the identification of targets in unstable
plaques to be used for molecular imaging. This is just one aspect of the application of molecular imaging to nuclear cardiology. In addition, novel molecular imaging agents may extend to monitoring gene and stem cell based therapy as well as response to novel therapies for the treatment of adverse remodeling in patients with heart failure. While we will discuss each of these targets of molecular imaging in detail below, we will start with an appraisal of metabolic and receptor imaging methods, which are based on cardiac myocyte biology. Specifically, SPECT imaging of fatty acid metabolism and quantitative PET analysis of substrate metabolism in clinically relevant conditions will be reviewed. In addition, β-adrenergic function in the heart will be reviewed.

SPECT Imaging of Fatty Acid Metabolism

Arguably, metabolic imaging represents a form of molecular imaging in that specific cellular processes are the targets of metabolic imaging. Specifically, the increased uptake and retention of FDG by ischemic myocardium is due to molecular signals responding to ATP depletion from ischemia that attempt to increase the energy supply of the heart muscle.253 This enhanced uptake of FDG in the ischemic myocardium has been utilized to detect ischemia in patients undergoing exercise treadmill testing.254 While FDG was injected at the time of exercise and therefore acute, active ischemia was detected in this study, there are data from animal studies that indicate that the glucose transporters responsible for enhanced postischemic glucose uptake, GLUT4, remain translocated to the cell surface for at least 1 hour after an ischemic insult.255 Furthermore, enhanced FDG uptake can be detected in the rat heart 24 hours after a short period of total ischemia.256 Further work is necessary to determine whether FDG or a molecular probe for GLUT4 translocation can be used as a memory marker for ischemia.

Another metabolic imaging agent, [125I]-β-methyl-iodophenyl-pentadecanoic acid (BMIPP), already shows promise as a potential tracer that can be used to identify an ischemic insult long after there is restoration of normal blood flow (“memory marker”). As a fatty acid analog, BMIPP is taken up and undergoes an ATP-dependent thioesterification, as do dietary fatty acids, but does not undergo significant mitochondrial β-oxidation and is essentially trapped in the lipid pool of the cell.257,258 BMIPP has been used extensively in Japan for the evaluation of cardiomyopathies and the severity of BMIPP defect has been shown to predict adverse outcomes in patients with hypertrophic cardiomyopathy.259 In the setting of cardiomyopathy, BMIPP defects tend to be disproportionately greater in regions with evidence of ischemia based on
thallium imaging (type B mismatching), suggesting a role for myocardial ischemia in the genesis of decreased BMIPP uptake.\textsuperscript{260} However, the BMIPP uptake defects can precede the development of abnormalities in oxygen consumption and glucose uptake as determined by quantitative PET, indicating that other factors, in addition to ischemia, are responsible for the changes in BMIPP uptake in the setting of hypertrophic cardiomyopathy.\textsuperscript{261}

BMIPP has also been used to evaluate other cardiomyopathies and it has been shown that patients with BMIPP/thallium type B mismatch were more likely to experience deterioration in their New York Heart Association Functional Class.\textsuperscript{262} Dynamic BMIPP imaging with kinetic analysis shows some promise as a method for differentiating ischemic from nonischemic cardiomyopathy.\textsuperscript{263} Furthermore, quantitative evaluation of the uptake of BMIPP can be used to determine the response to \(\beta\)-blocker therapy in patients with dilated cardiomyopathy.\textsuperscript{264,265}

As mentioned above, because the intracellular trapping of BMIPP is dependent on ATP content\textsuperscript{266} and because it tracks the initial steps of fatty acid oxidation, it would be expected that BMIPP might be applied to identify ischemic myocardium. In a study comparing resting BMIPP SPECT and Tl-201 SPECT to coronary angiography for the detection of CAD in patients receiving chronic hemodialysis, the sensitivity, specificity, and accuracy of BMIPP were 98.0, 65.6, and 90.0\%, respectively, while the sensitivity, specificity, and accuracy of Tl-201 were 84.7, 46.9, and 75.0\%, respectively.\textsuperscript{267} This is further supported by canine studies demonstrating rapid back diffusion of unmetabolized BMIPP out of severely ischemic myocardium.\textsuperscript{268} In a recent study of late BMIPP imaging of patients with inducible ischemia on Tl-201 SPECT imaging, it was found that BMIPP defects were present from 4 to 30 hours after the exercise-induced ischemia.\textsuperscript{269} While this study found an excellent sensitivity and specificity on the patient level, it was less predictive on the vascular territory level. Furthermore, BMIPP studies were not also performed before the stress test to determine if BMIPP defects were present before ischemia was induced. However, this study raises the possibility that BMIPP may be used as a memory marker for ischemia. In addition, moderate to large resting BMIPP defects are associated with higher cardiac event rates compared to absent or small defects in patients with suspected or known CAD.\textsuperscript{270} BMIPP may be superior to FDG for late imaging of ischemia because it does not require a cyclotron for production, making its use more practical in the clinical setting. Further studies defining the effects of patient characteristics such as diabetes and
heart failure, duration of BMIPP defects, and prognostic impact of the results of BMIPP imaging remain to be defined.

