METHODS

Single Photon Emission Computed Tomography With Thallium-201 During Adenosine-Induced Coronary Hyperemia: Correlation With Coronary Arteriography, Exercise Thallium Imaging and Two-Dimensional Echocardiography

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The feasibility, safety and diagnostic accuracy of single photon emission computed tomography (SPECT) with thallium-201 imaging during adenosine-induced coronary hyperemia were evaluated in 53 patients with and 7 without coronary artery disease proved by coronary angiography. Adenosine was infused intravenously at a dose of 0.14 mg/kg body weight per min for 6 min and thallium was injected at 3 min. Adenosine caused an increase in heart rate (68 ± 12 at baseline versus 87 ± 18 beats/min at peak effect, p < 0.0001) but no change in blood pressure. The sensitivity and specificity were 92% (95% confidence intervals 81% to 98%) and 100% (95% confidence intervals 59% to 100%), respectively; 20 (61%) of 33 patients with multivessel coronary artery disease were also correctly identified.

In 30 patients, the predictive accuracy of adenosine thallium imaging was slightly higher than that of exercise SPECT thallium imaging (90% versus 80%, p = NS) (95% confidence intervals 72% to 97% and 61% to 92%, respectively). In 25 patients, two-dimensional echocardiography during adenosine infusion disclosed a new wall motion abnormality in 2 (10%) of 20 patients with coronary artery disease; 80% of these patients had reversible thallium defects (p < 0.001). Side effects were mild and transient; aminophylline was used in only three patients.

Thus, adenosine SPECT thallium imaging provides a high degree of accuracy in the diagnosis of coronary artery disease. The results are comparable with those of exercise SPECT thallium imaging. Most reversible defects in the adenosine study are not associated with any transient wall motion abnormality.

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The mechanism of dipyridamole-induced coronary vasodilation and hyperemia appears to be increased blood levels of endogenous adenosine due to decreased cellular reuptake and metabolism (1,2).

Both oral and intravenous dipyridamole have been found to be useful in the diagnosis of coronary artery disease and risk stratification. The absorption rate and time to peak effect of oral dipyridamole are variable and the duration of study is longer with the oral than with the intravenous agent. Intravenous dipyridamole at the conventional dose of 0.56 mg/kg body weight may not produce maximal coronary vasodilation in all patients (3). Higher doses may be necessary in some patients but may produce more side effects. Dipyridamole imaging is frequently combined with handgrip or submaximal dynamic exercise to enhance the sensitivity of the test.

Adenosine, which is commercially synthesized, has been found to be a potent coronary vasodilator. In contrast to dipyridamole, adenosine has a rapid onset of action and an extremely short half-life (< 10 s).
Table 1. Demographic Characteristics of the 60 Patients

| Age (yr) | 62 = 5/Range 32-83 |
| Gender (M/F) | 39/21 |
| Systemic hypertension | 20 (33) |
| Diabetes mellitus | 9 (15) |
| Previous MI (by ECG) | 22 (37) |
| Typical angina pectoris | 41 (69) |

Coronary anatomy

| Visible collateral vessels | 3 (5) |
| Contractile ventriculography (n = 52) | |
| Akinesia/dyskinesia | 10 (19) |
| Hypokinesia | 10 (19) |
| Normal | 32 (62) |

Numbers in parentheses represent percents. ECG = electrocardiographic study; F = female; M = male; MI = myocardial infarction; VD = vessel disease (>50% diameter stenosis).

Wilson et al. (4) measured coronary blood flow with a 3F Doppler catheter in the normal left coronary artery in 10 patients. They found that maximal coronary vasodilation was achieved in 9 of 10 patients with an intravenous dose of 140 μg/kg per min. There were no significant side effects. Several recent preliminary reports suggested that adenosine thallium scintigraphy is a feasible, safe and accurate technique for the detection of coronary artery disease (5,6).

