Contributions of Nuclear Cardiology to Diagnosis and Prognosis of Patients With Coronary Artery Disease

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In the past decade, significant advances have been made in the ability to image the heart with radionuclide tracers under stress and resting conditions in patients with suspected or known coronary artery disease (CAD) for the detection of ischemia, determination of prognosis, assessment of myocardial viability, preoperative risk assessment for patients undergoing noncardiac surgery, and evaluation of the efficacy of revascularization in patients undergoing coronary artery bypass surgery or an interventional procedure.1

For many years, planar imaging and SPECT with 201Tl constituted the only scintigraphic techniques available for detecting CAD and assessing prognosis in patients undergoing stress perfusion imaging. The major limitation of 201Tl scintigraphy is the high false-positive rate observed in many laboratories, which is attributed predominantly to image attenuation artifacts and variants of normal that are interpreted as defects consequent to a significant coronary artery stenosis. Although quantification of 201Tl images improves specificity, the false-positive rate remains problematic, particularly in women and in obese patients. Breast attenuation artifacts in women are sometimes difficult to distinguish from perfusion abnormalities secondary to inducible ischemia or myocardial scar.

In recent years, new 99mTc-labeled perfusion agents have been introduced into clinical practice to enhance the specificity of SPECT and to provide additional information regarding regional and global left ventricular systolic function via ECG gating of images. It was immediately apparent that the uptake of these new 99mTc tracers is proportional to regional blood flow but plateaus earlier than 201Tl at hyperemic flows because extraction is reduced. It should be pointed out that the first-pass myocardial extraction fraction of 99mTc-tetrofosmin is lower than 99mTc-sestamibi by ≈10% to 15%, which may contribute to its lower sensitivity for detecting mild to moderate stenoses with vasodilator stress. A new 99mTc-labeled perfusion agent, 99mTc-N-NOET, presently under investigation shows a higher first-pass myocardial extraction than 99mTc-sestamibi or 99mTc-tetrofosmin and redistributes over time similar to 201Tl.3

Diagnosis of CAD

Exercise Perfusion Imaging

Perhaps 1 of the most significant advances in myocardial perfusion imaging in the past decade is the development of quantitative SPECT perfusion imaging. With planar imaging incorporating visual assessment of myocardial scintigrams, sensitivity and specificity for detection of CAD averaged 82% and 88%, respectively, in ≈4000 patients combined from multiple published series.4 The sensitivity and specificity of quantitative planar 201Tl scintigraphy were significantly higher at 91% and 89%, respectively, in 682 patients from studies published in the literature.5 With tomographic SPECT technology, sensitivity averaged 92% (range, 82% to 98%) with a specificity of 68% in 1447 patients combined from 6 studies in the literature. The specificity for CAD detection was only 68% (range, 44% to 91%), which is most likely attributed to a referral bias in which patients with abnormal scans are more likely to be referred for coronary angiography than patients with normal scans. The normalcy rate was 84%. The normalcy rate, used as a surrogate for specificity, is defined as the rate of normal perfusion scans in patients with <5% likelihood of CAD on the basis of clinical and ECG stress test data. It is of interest that the sensitivity of SPECT remains high (85%) for CAD detection in patients without prior myocardial infarction. As expected, the sensitivity for detection of single-vessel disease with SPECT 201Tl imaging averaged 83% compared with 93% for patients with angiographic 2-vessel disease and 95% for patients with 3-vessel disease.4

Variables that diminish sensitivity of SPECT 201Tl imaging for CAD detection are single-vessel disease, left circumflex coronary artery stenosis, branch vessel or distal stenosis, mild degree of stenosis (50% to 70% luminal narrowing), inadequate heart rate response with cessation of exercise caused by noncardiac symptoms, and antianginal therapy with nitrates or calcium blockers. As expected, sensitivity is enhanced in
patients with prior myocardial infarction, more extensive CAD, high-grade coronary stenosis, proximal location of stenosis, and presence of regional wall motion abnormalities. Quantitative scan analysis yields higher sensitivity and specificity values than visual assessment alone of stress and redistribution 201Tl scintigrams. In 1 study,\(^6\) stenosis severity was the most important determinant of an abnormal scan, followed by impaired treadmill exercise duration caused by cardiac symptomatology.

As indicated above, the overall specificity of 201Tl scintigraphy is suboptimal, which is due predominantly to a failure to recognize image attenuation artifacts. Although quantification of 201Tl images improves specificity, the false-positive rate still remains unacceptable. The false-positive defects are commonly observed in the inferobasal region toward the basilar segment of the left ventricle. In women, attenuation artifacts are caused by overlying breast tissue and are localized in the anterior wall and septum. In high diaphragm can cause attenuation artifacts in the inferior wall. Gated 99mTc perfusion imaging permits the assessment of systolic thickening of end diastole to end systole on SPECT tomograms. Recognition of normal systolic thickening in an area of hypoperfusion would direct the interpreter to the conclusion that a defect is an attenuation artifact rather than a myocardial scar. The latter would most likely be associated with reduced systolic thickening as assessed on gated tomograms. In a prospective study by Taillefer et al,\(^7\) the diagnostic accuracy of 201Tl SPECT and 99mTc SPECT perfusion imaging for detection of CAD in women was evaluated. Women in the study underwent both SPECT techniques, and many underwent coronary angiography. The overall sensitivities for detecting significant CAD were similar for 201Tl SPECT and 99mTc SPECT. The specificity, however, was only 67% for 201Tl SPECT when the definition of a significant stenosis was \(\geq 70\%\) reduction in luminal diameter (Figure 1). In the same women, 99mTc-sestamibi SPECT perfusion imaging alone increased specificity to 84%. When gated images were then also analyzed, specificity for CAD detection further improved to 92%. Thus, gated 99mTc-sestamibi imaging reduced the false-positive rate in these women from 33% with 201Tl to 8% with gated SPECT using 99mTc-sestamibi.