**George A. Beller:** BMIPP imaging has promise for detection of ischemic memory in the emergency room when patients have had prolonged ischemia, which has resolved prior to arrival to the hospital. Myocardial blood flow may have returned to normal but persistent metabolic dysfunction may exist. Thus, the BMIPP images may show a defect in the previously ischemic region in the face of a normal perfusion scan. This technique requires further study in a larger number of patients to determine its worth relative to other noninvasive techniques such as CT angiography and stress SPECT imaging that can be performed once the troponin levels have been shown to not be elevated.

**Quantitative PET Metabolic Imaging**

While the evaluation of myocardial viability with PET was discussed above in terms of the current state of the art of nuclear cardiology, the majority of these studies did not perform quantitative evaluation of metabolism. In contrast, quantitative assessment of myocardial metabolism may be used to provide important information concerning the regulation of substrate metabolism and mitochondrial function that can allow specific metabolic therapies to be developed to treat cardiac diseases, such as the use of the fatty acid oxidation inhibitor ranolazine in patients with chronic angina.\(^{271,272}\) PET, in contrast to the currently available SPECT methods, allows for quantitative evaluation of kinetic parameters associated with positron-emitting radiotracers; as mentioned previously, this is based on the detection of true positron/electron annihilation events by coincidence detection and the attenuation correction that is employed by PET.

Quantitative PET measurements have been used to estimate a variety of metabolic and hemodynamic parameters, including glucose uptake and phosphorylation, glucose oxidation, fatty acid uptake and oxidation, blood flow, and even mitochondrial membrane potential.\(^{273}\) While most of the earlier studies utilized a single PET radiotracer to evaluate a specific aspect of myocardial metabolism, the relatively short half-life of carbon-11 (\(t_{1/2} = 20.4 \text{ minutes}\)) and the ability to synthesize a variety of metabolically relevant tracers\(^{274}\) allows for the evaluation of several aspects of myocardial metabolism. Specifically, \([1-{\text{11C}}]\)glucose can be used to estimate glucose uptake and oxidation in the citric acid cycle, \([1-{\text{11C}}]\)palmitate, can be used to estimate fatty acid uptake, oxidation, and storage in the triacylglycerol pool and \([1-{\text{11C}}]\)acetate can be used to
determine oxygen consumption. Using these tracers, and sophisticated modeling, the changes in cardiac metabolism in the setting of obesity and insulin resistance, heart failure, and aging have been assessed. In premenopausal women either with or without evidence of obesity and insulin resistance, quantitative PET analysis demonstrated that, while there was no relationship between either glucose uptake or oxidation and the degree of insulin resistance, there was a direct correlation between myocardial fatty acid uptake and oxidation and the degree of insulin resistance. Furthermore, obesity was associated with decreased myocardial work efficiency as determined by myocardial consumption determined by \([1-^{13}C]\)acetate.

Studies in animal models and in humans have suggested that the failing adult heart reverts to a fetal pattern of gene expression, including genes involved in metabolic regulation. Studies utilizing multiple PET tracers to determine rates of metabolism indicate that, in patients with nonischemic cardiomyopathy, quantitative PET analysis of substrate metabolism demonstrated that rates of myocardial glucose uptake and oxidation were higher and rates of fatty acid uptake and oxidation were lower than in individuals with normal left ventricular function, despite similar myocardial blood flows and oxygen consumption. What remains to be determined is if this reversion to a greater reliance on glucose represents an adaptive or maladaptive response in the failing heart.

