Quantitative Adenosine $^{201}$Tl Single-Photon Emission Computed Tomography for the Early Assessment of Patients Surviving Acute Myocardial Infarction

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Background. We prospectively investigated whether adenosine $^{201}$Tl tomography (SPECT) could determine the extent of coronary artery disease, the presence of jeopardized myocardium, and the risk for in-hospital cardiac events in 120 clinically stable patients early (5±3 days) after myocardial infarction.

Methods and Results. All patients had coronary angiography and SPECT in close proximity. Adenosine SPECT identified 99% of infarct-related arteries and 82% of severely stenosed (≥70%) noninfarct arteries. Multivessel disease was accurately predicted in 69% of patients. Sixty-five percent of stenosed noninfarct arteries had matching thallium perfusion defects, and 92% of these were reversible. The specificity of adenosine SPECT was >90%. Thallium redistribution occurred often within infarct (59%) and noninfarct (92%) zones. The patency status of the arteries, however, did not predict the presence or extent of jeopardized myocardium. The perfusion defect size was larger ($p=0.0001$) in patients with (45±18%) than in those without (22±15%) in-hospital cardiac events. Furthermore, 90% of patients with events had a ≥20% perfusion defect compared with only 38% of those without events ($p=0.0001$). The positive-predictive accuracy for developing a cardiac event was 70% when the perfusion defect size was >30%. The ischemic defect was also larger in patients with (19±14%) than in those without (10±10%) events ($p=0.001$). The positive- and negative-predictive values for developing early postinfarction angina were 43% and 91%, respectively, when the ischemic defect was >12%.

Conclusions. In selected low-risk survivors of myocardial infarction, early quantitative adenosine SPECT is safe and accurate in detecting and localizing coronary stenoses, assessing the extent of jeopardized myocardium, and determining subsequent risk for in-hospital cardiac events. (Circulation 1993;87:1197-1210)

Key Words • scintigraphy, myocardial perfusion • pharmacology • vasodilation, coronary • myocardial ischemia • adenosine • $^{201}$Tl • computed tomography, single-photon emission

There is increasing clinical awareness that patients with myocardial infarction have a greater risk for subsequent cardiac events if they have marked left ventricular (LV) dysfunction,1–3 multivessel coronary artery disease,4,5 and/or residual myocardial ischemia.4–6 The latter may play a particularly important prognostic role in patients who have only moderately depressed LV function.7,8 For example, compared with patients with Q wave infarction, those with non-Q wave infarction have more residual ischemia surrounding the infarct zone7 and a higher reinfarction rate.7–11 Recent investigations have also suggested an increased risk of recurrent ischemic events in patients receiving thrombolytic therapy for myocardial infarction.12,13 Furthermore, after infarction many patients have detectable asymptomatic myocardial ischemia that appears to adversely affect prognosis.14

The submaximal exercise stress test before hospital discharge traditionally has been used to identify patients with residual myocardial ischemia after infarction. An ischemic ECG response to exercise is a good predictor of subsequent cardiac events.4–6 but it lacks sensitivity, so a normal submaximal exercise ECG does not necessarily indicate a favorable outcome when assessing individual patients.4 Exercise $^{201}$Tl perfusion scintigraphy is superior to the stress ECG for detecting jeopardized myocardium and determining cardiac risk.4,15–17 Furthermore, with the use of single-photon emission computed tomography (SPECT), the extent of jeopardized myocardium can be accurately quantified.18–21

Exercise testing is not feasible in many patients surviving myocardial infarction due to physical con-
strains. Moreover, maximal exercise is not recommended for several weeks after infarction, so the physician is limited to information obtained from a predischarge submaximal test during a time interval known to be associated with a high incidence of recurrent cardiac events. In this regard, a noninvasive alternative method of assessing the presence of jeopardized myocardium during the acute hospitalization, without the requirement of exercise, would add diagnostic flexibility to identifying high-risk patients before hospital discharge.

Pharmacological vasodilation with dipyridamole in conjunction with 201TI scintigraphy has been reported to detect high-risk patients after infarction.22–25 Dipyridamole, however, is an indirect coronary vasodilator that acts by blocking the cellular uptake of the primary vasodilator, adenosine.26 Furthermore, both oral and intravenous dipyridamole may be associated with significant side effects, which in some individuals can be long lasting and require theophylline administration for reversal.27,28 In contrast, the primary coronary vasodilator adenosine has an exceedingly short half-life of only several seconds29 and therefore affords a high degree of safety because its pharmacological effects disappear promptly on discontinuation of the drug infusion.30,31

Accordingly, we prospectively assessed the clinical value of quantitative 201TI SPECT during pharmacological coronary vasodilation with adenosine for determining the anatomic extent and location of coronary artery stenoses, the frequency and severity of residual myocardial ischemia, and whether the perfusion defect size and the presence or extent of residual ischemia could predict cardiac events in an otherwise low-risk, stable group of patients very early after acute myocardial infarction.

Methods

Patient Population

The patient population consisted of 120 consecutive patients (95 men and 25 women; mean age, 59±11 years; age range, 31–84 years) in whom we performed adenosine 201TI SPECT early (5±3 days) after acute myocardial infarction. Myocardial infarction was diagnosed if patients had chest pain lasting >30 minutes, typical ECG changes of infarction, and a characteristic rise and fall in plasma creatine kinase–MB activity. ECG criteria for acute Q wave infarction required ST segment elevation of at least 0.1 mV in two or more of the six precordial leads for anterior infarction; leads II, III, and aVF for inferior infarction; and leads I, aVL, V5, and V6 for lateral infarction, with the subsequent development of pathological Q waves. Non–Q wave myocardial infarction required new and persistent ST segment depression of at least 0.1 mV in the appropriate leads.