A study performed in a heterogeneous population of patients also demonstrated the value of gating of 99mTc-sestamibi SPECT images.\(^8\) This study showed that the addition of gating to standard perfusion 99mTc-sestamibi SPECT reduced the number of borderline interpretations from 89 to 29 in the total group of 285 patients. In the 137 patients with a pretest likelihood of CAD of \(\leq 10\%\), the addition of gated images added significantly to the percentage of interpretations that were designated as “normal” (74% to 93%) because of a reduction in “borderline-normal” and “borderline-abnormal” readings. Thus, the addition of ECG-gated 99mTc SPECT images to the reading of stress and rest perfusion images alone resulted in a significant shift in the final scan interpretations to a more normal designation in patients with a low pretest likelihood of CAD and to more abnormal readings in patients with known CAD.

Finally, ECG-gated SPECT yields important information about global left ventricular function that could previously be obtained only with a second test, such as radionuclide angiography, echocardiography, or contrast ventriculography.\(^9,10\) The ability to accurately measure left ventricular ejection fraction with 99mTc-sestamibi or 99mTc-tetrofosmin adds supplementary value to the procedure, particularly with respect to prognostication and assessment of viability.

A pooled analysis of studies using exercise 99mTc-sestamibi SPECT imaging yielded a 90% sensitivity for 99mTc-sestamibi and 83% specificity for 201Tl for the detection of CAD.\(^11\) Specificity for SPECT 99mTc-sestamibi was 93% compared with 80% for SPECT 201Tl, whereas the normalcy rate was 100% for 99mTc-sestamibi and 77% for 201Tl. In a phase III multicenter SPECT trial, detection of single-vessel disease was 90% for 99mTc-sestamibi imaging, which was \(\approx 20\%\) higher than the detection rate of single-vessel disease with the planar imaging approach in this phase III trial.\(^11\) Sensitivity for detecting 3-vessel disease was 98% for 99mTc-sestamibi SPECT imaging.

An alternative approach to performing rest and stress 99mTc-sestamibi imaging for detection of CAD and distinguishing reversible from nonreversible defects is a dual-isotope rest 201Tl/stress 99mTc-sestamibi SPECT imaging protocol. In this protocol, 3.5 mCi of 201Tl is injected at rest, with images acquired 10 minutes later. Exercise testing is performed immediately after acquisition of these rest images with 25 to 30 mCi of 99mTc-sestamibi injected at peak stress. Berman and coworkers\(^12\) reported a sensitivity and specificity of 91% and 75%, respectively, for CAD detection with this technique. The normalcy rate in patients with a low pretest likelihood of CAD was 95%. Defect reversibility, in a comparison of the resting 201Tl and 99mTc-sestamibi scintigrams, was comparable to the prevalence of defect reversibility on the standard rest/stress 99mTc-sestamibi SPECT technique.

![Figure 1. Specificity of 201Tl (open bars), 99mTc-sestamibi perfusion (striped bars), and gated 99mTc-sestamibi SPECT (speckled bars) imaging studies for both women without CAD and normal volunteers.\(^7\) Values are given for \(\geq 50\%\) and \(\geq 70\%\) stenosis as definition for significant CAD. Reprinted with permission from the American College of Cardiology.\(^7\)](file://C:/Users/End/Downloads/1466_Circulation_March_28,2000)
Pharmacological Stress Perfusion Imaging

Pharmacological stress imaging is an important alternative noninvasive approach for detecting CAD and assessing prognosis in patients who are unable to adequately exercise. Intravenous infusion of dipyridamole, adenosine, or dobutamine is an acceptable alternative to an exercise stress for determining the presence and extent of CAD using SPECT perfusion imaging with $^{201}$Tl or $^{99m}$Tc-sestamibi. Both dipyridamole and adenosine induce a 3- to 5-fold increase in myocardial blood flow with the standard doses. Although adenosine causes a greater increase in blood flow and more patients achieve a maximal flow increase than with dipyridamole, both adenosine and dipyridamole increase blood flow in normal myocardium in excess of that found with maximal exercise. Both have comparable detection rates for identifying functionally important coronary stenoses. The sensitivity for CAD detection for dipyridamole, adenosine, and dobutamine ranges from 89% to 91%. Specificity is also comparable among these 3 stressors, although the specificity for CAD detection might be slightly higher for adenosine compared with dipyridamole. Recent data suggest that in women adenosine perfusion imaging is significantly more sensitive than exercise imaging for detection of single-vessel disease. In men, the sensitivity and specificity for CAD detection were comparable for exercise and adenosine SPECT perfusion imaging with comparable specificities.

Patients with left bundle-branch block (LBBB) and angiographically normal coronary arteries often have abnormal septal defects on exercise SPECT perfusion imaging. The false-positive rate of septal defects in patients with LBBB for CAD detection is significantly lower with dipyridamole or adenosine perfusion imaging. Therefore, in such patients, vasodilator stress imaging is preferable to exercise imaging to determine whether CAD causes the LBBB pattern.

Side effects are somewhat greater with adenosine vasodilator stress imaging than with dipyridamole imaging. Of 9256 patients undergoing adenosine perfusion imaging, 82% had adverse side effects, the most common of which were flushing (37%), chest pain (35%), shortness of breath or dyspnea (35%), headache (14%), ECG ischemic changes (9%), and 8-V conduction block (8%). New adenosine $A_2A$-receptor agonists are under investigation for clinical use instead of dipyridamole or adenosine for vasodilator stress imaging. These $A_2A$-receptor agonists selectively dilate the coronary arteries without associated systemic hypotension or without the adenosine $A_1$-receptor agonist effects, such as AV block and nonspecific chest pain.

Intravenous dobutamine infusion is an alternative to vasodilator stress for myocardial perfusion imaging and is predominantly indicated in patients with pulmonary disease and bronchospasm. Dobutamine infusion produces flow heterogeneity in the presence of a significant coronary artery stenosis because it increases myocardial oxygen demand by increasing heart rate, blood pressure, and contractility. O’Keefe et al summarized the published studies in which dobutamine was used with perfusion scintigraphy. Sensitivity and specificity for CAD detection were 91% and 86%, respectively, in the 158 patients included in these 3 studies. Hays et al found that the sensitivity for single-, double-, and triple-vessel CAD was 84%, 82%, and 100%, respectively, in a group of patients undergoing SPECT dobutamine $^{201}$Tl imaging. Overall sensitivity for CAD detection was 86%, with a 90% specificity.