With the increasing longevity of individuals in developed countries combined with the increase in the size of the population of aged individuals, it is important to gain a greater understanding of the changes that occur in the aging heart. Furthermore, the aging heart has greater susceptibility to ischemic damage and older patients have a higher morbidity and mortality following myocardial infarction than younger adults. In aging animals, there is an increase in the rate of basal myocardial glucose uptake, suggesting a greater reliance on glucose metabolism. In patient-based studies, the rates of myocardial fatty acid uptake and oxidation under basal conditions decrease in older individuals (67 ± 5 years) compared to young adults (26 ± 5 years) based on quantitative PET measurements. While there was no increase in the rates of myocardial glucose uptake with aging in the older individuals, there was most likely a greater reliance on glucose metabolism for energy production by virtue of the decrease in fatty acid oxidation, a metabolic shift similar to that seen with heart failure. In contrast to the relatively intact insulin response in the aged heart, there is evidence from positron emission tomographic studies in humans suggesting that the increase in glucose uptake in response to hemodynamic stress is attenuated.
Specifically, while there is a 50% increase in glucose uptake in young adults in response to dobutamine infusion, myocardial glucose uptake does not change in older adults, although both myocardial fatty acid uptake and oxidation increased to a similar extent in young and old adults in that study. However, the metabolic disposal of glucose in response to dobutamine infusion (ie, glycolysis versus glucose oxidation) was not assessed in that study. As with the metabolic changes seen in the failing heart, the shift in substrate preference in the aged heart may be important in the ability of the aged heart to adapt to hemodynamic and metabolic stress and underscores the need for further basic studies to define the cellular changes that occur with aging as well as imaging studies to translate those basic studies to practical clinical application.

Assessment of Cardiac Sympathetic Innervation: Role of I-131-Metaiodobenzylguanidine

The role of the neurohormonal axis in congestive heart failure is now well-recognized and plays a predominant role in the treatment of the failing heart. One of the hallmarks of specific changes in the setting of congestive heart failure is the development of excess sympathetic tone and uncoupling of the $\beta$-adrenergic receptors. Therefore, the development of noninvasive methods to assess changes in the $\beta$-adrenergic signaling system in the failing heart and the response to therapy is important. The radiolabeled norepinephrine analog I-131-metaiodobenzylguanidine (MIBG) competes with norepinephrine for reuptake in presynaptic vesicles and can be used to assess sympathetic innervation and function in the heart. Animal and human studies demonstrated the ability of MIBG imaging to identify abnormal sympathetic function in failing hearts.288-291 Furthermore, in rats receiving anthracycline chemotherapeutic agents, MIBG imaging has been able to identify abnormalities in sympathetic innervation prior to the development of significant myocyte damage.292 Subsequent studies in humans have demonstrated that abnormalities in MIBG uptake precede changes in left ventricular function in patients treated with anthracycline chemotherapeutic agents.293,294 Myocardial MIBG imaging has been used to assess prognosis in patients with congestive heart failure. In a study of patients with either ischemic or nonischemic cardiomyopathy, MIBG uptake was a stronger predictor of survival than ejection fraction or left ventricular end-diastolic diameter.295 Several subsequent studies have confirmed the prognostic value of MIBG imaging in patients with congestive heart failure.296-298 Furthermore, MIBG uptake predicts whether a patient will require cardiac transplantation.299 With respect to a possible role for noninvasive
imaging in monitoring therapeutic response in the setting of heart failure, treatment of heart failure patients with the angiotensin converting enzyme inhibitor, enalapril, increases myocardial MIBG uptake, suggesting improved sympathetic function. Similarly, MIBG uptake can predict the response to β-blocker therapy in patients with congestive heart failure, and long-term treatment with β-blockers has been shown to improve cardiac sympathetic innervation. Furthermore, changes in MIBG uptake following institution of optimal therapy for congestive heart failure can be used to predict long-term survival.

In those patients with congestive heart failure who do not respond to medical therapy or coronary revascularization, cardiac transplantation must be considered. With cardiac transplantation, the donor heart becomes surgically denervated during the harvesting procedure and imaging studies show that MIBG uptake falls to 10% of normal values 2 hours after transplantation and is undetectable after 16 hours. However, there is evidence from studies using MIBG that about half of patients have scintigraphic evidence of reinnervation of the engrafted heart 1 to 2 years after transplantation, although the functional consequences of this reinnervation may be minimal.

