Role of nuclear cardiac imaging in myocardial infarction: Postinfarction risk stratification

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INTRODUCTION

Over the past two decades, advancements in nuclear cardiac imaging have greatly improved the overall evaluation of patients surviving acute myocardial infarction (AMI). Initially used only to detect the presence of AMI in patients with an unclear clinical diagnosis, nuclear cardiac imaging has matured into a technique that can now accurately assess individual patient risk among seemingly stable survivors of AMI based on the total left ventricular (LV) perfusion defect size (PDS), the extent of inducible ischemia, and the degree of LV dysfunction. Gated radionuclide angiography (RNA) and first-pass RNA were first used to assess LV ejection fraction (EF) and LV volumes—both strong independent predictors of survival. However, the development of technetium 99m–based perfusion agents enabled assessment of LV function by direct gating of the perfusion images. With the transition from planar to single photon emission computed tomography (SPECT) perfusion imaging, further refinements in risk stratification became possible. The introduction of quantitative SPECT analysis added a new dimension to risk stratification by affording an accurate estimate of the stress-induced LV PDS and the extent of scintigraphic ischemia. With advances in AMI therapeutics and the need for earlier risk assessment, pharmacologic vasodilators were developed as an alternative to treadmill exercise stress. Both adenosine and dipyridamole can be administered safely even within the first few days of AMI, allowing very early risk stratification based on the gated SPECT perfusion and functional results and thereby expediting appropriate patient care. Recent studies indicate that gated SPECT imaging may be used not only to assess initial patient risk but also to track subsequent risk based on the therapeutic effects of various medical and interventional strategies on the quantified extent of LV ischemia. If verified in larger clinical trials, stress myocardial perfusion SPECT may prove invaluable in guiding therapeutic decision making and in monitoring the benefits of these therapeutic measures.

NUCLEAR CARDIAC IMAGING FOR DIAGNOSIS OF AMI AND QUANTIFICATION OF INFARCT SIZE

The accurate detection of AMI is pivotal for directing appropriate patient treatment and became one of the early applications of nuclear cardiac imaging. AMI detection is feasible by use of both “hot” and “cold” imaging agents. Hot-spot imaging was first performed with Tc-99m pyrophosphate, but alternative radiopharmaceuticals have included indium 111 antimyosin and, more recently, Tc-99m–labeled glucarate and annexin V. Perfusion defect (cold) imaging is typically performed with thallium 201– or Tc-99m–based radiopharmaceuticals.

Tc-99m Pyrophosphate

Tc-99m pyrophosphate is a bone-seeking radiopharmaceutical that labels calcium phosphate deposited in the mitochondria of acutely necrotic myocardium. This type of imaging was helpful in diagnosing AMI in patients presenting late (>24 hours) after the onset of symptoms but should ideally be used within 1 to 3 days of infarction. The sensitivity and specificity of Tc-99m pyrophosphate for AMI detection vary depending on infarct size and the timing of imaging.

Both the intensity and pattern of myocardial tracer uptake predict outcome as an expression of infarct size. Patients with normal scans or small areas of scintigraphic uptake have an excellent prognosis, whereas morbidity and mortality rates rise sharply as the extent and intensity of myocardial uptake increase. The doughnut scintigraphic pattern predicts a particularly poor clinical outcome and is exemplified by intense tracer uptake in the peripheral area of infarction, with less central uptake. Patients who have persistently positive scans after AMI are another high-risk group for...
the development of congestive heart failure, angina, and ventricular dyssynergy. This agent is no longer used clinically because of its limited diagnostic accuracy and inability to detect AMI in its earliest stages.

**In-111 Antimyosin**

In-111–labeled murine antimyosin antibody has also been used as a marker of cell death during AMI. Once myosin is exposed to the extracellular matrix as a result of irreversible damage to the cell membrane, it can be imaged by use of radiolabeled monoclonal antibodies derived from the inoculation of mice with human myosin.

In-111–labeled antimyosin is highly specific (100%) and sensitive (92%) for the detection of acute myocardial necrosis, and its uptake is maximal in areas with the most severe impairment in blood flow. As with pyrophosphate, the intensity and extent of In-111 antimyosin accumulation predict outcome in patients with acute coronary syndromes (ACS). Patients with extensive antimyosin uptake have a several-fold higher risk for future death or myocardial infarction (MI) as compared with patients with little or no uptake. Simultaneous dual-isotope SPECT imaging with Tl-201 and In-111 antimyosin can distinguish acute necrosis from previous infarction, as compared with patients with little or no uptake. Simultaneous dual-isotope SPECT imaging with Tl-201 and In-111 antimyosin can distinguish acute necrosis from previous scar.

The limitations of In-111 antimyosin are its long half-life and slow blood clearance, which preclude early identification of AMI. Furthermore, because In-111 antimyosin uptake may be seen up to 9 months after an acute event, it is unreliable for distinguishing old from new AMI.

**Tc-99m Glucarate and Annexin V**

Tc-99m glucarate, a glucose analog, accumulates rapidly and specifically in very recent infarction and far earlier than observed with antimyosin or pyrophosphate. Advantages of this agent are that (1) imaging can be performed within 1 to 2 hours of injection, (2) uptake is specific for necrotic tissue, and (3) tracer delivery is less dependent on myocardial blood flow because of the small molecular size of glucarate. However, given that Tc-99m glucarate primarily targets histones, which rapidly disintegrate within hours after necrosis, the clinical window for imaging appears to be limited to within 9 hours of AMI onset. The clinical utility of this agent is yet to be determined.