Exercise or pharmacological stress myocardial perfusion imaging provides significant supplementary diagnostic information to stress ECG variables for detecting CAD among patients presenting with chest pain. The reason is that both the sensitivity and specificity of exercise ECG stress testing are suboptimal for CAD detection. Gianrossi et al performed a meta-analysis of 147 published studies in the literature in which the exercise ST-segment response was compared with coronary angiographic findings. The mean sensitivity for detection of CAD in these studies was 68%, with a specificity of 77%. The extent of CAD certainly affects the sensitivity of the exercise ST-segment response. Sensitivity for detection of single-vessel disease with ECG stress testing alone ranges from 50% to 55%. Sensitivity is also significantly reduced in patients who are unable to achieve ≥85% of their maximum predicted heart rate for their age. In the presence of baseline ECG abnormalities, exercise-induced ST-segment depression may be nonspecific for ischemia, which considerably lowers the specificity of the test.

Prognostic Value of Stress Perfusion Imaging

The prognostic value of exercise and pharmacological stress perfusion imaging has been established in thousands of patients evaluated in multiple clinical studies. The major goal of noninvasive risk stratification with stress perfusion imaging in either patients presenting with undiagnosed chest pain or patients with known CAD is the identification of subsets at high risk of cardiac death or nonfatal infarction so that prompt referral to invasive strategies can be undertaken. Conversely, patients at low risk of future cardiac events on the basis of scintigraphic findings can be spared unnecessary referral for invasive evaluation.

The major prognostic variables on stress perfusion images predictive of future cardiac events are a large defect size (≥20% of the left ventricle), defects in >1 coronary vascular supply region suggestive of multivessel CAD, defect reversibility reflective of inducible ischemia in multiple myocardial scan segments, a large number of nonreversible defects even in the supply region of a single coronary artery, transient or persistent left ventricular cavity dilation from stress to rest images, increased lung $^{201}$Tl uptake on $^{30}$Tl scintigraphy, and a resting left ventricular ejection fraction measured on $^{99m}$Tc gated SPECT imaging of <40%.

Perhaps 1 of the most valuable features of exercise or pharmacological stress perfusion imaging with $^{201}$Tl or a $^{99m}$Tc-labeled agent is its excellent negative predictive value for predicting low mortality and myocardial infarction rates in patients with totally normal scans. Patients with normal perfusion studies at peak stress have a <1%/y combined mortality and nonfatal infarction rate and are thus often spared further invasive evaluation for assessment of their symptoms.

One of the first published reports of the prognostic value of exercise $^{201}$Tl imaging by Brown et al revealed that the number of reversible $^{201}$Tl defects was the best predictor of...
death or nonfatal infarction in 100 patients without prior myocardial infarction. In that study, neither the number of stenotic arteries on angiography nor the presence of inducible ST-segment depression on exercise electrocardiography provided significant supplementary prognostic information to the scintigraphic data. Similarly, Ladenheim et al27 identified the number of myocardial segments with reversible $^{201}$TI defects and exercise heart rate as the only independent predictors of future cardiac events in 1689 CAD patients without prior infarction. Other studies with either planar or SPECT $^{201}$TI scintigraphy confirmed these earlier studies and showed that when assessment of variables for myocardial perfusion imaging is added to information solely obtained from the clinical history, physical examination, and exercise treadmill results, incremental prognostic information is obtained.23,24 Perhaps the largest prognostic study with SPECT $^{201}$TI imaging is by Machecourt et al,25 who followed up 1926 patients for 33 months after exercise $^{201}$TI SPECT imaging. The cardiac mortality rate was 0.42%/y in patients with normal scans and 2.1%/y in patients with abnormal scans. When ≥3 scan territories were involved, the relative risk of cardiac death increased to 24.

The prognostic value of stress $^{99m}$Tc-sestamibi perfusion imaging is comparable to that reported with $^{201}$TI imaging. Iskander and Iskandrian26 analyzed 14 prognostic studies comprising more than 12 000 patients with respect to the prognostic value of the perfusion imaging data. In these patients, normal stress SPECT $^{99m}$Tc-sestamibi images were associated with an average annual hard event rate of 0.6%. Patients with abnormal images had a 12-fold-higher event rate at 7.4% annually (Figure 2). Berman et al27 demonstrated the incremental prognostic value of exercise $^{99m}$Tc-sestamibi imaging in 1702 patients who were followed up after testing for 20±5 months. In this study, patients were divided into low, intermediate, and high pretest likelihood of CAD on the basis of clinical and exercise ECG stress test data. $^{99m}$Tc-sestamibi scan results further separated patients into lower and higher subgroups. A very important finding in this article was that the cardiac event rate for patients with normal scans was low for all levels of pretest likelihood of CAD after acquisition of exercise ECG stress test results. For example, of the 90 patients who were classified as having a >85% likelihood of CAD after the exercise treadmill test and who had a normal scan, none had a cardiac event during follow-up. The rates of referral for catheterization after $^{99m}$Tc-sestamibi SPECT imaging was also very low in patients with normal perfusion studies, even if they had a high likelihood of CAD when only the clinical and exercise stress test results were analyzed.