As noted above in the discussion of SPECT perfusion imaging in diabetic patients, one of the risk factors for an abnormal perfusion study in asymptomatic diabetic patients is the complication of autonomic dysfunction. There is increasing interest, for both the assessment of diabetic autonomic neuropathy and the assessment of autonomic function in the setting of congestive heart failure, in the use of MIBG scintigraphy. MIBG is taken up in presynaptic vesicles, tracing the reuptake of norepinephrine, and therefore, can be used to assess sympathetic function. While MIBG defects are observed in patients with both insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus, the severity and distribution of MIBG defects have been shown to differ between the two diseases, although baseline differences in the two groups, with respect to duration of diabetes and patient age, may account for some of the differences. The changes in autonomic innervation can occur relatively early in the course of diabetes, with alterations in MIBG uptake being observed in patients with newly diagnosed insulin-dependent diabetes, and persist in long-standing diabetes, although the scintigraphic abnormalities can be partially normalized with insulin therapy or with the use of aldose reductase inhibitors. MIBG has been used to elucidate the role of autonomic dysfunction in left ventricular dysfunction in the diabetic heart (diabetic cardiomyopathy).

Two studies of the left ventricular response to exercise in diabetic patients
have demonstrated that the inability to augment the LVEF in response to either bicycle or handgrip exercise is associated with abnormal cardiac MIBG uptake compared to nondiabetic individuals or diabetic patients with a normal increase in LVEF during exercise. However, the inotropic response of the left ventricle to dobutamine infusion is normal in these patients, indicating that an inability to augment left ventricular contractility in response to exercise in diabetic patients is related to autonomic dysfunction and not to primary abnormalities in the β-adrenergic receptor system in the diabetic heart. Furthermore, abnormal heart/mediastinal ratios, abnormal washout rates, and MIBG scintigraphic defects identify diabetic patients with hypoglycemic unawareness, a critical complication of diabetes given the importance of tight glycemic control with its associated risk of hypoglycemia.

George A. Beller: I-123 MIBG is presently undergoing evaluation in a multicenter trial in the United States to assess its prognostic value in patients with a depressed ejection fraction. The idea is that this noninvasive imaging technique might identify patients who would benefit most from an ICD to prevent sudden cardiac death.

Molecular Imaging: General Concepts for Targets and Technical Considerations for Molecular Imaging

Molecular imaging holds the promise of providing new information concerning early steps in the progression of several cardiovascular diseases. However, there are several important aspects of nuclear molecular imaging that will require further technologic advances. First, molecular imaging agents are, for the most part, concentrated in areas with increased expression or activity of a relevant target but not taken up by normal tissue and are therefore “hot-spot” imaging agents. This becomes important in image acquisition. Specifically, in contrast to perfusion imaging agents that are taken up diffusely by normal myocardium but taken up to lesser extents by ischemic tissue (“cold-spot” imaging) and therefore allowed relatively easy scintigraphic identification of the heart, hot-spot imaging agents, if they are taken up by small, discreet areas, do not allow for easy anatomic localization.

Several registration methods can be used to overcome this problem of hot-spot imaging. First, a cold-spot perfusion-imaging agent can also be administered, allowing for registration of the two image sets and anatomic localization of the hot-spot agent. However, this method is hampered by
the need to use two agents that must have different photopeak energies for simultaneous imaging or injections that are separated temporally, which may affect the registration of the images unless there is precise repositioning of the subject. A second method involves registration of the hot-spot imaging agent with an anatomic image acquired by CT or MRI. With the increasing use of CT for attenuation correction and the incorporation of CT in hybrid SPECT/CT and PET/CT cameras, this latter method for hot-spot imaging seems the most likely to achieve widespread acceptance. Furthermore, with the use of multislice, diagnostic CT scanners with high-speed acquisition, a hybrid nuclear/CT camera can be used to obtain molecular images using nuclear tracers as well as anatomic information from CT (Fig 9), including assessment of coronary stenoses from CT angiography and coronary calcium scoring and potentially even right and left ventricular function.323

A second concern with molecular imaging centers on the fact that some of the targets may be expressed in low levels, resulting in only small amounts of radiolabeled ligand bound to the target of interest, which
would be below the limits of detection with noninvasive nuclear imaging.\textsuperscript{324,325} Although this may be a theoretic concern, given the sensitivity of SPECT and PET systems,\textsuperscript{326} other methods of detection of radiotracer accumulation could be employed, including the use of catheters equipped with radiation detectors. While such methods are obviously invasive, they may be used to identify clinically significant targets, such as vulnerable plaques, when the signal is below the limit of detection of noninvasive imaging systems.