This report summarizes our experience with intravenous adenosine-induced coronary hyperemia in conjunction with thallium-201 as the imaging agent for single photon emission computed tomography (SPECT). The results in these 60 patients were compared with those of coronary arteriography, exercise SPECT thallium imaging and wall motion analysis by two-dimensional echocardiography.

Methods

Study patients (Table 1). The 60 patients included in this study underwent diagnostic cardiac catheterization and coronary angiography for suspected coronary artery disease. None had recent myocardial infarction (within 1 week), unstable angina pectoris, greater than first degree atrioventricular (AV) block, asthma or chronic obstructive pulmonary disease and none were taking theophylline-containing medication.

There were 39 men and 21 women. The pertinent demographic data and results of coronary angiography are listed in Table 1. All 60 patients underwent intravenous adenosine thallium-201 imaging within 32 days of arteriography; 30 of the patients also had treadmill exercise thallium-201 imaging. These two perfusion studies were performed within 1 month of each other. All patients had stable symptoms and antiangiinal therapy remained unchanged between the studies. As the study progressed, we became interested in the relation between the perfusion pattern and the wall motion abnormality. Thus, in the last 25 of the 60 patients, serial two-dimensional echocardiograms were obtained during intravenous adenosine infusion.

The investigational nature of the study was explained to the patients and all signed a consent form approved by the Institutional Review Board of our hospital. These patients were not consecutive and the selection was based on willingness of physicians and patients to participate in the study. Patients who had both exercise and adenosine studies did not differ from the remaining patients who had only the adenosine study.

Coronary arteriography. The procedure was performed in multiple projections using standard techniques. The degree of coronary stenosis was visually assessed by two experienced angiographers unaware of scintigraphic findings. Significant coronary artery stenosis was defined as ≥50% diameter stenosis in any of the major coronary arteries or their branches; 53 patients had significant coronary artery disease and 7 patients had normal coronary arteries or mild luminal irregularities (<30% diameter narrowing).

Exercise testing. All patients underwent symptom-limited treadmill exercise testing in the fasting state with the standard or modified Bruce protocol. A 12 lead electrocardiogram (ECG) and blood pressure measurements were obtained at baseline and at each minute of exercise. Exercise end points were excessive fatigue, dyspnea, dizziness, moderate to severe angina, hypotension, >2 mm ST segment depression or significant arrhythmias. Nitrates and beta-adrenergic and calcium channel blockers were withheld on the morning of the test. At peak exercise, thallium-201 (3.5 mCi) was injected intravenously and patients exercised for 1 min before termination of the test.

Adenosine infusion protocol (Fig. 1). As for exercise
testing, antianginal medication was withheld on the morning of the test only. No patient had coffee or tea or caffeine-containing products on the morning of the test. Patients were studied in the fasting state in the supine position with the head elevated to about 30°. The heart rate, blood pressure and 12 lead ECG were recorded at baseline study. Intravenous infusion of adenosine (Adenoscan, Medco Research) was initiated at a dose of 0.14 mg/kg per min administered with use of an infusion pump and continued for a total of 6 min. At the end of the 3rd min of infusion, a 3.5 mCi (130 MBq) dose of thallium-201 was injected intravenously. A 12 lead ECG was continuously monitored and recorded at each minute of adenosine infusion. Perfusion imaging began within 5 min and at 4 h after thallium injection. The PR interval was measured at baseline study and during each minute of infusion and recovery. The results of the exercise and adenosine ECG were interpreted as positive, negative or nondiagnostic as previously described (7).