In another publication from this group, Hachamovitch et al28 showed that the catheterization rate was only 1% in 834 patients who had an intermediate Duke treadmill score after exercise testing but a low-risk $^{99m}$Tc-sestamibi stress perfusion scan. Interestingly, the combined death and infarction rate in 834 patients with an intermediate Duke treadmill score and a normal scan was 0.4%/y. In contrast, those with an intermediate Duke treadmill score and a high-risk SPECT scan had an 8.9% annual combined cardiac death and nonfatal infarction rate (Figure 3). Exercise $^{99m}$Tc-sestamibi perfusion imaging variables provide even greater incremental prognostic value for women than men.29,30 In the study by Hachamovitch et al,29 receiver-operating characteristic analysis demonstrated superior discrimination for the nuclear scan results in identifying high-risk women than in men (area under curve, 0.84 in women versus 0.71 in men). In the study by Marwick et al,30 the number of abnormal territories in the distribution of the 3 major coronary arteries remained the strongest correlate of mortality after adjustment for exercise variables in 3402 women analyzed. Boyne et al31 determined the ability of exercise $^{99m}$Tc-sestamibi SPECT imaging to predict adverse events in a population with a considerable number of women. In patients with normal scans, the combined cardiac death and nonfatal infarction rate was 0.8%/y compared with a 5.4%/y event rate in patients with abnormal scans.

Good exercise tolerance on treadmill testing is associated with a favorable prognosis. However, even in patients who achieve stage IV or greater on the Bruce protocol, exercise myocardial perfusion imaging provides significant additional prognostic value.32 In such patients, Chatziioannou et al32 reported that with the use of Cox proportional-hazards regression analysis, myocardial perfusion imaging was an excellent predictor of cardiac events (global $\chi^2=13.2$; $P<0.001$; relative risk=8), but exercise ECG variables or the addition of
the Duke treadmill score risk categories had no predictive power (Figure 4).

The extent of hypoperfusion on poststress $^{99m}$Tc-sestamibi images can be factored into a decision-making process relative to selecting medical therapy or revascularization. Patients with mild reversible perfusion defects judged to be not high risk can most often be treated medically, whereas patients with high-risk SPECT reversibility findings are candidates for further invasive strategies. O’Keefe et al.\(^3\) undertook a follow-up study in patients with mild to moderate SPECT reversibility, only 9% of whom were initially referred for coronary angiography. With medical therapy, the unadjusted actuarial 3-year event rate for cardiac death or nonfatal infarction was only 2% in the medically managed patients with non–high-risk SPECT reversibility. Only 4% of patients crossed over to subsequent coronary revascularization during follow-up. This study suggested that the results of SPECT imaging assisted in deciding which patients could do well with initial medical therapy as reflected by the low mortality and infarction rates at 3 years of follow-up.

Hachamovitch et al.\(^3\) also found a low annual cardiac death rate (0.8%/y) in patients with mildly abnormal stress perfusion scans who received medical therapy compared with an annual cardiac death rate of 0.9% in patients with mildly abnormal scans who underwent revascularization. This was an observational retrospective analysis of patients who underwent either medical or revascularization therapy after stress $^{99m}$Tc-sestamibi testing. In that study, patients with moderately abnormal or severely abnormal scans appeared to benefit from revascularization early after nuclear testing (Figure 5).

Pharmacological stress imaging can also be used for prognostication in patients with chronic CAD and in asymptomatic patients with aortic or peripheral vascular disease who are scheduled for major vascular surgery. High-risk imaging variables are comparable to those described previously for exercise perfusion imaging. Table 1 shows the prognostic value of adenosine-stress SPECT imaging in 1159 consecutive patients.\(^3\) Patients with a low summed stress score had a cardiac death rate of only 0.9%/y and a combined death and nonfatal infarction rate of 1.6%/y. As the summed stress score became more severe, the cardiac event rate substantially increases, rising to a mortality rate of 7.4% with a severely abnormal scan.

<table>
<thead>
<tr>
<th>Summed Stress Score</th>
<th>Total</th>
<th>Normal (0–3)</th>
<th>Mildly Abnormal (4–8)</th>
<th>Moderately Abnormal (9–13)</th>
<th>Severely Abnormal (&gt;13)</th>
</tr>
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<tbody>
<tr>
<td>Hard events, %/y</td>
<td>4.9</td>
<td>1.6</td>
<td>3.5</td>
<td>5.7</td>
<td>10.6†</td>
</tr>
<tr>
<td>Cardiac death, %/y</td>
<td>6.6</td>
<td>0.9</td>
<td>0.9</td>
<td>3.4</td>
<td>7.4†</td>
</tr>
<tr>
<td>Early catheterization, %</td>
<td>14.1</td>
<td>3.8</td>
<td>9.7</td>
<td>23.1</td>
<td>27.2†</td>
</tr>
</tbody>
</table>

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* The denominator for the hard event calculation is based on the censored population (n=1079); the denominator for early catheterization is the entire population (n=1159).
† Significantly different as a function of summed stress score.
and $1229 greater for low-, intermediate-, and high-risk patients undergoing initial cardiac catheterization compared with those having stress perfusion imaging as the initial test for CAD detection. The cardiac death rate and nonfatal infarction rate in the 5826 patients undergoing initial stress perfusion imaging for assessment of stable angina were both 2.8% compared with 3.3% and 3.0%, respectively, for the 5423 patients who were referred directly for cardiac catheterization as the initial diagnostic strategy. Thus, stress myocardial perfusion imaging may serve as a gatekeeper for referral for cardiac catheterization. This strategy, in which referral for cardiac catheterization is “ischemia driven,” could reduce healthcare costs because coronary angiography could be avoided in patients with low-risk radionuclide perfusion studies regardless of clinical characteristics, treadmill exercise test results, and even coronary angiographic findings. The latter is possible because of the low risk for subsequent cardiac death and infarction in patients with demonstrated angiographic coronary disease and normal perfusion scans.37

Figure 7 is a proposed decision-making algorithm for stable patients with an intermediate or high pretest likelihood of CAD who are referred for stress SPECT imaging, which is derived from the prognostic data summarized above.