Small animal models are used increasingly in every aspect of biomedical research. In particular, transgenic mouse models of disease represent powerful tools for research because of the ability to either silence or increase the expression of proteins of interest in an intact animal. However, these powerful models of disease come at both high monetary and high technical expense. Therefore, it is essential to be able to perform serial in vivo studies in transgenic mice to characterize the temporal changes in organ systems that occur with the genetic manipulations without performing terminal studies at multiple time points that require large numbers of precious strains. In response to this need, noninvasive imaging systems have been developed to perform SPECT, PET, CT, MR, ultrasound, and in vivo fluorescent studies in small animals.

With respect to nuclear imaging methods, micro-PET and micro-SPECT systems have both been developed. The two systems have strengths that are in many ways unique and based on the physical characteristics and constraints of the systems. The fundamental aspect of PET that distinguishes it from SPECT is that the positron-emitting tracer travels a defined distance in the environment (2 to 7 mm) before it interacts with an electron in the annihilation event. The current PET systems used for small animal imaging have a resolution just over 1 mm.\textsuperscript{327-329} In a study assessing the ability of micro-PET to evaluate left ventricular function as well as metabolism in mice with cardiomyopathy caused by knockout of the surviving gene, left ventricular volumes determined by PET correlated well with volumes determined by magnetic resonance imaging.\textsuperscript{330} In contrast, SPECT tracers emit their gamma photon at the site of decay. As a result of this difference, the resolution of both PET and micro-PET are limited by the physical properties of the positron-emitting radionuclide and this resolution is inferior to that of micro-SPECT. This inherent limitation in resolution for micro-PET is balanced by the greater range of radiotracers available for PET due to the relatively greater ability to produce radioligands based on carbon-11 and fluorine-18 radiochemistry compared to the addition of bulky Tc-99m or I-123 atoms to ligands.
Pinhole collimation systems, which enlarge the scintigraphic images, have been developed to increase the resolution of SPECT cameras for application to small animal models and have evolved to include multiple pinholes to increase resolution and decrease the amount of camera rotation needed to acquire images.\textsuperscript{331-333} Studies of left ventricular function using both gated myocardial perfusion SPECT and GBPS using a micro-SPECT system in rats have shown a high degree of reproducibility for both methods in serial studies performed 1-week apart.\textsuperscript{334} In addition, micro-SPECT systems have been used to identify perfusion defects and left ventricular function using Tc-99m tetrofosmin in mice.\textsuperscript{335}

**Molecular Imaging of Angiogenesis**

In the heart, angiogenesis occurs as an adaptive response to ischemia and several trials have attempted to exploit growth factors involved in the angiogenic process to improve nutritive blood flow to ischemic myocardium.\textsuperscript{336-339} While those studies have demonstrated varying degrees of success, they have relied on either angiographic evidence of myocardial blushing or improvement in myocardial perfusion using Tc-99m sestamibi to evaluate the presence of angiogenesis indirectly. Because the process of angiogenesis is complex and specific protocols may be necessary to treat with growth factors to optimize the angiogenic response, specific targets are needed to identify the angiogenic process. One such target is the integrin \( \alpha v \beta 3 \), which is important in the intercellular adhesion of endothelial cells and plays an important role in angiogenesis.\textsuperscript{340} Based on the studies of tumor angiogenesis, in which \( \alpha v \beta 3 \) has been shown to be a good target for imaging, studies in rat and canine models of reperfused infarct have demonstrated enhanced uptake of radiolabeled ligands for \( \alpha v \beta 3 \) in regions with angiogenesis and specific binding of the radioligand to endothelial cells in the peri-infarct area.\textsuperscript{341} Injection of similar radioligands of \( \alpha v \beta 3 \) in rats with occlusion of a unilateral femoral artery demonstrated temporal changes in uptake of the tracer in the ischemic limb compared to the nonischemic limb by in vivo imaging,\textsuperscript{342} suggesting that \( \alpha v \beta 3 \) plays a role in angiogenesis at a specific time during the angiogenic process.