Patients were excluded from imaging if they had postinfarction chest pain or cardiogenic shock or were receiving intravenous nitroglycerin or inotropic agents. Patients with signs and symptoms of LV dysfunction on the day of the adenosine SPECT study were excluded until stabilized. Additional exclusion criteria were persistent second- or third-degree atrioventricular (AV) block, a history or clinical findings of reactive airway disease, and the need for methylxanthines. Patients taking dipyridamole had this drug discontinued 24 hours before the test. Cardiac catheterization was performed in all patients within 1±16 days of tomographic imaging. The 120 patients studied represented 48% of those admitted to our coronary care unit with the diagnosis of acute myocardial infarction during the enrollment period.

The resultant study population consisted of 61 patients with anterior, 41 patients with inferior, and 18 patients with lateral myocardial infarction. Ninety-five patients had Q wave infarction, and 25 patients (21%) had non–Q wave infarction. Forty-six percent of patients (55 of 120) received thrombolytic therapy during the early stages of infarction with either streptokinase or recombinant tissue-type plasminogen activator.

Ninety-two patients were clinically stable without any evidence of congestive heart failure (Killip class I), 23 patients had mild heart failure (Killip class II), and five patients had pulmonary edema (Killip class III) earlier in the course of their myocardial infarction but were stabilized and free of pulmonary edema by the time of adenosine testing. Nineteen patients with prior coronary artery bypass grafting were included only in the prognosis analysis due to the difficulty in assessing the significance of perfusion defects in patients with prior bypass grafting.

Protocol for Adenosine Administration

Adenosine was supplied as a sterile, isotonic aqueous solution at a concentration of 6 mg/mL (2-mL vials). Ten vials were diluted in 30 mL of normal saline to provide a final concentration of 2.4 mg/mL for intravenous administration. Adenosine was infused into a peripheral antecubital vein using a computer controlled pump infusion system with stepwise dose increments every minute. The initial infusion rate was 50 μg · kg⁻¹ · min⁻¹ and was increased to 75, 100, and, finally, 140 μg · kg⁻¹ · min⁻¹ at 1-minute intervals. This dosage has been previously shown to be well tolerated in virtually all individuals.30,31

After 1 minute at the highest adenosine dose, 3 mCi 201TI was injected as a bolus in a contralateral vein and rapidly flushed with 10 mL of normal saline. The adenosine infusion then was maintained at the highest dose for an additional 3 minutes after the thallium injection. Vital signs and a 12-lead ECG were obtained immediately before, at every minute during, and for the first 5 minutes after the adenosine infusion. Vital signs and 12-lead ECGs then were recorded every 10 minutes for 30 minutes.

Single-Photon Emission Computed Tomography

201TI SPECT was performed by the method previously reported from our laboratory.32 Images were acquired using a large field-of-view, single-crystal rotating gamma camera (ADAC ARC 3000-3300) equipped with a high-resolution, parallel-hole collimator with a septal length and thickness of 33 and 0.15 mm, respectively. Image acquisition was performed over a 180° anterior arc, at 6° intervals, and for 40 seconds per frame. Imaging began 5 minutes after completion of the adenosine infusion and was repeated 4 hours later. Twenty-four–hour imaging was performed in patients with persistent defects at 4 hours, using a longer imaging time of 60 seconds per frame.

Transaxial reconstruction used a back projection technique with a Butterworth (order, 5) high-pass filter
Computer Quantification of Tomographic Images

The $^{201}$TI tomographic images were quantified using computerized two-dimensional polar maps of the threedimensional myocardial radioactivity. The initial and 4-hour delayed maps were generated independently and normalized through use of a circumferential profile analysis, which has been described in great detail.\textsuperscript{21,32} The presence and extent of thallium redistribution (ischemia) were determined by subtracting the initial polar map from the normalized delayed polar map on a pixel-by-pixel basis so as to generate a “redistribution” polar map.

The initial and redistribution polar maps for each patient were statistically compared with their corresponding adenosine normal data base maps previously generated in our laboratory. The adenosine normal data base consisted of 50 individuals who were at low risk for coronary artery disease in that they had either no chest pain or nonanginal pain, no prior cardiac history, normal resting ECGs, and less than three cardiac risk factors. In addition, all subjects had visually normal tomograms. Separate data bases for men and women were not used in this study because of our previous experience showing no significant differences in the detection or quantification of perfusion defects when sex-specific versus mixed-sex data bases are used with our software.\textsuperscript{34} A pixel in the patient’s initial polar map was considered abnormal if its count activity was $>2.5$ SDs below the mean count for the corresponding pixel in the normal data base. The extent redistribution occurring within the initial stress defect was determined by comparing the redistribution map of the patient with that of the normal data base. A pixel in the patient’s redistribution polar map was considered abnormal when its activity increased by $>2.5$ SDs above the corresponding mean count activity for that pixel in the normal data base. The initial perfusion defect size and the extent of redistribution then were expressed as the percentage of abnormal pixels within the initial and redistribution polar maps, respectively.