Risk Stratification After Acute Myocardial Infarction
Radionuclide techniques can be clinically useful in the evaluation of patients who have had an acute myocardial infarction with respect to determining infarct size, assessing the degree of myocardial salvage after reperfusion, determining myocardial viability in infarct zones of resting asynergy, and detecting inducible myocardial ischemia within or remote from the infarct zone with exercise or pharmacological stress.38–42

High-risk myocardial perfusion imaging variables in patients undergoing stress scintigraphy before discharge after acute myocardial infarction are (1) reversible defects within the infarct zone, (2) a multivessel disease scan pattern, (3) a large nonreversible defect corresponding to a large infarct size or cumulative zone of nonviability (new and old infarction), (4) transient left ventricular cavity dilation from stress to rest imaging, (5) increased lung/201 Tl uptake when that tracer is used, and (6) resting ejection fraction <40% on gated SPECT. A pooled analysis performed by Shaw et al43 combining studies relevant to exercise stress myocardial perfusion imaging after myocardial infarction showed the mortality rate to be 7.1% in patients with a stress-induced reversible defect on stress imaging compared with 1.6% in those without a reversible defect. Similarly, patients with multiple defects in 1 coronary supply region had a 16.7% combined death or myocardial infarction rate compared with a 2% event rate in patients without a multivessel disease scan pattern. In the era before thrombolytic therapy, Gibson et al44 used submaximal exercise 201 Tl scintigraphy before hospital discharge and demonstrated that ~50% of patients with an uncomplicated myocardial infarction who had a high-risk scan experienced a subsequent cardiac event (cardiac death, nonfatal infarction, or rehospitalization for class III or IV angina). In contrast, the event rate was only 6% in patients with a low-risk scan (a nonreversible defect in the infarct zone). In that study, perfusion scan variables separated high- and low-risk subgroups better than exercise ECG stress variables. In fact, scintigraphic variables separated risk-stratified patients better than coronary angiographic variables. A review of prior studies including symptom-limited or exercise stress testing after myocardial infarction showed an overall sensitivity of only 27% for detecting patients at risk for future cardiac death or infarction.48 As a result, the cardiac event rate in patients with a negative exercise stress test was high, and no significant overall predictive value of ST-segment depression was found. In the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial,49 36% of patients in the conservative group had reversible 201 Tl defects on planar imaging without ST-segment changes, whereas only 8% had ST-segment changes without reversible 201 Tl defects.
Dakik et al.\(^6\) reported that quantitative 201Tl SPECT imaging performed with exercise stress in postinfarction patients who had received thrombolytic therapy provided significant incremental prognostic value, whereas coronary angiography did not further improve the model that comprised clinical, ejection fraction, and 201Tl SPECT variables. Patients with defects of <20% of the left ventricle had a very low subsequent event rate, and separation of high- and low-risk subgroups by use of this quantitative imaging variable was comparable to that achieved with coronary angiography, for which patients with single-vessel disease were defined as comprising the low-risk group and those with multivessel disease were designated as the high-risk group.

Exercise or pharmacological 99mTc-sestamibi imaging can be used as an alternative to 201Tl stress scintigraphy for risk stratification after myocardial infarction. Travin et al.\(^6\) reported that the presence of either ischemia seen on SPECT 99mTc-labeled sestamibi imaging or defects detected in multiple vascular regions identified 92% of patients who subsequently experienced an event after hospital discharge. By Cox regression analysis of clinical, ECG stress test, and image variables, the number of ischemic defects on SPECT 99mTc-sestamibi imaging was the only significant correlate of future events in patients with >3 reversible 99mTc-sestamibi defects having an event rate of 38%. Vasodilator stress imaging can be substituted for exercise imaging and can be performed early after infarction with a high degree of safety. In a study by Brown et al.,\(^5\) infarct-zone 201Tl redistribution was the only significant predictor of in-hospital or late cardiac events. In-hospital ischemic cardiac events were seen in 45% of patients with ischemia on 201Tl scintigraphy. A larger multicenter trial\(^6\) in which dipyridamole 99mTc-sestamibi was performed 2 to 4 days after admission for acute myocardial infarction showed that extent and severity of defect reversibility had significant incremental prognostic value when added to clinical and stress variables for predicting in-hospital cardiac events. In that study, for patients with a low-risk dipyridamole SPECT 99mTc-sestamibi scan, the cardiac event rate at 2 years was <2%/y (death, nonfatal infarction, or coronary bypass surgery).

In summary, considerable evidence suggests that early predischarge exercise or pharmacological stress myocardial perfusion imaging in patients with uncomplicated acute myocardial infarction can adequately stratify patients into high- and low-risk subgroups. Very early imaging at 2 to 3 days after admission with pharmacological vasodilator imaging is safe and provides significant prognostic information for subsequent outcome. Now, the 2 most powerful predictors of prognosis (total defect size and resting left ventricular ejection fraction) can be assessed with a single test with gated 99mTc-sestamibi SPECT technology.

Detection of Myocardial Viability

The noninvasive assessment of myocardial viability has proved clinically useful for distinguishing hibernating myocardium from irreversibly injured myocardium in patients with chronic ischemic heart disease or a recent myocardial infarction who exhibit marked regional and global left ventricular dysfunction.\(^50\)–\(^54\) The accurate noninvasive determination of myocardial viability is critically important for clinical decision making. It allows for the selection of patients with CAD and resting left ventricular dysfunction who benefit most from revascularization strategies. Patients with substantial zones of viability and asynergic myocardium should demonstrate improved function and overall better outcomes after revascularization than patients whose left ventricular dysfunction is attributed to extensive myocardial scar.

A number of radionuclide techniques can be satisfactorily used to assess myocardial viability in patients with ischemic cardiomyopathy. 201Tl is the imaging agent most often used with SPECT imaging for determination of myocardial viability. The reason is that the delayed uptake of 201Tl on rest-redistribution imaging is related to myocardial cellular integrity. Several groups have shown that >70% of segments showing >50% or >60% 201Tl uptake on 3- to 4-hour rest 201Tl redistribution scintigrams will demonstrate improved systolic function after revascularization.\(^52\)–\(^55\) The greater the number of viable segments detected preoperatively, the greater is the improvement in left ventricular ejection fraction postoperatively.\(^55\)

Although 99mTc-labeled perfusion agents, such as sestamibi and tetrofosmin, do not show significant redistribution over time after being injected intravenously, several studies have shown comparable accuracy for viability detection between these agents and 201Tl.\(^57\)–\(^59\) This is thought to be due to high extraction of these tracers in the region of low flow in which myocytes are viable. These agents bind to the mitochondrial membrane and require an intact mitochondrial membrane potential for intracellular binding.