**Molecular Imaging of Remodeling and Apoptosis**

Ventricular remodeling is a critical step in the initiation and progression of heart failure.\textsuperscript{343,344} The importance of remodeling in the heart is underscored by the many studies that demonstrate that therapies aimed at minimizing remodeling in the infarcted and failing heart are beneficial.\textsuperscript{345,346} Two of the major processes implicated in ventricular remod-
eling are changes in extracellular structural proteins and myocyte cell loss through apoptosis. The extracellular matrix proteins represent a pool of structural proteins with a dynamic but stable turnover. In the setting of heart failure, there is an increase in the degradation of these proteins that is mediated through the action of proteases including the matrix metalloproteinases (MMPs). The recent introduction of ligands for MMPs has allowed for the development of radiotracers that may be used to monitor MMP activity. In a mouse model of myocardial infarction, uptake of the indium-111-labeled MMP ligand, RP782, was increased over threefold in the infarcted area based on gamma well counting and the Tc-99-labeled MMP ligand, RP805, could be identified by planar and SPECT imaging up to 3 weeks after infarction (Fig 10). Interestingly, there was also evidence of increased RP805 accumulation in remote, noninfarcted regions of myocardium, demonstrating that the remodeling process is a global phenomenon. While this study demonstrates the promise of MMP imaging in the process of remodeling, there are several important technical and biological aspects of MMP imaging that must be understood before MMP imaging can have a significant clinical impact. First, there are numerous MMPs that have been identified, and their time courses for activation and deactivation following a myocardial infarction vary. Therefore, it is difficult to know which specific MMP, if any, is the most important in the remodeling process. Second, the currently available radioligands show only modest selectivity for specific MMPs.

Apoptosis plays an important role in the remodeling process and increases in the number of apoptotic cardiomyocytes can be seen in explanted hearts.
from patients with either ischemic or nonischemic cardiomyopathy compared to autopsy specimens obtained from individuals without evidence of cardiac disease who died in motor vehicle accidents.\textsuperscript{351} The apoptotic pathway has been characterized in great detail, allowing for the identification of potential molecular targets for noninvasive imaging of apoptosis. Specifically, activation of the apoptotic pathway leads to translocation of phosphatidylserine from the cytoplasmic leaf of the cell-surface lipid bilayer to the extracellular leaf. This translocation makes phosphatidylserine available to the cell-impermeant protein annexin-V, which has a high affinity for binding to phosphatidylserine and has been used for many years for the histologic assessment of apoptosis. Studies of annexin-V tagged with Tc-99m have demonstrated the ability of this radioligand to identify regions with increased rates of apoptosis. In patients with histologic evidence of cardiac transplant graft rejection, there is evidence of increased Tc-99m-annexin-V uptake,\textsuperscript{352} suggesting that noninvasive imaging with agents directed against the rejection process, including apoptosis, may eventually be used to monitor patients following transplantation without requiring endomyocardial biopsies.

**Molecular Imaging of Atherosclerosis**

The current state of the art in nuclear cardiac imaging involves imaging atherosclerosis indirectly based on the reduction in coronary blood flow caused by atherosclerotic stenoses. However, the ability to detect these myocardial perfusion defects requires the presence of a stenosis of at least 90% to create flow heterogeneity of a sufficient severity to be able to detect it with currently available technologies. As mentioned earlier in this review, the currently available SPECT techniques are able to identify these lesions with a high degree of sensitivity and specificity allowing for the evaluation of patients with chronic stable CAD. However, the current techniques do not allow for the detection of vulnerable plaques, which tend to cause less luminal narrowing but are at higher risk of rupturing and causing acute myocardial infarction. Therefore, the development of molecular imaging agents that identify specific targets in vulnerable plaques are needed to identify patients at elevated risk of plaque rupture. The process of atherogenesis is beyond the scope of the present discussion and the reader is directed to several recent, comprehensive reviews of atherogenesis for a more in-depth discussion of the process.\textsuperscript{353-357} However, several potential targets for identifying the vulnerable plaque have been suggested: the lipid pool, inflammation, fibrous cap erosion, and plaque remodeling.

One of the main components of the atherosclerotic lesion is the lipid
core, which develops from deposition of low density lipoproteins (LDL) in the vessel wall. To evaluate the lipid pool as a potential target for imaging, LDL particles have been labeled with Tc-99m. Studies using these radiolabeled LDL particles have suggested that this may be one possible method of identifying atherosclerotic lesions, although the technique has been hampered by incomplete clearance of radiolabeled LDL particles from the blood pool, decreasing the target-to-background activity ratio. However, studies aimed at optimizing the signal attained from radiolabeled LDL particles are being performed.