The vascular territories of the three major coronary arteries were assigned in the following manner: anteroseptal, anterior, and anterolateral regions to the left anterior descending coronary artery (LAD); inferior, posterior, and posteroseptal regions to the right coronary artery (RCA); and lateral and posterolateral regions to the circumflex coronary artery (Cx). Apical defects were assigned to the same coronary artery as the adjacent region with abnormal perfusion. The patient’s initial polar map was considered abnormal if a $\geq 3\%$ focal perfusion defect was found within a given vascular territory. This criterion has led to a high sensitivity for detecting coronary artery disease both in individual patients and in all three vascular territories while maintaining a high specificity.\textsuperscript{32}

Exercise $^{201}$TI Tomography

Twenty-six patients also underwent subsequent treadmill exercise scintigraphy with the Bruce protocol at the request of their cardiologist. Blood pressure, heart rate, and a 12-lead ECG were recorded at 1-minute intervals with the latter monitored continuously throughout the study. At peak exercise, 3 mCi $^{201}$TI was injected intravenously and flushed with a saline solution. The patients then were encouraged to exercise an additional 30–60 seconds after the radionuclide injection. Acquisition and analysis of these SPECT images were performed in a similar fashion as with adenosine SPECT, except for the use of an appropriate exercise normal data base.

Coronary Angiography

Selective coronary cineangiography was performed in multiple views with standard techniques. The presence of collateral circulation to all stenotic vessels was noted. Coronary stenoses were measured with calipers by an experienced angiographer blinded to the scintigraphic results and expressed as percent luminal diameter stenosis. Stenosis severity was graded as normal ($\leq 25\%$), insignificant ($26\%$–$50\%$), moderate ($51\%$–$69\%$), or severe ($\geq 70\%$) stenosis. The interobserver agreement for defining vessels as normal or having only insignificant stenosis versus those with significant ($>50\%$) stenosis has been shown to be $96\%$ and $99\%$, respectively, at our institution.\textsuperscript{32} Furthermore, intraobserver agreement for classifying vessels as having moderate ($51\%$–$69\%$) or severe ($\geq 70\%$) stenosis is $84\%$, with small mean absolute differences in percent diameter stenosis between two experienced angiographers ($7.3\pm 8.7\%$; median, $4\%$).\textsuperscript{32}

Cardiac Events

The patient medical records were reviewed to determine who had a cardiac event during the initial hospitalization. Cardiac events were defined as the development of clinical congestive heart failure; recurrent chest pain with associated transient ST segment changes; reinfarction, defined as a secondary rise in plasma creatine kinase–MB in a patient with associated ST changes and/or chest pain; sustained ventricular tachycardia or fibrillation beyond the initial 24-hour period after infarction; and death. Coronary revascularization with angioplasty or bypass surgery was considered a distinct cardiac event only when preceded by recurrent chest pain because the decision to perform these procedures was influenced in most cases by the scintigraphic results rather than by a change in the patient’s clinical status.

Statistical Analysis

Sensitivity was defined as the number of true-positive scans multiplied by 100 divided by the true-positive plus false-negative scans. Specificity was defined as the number of true-negative scans multiplied by 100 divided by the true-negative plus false-positive scans. The positive-predictive value was defined as the number of true-positive scans multiplied by 100 divided by the total number of positive results. The negative-predictive value was defined as the number of true-negative results multiplied by 100 divided by the total number of negative results. The overall predictive value was defined as the true-positive plus true-negative results multiplied by 100 divided by the total results.

Changes in heart rate, blood pressure, and ECG intervals from baseline to peak adenosine infusion and
comparisons of perfusion defect size in patients having both adenosine and exercise scintigraphy were analyzed with the use of paired \( t \) tests. Comparisons of extent thallium redistribution in patients with Q wave and non-Q wave infarction and of the extent redistribution in infarct and noninfarct zone perfusion defects, relative to coronary patency and the presence of collaterals, were analyzed with the use of unpaired \( t \) tests. Comparisons of perfusion defect size in patients 1) with Q wave versus non-Q wave infarction, 2) with anterior versus inferior versus lateral infarction, 3) with differing Killip classes, 4) with or without thrombolytic therapy, and 5) with and without cardiac events also were analyzed with the use of unpaired \( t \) tests. When a normal distribution was not present, the Wilcoxon rank sum test was used. All comparisons of sensitivity, all analyses comparing the frequency of redistribution among defects supplied by patent and occluded vessels and in infarct and noninfarct zone perfusion defects, and all analyses comparing the frequency of cardiac events based on the perfusion defect size and the presence of infarct zone redistribution were performed using the \( \chi^2 \) test. Linear regression analysis was used to determine the correlation for perfusion defect size in patients having both exercise and adenosine scintigraphy and to determine the intraobserver and interobserver reproducibility of our quantitative SPECT analysis. All data are expressed as mean±SD. A value of \( p<0.05 \) was considered significant.

**Results**

**Hemodynamic, ECG, and Side Effect Profiles of Adenosine**

Adenosine infusion increased the mean heart rate (76±14 to 92±16 beats per minute, \( p<0.001 \)) but decreased the mean systolic (120±18 to 106±17 mm Hg, \( p<0.001 \)) and diastolic (74±10 to 65±12 mm Hg, \( p<0.001 \)) blood pressures.

Although adenosine prolonged the PR interval (169±28 to 175±29 msec, \( p<0.0001 \)), no significant alterations in the QRS (90±27 to 91±30 msec) or QT (367±49 to 371±50 msec) intervals were observed from baseline to peak infusion rate, respectively. Twenty-five patients (25%) developed first-degree, four patients developed transient type 1 second-degree, and no patient developed third-degree AV block.

The side effects observed during adenosine administration are shown in Table 1. All side effects resolved within 1–2 minutes of terminating the infusion. No patient developed a serious adverse reaction to adenosine such as severe hypotension (systolic blood pressure, <80 mm Hg), bronchospasm, myocardial infarction, or death. One patient developed severe chest pain that resolved after termination of the infusion and administration of sublingual nitroglycerin. Thirteen patients developed transient ST depression during adenosine infusion.