PET is considered by many to be the standard of reference for noninvasive detection of viability with nuclear cardiology techniques.\(^50\) The most common methodology for determining viability by PET uses 11N-labeled ammonia as the perfusion tracer and 18F-fluorodeoxyglucose (FDG) as the metabolic marker for glucose utilization. A myocardial zone of asynergy is determined to have preserved viability when there is a “mismatch” between perfusion and FDG uptake. Patients with a “mismatch” pattern will often show improved regional and global left ventricular function after revascularization, whereas patients with a concordant reduction in perfusion and FDG uptake, referred to as a “match” pattern, have predominantly scar and do not show significant improvement in regional and global function after revascularization. FDG imaging can now be undertaken with a SPECT camera and a 511-keV collimator.\(^51\) With this approach, perfusion is assessed with 201Tl or a 99mTc-labeled agent, and FDG is administered for the assessment of metabolism.

Observational studies of patients who have undergone preoperative viability testing have demonstrated that patients with poor viability preoperatively who still undergo coronary bypass surgery have a high rate of early and late cardiac death or need for transplantation compared with patients with greater viability.\(^52\)–\(^54\) Figure 8 shows the survival free of cardiac death or transplantation in patients with greater viability compared with those with lesser viability by quantitative 201Tl scan analysis who underwent coronary bypass surgery. In 70 patients with multivessel CAD and left
ventricular ejection fractions of <40% who underwent preoperative quantitative ²⁰¹Tl scintigraphy, there were 6 cardiac deaths and no heart transplants in patients judged to have greater viability compared with 15 cardiac deaths and 2 transplants in patients judged to have lesser viability with the use of a quantitative viability index based on number of myocardial segments with ≥50% ²⁰¹Tl uptake on delayed rest scintigraphy. Other studies have shown comparable outcomes in patients with poor viability compared with good viability after revascularization.

Other observational studies have determined outcomes in patients with substantial zones of myocardium judged to be viable by radionuclide techniques who have then undergone either medical therapy or coronary revascularization. In such retrospective analyses, patients with extensive zones of viable myocardium had substantially better event-free survival with revascularization compared with medical therapy. Similarly, improvement in heart failure symptoms and enhanced exercise tolerance after revascularization is proportional to the number of preoperative viable myocardial segments that are revascularized.

Taken together, the clinical studies published in the literature to date indicate that the noninvasive assessment of myocardial viability in patients with severe CAD and left ventricular dysfunction assists in the decision-making process in identifying which patients with ischemic cardiomyopathy will benefit the most from revascularization strategies. The greater the extent of preoperative viability as assessed by quantitative SPECT techniques or by PET imaging, the better the short- and long-term outcomes are with respect to survival, heart failure symptoms, and exercise tolerance.

Mental Stress Testing
The traditional approaches to stress imaging, as previously discussed, have involved either physical exercise or pharmacological stress with either vasodilators, such as dipyridamole and adenosine, or dobutamine. These approaches clearly have been successful in identifying significant coronary stenosis. However, it is also clear that most acute coronary events do not occur under conditions of physical exercise. This observation, as well as others relating to the occurrence of significant cardiovascular morbidity and mortality in association with stressful catastrophic events, has led investigators to consider the potential importance of mental stress in assessing cardiovascular risk.

Laboratory protocols involving mental stress have been established in patients with significant CAD. In these protocols, the imaging response to mental stress has been achieved using radionuclide angiocardiography, either with direct blood pool imaging or with nonimaging detectors. In either circumstance, abnormal responses defined by a decrease in ejection fraction and/or development of regional wall motion abnormality have been noted in up to 50% of patients with significant CAD. Abnormalities have been related to specific psychological profiles. In addition, the presence of an abnormal study has been associated with significant cardiovascular risk. The major physiological correlates of an abnormal response to mental stress have involved elevation of plasma catecholamines and an associated rise in peripheral vascular resistance.

These responses are reproducible and may be blunted by specific pharmacotherapy. Mental stress testing offers the potential for an alternative form of stress testing in specified populations of predisposed individuals with CAD. It is anticipated that this will be an additional frontier for further study.

Advances in Instrumentation and Radiopharmaceuticals
The current contributions of nuclear cardiology to the understanding of diagnosis and prognosis in patients with CAD have been developed almost exclusively with myocardial perfusion imaging, initially using planar scintigraphy and more recently including SPECT. At an earlier phase of the field, important prognostic data were generated from radionuclide angiography. Presently, the role of radionuclide angiography has been for the most part subserved and incorporated into perfusion imaging studies. The elegant studies performed in many laboratories defining the prognostic relevance of nuclear imaging in CAD have established a standard for all fields which has been based on rigorously conducted studies and equally rigorous analysis. However, for the field to continue to grow, it is important to move to new frontiers beyond conventional stress perfusion imaging. With this in mind, a number of important advances have been or are in the process of being developed. The domains of study involve instrumentation, conventional radioactive tracer development, and the union of nuclear cardiology with molecular biology to develop a “molecular imaging” approach to the study of CAD.

Instrumentation Advances
Several important advances in instrumentation have occurred recently. Some have been incorporated into clinical imaging, and others are still in the process of being developed, standardized, and validated. One such advance involves quantification of myocardial radionuclide distribution. Nuclear cardiology, by definition, is eminently quantitative. However, approaches to the quantification of myocardial tracer distribution have been far from uniform.

In addition, quantification has been predominately relative, ie, comparing...
count profiles in 1 region to another as opposed to measuring regional distribution in absolute terms. Current computer quantification has generally involved either circumferential profile or polar map displays. Both forms of quantification have been related to normal databases with individual perfusion tracers. It is anticipated that over the next several years there will be far greater uniformity of these displays and analyses.