Atherogenesis is increasingly being appreciated as a disease caused, at least in part, by inflammation and several studies have tried to identify active atherosclerotic plaques based on the presence of inflammation. Studies in patients with embolic strokes or transient ischemic attacks have demonstrated the presence of increased FDG uptake in the culprit carotid artery at the site of carotid stenosis identified by computed tomography compared to individuals with asymptomatic carotid disease. Animal studies of atherosclerosis indicate that this increased uptake of FDG is due to the accumulation of leukocytes and macrophages at the site of plaque rupture and not due to enhanced uptake by the neointima. While these studies demonstrate the ability to identify regions of plaque rupture in arteries with minimal uptake of glucose by surrounding tissue (ie, the carotids and aorta), it may be more difficult to identify sites of coronary vascular inflammation because of the relatively greater metabolic rate of the surrounding myocardium resulting in decreased target-to-background ratios.

In addition to the angiogenic process in ischemic tissue discussed above, studies have also suggested that αvβ3 is important in vascular remodeling and may be used to evaluate vascular injury and atherosclerosis. Specifically, in a mouse carotid injury model, changes in the uptake of a radioligand for αvβ3 paralleled the changes in the rate of cellular proliferation in the neointima.

Plaque remodeling, like left ventricular remodeling, discussed above, involves both apoptosis and activation of MMPs and this process of remodeling may represent a target for atherosclerosis imaging. In a study of a porcine model of atherosclerosis, animals with coronary artery injuries fed a high cholesterol diet to accelerate the atherosclerotic process underwent SPECT imaging with Tc-99m-labeled annexin V and autoradiographic and histologic analysis of the coronary vessels. Almost 60% of the coronary lesions were identified by SPECT imaging, while none of the normal coronary arteries had evidence of labeling by annexin V. In the 40% of atherosclerotic lesions that were not identified by
annexin V imaging, the percentage of apoptotic cells in the lesions was four times lower than in the lesions identified by annexin V imaging. Interestingly, the apoptotic cells in that study were predominantly vascular smooth muscle cells, while in a previous study of atherosclerosis in the rabbit aorta, macrophages were the predominant cell type found to be apoptotic. While further work is necessary to characterize the cell types in the atheroma that are identified by apoptotic imaging with annexin V and to determine if this molecular imaging agent can be used to identify vulnerable plaques, these studies demonstrate that atherosclerotic plaques, especially those in the coronary vessels, can be imaged noninvasively using radiolabeled molecular imaging agents.

**Molecular Imaging of Stem Cell and Gene Therapy**

Two issues of concern in the evaluation of stem cell therapy that can potentially be assessed by noninvasive measures are engraftment of the stem cells at the desired site and differentiation of the stem cell to the desired phenotype. Several methods of labeling stem cells to follow engraftment have been utilized in animal models. Indium-111 tagging of bone marrow derived stem cells and myoblasts has been used to track engraftment in rats and pigs following intravenous infusion of the stem cells. In one study, tracking of radiolabeled mesenchymal stem cells showed engraftment in infarcted myocardium, while magnetic resonance imaging could not identify ferromagnetically tagged stem cells in the region of infarct, although a subsequent study from the same group demonstrated the ability of magnetic resonance imaging to identify signal from the ferromagnetic particles used to tag stem cells in the infarcted region.

Tagging of cells with agents like In-111 for nuclear imaging, or ferromagnetic particles for magnetic resonance imaging, only allows for the ability to localize signal and does not indicate that viable, engrafted cells are present. Furthermore, because of the half-life of In-111 tagging of stem cells prior to injection or infusion does not allow for late or serial imaging of stem cell engraftment. A third concern about In-111 tagging of stem cells centers on the dose-dependent toxic effects on the cells, potentially inhibiting replication of the stem cells. Similar concerns about labeling stem cells with Tc-99m have also been raised. Therefore, it is more desirable to utilize a reporter gene system that allows for serial assessment of engraftment of stem cells. Such a system has been developed that relies on expression of reporter genes such as the herpes simplex type 1 thymidine kinase gene (HSV-tk).
HSV-tk can phosphorylate fluorine-18-labeled guanine nucleotide substrates (e.g., 9-(4-[18F]-fluoro-3-hydroxymethylbutyl)guanine ([18F]-FHBG)), trapping them in cells in a fashion analogous to the trapping of FDG in viable cells through phosphorylation by hexokinase. The HSV-tk reporter gene system for noninvasive imaging was initially developed for use in gene therapy. Specifically, efficacy of gene therapy can be assessed using reporter gene constructs. In studies of the effects of adenoviral delivery of the vascular epidermal growth factor (VEGF) gene on angiogenesis, an adenoviral construct including both the therapeutic VEGF gene and the HSV-tk reporter gene was injected into the peri-infarct region in rats and [18F]-FHBG was used to monitor gene expression noninvasively. Using this system, gene expression was found to peak 1 day after adenoviral injection and remain detectable for 2 weeks. Histologic evaluation demonstrated an increase in capillary and small-vessel formation, although there was no evidence of therapeutic benefit based on changes in blood flow, FDG uptake, or regional function. While the results of this particular study do not indicate a therapeutic benefit for this particular protocol, it acts as proof of concept for the reporter gene method to monitor gene therapy noninvasively.