Annexin V is an endogenous intercellular protein that has a high affinity for phosphatidylserine, an intracellular phospholipid that is expressed on the cell membrane surface in early (and potentially reversible) apoptosis.

**Cold Imaging with TI-201/Tc-99m Agents**

Rest myocardial perfusion imaging with TI-201 and, particularly, Tc-99m agents can estimate both myocardium at risk during acute coronary artery occlusion and, ultimately, final infarct size. In animal models of permanent coronary occlusion, initial TI-201 activity within the infarct zone correlates very well with coronary blood flow as measured by radiolabeled microspheres. However, this agent has limitations in acute imaging, as the relative gradient in TI-201 activity between normal and infarcted myocardium decreases over time as this isotope washes out from normal regions, thereby simulating an artificial reduction in scintigraphic infarct size. This phenomenon is exaggerated after coronary reperfusion, where TI-201 concentrations not only decrease in normal regions but steadily increase within the ischemic zone. To assess myocardium at risk, imaging must be performed before coronary reperfusion—an untenable requirement.

An alternative radiopharmaceutical for assessing myocardium at risk and final infarct size is Tc-99m sestamibi, as this isotope minimally redistributes once it is taken up by the myocardium. Animal investigations with sestamibi demonstrate close correlations between its initial uptake and occluded flows by radiolabeled microspheres, and the gradient in count activity between normally perfused and infarcted zones remains relatively constant over time.

In animal models of coronary occlusion, there is a close correlation between scintigraphic and pathologic infarct size (Figure 1), which is not influenced by the early reactive hyperemia observed after rapid reperfusion (Figure 2). Thus rest sestamibi imaging during AMI can estimate the extent of myocardium at risk after coronary reperfusion and final infarct size independent of temporal restraints. Rest myocardial perfusion SPECT has important clinical applications in the evaluation of patients with suspected AMI. A normal study virtually excludes the diagnosis of AMI, allowing for early hospital discharge and further outpatient testing as clinically indicated. Although an abnormal rest study can represent a composite of “old” and “new” infarction, the quantified PDS clearly predicts outcome. In the Western Washington Study, patients with a resting LV PDS of 20% or greater by TI-201 SPECT had a significantly higher mortality rate than those with smaller infarcts.
Figure 1. Comparison of tomographic (SPECT) and pathologic infarct sizes in 13 dogs with permanent coronary occlusion. *NS*, Not significant; *LV*, left ventricle; *TTC*, triphenyltetrazolium chloride. (Modified and used with permission from Verani MS, Jeroudi MO, Mahmarian JJ, et al. Quantification of myocardial infarction during coronary occlusion and myocardial salvage after reperfusion using cardiac imaging with technetium-99m hexakis 2-methoxyisobutyl isonitrile. J Am Coll Cardiol 1988;12:1573-81.)

Figure 2. Comparison of planar scintigraphic defect size during occlusion and after reperfusion with pathologic infarct size in 12 dogs. Note the final scintigraphic infarct size after reperfusion is similar to the pathologic infarct size. The difference between the initial defect during occlusion and the final infarct size after reperfusion is the extent of myocardial salvage. *NS*, Not significant; *TTC*, triphenyltetrazolium chloride. (Modified and used with permission from Verani MS, Jeroudi MO, Mahmarian JJ, et al. Quantification of myocardial infarction during coronary occlusion and myocardial salvage after reperfusion using cardiac imaging with technetium-99m hexakis 2-methoxyisobutyl isonitrile. J Am Coll Cardiol 1988;12:1573-81.)
results have been reported with rest Tc-99m sestamibi infarct sizing\(^3\) (Figure 3). Infarct size as determined by rest Tc-99m sestamibi SPECT is now commonly used as a surrogate marker for death in clinical trials assessing therapies during AMI\(^{35-41}\).

**RISK STRATIFICATION WITH GATED RNA: ASSESSMENT OF LV FUNCTION**

Gated RNA is an accurate\(^{42}\) and highly reproducible\(^{43}\) technique for assessing LVEF and LV volumes at rest and during supine bicycle exercise. Studies can be performed directly in the coronary care unit, allowing rapid assessment of LV hemodynamics in AMI patients.

**Rest LVEF**

Early studies have demonstrated that the resting LVEF measured by RNA\(^{33,44}\) and other techniques\(^{45-47}\) is the single best long-term predictor of death in survivors of AMI. In the Multicenter Post Infarction Research Group (MPRG)\(^44\) study, the 1-year mortality rate among 799 survivors of AMI was 9%, but 60% of all deaths occurred in the 33% with an LVEF lower than 40%. A very high mortality rate of 47% was observed in the small 3% of patients with an LVEF lower than 20% (Figure 4).

The important prognostic information obtained from LVEF has been confirmed in patients receiving reperfusion therapy during AMI. In the study by Simoons et al.,\(^45\) 1- and 3-year mortality rates increased with worsening LVEF lower than 40%, irrespective of whether patients received streptokinase or placebo (Figure 5). In the series by Dakik et al.,\(^48\) the LVEF was the only significant predictor of infarct-free survival, with the relative risk of death or nonfatal MI doubling for every 10% decrease in LVEF. Curiously, survival in patients with a depressed LVEF appears to be better in those who receive thrombolytic therapy\(^{49,50}\) as compared with historic control subjects\(^{44}\) (Figure 4). This may be a result of transient myocardial stunning after thrombolysis, which can spuriously overestimate cardiac risk if the LVEF is measured before recovery in function.\(^{51}\) Beyond this caveat, the final LVEF remains an important predictor of long-term survival irrespective of initial therapy during AMI.