As described previously, a major advance in myocardial perfusion imaging has involved the ability to perform ECG gated SPECT studies, predominately with 99mTc perfusion tracers as sestamibi or tetrofosmin.80 Recent data suggest that this analysis also can be performed with 201TI SPECT. Gated SPECT provides not only information relevant to regional systolic function but also relevant data concerning left ventricular volumes and global left ventricular function. Volume and ejection fraction measurements have correlated well with standard measures of left ventricular ejection fraction. Measurements of ventricular function may also be obtained immediately after exercise, thereby providing another index of ischemic dysfunction. The power of gated SPECT allows one to determine ischemia, scar, and regional and global left ventricular function from a single study. One recent study has already demonstrated the relevance of this technique for assessing prognosis.81

Perhaps the most exciting aspect of instrumentation research involves the development of transmission-emission tomographic systems that provide attenuation and scatter correction reconstruction algorithms.82 Although this technique generically has contained a great deal of commercial variability, promising results have been published in the literature. The ability to deal effectively with attenuation and its intrinsic problems with respect to SPECT imaging, particularly the modulation of false-positive results, is a substantial advance. This can play a major role in dealing with artifacts resulting from breast and diaphragmatic attenuation. At the present time, many systems have not been validated effectively, and some controversy exists concerning intermediate clinical applicability. Nevertheless, this imaging technology should provide SPECT imaging with a level of accuracy and quantitative power heretofore achieved only with PET perfusion imaging.

Another recent development with potential for novel categorization of patients with CAD involves the use of PET radioactive tracers imaged with new unique SPECT equipment. The combined PET/SPECT cameras allow imaging of PET tracers such as FDG, a commonly used tracer for myocardial viability studies with PET. The approach involves either specially collimated SPECT cameras or specially designed coincidence-detecting SPECT cameras.83 Such an approach, when combined with exercise perfusion imaging, could allow the comprehensive definition of ischemia, scar, and viability in patients with left ventricular dysfunction and CAD.84,85 Currently, such studies can be performed only in PET centers. Other instrumental advances, such as SPECT studies of equilibrium radionuclide angiograms,79 3-dimensional displays of data,79 and widespread networking,86 promise to have significant impact on the field.

### New Imaging Agents

Important advances also have occurred in the area of radioactive tracer pharmaceutical development (see Table 2). Over the past decade, a number of new 99mTc-labeled perfusion agents have been developed. Although currently 99mTc-sestamibi and 99mTc-tetrofosmin have been approved throughout the world and are widely used, several other proposed Tc-labeled radiopharmaceuticals have been evaluated but have not received wide acceptance and are no longer in use. Others, such as 99mTc-N-NOET, are currently under study.3 It is clear that the ideal myocardial perfusion imaging radiopharmaceutical is not yet available, and the opportunity for significant developmental growth in this area remains. Issues relating to the relationship between myocardial tracer uptake and flow under various physiological circumstances, imaging characteristics, and biological properties, including uptake by adjacent organs, all affect the less-than-optimal nature of currently available tracers. The optimally developed flow-related tracer should provide better resolution with respect to definition of less critical physiological stenoses, such as those in the range of 40% to 75% of luminal diameter. Its myocardial uptake with respect to flow should be linear across the broad range of myocardial blood flow occurring under conditions of rest and stress.

A number of other approaches are suitable for imaging patients with CAD. Each has potential for dealing with diagnostic and prognostic issues of consequence. Newer radioactive tracers that have increased myocardial uptake in the presence of tissue hypoxia are currently under active experimental evaluation. Two classes of 99mTc-labeled hypoxia agents have been studied with encouraging results in experimental models.87,88 Such agents, depending on the degree of tissue hypoxia, may allow definition of ischemic myocardial regions of zones of increased radioactive tracer accumulation.

Other approaches have focused on the metabolic consequences of ischemia. With respect to single photon agents, most work has involved free fatty acid imaging with 123I iodophenyl pentadecanoic acid and 123I beta methyl-iodophenyl pentadecanoic acid.89 These 2 radiolabeled fatty acids provide insight into the metabolic state of myocardium as reflected by fatty acid uptake and utilization. 123I beta

### TABLE 2. New Radiopharmaceutical Approaches for Nuclear Cardiology

<table>
<thead>
<tr>
<th>Myocardial perfusion</th>
<th>N-NOET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial fatty acid metabolism</td>
<td>IPPA, BMIPP</td>
</tr>
<tr>
<td>Neuronal integrity</td>
<td>MIBG</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Glucurate</td>
</tr>
<tr>
<td>Vascular proliferating smooth muscle</td>
<td>Z2D3 endothelin derivatives, diadenosine, polyphosphate</td>
</tr>
<tr>
<td>Vascular lipid pools</td>
<td>Antibody to oxidized LDL cholesterol</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Annexin V</td>
</tr>
<tr>
<td>Gene expression</td>
<td>PET reporter genes/reporter probes, antisense oligodeoxynucleotides</td>
</tr>
</tbody>
</table>

See text for details and references.

IPPA indicates 123I iodophenyl pentadecanoic acid; BMIPP, 123I beta methyl-iodophenyl pentadecanoic acid; MIBG, 123I metaiodobenzylguanidine imaging.
methyl-iodophenyl pentadecanoic acid, by virtue of its chemical structure, is trapped within the myocyte, whereas $^{123}$I iodophenyl pentadecanoic acid undergoes active metabolism. These agents have been used most extensively in Japan. Their long-term potential with respect to clinical imaging in CAD remains to be defined.

Another important functional imaging approach involves $^{123}$I metaiodobenzylguanidine imaging, which provides information concerning presynaptic neuronal occupancy. Work with this tracer has involved studies of congestive heart failure in which important prognostic impact has been noted in the presence of decreased $^{123}$I metaiodobenzylguanidine uptake and in specified states resulting in cardiac arrhythmias. At the present time, it would appear as if this imaging approach would have its major role in the population with congestive heart failure.

One of the first nuclear approaches to CAD involves the imaging of necrotic myocardium in acute myocardial infarction with $^{99m}$Tc-pyrophosphate. This particular approach is no longer used. Newer agents, such as radiolabeled antmyosin antibodies, were also used initially but also are not now widely used. $^{99m}$Tc-glucarate has been proposed as a necrosis marker, which provides extremely early visualization of acute myocardial infarction. This approach is still under study.