**Coronary Angiographic Findings**

In the 101 patients without prior coronary artery bypass grafting, coronary angiography identified 51 patients with one-vessel, 38 patients with two-vessel, and 11 patients with three-vessel disease. One patient with a lateral infarction who received thrombolytic therapy had only an insignificant stenosis (39%) in the obtuse marginal artery.

Of the 160 vessels with significant (>50%) coronary stenoses, 43 (27%) had moderate (51–69%) and 117 (73%) had severe (≥70%) involvement. One hundred twelve arteries were normal, whereas 31 had insignificant coronary stenoses.

**Reproducibility of Quantitative SPECT**

The intraobserver and interobserver reproducibilities for SPECT in quantifying the total perfusion defect size and the extent redistribution were determined in a random sample of 29 patients who had initial perfusion defects ranging from 0% to 66%. The intraobserver comparisons using linear regression analysis yielded highly significant \( (p<0.0001) \) correlation coefficients of 0.99 for the total defect size, 0.99 for the extent scar, and 0.97 for the extent redistribution. The regression equation for the extent redistribution comparison was as follows: extent redistribution\(_{i} = 0.5 + 1.1 \times \text{extent redistribution}_{o} \).

The interobserver comparisons likewise were highly correlated \( (p<0.001) \) with coefficients of 0.98 for total defect size, 0.97 for extent scar, and 0.93 for the extent redistribution. The linear regression equation for the extent redistribution comparison was as follows: extent redistribution\(_{i} = 2.2 + 0.97 \times \text{extent redistribution}_{o} \).

**Detection of Individual Vessel Stenoses**

The overall sensitivity for detecting coronary stenoses was 87%, with 88% of LAD, 94% of RCA, and 74% of Cx stenoses correctly identified. Importantly, of the 21 vessels not detected by tomography, 15 (71%) had only

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Percent of patients</th>
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<tbody>
<tr>
<td>Flushing</td>
<td>36</td>
</tr>
<tr>
<td>Chest pain</td>
<td>22</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21</td>
</tr>
<tr>
<td>Headache</td>
<td>17</td>
</tr>
<tr>
<td>Neck, throat, or jaw pain</td>
<td>15</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
</tr>
<tr>
<td>ST segment depression</td>
<td>13</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>7</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td>3</td>
</tr>
<tr>
<td>Sour taste</td>
<td>3</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Any symptom</td>
<td>76</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate (51–69%)</td>
<td>All vessels 65 (28/43) Infarct-related artery 100 (17/17)† Noninfarct-related artery 42 (11/26)</td>
</tr>
<tr>
<td>Severe (≥70%)</td>
<td>95 (111/117)* Infarct-related artery 100 (83/83)‡ Noninfarct-related artery 82 (28/34)*</td>
</tr>
<tr>
<td>All stenoses</td>
<td>87 (139/160) Infarct-related artery 100 (100/100)† Noninfarct-related artery 65 (39/60)</td>
</tr>
</tbody>
</table>

\*\( p=0.0001 \) vs. moderate stenosis.  
†\( p=0.0001 \) vs. noninfarct-related artery.  
‡\( p=0.002 \) vs. noninfarct-related artery.
moderate (51–69%) stenoses. The overall sensitivity was significantly higher for detecting severe (≥70%) compared with moderate (51–69%) vessel stenoses (95% versus 65% \(p=0.0001\), respectively) (Table 2).

The sensitivity for detecting perfusion abnormalities within the vascular territory of all infarct-related arteries was 99% (100 of 101). All patients with anterior and inferior infarctions were correctly identified, but one patient with a small lateral infarction (peak creatine kinase–MB, 42 IU) had a normal SPECT study.

The overall sensitivity was significantly lower for detecting noninfarct compared with infarct-related coronary artery stenoses (Table 2). However, this was due primarily to the poor sensitivity (42%) for detecting only moderate (51–69%) stenosis within noninfarct arteries. Sensitivity improved dramatically to 82% \(p=0.0001\) for noninfarct arteries with severe (≥70%) stenoses.

Adenosine SPECT correctly identified 100% (51 of 51) of patients with one-vessel disease as having only one involved vessel, whereas 63% (24 of 38) of patients with two-vessel and 91% (10 of 11) of patients with three-vessel disease were correctly predicted to have multivessel coronary stenoses. Furthermore, the test correctly identified 100% (51 of 51) of all significantly (>50%) stenosed arteries in patients with one-vessel, 82% (62 of 76) of those with two-vessel, and 79% (26 of 33) of all stenosed arteries in patients with three-vessel disease.

The specificity of adenosine SPECT was 96% for the 143 coronary arteries with ≤50% stenosis. The specificities were comparably high within the vascular territories of the LAD (100%), RCA (100%), and Cx (97%).

The positive, negative, and overall predictive values using adenosine SPECT were 99%, 89%, and 93%, respectively.

**Redistribution Patterns in Infarct and Noninfarct Zones**

Ninety-nine percent (100 of 101) of infarct zone vascular territories were abnormal by quantitative SPECT analysis, and most (59%) demonstrated thallium redistribution. The extent of redistribution within these perfusion defects was 55±20% (Table 3).

Thirty-four of 49 patients (69%) with multivessel disease had perfusion defects outside the infarct zone, and 31 of these patients (91%) also had thallium redistribution. For the 60 stenosed noninfarct coronary arteries, there were 39 corresponding perfusion defects, of which 36 (92%) demonstrated redistribution. The extent of redistribution within these defects was 69±25% (Table 3).