**LV Volumes**

LV enlargement significantly increases the mortality rate in patients with AMI, particularly when there is coexisting myocardial dysfunction.\(^{52}\) LV dilation develops early, particularly in patients with anterior infarction who generally have the greatest degree of initial LV dysfunction and in whom early infarct zone expansion is therefore most likely to develop.\(^{33,54}\) Remodeling continues after the acute phase of infarction, but the progressive increase in both LV end-diastolic and end-systolic volumes is generally limited to those with an initial LVEF of 40% or lower\(^{55}\) (Figure 6). Patients with an LVEF lower than 40% in whom LV expansion develops have a significantly higher mortality rate as compared with those who do not.\(^{47}\)

**Stress Gated RNA**

Although the rest LVEF identifies patients at high risk for death,\(^{33,44-46,48-50}\) the presence of exercise-
induced ischemia by RNA may further improve risk stratification.56-63 (Table 1). This may also be true for patients who receive thrombolytic therapy, where exercise-induced ischemic LV dysfunction is frequently ob-


Figure 5. Survival rate of patients based on various LVEF cutoff values and initial therapy during acute infarction. No difference in survival rate was observed between patients treated with streptokinase (solid lines) or conventional therapy (dashed lines) within a given range of LVEF. (Used with permission from Simoons ML, Vos J, Tijssen JG, Verheugt FWA, Cats VM. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. J Am Coll Cardiol 1989;14:1609-15.)
In the Thrombolysis in Myocardial Infarction (TIMI) phase II trial, 59% of patients had an ischemic response, defined as either a less than 5% increase (48%) or a greater than 5% decrease (11%) in exercise LVEF. The rest LVEF (Figure 4), peak exercise LVEF, and change in LVEF with exercise all predicted survival, but the exercise variables did not improve predictive accuracy over the rest LVEF alone. Exercise LVEF variables may better predict nonfatal ischemic cardiac events, which were not evaluated in this trial. Although important from an historical perspective, exercise gated RNA has been largely supplanted by gated SPECT perfusion imaging for risk stratification.

### Table 1. Gated exercise radionuclide angiography for risk assessment after acute myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Follow-up (mo)</th>
<th>Events</th>
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<th>Positive predictive accuracy (%)</th>
<th>Negative predictive accuracy (%)</th>
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<td>Candell-Riera et al&lt;sup&gt;56&lt;/sup&gt;</td>
<td>115</td>
<td>12</td>
<td>D/RMI/A/CHF/REV</td>
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<tr>
<td>Corbett et al&lt;sup&gt;57&lt;/sup&gt;</td>
<td>61</td>
<td>9.6</td>
<td>D/RMI/A/UA/CHF</td>
<td>Δ LVEF &lt;5%</td>
<td>97</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>Corbett et al&lt;sup&gt;59&lt;/sup&gt;</td>
<td>117</td>
<td>8.3</td>
<td>D/RMI/A/UA/CHF</td>
<td>Δ LVEF &lt;5%</td>
<td>95</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>Nicod et al&lt;sup&gt;61&lt;/sup&gt;</td>
<td>42</td>
<td>8</td>
<td>D/RMI/UA</td>
<td>Δ LVEF &lt;5%</td>
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<td>Hung et al&lt;sup&gt;60&lt;/sup&gt;</td>
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<td>Δ LVEF &lt;5%</td>
<td>63</td>
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</table>


A, exertional angina; CHF, congestive heart failure; D, death; Ex, exercise; REV, revascularization; RMI, recurrent myocardial infarction; UA, unstable angina.
diagnostic (ECG) ischemia predicted subsequent cardiac death. Other important predictors of death included a poor exercise effort (<4 metabolic equivalents) and exercise-induced angina, hypotension, or ventricular arrhythmias. In an early study from the Montreal Heart Institute, the 1-year mortality rate among all patients was 9.5% but death occurred almost exclusively in the 30% of patients with ECG ischemia. Patients without ischemia had only a 2.1% mortality rate as compared with a 27% mortality rate in those with ST-segment depression.64

Although submaximal exercise ECG testing predicts death in stable patients after AMI, it was of limited value in predicting other morbid events (Figure 7). In an attempt to improve risk stratification, investigators combined submaximal treadmill exercise with myocardial perfusion scintigraphy (Table 2).74-78 In a landmark study from Gibson et al.75 140 seemingly low-risk patients were evaluated with submaximal exercise Tl-201 scintigraphy and coronary angiography and were observed for 15 ± 12 months. The presence of scintigraphic ischemia, particularly when involving multiple vascular territories, was the most powerful prognosticator. The scintigraphic variables were superior to the treadmill exercise variables in defining high-risk and particularly low-risk individuals (Figure 8).

More recently, Travin et al.76 demonstrated the value of submaximal exercise Tc-99m sestamibi SPECT in stratifying risk after AMI. Ischemic ECG changes were observed in only 23% of the 134 patients, whereas 70% had scintigraphic ischemia. The cardiac event rate in patients without scintigraphic ischemia was only 7% versus 19% in those with ischemia. The extent of ischemia further predicted outcome, with a 12% event rate in those with 1 or 2 ischemic defects versus 38% in patients with 3 ischemic defects or more. By Cox regression analysis of clinical, exercise treadmill, and scintigraphic variables, only the number of ischemic defects on SPECT predicted outcome.