**Molecular Imaging**

The next frontier of nuclear cardiology with respect to understanding CAD and ultimately assessing diagnosis and prognosis involves the application of the principles of molecular and cellular biology to myocardial and vascular imaging. With such approaches, it should be possible to explore a variety of pathophysiological mechanisms that substantially affect human CAD. Issues relating to presence of significant atherosclerosis, plaque vulnerability, myocardial necrosis, apoptosis, and gene expression should all be accessible with modern nuclear imaging techniques. The field has already seen initial studies that have established proof of principle (see Table 2).

A major challenge to the field involves the imaging of components of the vascular wall. Such approaches require both innovative chemistry and new instrumentation, which will allow high resolution of relatively small targets. Because one generally will be defining areas of interest as those of increased or enhanced radiopharmaceutical uptake, specific issues relating to target size, target to background ratios, and ultimate system resolution may be appropriately modulated to produce realistically defined results.

With respect to imaging the vascular wall, a number of different targets have already been studied. These involve proliferating smooth muscle cells, macrophages, and lipid pools. An antibody against an antigenic component of proliferating smooth muscle cells has been studied in both experimental animals and humans. The nature of this antigen has not as yet been defined biochemically. Narula et al demonstrated that a murine monoclonal antibody (Z2D3) generated against homogenized human atherosclerotic plaque was highly specific for proliferating smooth muscle cells. When studied in a rabbit atherosclerosis model, increased uptake was demonstrated in vivo, ex vivo, and by macroau-

toradiography. Carrio et al recently demonstrated that the same radiopharmaceutical could be used to image atherosclerotic plaque in human carotid arteries. Imaging in humans was accomplished with both planar and SPECT techniques. This latter study was the first to demonstrate the feasibility of targeting atherosclerotic lesions with a specific radiolabeled antibody against a component of the vascular wall. Elmaleh et al applied to imaging the concept that ATP and its analogs are significant inducers of aortic medial smooth cell proliferation from the rat aorta in culture. These investigators hypothesized that $^{99m}$Tc-diadenosine polyphosphate could be used for the noninvasive imaging of active atherosclerotic lesions. With $^{99m}$Tc labeling, significant uptake of diadenosine tetraphosphates was noted in vivo and ex vivo.

Additional studies have applied to imaging the principle that endothelin receptors are present on the sarcolemmal surface of smooth muscle cells. Because the atherosclerotic process is characterized in part by proliferation of migration of vascular smooth muscle cells and because endothelins influence cell proliferation, it was thought that imaging with radiolabeled endothelin derivatives could play a role in imaging. Indeed, in a rabbit atherosclerosis model created by balloon denudation of the aorta and high cholesterol feeding, in vivo imaging of a $^{99m}$Tc endothelin analog allowed detection of increased uptake in the aorta a short time after injection. This was confirmed by tissue counting and ex vivo imaging. In addition, the accumulation of the endothelin derivative correlated with the number of smooth muscle cells but not with either the amount of macrophages present or the area of maximum plaque thickness. These studies have demonstrated the feasibility of imaging strategies for identifying atherosclerotic vasculature on the basis of smooth muscle cell proliferation within lesions.

Because the atherosclerotic lesion clearly contains lipids and cholesterol, it would seem appropriate also to attempt to image the lipid pool. Earlier attempts at this strategy met with only limited success. Recently, Tsimikas et al used imaging with a radiolabeled monoclonal antibody for oxidized LDL cholesterol as a means of imaging atherosclerotic lesions. In this initial study, uptake was demonstrated in lipid laden regions of the aorta of rabbits with heritable hyperlipidemia. Uptake was greatest in areas with abundant foam cells and in lipid-rich necrotic core areas of lesions. In vivo scintigraphy also demonstrated significant uptake.

Other appropriate targets for vascular imaging would obviously include the endothelium, macrophages, and antigens specific to neovascularization. With respect to the endothelium, antibodies against adhesion molecules have already been studied in vitro systems and should also be applicable to nuclear imaging strategies. Preliminary studies with a nonimaging probe and FDG have demonstrated increased uptake of the tracer at the site of active atherosclerotic lesions, presumably because of the metabolic activity of macrophages. It has been demonstrated with MRI in experimental tumor angiogenesis that $\alpha\beta$ activity can be imaged as an index of angiogenesis, at least in experimental tumors.

Another area of interest with respect to novel imaging strategies involves the potential imaging by nuclear tech-
niques of the process of apoptosis. Blankenberg et al. recently reported the ability to image of apoptosis based on the principle that annexin V, an endogenous human protein with a high affinity for membrane bound phosphatidylserine, can be used in vitro to detect apoptosis before other changes are noted. A $^{99m}$Tc-labeled annexin V has been used to image apoptosis in a number of experimental models in vitro, including cardiac allografts.

One of the most exciting new directions in nuclear imaging involves the imaging of gene expression. Two general approaches have been developed to date. One involves imaging gene expression with reporter gene/reporter probe systems to image the expression of endogenous or exogenous genes. The second involves the use of antisense oligodeoxynucleotides that are radionuclide labeled and targeted at a specific mRNA of a particular gene (RASON). Both techniques are in their earliest phases of study. Both have been used for in vivo imaging in mice. One gene/reporter probe system that has been imaged with PET involves the herpes simplex virus type 1 thymidine kinase gene ($\text{HSV1-tk}$) and $^{18}$F ganciclovir. Preliminary results are extremely exciting and offer a generic approach applicable to both PET and conventional SPECT technology. Such “micro” PET and SPECT cameras and their widespread availability are likely to have a major impact on modern biologic research and long-term sequential in vivo studies involving gene expression and its manipulation therapeutically (Figure 9).

Thus, the field of nuclear cardiology has great promise for future progress with advances in technology and emergence of new imaging modalities and applications. Much research needs to be undertaken, and the ability to test novel radiopharmaceuticals in small animals will surely contribute to advancing the field of nuclear cardiology.

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Key Words: imaging × coronary disease × thallium-201 × technetium-99m-sestamibi
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