Redistribution was observed more frequently in noninfarct than in infarct zone perfusion defects (92% versus 59%, \(p=0.01\)), and the extent of redistribution was also larger in the former (69±25% versus 55±20%, \(p=0.005\)) (Table 3).

**Redistribution Patterns in Patients With Patent Versus Occluded Infarct- and Noninfarct-Related Arteries**

Coronary stenosis severity was similar for infarct-related arteries perfusing vascular territories with and without redistribution (86±16% versus 81±18%, respectively). Likewise, coronary stenosis severity was similar for noninfarct arteries perfusing myocardium with and without redistribution (80±17% versus 89±18%, respectively).

Redistribution occurred as frequently within the vascular territories of patent (60 of 86, or 69%) as that of occluded (36 of 54, or 67%) arteries, whether they perfused the infarct or noninfarct zone (Table 4). The extent of thallium redistribution within these perfusion defects also was similar regardless of vessel patency (Table 3). The extent of redistribution, however, was greater within defects corresponding to noninfarct than to infarct-related arteries (Table 3). Thus, although the presence and extent of thallium redistribution were greater in noninfarct than in infarct zones, the patency or nonpatency of the vessel did not predict whether the myocardium was viable. This is illustrated in Figure 1.

**Table 3. Extent Redistribution in Infarct and Noninfarct Zone Perfusion Defects**

<table>
<thead>
<tr>
<th></th>
<th>Overall (%)</th>
<th>Patent artery (%)</th>
<th>Occluded artery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct zone (n=100)</td>
<td>55±20</td>
<td>54±20</td>
<td>56±20</td>
</tr>
<tr>
<td>Noninfarct zone (n=38)</td>
<td>69±25*</td>
<td>69±26†</td>
<td>69±24‡</td>
</tr>
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</table>

*p<0.005 vs. infarct zone.
†p<0.05 vs. infarct zone.
‡p<0.01 vs. no collaterals.
§p<0.0003 vs. no collaterals.

**Table 4. Redistribution Patterns in Infarct and Noninfarct Zones: Relation to Vessel Patency**

<table>
<thead>
<tr>
<th></th>
<th>Patent artery (n=86)</th>
<th>Occluded artery (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete R Partial R No R</td>
<td>Complete R Partial R No R</td>
</tr>
<tr>
<td>Infarct zone</td>
<td>8 (13%) 27 (45%) 25 (42%)</td>
<td>5 (13%) 19 (47%) 16 (40%)</td>
</tr>
<tr>
<td>Noninfarct zone</td>
<td>13 (50%)* 12 (46%) 1 (4%)†</td>
<td>6 (43%)† 6 (43%) 2 (14%)</td>
</tr>
<tr>
<td>Infarct/noninfarct zones</td>
<td>21 (24%) 39 (45%) 26 (31%)</td>
<td>11 (21%) 25 (46%) 18 (33%)</td>
</tr>
</tbody>
</table>

R, redistribution.

*p=0.0005 vs. infarct zone; †p=0.02 vs. infarct zone.
FIGURE 1. Selected tomographic slices and polar maps in two postinfarct patients who had a patent left anterior descending coronary artery (LAD). Despite a patent vessel, the first patient (panel A) showed no evidence of thallium redistribution from the initial to the delayed (4- and 24-hour) reoriented (REOR) images, whereas the tomographic slices in the second patient (panel B) demonstrated a largely reversible perfusion defect (81%) from the initial (adenosine) to the delayed (redistribution) images. The initial stress defects are identified by white arrows. The quantified perfusion defect sizes in the polar map of the first and second patients are 25% (panel C, facing page) and 70% (panel D, facing page), respectively. After left internal mammary graft placement the second patient now has only a 15% perfusion defect remaining on repeat adenosine testing (panel E, facing page), indicating that most of the abnormally perfused myocardium was viable. Red and black in the polar map represent normal and abnormal myocardial perfusion, respectively. The angiographic patency of the infarct artery was not a predictor of jeopardized myocardium in the first patient, although the second patient had a large region of viable tissue. RCA, right coronary artery; LCX, left circumflex artery.
Importance of Collaterals for Maintaining Myocardial Viability in Totally Occluded Arteries

Of the 54 vessels with complete occlusion, 40 involved the infarct, and 14 involved the noninfarct zones (Table 5). Forty-three of these 54 occluded vessels (80%) were supplied by collaterals, which were present in 78% of infarct and 86% of noninfarct arteries. Importantly, thallium redistribution occurred more frequently within the vascular territories of occluded vessels with (77%) than within those without (27%) collaterals \( (p=0.002) \). Furthermore, the extent of redistribution within the perfusion defects also was significantly greater when occluded vessels were supplied by collaterals (Table 3). Figure 2 illustrates the importance of collaterals for maintaining myocardial viability.

Perfusion Defect Size Related to Site and Severity of Clinical Infarction

Patients with anterior infarction had a larger LV perfusion defect size \( (42\pm18\%) \) than did those with inferior \( (22\pm15\%, \ p=0.0001) \) or lateral \( (22\pm16\%, \ p=0.0008) \) infarction. Patients in Killip class I had a significantly smaller perfusion defect size \( (27\pm17\%) \) than did those in Killip class II \( (51\pm15\%, \ p=0.0001) \) or III \( (56\pm10\%, \ p=0.002) \). However, most of the patients in Killip class II or III had anterior infarction \( (22\) of 24, or 92\%) , whereas most of those in Killip class I had inferior and lateral infarctions \( (45\) of 77, or 58\%).