**RISK STRATIFICATION WITH PHARMACOLOGIC STRESS MYOCARDIAL PERFUSION SCINTIGRAPHY**

The introduction of pharmacologic vasodilators as an alternative to submaximal exercise stress allowed for
Table 2. Comparison of exercise versus pharmacologic coronary vasodilators for risk assessment after acute myocardial infarction

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Positive predictive accuracy (%)</th>
<th>Negative predictive accuracy (%)</th>
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<tr>
<td>IZ RD</td>
<td>42</td>
<td>77</td>
</tr>
<tr>
<td>IZ RD</td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>RD</td>
<td>59 (86)*</td>
<td>94</td>
</tr>
<tr>
<td>RD</td>
<td>31</td>
<td>97</td>
</tr>
<tr>
<td>RD</td>
<td>20</td>
<td>96</td>
</tr>
<tr>
<td>NIZ RD</td>
<td>26 (42)*</td>
<td>88</td>
</tr>
<tr>
<td>RD</td>
<td>22</td>
<td>94</td>
</tr>
<tr>
<td>RD</td>
<td>33</td>
<td>94</td>
</tr>
<tr>
<td>RD</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>RD (5% LV)</td>
<td>42</td>
<td>90</td>
</tr>
<tr>
<td>RD</td>
<td>36</td>
<td>92</td>
</tr>
<tr>
<td>RD</td>
<td>50</td>
<td>97</td>
</tr>
</tbody>
</table>


IZ, Infarct zone; LV, left ventricle; NIZ, noninfarct zone; RD, redistribution; REV, coronary revascularization; UA, unstable angina.

*Positive predictive accuracy for ischemia in multiple vascular territories is shown in parentheses.

Figure 8. Kaplan-Meier event-free survival curves in 140 stable patients with AMI based on the presence of ischemia as assessed by the submaximal exercise test and Tl-201 scintigraphy. The Tl-201 scintigraphic results best predicted risk for subsequent cardiac events. RD, Redistribution. (Adapted and used with permission from Gibson RS, Watson DD, Craddock GB, et al. Prediction of cardiac events after uncomplicated myocardial infarction: a prospective study comparing predischarge exercise thallium-201 scintigraphy and coronary angiography. Circulation 1983;68:321-36.)
an earlier assessment of risk and expanded noninvasive testing to those patients who had physical limitations to exercise.

Pharmacologic vasodilators maximize heterogeneity in coronary blood flow and can thereby accurately identify the extent of LV hypoperfusion and residual ischemia.\textsuperscript{79,80} Whereas submaximal exercise may underestimate the extent of inducible ischemia by SPECT\textsuperscript{81} and thereby underestimate risk, pharmacologic vasodilators, particularly adenosine, induce a similar PDS as observed with maximal exercise stress.\textsuperscript{82} Given that pharmacologic stress testing can be safely performed even within 1 to 2 days after AMI, high- and low-risk patients can be identified early and treated accordingly.\textsuperscript{83-85} For these reasons, dipyridamole and adenosine have become preferable to exercise stress for assessing risk in stable patients after AMI. The scintigraphic risk variables identified with exercise stress have been confirmed in studies using dipyridamole and adenosine (Table 2).\textsuperscript{86-92}

**Dipyridamole SPECT**

Leppo et al\textsuperscript{86} first investigated the role of dipyridamole TI-201 scintigraphy for risk stratification after uncomplicated AMI. In this study the presence of TI-201 redistribution was the only significant predictor of cardiac death or recurrent AMI. Brown et al\textsuperscript{87} demonstrated the safety of dipyridamole in 50 stable patients imaged very early (mean, 62 ± 121 hours) after hospitalization. No patient had a complication with dipyridamole administration. The only significant predictor of in-hospital and late cardiac events among clinical, scintigraphic, and angiographic variables was the presence of infarct-zone TI-201 redistribution. Conversely, none of the patients without redistribution had a subsequent cardiac event during the ensuing year.

Recently, Brown et al\textsuperscript{91} reported the results of a large multicenter trial evaluating the relative efficacy of dipyridamole versus exercise SPECT for predicting early and late cardiac events. A semiquantitative summed stress score (SSS) and summed difference score (SDS) were generated to assess the size of the stress-induced perfusion defect and the extent of scintigraphic ischemia, respectively. The only multivariate predictors of in-hospital events among clinical, dipyridamole stress ECG, and scintigraphic variables were the SSS, SDS, and peak creatine kinase level. Multivariate predictors of death or MI after hospital discharge were the dipyridamole SPECT-derived SSS and SDS and anterior infarction location. The extent of scintigraphic ischemia (ie, SDS) further improved risk stratification, particularly in patients with intermediate-sized perfusion defects (Figure 9). Risk stratification was significantly better with dipyridamole than with submaximal exercise SPECT.

**Adenosine SPECT**

The role of adenosine TI-201 SPECT for detecting residual ischemia and predicting in-hospital cardiac events was first reported in 120 stable survivors of AMI who were imaged early (5 ± 3 days) after infarction.\textsuperscript{84}
The overall sensitivity of SPECT for detecting significant (>50%) coronary artery disease (CAD) by coronary angiography was 87%. Sixty-three percent of patients with double-vessel CAD and ninety-one percent of patients with triple-vessel CAD were accurately predicted to have multivessel involvement. Although scintigraphic ischemia was common within the infarct (59%) and noninfarct (63%) zones, neither angiographic patency nor the presence of collaterals predicted the presence of scintigraphic ischemia. In this regard, angiographic information alone is a poor predictor of myocardial viability and might be misleading when deciding the appropriateness of coronary revascularization. The adenosine-induced LV PDS identified a high-risk group for in-hospital complications (Table 3). No patient with a small (<10%) LV PDS had an in-hospital cardiac event, as compared with 51% of those with larger defects.