Thallium-201 SPECT imaging. Our method for standard SPECT thallium studies has been previously described in detail (8). Images are acquired using a circular orbit over a 180° range, starting at the 45° right anterior oblique projection and ending at the 45° left posterior oblique projection. Each of 32 projections was acquired using a 64 x 64 matrix at 40 s/image. Each projection was corrected for nonuniformity using a 30 million count cobalt-57 flood. A standard filtered-back projection technique was applied using a Ramp-Hanning filter with a cutoff frequency of 0.83 cycles/cm to generate transaxial slices. No scatter or attenuation correction was used. From these transaxial images, the long axis of the left ventricle was identified and oblique angle images were generated in the short-axis, vertical long-axis and horizontal long-axis orientations. Thirty-two planar images were reviewed in a cine loop mode to evaluate extracardiac activities and motion artifact. In addition, a sinogram using a cross-correlation function was also examined to specifically identify any abrupt motion during the study. Oblique-angled tomograms were reconstructed on the basis of the long axis of the heart. Thus, these tomograms from initial and 4 h delayed studies were presented in the same manner. To match initial and 4 h delayed slices, eight initial tomograms were displayed on the top and the corresponding eight delayed slices on the bottom of the screen with an appropriate display window. Thus, the nature of the perfusion abnormality was evaluated easily, comparing the initial and 4 h delayed tomograms at the same level.

Three short-axis slices at the apical, mid and basal levels were selected. Each slice was divided into six segments: anterior, inferior, high septal, low septal, high lateral and low lateral. The apical perfusion pattern was assessed in two segments at the mid level in the vertical long-axis slice. There were 20 segments per patient per study.

The initial and 4 h delayed images were interpreted by two experienced observers without knowledge of the results of cardiac catheterization or other tests. A perfusion abnormality on the initial image that demonstrated complete or partial redistribution in the delayed images involving ≥25% of the segment was considered to represent ischemia. A perfusion abnormality that remained unchanged in the delayed images was considered a fixed defect or scar.

Two-dimensional echocardiography. Two-dimensional echocardiograms were continuously monitored and recorded at baseline study and at each minute during adenosine infusion and approximately 30 min into recovery. A commercially available phased array imaging system (Model 500, Hewlett-Packard) was used to obtain multiple images in four standard views (parasternal long- and short-axis and four and two chamber views whenever possible). Regional wall motion was evaluated semiquantitatively at rest and during and after adenosine infusion by two experienced observers who had no knowledge of angiographic or scintigraphic findings. For the purpose of analysis, the left ventricle was divided into five segments: anterior, lateral, inferior, septum on the short-axis view at the level of papillary muscle and the apex on the two chamber view. The evaluation was based on subjective interpretation of segmental wall motion and the degree of systolic thickening. Wall motion was graded as: 0 = hyperkinetic, 1 = normal, 2 = hypokinetic, 3 = akinetic and 4 = dyskinetic.

The test was considered positive if a transient wall motion abnormality was detected that was absent or of lesser degree before adenosine infusion. A wall motion abnormality that did not worsen during adenosine infusion was defined as a fixed abnormality or scar. A wall motion score index was derived by adding the scores assigned to each segment and dividing the final score by the number of segments visualized. The wall motion score index of a normal ventricle is 1. Segments with suboptimal image quality were excluded from analysis. The interobserver variability assessed in 17 randomly selected patients was small (r = 0.91, p < 0.0001). Similarly, the intraobserver variability was small (r = 0.92, p < 0.0007). The site of the wall motion abnormality in relation to vascular territory was similar to that used for thallium imaging.

Statistical analysis. The following calculations were used:

- Sensitivity (%) = 100 × (true positives)/(true positives + false negatives);
- Specificity (%) = 100 × (true negatives)/(true negatives + false positives);
- Positive predictive value (%) = 100 × (true positives)/(true positives + false positives);
- Negative predictive value (%) = 100 × (true negatives)/(true negatives + false negatives);
- Predictive accuracy (%) = 100 × (true positives + true negatives)/total number of patients.

A true positive result is defined as an abnormal test result in a patient with coronary artery disease; a true negative result is defined as a normal test result in a patient with no coronary artery disease; a false positive result is an abnormal test result in a patient with no coronary artery disease; a false result is a normal test result in a
patient with coronary artery disease. The 95% confidence intervals were used when indicated.