Scintigraphic Results Depending on Type of Infarction and Treatment Strategy

Patients with Q wave infarction had a larger perfusion defect size than those with non-Q wave infarction \( (36\pm19\% \) versus \( 17\pm11\%, \ p=0.0001) \), regardless of the site of infarction or the extent of coronary artery disease. Patients with non-Q wave infarction were more likely than were those with Q wave infarction to have a patent infarct-related artery \( (81\% \) versus \( 56\%, \ p<0.05) \) but had a similar frequency \( (63\% \) versus \( 59\%) \) and extent of infarct zone redistribution \( (35\pm27\% \) versus \( 38\pm26\%, \ p=NS) \). Patients who received thrombolytic therapy compared with those who did not had a greater extent of redistribution within infarct zone perfusion defects \( (42\pm25\% \) versus \( 32\pm26\%, \ p=0.03) \) and a higher prevalence of a patent infarct-related artery \( (80\% \) versus \( 41\%, \ p=0.0005) \).

Adenosine Scintigraphy: Comparison With Exercise SPECT

Twenty-six patients initially studied with adenosine had an exercise test within the following 6 months. Nine of the 26 patients had an intercurrent revascularization procedure, whereas 17 did not. All of these 17 patients had an adenosine and exercise SPECT study within close temporal relation \( (mean, \ 31\pm29 \) days; range, \ 3-107 \) days). In these 17 patients, the number of abnormally perfused vascular territories identified with adenosine and exercise SPECT was similar \( (23 \) versus \( 24, \ p=NS) \), as was the extent redistribution within these defects \( (43\pm31\% \) versus \( 37\pm24\%, \ p=NS) \). The overall quantified perfusion defect size \( (31\pm21\% \) versus \( 29\pm16\%) \) and the defect size demonstrating no redistribution \( (19\pm16\% \) versus \( 20\pm13\%) \) were similar in patients studied by adenosine and exercise SPECT,
TABLE 5. Prevalence of Redistribution Associated With Occluded Infarct and Noninfarct Arteries: Relation to Coronary Collaterals

<table>
<thead>
<tr>
<th>IRA</th>
<th>NIRA</th>
<th>Total</th>
<th>IRA</th>
<th>NIRA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/31 (71%)*</td>
<td>11/12 (92%)</td>
<td>33/43 (77%)†</td>
<td>29 (22%)</td>
<td>1/2 (50%)</td>
<td>3/11 (27%)</td>
</tr>
</tbody>
</table>

IRA, infarct-related artery; NIRA, noninfarct-related artery.
* P=0.009 vs. no collaterals.
† P=0.002 vs. no collaterals.

Relation Between Cardiac Events and Adenosine Perfusion Defects

Of the total 120 patients studied, 52 had an uneventful postinfarction course (group 1), whereas 14 had recurrent chest pain (group 2), and 27 developed congestive heart failure (n=25) (of whom one died) or had incessant ventricular tachycardia (n=2) (group 3). Seven of the 14 group 2 patients went on to have revascularization with either angioplasty (n=5) or coronary artery bypass surgery (n=2). Twenty-seven additional patients were clinically stable throughout their hospitalization but had revascularization procedures performed at the discretion of their private cardiologist; most of these patients had infarct zone redistribution on their adenosine thallium tomograms (59%). These patients were excluded from the prognostic analysis.

The overall perfusion defect size was significantly larger (P=0.0001) in patients with (45±18%) compared with those without (22±15%) postinfarction complications (Table 6). Furthermore, 90% (37 of 41) of patients with complications had a perfusion defect size involving ≥20% of the left ventricle compared with only 38% (20 of 52) of those without complications (P=0.0001). All group 2 patients had a perfusion defect size ≥10%, and all group 3 patients had a defect size ≥23%. Although the positive-predictive accuracy for cardiac events was only 51% (41 of 80) when the defect size was ≥10%, it increased to 70% (35 of 50) when the defect size was >30%. No patient with a perfusion defect <10% had a complication (negative-predictive value, 100% for perfusion defects <10%).

The presence of thallium redistribution, which denoted myocardial ischemia, also was an important predictor of cardiac events. The size of the perfusion defect demonstrating redistribution was larger in patients with (19±14%) than in those without (10±10%) complications (P=0.001). The ischemic perfusion defect size was significantly larger in both group 2 (21±16%, P=0.01) and group 3 (18±14%, P=0.004) patients compared with those without complications (Table 6). Seventy-one percent of group 2 patients (10 of 14) had a >12% ischemic perfusion defect compared with only 25% (13 of 52) of patients without complications (P=0.001). The positive-predictive value of a >12% ischemic perfusion defect for the development of postinfarction chest pain was 43% (10 of 23), but the negative-predictive value was very high (91%). The extent of thallium redistribution was an important predictor of subsequent postinfarction chest pain but not necessarily whether it involved the infarct or noninfarct zone. Infarct zone redistribution occurred as frequently in patients with recurrent chest pain (group 2) (86%, or 12 of 14) as in those without complications (67%). Likewise, noninfarct zone redistribution occurred with a similar frequency in group 2 (43%) and group 1 (29%) patients, although the extent redistribution was greater in the former patients (86±11% versus 62±33%, P=0.02).

Discussion

The present approach to risk stratification of patients surviving acute myocardial infarction has emerged from a large body of clinical studies. Many reports have emphasized the high incidence of cardiac events in patients during the first 4–6 weeks after infarction and the prognostic importance of residual myocardial ischemia, identified with exercise testing, in predicting these early events.努力. Efforts at risk stratification have focused on detecting residual ischemia with either exercise ECG or perfusion scintigraphy. This typically entails a limited treadmill evaluation before hospital discharge followed by a maximal exercise test at 4–6 weeks. Through early detection of residual ischemia, the clinician may have time to carefully plan either an aggressive pharmacological or invasive strategy for the individual patient surviving myocardial infarction.