A subsequent trial from the same group assessed the long-term prognostic importance of performing adenosine T1-201 SPECT early after AMI. Clinical predictors of risk were patient age, sex, prior history of AMI, and prior coronary revascularization. Scintigraphic risk predictors were the LVEF (P < .0001), the quantified LV PDS (P < .0001), and the absolute extent of scintigraphic ischemia (P < .000001) (Figure 10). Multivariate analysis incorporating clinical, angiographic, and scintigraphic variables identified only the absolute extent of scintigraphic ischemia and LVEF or total PDS and infarct zone ischemia as independent predictors of risk (Figure 11). Chi-square analysis with a baseline model of clinical variables demonstrated improved risk stratification when LVEF and total and ischemic PDS were added in an incremental fashion. The addition of coronary angiographic findings did not improve the clinical model.

To validate these retrospective results, a more recent study prospectively risk-stratified patients according to their initial adenosine-induced PDS and the extent of scintigraphic ischemia. Patients with a small (<20%) LV PDS were classified as low risk, patients with a large (≥20%) but predominantly nonischemic (<10%) PDS as intermediate risk, and patients with a large (≥20%) and predominantly ischemic (≥10%) LV PDS as high risk. High-risk patients who were considered good revascularization candidates after coronary angiography underwent randomization to receive either intensive anti-ischemic medical therapy or coronary revascularization, whereas the remainder received medical therapy as tolerated.

Patients classified as low risk had a relatively low overall cardiac event rate (17%), with no deaths and few reinfarctions (7%) over a period of 11 ± 5 months, whereas patients classified as intermediate risk had an overall higher event rate (29%). High-risk patients who were not randomized had a significantly higher event rate than those with scintigraphic scar (78% vs 29%, P < .001) despite a comparable LVEF of 36%. This was also true when events were limited to death and nonfatal reinfarction (Figure 12). These data imply that stable patients after AMI who have either a small or predominantly nonischemic PDS can generally be treated conservatively, with aggressive anti-ischemic therapy reserved for those with large reversible defects who are at high risk for subsequent cardiac events. This paradigm is further supported by a more recent study focusing on patients with a remote (>6 months) history of AMI, in which a very low annual event rate of 0.6% was observed in patients who had only a small MI and no inducible ischemia.

### RISK STRATIFICATION WITH PERFUSION SCINTIGRAPHY IN THE THROMBOLYTIC ERA

Myocardial perfusion scintigraphy remains an accurate method for risk-stratifying patients after acute reper-
fusion therapy. Much of the initial controversy surrounding the prognostic accuracy of scintigraphy in this population grew from concern over the low mortality rate reported in patients who received acute reperfusion therapy. Much of the initial controversy surrounding the prognostic accuracy of scintigraphy in this population grew from concern over the low mortality rate reported in patients who received acute reperfusion therapy.

**Figure 10.** Kaplan-Meier curves depicting freedom from cardiac events on the basis of LV PDS and EF (A) and quantified extent of LV ischemia (QISCH) (B). The total PDS and global LVEF were inversely related and provided similar prognostic information. QISCH was the best univariate predictor of risk and did so irrespective of initial therapy during acute infarction. **Thick lines** in B, Early reperfusion therapy; **thin lines**, no early reperfusion therapy. (Used with permission from Mahmarian JJ, Mahmarian AC, Marks GF, Pratt CM, Verani MS. Role of adenosine thallium-201 tomography for defining long-term risk in patients after acute myocardial infarction. J Am Coll Cardiol 1995;25:1333-40.)

**Figure 11.** Cox regression models displaying 1-year risk for a cardiac event according to LVEF and total LV ischemia (A) or scintigraphic variables (B). **Diagonal lines**, Representative isobars of percent risk. Patient risk for any cardiac event increases as total LV ischemia increases and LVEF decreases (A) or as total PDS and percent infarct zone ischemia increase (B). For any given LVEF (A) or PDS (B), risk varies widely depending on the amount of ischemia. LVEF and scintigraphic results for each of the 92 patients who did (solid circles) or did not (open circles) have a subsequent cardiac event over the entire follow-up period are plotted against their calculated risk at 1 year (A and B). (Used with permission from Mahmarian JJ, Mahmarian AC, Marks GF, Pratt CM, Verani MS. Role of adenosine thallium-201 tomography for defining long-term risk in patients after acute myocardial infarction. J Am Coll Cardiol 1995;25:1333-40.)
therapy. Risk stratification via any test is of little clinical value when applied to a very low-risk population. However, patients undergoing acute coronary reperfusion commonly return with other nonfatal cardiac events such as recurrent AMI and particularly readmission for unstable angina.

Another concern was that the prevalence of ischemia in patients receiving thrombolytic therapy may be significantly lower than previously reported. This is apparently true for exercise-induced ECG ischemia, which has decreased from a prevalence of approximately 31% to 15%. The prevalence of scintigraphic ischemia has decreased to a lesser degree in that approximately 46% of patients still demonstrate ischemia on perfusion scintigraphy.

Exercise and pharmacologic stress myocardial perfusion imaging can predict subsequent outcome in patients receiving thrombolytic therapy. Tilkemeier et al compared submaximal planar TI-201 scintigraphy in 171 patients who did or did not have interventions (ie, primary angioplasty or thrombolytic therapy) during AMI. The positive predictive value of exercise-induced scintigraphic ischemia for predicting subsequent events was similar in both groups (36% vs 33%, respectively). Travin et al observed 87 patients after submaximal exercise SPECT, 34 of whom received thrombolytic therapy. The number of ischemic segments predicted subsequent cardiac events equally well irrespective of initial therapy.