Data are presented as mean values ± SD when appropriate. Chi-square analysis and Student's t-test were used for comparison. A p value <0.05 was considered statistically significant.

Results

Coronary angiography in the 60 patients showed that 53 patients had significant coronary artery disease: 20 had one vessel, 16 had two vessel and 17 had three vessel disease (Table 1). The remaining seven patients had normal coronary arteries or minor luminal irregularities.

Hemodynamic responses to intravenous adenosine (Table 2). Heart rate increased from a mean of 68 ± 12 beats/min at baseline study to 87 ± 18 beats/min at peak infusion (p < 0.0001). There were no significant changes in diastolic and systolic blood pressure. The rate-pressure product (heart rate × systolic blood pressure) increased significantly during adenosine infusion.

Side effects of intravenous adenosine (Table 3). Side effects were reported in 88% of patients and were mostly mild in nature. They included headache (20%), flushing (58%), nausea (8%), abdominal discomfort (2%), dizziness (8%) and dyspnea (13%). Chest pain occurred in 23 patients (38%) and ST segment depression in 8 (13%). Of the 23 patients with chest pain, 21 had coronary artery disease and 2 had a normal coronary angiogram. Side effects were transient, except in three patients in whom premature termination of adenosine and treatment with aminophylline were necessary (for hypotension, severe dyspnea or angina, respectively). Two of these patients, including the patient with hypotension, had a normal coronary angiogram. In the remaining patients, side effects resolved promptly within 1 min of termination of adenosine infusion. No patient had prolonged chest pain, myocardial infarction or ventricular arrhythmias.

The PR interval increased from 0.17 ± 0.02 to 0.19 ± 0.03 s in the group as a whole (p < 0.001); eight patients (13%) developed first degree AV block, but none had second or third degree AV block during adenosine infusion. In six patients with mild baseline first degree AV block, there was no further prolongation of the PR interval.

Comparison of adenosine SPECT thallium-201 imaging with coronary angiography (Table 4). The sensitivity and specificity were 92% and 100%, respectively (95% confidence intervals 81% to 98% and 59% to 100%, respectively). Positive and negative predictive values were 100% and 64%, respectively, and overall predictive accuracy was 93%. In the 49 patients with an abnormal image, the perfusion defects were reversible in 39 and fixed in 10. There were a mean of 3.2 ischemic segments per patient. Of the 10 patients with a fixed defect, 6 had a Q wave myocardial infarction and 5 had one vessel coronary artery disease. Of the 33 patients with multivessel disease by coronary angiography, 20 had a multisegment (multivessel) thallium abnormality.

The coronary anatomy in four patients with coronary artery disease and a normal adenosine SPECT thallium image (false negative responses) is listed in Table 5. Two of these patients had mild coronary artery disease; all four patients had one vessel disease. All seven patients with normal coronary arteries or minor luminal irregularities had a normal image. Images were uniformly of high quality (Fig. 2).

Comparison of adenosine with exercise SPECT thallium imaging (Table 6). Thirty patients underwent both adenosine and exercise studies within 1 month of each other. There were 25 patients with and 5 patients without coronary artery disease. The heart rate, systolic blood pressure and rate-pressure product were significantly higher during exercise than during adenosine infusion and more patients had

Table 3. Side Effects of Adenosine in the 60 Patients

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Baseline</th>
<th>Peak Effect</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>8 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>23 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST depression ≥ 1 mm</td>
<td>8 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First degree AV block</td>
<td>8 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocardiac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>35 (58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminophylline treatment</td>
<td>3 (5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses represent percent. AV = atrioventricular.