With respect to the use of the HSV-tk reporter system in stem cells, engrafted cells expressing HSV-tk, which is not expressed in uninfected mammalian cells, could be identified noninvasively using [18F]-FHBG. Using this technique, animal studies have demonstrated engraftment of cardiomyoblasts following direct myocardial injection. While these previous studies utilized viral promoter elements to drive expression of the therapeutic and reporter gene, it is possible to utilize tissue-specific promoters to drive the expression of the genes. In this way, it would be possible to monitor engraftment and differentiation of stem cells into cardiac myocytes, for example, by designing reporter gene constructs driven by a cardiac-specific promoter such as the myosin light chain, MLC-2v, or the α-myosin heavy chain, α-MHC. Another interesting use of reporter genes utilizes the sodium/iodide symporter gene, which when injected directly into rat myocardium resulted in focal uptake of I-123. In fact, cardiac-specific expression of the sodium/iodide symporter gene has been achieved with use of the α-MHC promoter in transgenic mice, with enhanced uptake of I-123 in the heart.

George A. Beller: Drs Russell and Zaret elegantly describe the potential applications of nuclear cardiology for molecular imaging of both the myocardium and the vascular system. This is an area that radionuclide imaging has demonstrated great promise, particularly for the goal of identifying vulnerable...
plaques that are lipid laden and inflamed. Molecular imaging data could be used as surrogate endpoints to determine the efficacy of new therapeutic modalities like gene therapy and stem cell therapy. Such techniques could be used clinically to monitor angiogenesis and enhanced metabolic activity. Apoptosis imaging in heart failure in response to new cardioprotective drugs would be of great value in identifying which patients respond favorably to an intervention. Studies in the molecular imaging field are being advanced with the use of micro-PET and micro-SPECT for imaging of small animals like knockout mice.

Concluding Remarks

Currently, nuclear cardiac imaging is an important diagnostic tool that provides valuable information concerning myocardial perfusion, function, and viability. While these techniques will remain an essential part of the evaluation of patients with cardiovascular diseases, molecular imaging has the potential of bringing new targets for diagnosis, prognosis, and therapeutic monitoring to nuclear cardiology. While the molecular imaging agents discussed in this review may not be the agents that will eventually be used for clinical studies, they certainly provide the proof of principle that supports further investigation in the field.

George A. Beller: This is one of the best reviews in recent years on the current status of nuclear cardiology and demonstrates the great advances made in the field over the past 25 years. Drs Russell and Zaret provide a state of the art summary of all the applications of stress and rest perfusion and function imaging and highlight many of the new clinical applications of the various SPECT and PET techniques. They finish with a superb glimpse of the future where nuclear cardiology will undergo a transformation to also include molecular imaging applications that will provide noninvasive information on biological processes such as plaque inflammation and angiogenesis. The field is not stagnant as reflected by all the work summarized in this review. Finally, it is clear that nuclear cardiology will be performed in a multimodality manner in the future with hybrid imaging technology emerging such as with SPECT-CT and PET-CT. Even nuclear imaging data fused with MRI scans will surely emerge in the future as issues with registration of images from different modalities are achieved.

REFERENCES

18. Tartagni F, Dondi M, Limonetti P, et al. Dipyridamole technetium-99m-2-methoxy...


89. Grossman GB, Garcia EV, Bateman TM, et al. Quantitative Tc-99m sestamibi attenuation-corrected SPECT: development and multicenter trial validation of


artery disease and severe left ventricular dysfunction. The importance of myocardial viability. Eur J Heart Fail 2003;5:85-93.


305. Lotze U, Kaepplinger S, Kober A, et al. Recovery of the cardiac adrenergic nervous function...


337. Udelson JE, Dilsizian V, Laham RJ, et al. Therapeutic angiogenesis with recom-