Dakik et al studied 71 patients who received thrombolytic therapy during AMI and underwent exercise TI-201 SPECT and coronary angiography before hospital discharge. The LVEF ($P < .005$) and the exercise-induced total ($P = .002$) and ischemic ($P < .0005$) SPECT PDS were all strong univariate predictors of subsequent cardiac events over a follow-up period of 26 ± 18 months. None of the treadmill exercise variables predicted subsequent outcome. By multivariate analysis, the best predictors of risk were the LVEF (relative risk of 1.85 for a 10% decrease) and quantified ischemic PDS (relative risk of 1.38 for a 5% increase). The LVEF and scintigraphic variables significantly contributed to predicting risk beyond the clinical variables alone, with no additional information gained from the angiographic results (Figure 13).

These results with submaximal exercise testing have been confirmed in patients studied with pharmacologic vasodilators. Brown et al reported separation of high and low risk with dipyridamole sestamibi SPECT in patients who received thrombolytic therapy ($P = .02$). Mahmarian et al likewise showed that adenosine TI-201 SPECT could predict events equally well in patients who did or did not receive thrombolytic therapy during AMI based on the quantified ischemic PDS (Figure 10). These data all indicate that the resultant extent of residual scintigraphic ischemia, rather than the initial reperfusion strategy per se, best predicts future cardiac risk. As post-thrombolysis patients who lack ischemia by noninvasive testing have an excellent prognosis, it seems unlikely that coronary revascularization in this population would further improve outcome.
NUCLEAR CARDIAC IMAGING IN THE CURRENT ERA OF INTERVENTIONAL CARDIOLOGY

There is growing acceptance that a routine invasive strategy should be the community standard of care for evaluating and treating ACS patients. This is largely fueled by (1) the therapeutic advantage of primary percutaneous coronary intervention (PCI) over thrombolytic therapy for treatment of ST-elevation AMI, (2) evidence of early and clinically unpredictable reinfection in patients who receive thrombolytics, and (3) results of randomized ACS trials showing an advantage of a routine invasive strategy over a conservative approach in preventing subsequent cardiac events.

First, primary PCI is increasingly recognized as the

Figure 13. Incremental prognostic value of LVEF and TI-201 SPECT variables. The bars depict the $\chi^2$ statistics for clinical variables; clinical variables and LVEF; clinical, LVEF, and SPECT variables; and clinical, LVEF, SPECT, and angiographic variables. (Used with permission from Dakik HA, Mahmarian JJ, Kimball KT, et al. Prognostic value of exercise thallium-201 tomography in patients treated with thrombolytic therapy during acute myocardial infarction. Circulation 1996;94:2735-42.)

treatment of choice for restoring coronary blood flow, preventing reinfarction, and improving survival in patients with ST-elevation AMI. In patients who receive primary PCI as initial treatment, further risk stratification by use of noninvasive imaging would seem moot. However, despite growing support for performing PCI over thrombolytic therapy, only approximately 18% of patients currently undergo primary PCI in the United States, with most receiving either thrombolytic agents (52%) or no reperfusion therapy (30%). Stabilized patients not treated with primary PCI are good candidates for noninvasive risk stratification. In patients who do have primary PCI, SPECT might still be selectively used to assess for ischemia outside the infarct zone in those with multivessel CAD, as well as to identify viable myocardium within the infarct zone and thereby predict recovery of LV function in patients with myocardial stunning.

Second, concern has been raised that patients who receive thrombolytic agents are at high risk for early reinfarction and that “watchful waiting” before performing noninvasive testing is not acceptable. Recent data from the TIMI group in 20,101 patients indicate that 4.2% of patients who received thrombolytic therapy had reinfarction during their index hospitalization. Furthermore, patients with reinfarction had a significantly higher 30-day and 2-year mortality rate as compared with those who did not (16.4% vs 6.2% and 19.6% vs 10.1%, respectively; \( P < .001 \)). Reinfarction occurred less frequently among patients who underwent revascularization (1.4% vs 4.7%, \( P < .001 \)), with improved subsequent survival (\( P < .001 \)). These data support that an early invasive approach is good clinical practice—a pre-emptive strike to avoid an ensuing bad outcome. Although the cost efficacy of performing coronary angiography in all patients to improve outcome in the small 4% destined to have reinfarction requires further investigation, a watchful waiting approach also appears undesirable.

Finally, a routine invasive approach was shown to be superior to a conservative strategy in two recent large randomized ACS trials. In the Fast Revascularization during InStability in Coronary artery disease (FRISC) study, 2,457 patients were randomized to either an early invasive strategy or a conservative strategy with selective angiography in those demonstrating myocardial ischemia. Most patients (96%) randomized to the invasive strategy had coronary angiography within 7 days of admission, and 78% had either coronary artery bypass surgery (35%) or coronary angioplasty (43%). Conversely, coronary angiography was performed in only 47% of patients assigned to the conservative limb, with 36% undergoing coronary revascularization. The infarct-free survival rate was significantly better at 6 months (90.6% vs 87.9%, \( P = 0.031 \)) and at 1 year (89.6% vs 85.9%, \( P = .005 \)) in patients assigned to the invasive versus the conservative strategy, respectively.