The present study is the first to demonstrate that quantitative adenosine 201TI SPECT is a safe technique that is well suited to determine the extent of abnormal myocardial perfusion and the presence of viable, jeopardized myocardium very early after infarction. We also report several observations of potential clinical importance: that redistribution occurs frequently within infarct zone perfusion defects and that the angiographic finding of a totally occluded infarct-related artery should not be considered synonymous with irreversible injury because large amounts of jeopardized yet salvageable myocardium may still be present within the infarct zone, especially in patients with a well-developed collateral circulation. Our data indicate that patients who have large perfusion defects, myocardial ischemia, or both with quantitative adenosine SPECT are at high risk for in-hospital cardiac events. These observations have practical significance in the selection of individual cases for pharmacological management of ischemia or when bypass surgery or angioplasty is being considered. By identifying regions of jeopardized myocardium, adenosine SPECT may aid in planning optimal revascularization.
Unlike perfusion scintigraphy, the presence and extent of jeopardized myocardium cannot be evaluated by coronary angiography even when combined with predischarge limited exercise testing because ECG identification of ischemia within the infarct zone is not feasible. The data from our limited number of patients who had concomitant adenosine and exercise scintigraphy would indicate that both stressor modalities are comparable in detecting the location and extent of myocardial ischemia. The major advantages of adenosine SPECT, however, are the feasibility to detect jeopardized myocardium very early after infarction and the capability for evaluating patients unable to perform adequate exercise.

**Sensitivity of Quantitative Adenosine SPECT**

The 87% overall detection of significantly stenosed arteries with adenosine SPECT is similar to previous reports with exercise scintigraphy,32,34–37 adenosine,38 and after oral49 or intravenous40,41 dipyridamole in patients with stable coronary artery disease. This overall high sensitivity for detecting individual stenoses, however, was influenced by the large number of infarct-related arteries. Considerably less noninfarct than infarct arteries were detected in the present study, but this may have been due to the large number of noninfarct arteries with only moderate stenosis (43%). The poor scintigraphic detection of vessels with moderate (51–69%) stenosis is consistent with known concepts of coronary flow reserve42,43 and adenosine’s mechanism of action.44,45 Adenosine induces a fourfold to sixfold increase in coronary blood flow in normal arteries by maximizing arteriolar vasodilation but may induce only minimal additional vasodilation in severely stenosed vessels. The resultant inhomogeneity in blood flow and possible myocardial ischemia46 create an unequal thallium distribution recognized scintigraphically as a perfusion defect. Coronary angiography can localize focal stenoses but cannot determine which ones are functionally important. The low sensitivity for detecting vessels with moderate stenosis in the present study is similar to that reported with exercise SPECT47 and is not unexpected when an abnormal scintigraphic result is predicated on the angiographic findings alone rather than on a physiological parameter such as coronary flow reserve.

**Scintigraphic Redistribution Within the Infarct Zone**

The high frequency of scintigraphic redistribution observed within the infarct zone (59%) may have been related to the large percentage of patients who received thrombolytic therapy (49%) or had non–Q wave myocardial infarction (16%). Furthermore, 59% of patients received thrombolytic therapy, presented with non–Q wave infarction, or both. These patients commonly achieve vessel patency within the early hours of myocardial infarction and thus have smaller infarcts by enzymatic,7,8 hemodynamic,7,8 and scintigraphic criteria.49 However, myocardium salvaged by early reperfusion often is jeopardized and leads to a higher incidence of recurrent ischemic events. The similarity of our results with those reported for exercise scintigraphy7 indicates that quantitative adenosine SPECT also may be used to effectively risk-stratify patients after infarction but at an even earlier time.

**Scintigraphic Redistribution Versus Coronary Anatomy: The Importance of Collaterals**

Angiographic patency of the infarct or noninfarct arteries and the residual stenosis severity did not predict the presence of scintigraphic redistribution within or outside the infarct zone. Redistribution occurred as frequently within vascular territories supplied by patent or occluded vessels, regardless of perfusion defect location. These results are consistent with a previous report in patients achieving myocardial reperfusion with streptokinase during acute infarction.50 Our data also suggest that collateral blood flow to occluded arteries appeared to contribute significantly to maintaining myocardial viability. Seventy-seven percent of occluded vessels supplied with collaterals had evidence of redistribution within their respective vascular beds compared with only 27% of occluded vessels without visible collaterals (p = 0.002). The importance of collaterals was most dramatically illustrated within the noninfarct zone, where 92% of occluded vessels receiving collaterals showed evidence of myocardial thallium redistribution.

The higher prevalence of redistribution within non–infarct (92%) than within infarct (71%) zones supplied by collaterals may be related to the slower progression of occlusive disease in the former. Previous studies have shown that angiographically demonstrable collaterals are present only after stenosis severity is >90%,51,52 Furthermore, collaterals can be demonstrated in virtually all patients with subtotal stenoses but in only approximately 20% of those with less severe stenoses when blood flow is abruptly interrupted during coronary angioplasty.53 Recent reports indicate that most patients will have <90% residual stenosis in the infarct-related artery after thrombolysis, and as many as 20% will have <50% stenosis.12,13,54 Because infarction due to acute plaque rupture and thrombosis occurs in many patients with only moderate stenoses, it is not surprising that few patients will demonstrate adequate collaterals to the infarct artery during the early hours of total occlusion.55,56 In these patients, myocardial necrosis will be complete before collaterals develop, whereas in patients with severe stenosis, collaterals may protect the myocardium from infarction when occlusion finally occurs. This concept is supported by retrospective reports suggesting that patients with initially severe stenoses have smaller (usually non–Q wave) infarctions compared with those with less severe stenoses.57 Moreover, a smaller enzymatic infarct size is observed in patients with, compared with those without, collaterals to the occluded infarct-related artery during the early hours of myocardial infarction.58