In the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) trial, 2,200 patients with unstable angina or non–Q-wave AMI were randomized to either an invasive or conservative strategy. In the invasive strategy, 97% of patients had coronary angiography before hospital discharge and 61% had either coronary angioplasty with stenting (41%) or bypass surgery (20%). In the conservative limb, 51% had coronary angiography and 37% had either angioplasty (24%) or bypass surgery (13%) during the initial hospitalization. At 6 months, the primary endpoint of death, nonfatal AMI, and readmission for unstable angina was significantly lower in the invasive (15.9%) versus the conservative strategy (19.4%) group (\( P = 0.025 \)), as was the combined endpoint of death/nonfatal AMI (4.7% vs 7%, respectively; \( P = 0.02 \)).

At first blush, these results appear impressive. How-
Figure 16. Representative stress-only short-axis (SA) (upper 2 panels) and vertical long-axis (VLA) (lower 2 panels) tomographic images of a patient at baseline and at 8 weeks after administration of intracoronary Ad5FGF-4 gene therapy. The corresponding quantitative polar maps are shown on the right. The adenosine-induced ischemic anterior perfusion defect improves dramatically from baseline to week 8, as reflected by a reduction in PDS from 26% to 6%. The ischemic (green) area of the polar map resolves, whereas the scarred region (black) remains unchanged over the 8-week period. [Modified and used with permission from Grines CL, Watkins MW, Mahmarian JJ, et al, for the Angiogenic GENE Therapy (AGENT-2) study group. A randomized, double-blind, placebo-controlled trial of Ad5FGF-4 gene therapy and its effect on myocardial perfusion in patients with stable angina. J Am Coll Cardiol 2003;42:1339-47.]

Figure 17. Sequential adenosine Ti-201 SPECT images (left) and polar maps (right) in a patient after AMI. On initial baseline SPECT (SPECT 1), the polar map shows a large (49%) primarily ischemic (37%) LV PDS (dark green) in the left anterior descending (LAD) coronary artery vascular territory with minimal scar (12%) (black). After angioplasty of the LAD, the ischemic defect is no longer present (SPECT 2) with only a small comparable residual scar (10%) as seen on baseline SPECT. (Used with permission from Mahmarian JJ. Risk assessment in acute coronary syndromes [chapter 11-iii]. In: Iskandrian AE, Verani MS, editors. Nuclear cardiac imaging: principles & applications. 3rd ed. Oxford: Oxford University Press, Inc; 2002:207-243.)
ever, both trials compared a “state-of-the-art” interventional approach with a suboptimal conservative strategy of submaximal treadmill testing with variable and poorly documented anti-ischemic medical therapy. Submaximal treadmill testing is insensitive in identifying myocardial ischemia and has a poor negative predictive accuracy for identifying low-risk patients. Furthermore, the degree to which medical therapy reduces ischemia is uncertain in patients with low-risk features. Therefore, the demonstration of reduction in ischemia with intensive medical therapy might be an important and clinically relevant endpoint in the postinfarction population. Figure 18. Mean quantified total, ischemic, and scar PDS at baseline (SPECT 1) and after anti-ischemic medical or revascularization therapies (SPECT 2). (Used with permission from Dakik HA, Kleiman NS, Farmer JA, et al. Intensive medical therapy versus coronary angioplasty for suppression of myocardial ischemia in survivors of acute myocardial infarction. A prospective, randomized pilot study. Circulation 1998;98:2017-23.)

therapy was administered in patients with residual ischemia is unclear. This is particularly relevant because patients in the conservative strategy group only crossed over to coronary angiography when ischemia was considered severe by treadmill testing. As treadmill exercise was used in both of these trials, many patients randomized to the conservative strategy had a recurrent cardiac event during the “watchful waiting” period—before the index stress test could be safely performed.

Beyond these ACS trials, several randomized studies in patients with AMI have shown no significant prognostic advantage between an invasive or a conservative approach. The Veterans Affairs Non Q-Wave Infarction Strategies in Hospital (VANQWISH) study, however, is the only one of these trials that selected myocardial perfusion scintigraphy as the noninvasive testing modality. In this study, significantly higher rates of coronary angiography (94% vs 48%) and revascularization (44% vs 33%) were observed in the invasive versus conservative limbs despite a comparable 1-year infarct-free survival rate (76% vs 81%) (Figure 14). A recent analysis from the VANQWISH investigators demonstrated that the conservative strategy was more cost-effective than the routine invasive approach. A pooled analysis of ACS trials has not demonstrated a survival advantage with a routine invasive approach over a conservative approach.

It is generally accepted that clinically high-risk patients with AMI should undergo coronary angiography with the intent to revascularize. However, the rationale behind a noninvasive conservative approach is that most patients are not clinically high risk and will remain stable during the initial hospitalization, allowing adequate time to accurately identify high- and low-risk patients based on the results of noninvasive testing. Gated SPECT imaging can readily identify which stable patients are at high risk based on the extent of residual myocardial ischemia, a perfusion pattern suggesting multivessel CAD, and the degree of LV dysfunction. With the introduction of pharmacologic vasodilators, in lieu of exercise stress, perfusion imaging can be performed safely even within 1 to 2 days of admission, allowing very early risk stratification and selective targeting of invasive procedures to scintigraphically high-risk patients who are most likely to benefit from this approach.

**ASSESSING THERAPY AND TRACKING CARDIAC RISK WITH SEQUENTIAL IMAGING**

Serial gated RNA can accurately assess individual and group effects of various therapies on LVEF and LV volumes. Likewise, serial rest Tc-99m sestamibi SPECT during AMI can define the extent of jeopardized myocardium during acute coronary occlusion and the degree of myocardial salvage after a given therapeutic intervention. Serial rest Tc-99m sestamibi SPECT has been popularized as a method by which to assess the benefits of reperfusion therapy on infarct size (Figure 15).