**Scintigraphic Redistribution: Distinguishing Viable Myocardium From Scar**

Perfusion defect reversibility in this study was considered synonymous with jeopardized, but viable myocardium, although lack of reversibility does not necessarily indicate scar.59–61 There is convincing evidence in the literature that delayed 201Tl redistribution within an initial defect reflects underperfused but viable myocardium.59,60,62–66 This has been carefully studied in the animal model62–64 and recently reported after coronary occlusion and reperfusion.64 Furthermore, clinical studies demonstrate that reversible perfusion defects re-
solve after coronary revascularization with preservation of regional left ventricular function. Current literature also supports that lack of redistribution at 4 hours may occur in viable myocardium but is much less likely when late (24-hour) imaging is performed. Factors responsible for defect nonreversibility in some infarct patients may be 1) complete myocardial necrosis within the infarct zone, 2) low serum thallium blood levels (which may improve after thallium reinfarction), or 3) poor myocardial delivery of thallium through severely stenosed arteries, which slows its uptake by viable tissue within the infarct zone. For this reason, patients in the present study with persistent defects at 4 hours all returned for late (24-hour) imaging so as to minimize nonreversibility due to temporal limitations. Furthermore, the high rate (92%) of redistribution within myocardial regions perfused by occluded noninfarct arteries with collaterals would indicate that given enough time, thallium eventually may reach abnormally perfused areas through collaterals. This also has been reported by other investigators. Although many of the nonreversible perfusion defects probably did reflect completed infarction, myocardial viability may still have been underestimated in the present study because thallium reinfarction at 24 hours was not performed as part of the imaging protocol.

Study Limitations

Although adenosine has an exceedingly short half-life and was administered safely in all patients in the present study, certain patients should not receive adenosine due to the potential for serious side effects. Patients with a history of reactive airway disease may develop bronchospasm, and those with sick sinus syndrome or greater than first-degree AV block may develop more serious conduction abnormalities. Furthermore, patients with a borderline low blood pressure may develop more severe hypotension. Last, patients should not be given adenosine for at least 12 hours after a dose of dipyridamole because it potentiates the effects of adenosine.

Clinical Implications

The present study demonstrates that quantitative adenosine SPECT is a safe, sensitive test for detecting and localizing the site of stenoses both within and outside the infarct zone and can provide a very early assessment of jeopardized myocardium in carefully selected patients after myocardial infarction. Recent studies with dipyridamole thallium scintigraphy early after infarction emphasize that the presence of jeopardized myocardium, particularly within the infarct zone, is the best predictor of both in-hospital and late cardiac events. The present study also emphasizes that the presence and extent of ischemia identified with adenosine SPECT are important very early predictors of recurrent chest pain and that the size of the quantified perfusion defect can predict high-risk patients for in-hospital cardiac events in an otherwise low-risk population. Furthermore, in patients with recurrent chest pain, most of the perfusion defect was due to ischemia, whereas in those with heart failure or death, most of the defect was due to myocardial scar. No patient with a perfusion defect involving <10% of the myocardium had a cardiac event. These prognostic findings with adenosine SPECT, although clinically relevant, were derived from a stable low-risk cohort of patients and should not be generalized to all postinfarction patients, particularly those with a complicated early postinfarction course.

In this new era of routine thrombolytic therapy for treating myocardial infarction, patients can be anticipated to have smaller infarcts but more residual myocardial ischemia. The coronary angiographic findings are a poor predictor of future cardiac events in the postinfarction population and cannot determine the extent of myocardium perfused by a given coronary artery. The results of the present trial suggest that the angiographic findings alone also are a poor indicator of myocardial viability and actually may be misleading if it is assumed that a patent infarct-related artery implies viability within the infarct zone. Combining imaging of thallium redistribution with adenosine SPECT will provide a total package for understanding anatomic relationships and the potential for myocardial viability.

Table 6. Adenosine SPECT Perfusion Defect Size: Cardiac Events

<table>
<thead>
<tr>
<th></th>
<th>No complications (n=52)</th>
<th>Chest pain (n=14)</th>
<th>CHF/death/VT (n=25/1/2)</th>
<th>Total complications (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDS (total)</td>
<td>22±15%</td>
<td>33±19%*</td>
<td>51±14%†</td>
<td>45±18%‡</td>
</tr>
<tr>
<td>PDS (ischemia)</td>
<td>10±10%</td>
<td>21±16%†</td>
<td>18±14%§</td>
<td>19±14%‖</td>
</tr>
<tr>
<td>PDS (scar)</td>
<td>12±10%</td>
<td>12±8%</td>
<td>33±10%‡</td>
<td>26±16%§</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; PDS, perfusion defect size; VT, ventricular tachycardia.

* p=0.047 vs. no complications.
† p=0.01 vs. no complications.
‡ p=0.0001 vs. no complications.
§ p=0.004 vs. no complications.
‖ p=0.001 vs. no complications.
versely, an occluded infarct-related artery may be wrongly interpreted to imply a completed infarction when substantial amounts of jeopardized myocardium often remain intermixed with or surrounding the scar. Further investigation is needed to determine whether the earlier detection of both the extent and severity of jeopardized myocardium by quantitative adenosine SPECT can more precisely define long-term cardiac risk and better guide therapy than the important information obtained by traditional submaximal exercise scintigraphy.

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