Gated myocardial perfusion scintigraphy is most studied for assessing changes in stress-induced perfusion defects after various anti-ischemic medical and revascularization therapies. Studies in patients with...
chronic CAD have shown improvements in stress-induced scintigraphic ischemia with single and combination medical therapies\textsuperscript{119-123} and, more recently, in angiogenesis studies using growth factors\textsuperscript{124,125} (Figure 16). As a result of the known high reproducibility of quantitative sequential SPECT imaging,\textsuperscript{126} both mean and individual treatment effects can be observed (Figure 17). Although the significance of such changes requires confirmation, a reduction in the quantified PDS would appear to predict a reduction in risk for subsequent cardiac events. In the study by Dakik et al\textsuperscript{123} sequential adenosine SPECT was used to assess the relative benefit of intensive medical therapy versus coronary angioplasty in suppressing myocardial ischemia and improving outcome. The adenosine-induced LV PDS was significantly reduced after anti-ischemic therapy and almost entirely attributable to a reduction in the ischemic PDS (Figure 18). The total PDS and ischemic PDS were comparably reduced with medical therapy and coronary angioplasty (Figure 19). The event-free survival rate was superior in the 25 patients (13 revascularized and 12 medically treated) who had a significant ($\geq 9\%$) reduction in PDS (96\%) as compared with those who did not (65\%) ($P = .007$) (Figure 20). A 40\% 1-year event rate was anticipated based on the initial SPECT results. Thus patients who did not reduce their PDS with anti-ischemic therapy continued to have events at an expected rate. Similar results have been reported with planar thallium scintig-

**Figure 21.** Adenosine Tc-99m sestamibi myocardial perfusion tomographic (SPECT) images (left) and polar maps (right) of a 41-year-old man who received thrombolytic therapy for AMI. Once stabilized, the patient underwent baseline SPECT (top panel) on day 2 after admission. The baseline study shows a predominantly ischemic perfusion defect in the left anterior descending and right coronary artery vascular territories with a large total PDS of 33\% (26\% ischemia, green; 7\% scar, black). The patient was treated medically with aspirin, long-acting nitrates, $\beta$-blockers, and calcium antagonists. Simvastatin was given to treat hyperlipidemia. The patient returned for repeat SPECT (bottom panel) 6 weeks later, which showed an almost entirely normal study. He remains asymptomatic 2 years later.
Scintigraphy in patients with chronic CAD. These preliminary data indicate that myocardial perfusion scintigraphy may be used not only to assess initial risk but also to track subsequent risk after AMI by evaluating the efficacy of various therapies on myocardial ischemia (Figure 21).

FUTURE DIRECTIONS

The role of nuclear cardiac imaging in AMI continues to evolve. Although scintigraphic variables predict subsequent outcome in patients after AMI, most reported patient series have been relatively small and overshadowed by larger ACS trials, which generally did not incorporate myocardial perfusion scintigraphy as the noninvasive methodology for patient assessment. Although VANQWISH was a large, prospective, randomized trial that used perfusion imaging to assess risk, this study has been criticized because of the inordinately high initial mortality rate among revascularized patients. Furthermore, VANQWISH used subjective planar imaging to assess for ischemia rather than a quantitative assessment of ischemia with SPECT.

The Adenosine Sestamibi Post-Infarction Evaluation Trial (INSPIRE) is a soon-to-be-completed prospective, multicenter, randomized study that will evaluate the role of perfusion scintigraphy in defining initial risk and subsequent patient outcome after anti-ischemic therapies (Figure 22). This trial has enrolled 728 clinically stable patients with Q-wave and non-Q-wave AMI who underwent adenosine Tc-99m sestamibi gated SPECT within the first several days of AMI. Therapeutic decision making was based on the quantified size of the total LV PDS, the extent of residual ischemia, and the LVEF.

A core laboratory interpreted all nuclear studies online so that sites could be notified of SPECT results on the day of imaging. Patients with a small quantified PDS (<20%) were considered at low risk and medically treated, whereas patients with a large (≥20%) and ischemic (≥10%) LV PDS were considered at high risk for subsequent cardiac events. High-risk patients with an LVEF lower than 35% were directed to undergo coronary angiography with the intent to revascularize, whereas those with an LVEF of 35% or greater were randomized to either intensive medical therapy or coronary revascularization. Crossover to coronary angiography in the medical therapy group was allowed only for protocol-defined clinical indications. As in other recent trials, INSPIRE used state-of-the-art interventional approaches. However, unlike other studies, the medical therapy regimen in this trial was intensive, multifaceted, and prospectively defined. Preliminary results from INSPIRE in the 205 randomized patients who had sequential SPECT imaging show a significant overall reduction in total and ischemic PDS in the majority of treated patients (79%). Whether a change in PDS after therapy tracks subsequent patient outcome awaits confirmation after compilation of the INSPIRE cardiac event data. All patients are anticipated to have at least a 1-year follow-up visit to assess prognosis.

Depending on the results of INSPIRE, larger prospective trials may be justified to further evaluate the role of nuclear cardiac imaging in evaluating and treating the broader spectrum of ACS patients. Subsequent trials might potentially incorporate vascular imaging of the coronary bed so as to identify vulnerable plaques in arteries perfusing ischemic territories and thereby better predict which patients with ischemia are likely to have a
subsequent cardiac event. Imaging the sympathetic nerve system with agents such as metaiodobenzylguanidine might determine which patients are at high risk for ventricular dysrhythmias or progressive heart failure and death. These types of novel and innovative developments will define the future role of nuclear cardiac imaging for guiding therapeutic decision making in patients surviving AMI.

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