Table 4. Comparison of Adenosine SPECT Thallium Imaging With Coronary Angiography in the 60 Patients

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Predictive accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>92% (49/53)</td>
<td>100% (77)</td>
<td>100% (49/49)</td>
<td>64% (7/11)</td>
<td>93% (56/60)</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent percent. AV = atrioventricular.
ST segment depression during exercise. The exercise test was considered inconclusive in four patients because of submaximal stress or baseline ECG changes; results were normal in 10 patients and abnormal in 16 patients.

Although the sensitivity, predictive accuracy and negative predictive value were slightly higher with adenosine than with exercise, the differences did not reach statistically significant levels, possibly because of the small number of patients (Table 7). There was also good agreement between the two techniques in the diagnosis of the number of diseased vessels. Thus, of the 12 patients with multivessel disease by angiography, 8 had a multisegment (multivessel) thallium abnormality by exercise SPECT imaging and 6 by adenosine SPECT imaging (p = NS).

Comparison of adenosine echocardiography with adenosine SPECT thallium-201 imaging and coronary angiography (Table 8). Of the 60 patients, the last 25 underwent serial two-dimensional echocardiography during adenosine infusion. No patient was excluded because of poor image quality, but 25 of 125 segments were of suboptimal image quality and were excluded from analysis. Only 2 (10%) of 20 patients with coronary artery disease developed a new wall motion abnormality during adenosine infusion; 1 of the 2 had three vessel disease, the other had one vessel disease. Eight additional patients had a wall motion abnormality at rest that did not worsen during adenosine infusion. The wall motion score index was $1.4 \pm 0.3$ at baseline study and $0.7 \pm 0.8$ at peak effect (p = 0.001); 32 segments (32%) showed an improvement in wall motion (hyperkinesia).

This hyperkinetic response was seen in 10 (40%) of the 25 patients. The sensitivity of adenosine SPECT thallium im-

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**Table 5. Coronary Anatomy in Four Patients With False Negative Adenosine SPECT Thallium Imaging Results**

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Adenosine Thallium</th>
<th>Exercise Thallium</th>
<th>RCA (%)</th>
<th>LAD (%)</th>
<th>D (%)</th>
<th>LCx (%)</th>
<th>M (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>NA</td>
<td>30</td>
<td>50</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>—</td>
<td>0</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>70</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

D = diagonal branch; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; M = marginal branch; NA = not available; % = percent stenosis; Pt. = patient; RCA = right coronary artery; — = normal.
Aging was significantly higher than that of adenosine two-dimensional echocardiography (Table 8). If absence of hyperkinesia was considered an abnormal response, the sensitivity of two-dimensional echocardiography was 60%.

**Discussion**

**Adenosine versus dipyridamole thallium scintigraphy.** Previous studies (1,2) have demonstrated the clinical usefulness of dipyridamole thallium scintigraphy. This technique permits the accurate diagnosis of coronary artery disease, assessment of jeopardized myocardium and identification of patients at risk for a subsequent cardiac event after myocardial infarction and before major noncardiac surgery (1,2).

*Dipyridamole has been frequently combined with handgrip or submaximal treadmill exercise to further increase coronary blood flow by increasing myocardial oxygen demand. However, a recent report (3) suggested that intravenous dipyridamole at the dose of 0.56 mg/kg may not produce maximal coronary vasodilation in all patients, and the addition of handgrip exercise did not significantly augment coronary blood flow.*

*The mechanism of dipyridamole-induced coronary hyperemia appears to be related to the increased level of endogenous adenosine, which is a potent coronary arteriolar vasodilator. The primary action of dipyridamole is to inhibit the cellular reuptake of adenosine and metabolism by adenosine deaminase, thus increasing the interstitial adenosine concentration. Other actions of dipyridamole include inhibition of phosphodiesterase and increased prostacyclin synthesis (9,10). A recent report (11) suggests that adenosine interacts with adenosine-A1 receptors on vascular smooth muscle cells and activates a particulate guanylate cyclase to increase cyclic guanosine monophosphate production, which ultimately leads to vasorelaxation by complex mechanisms of signal transduction. Adenosine also stimulates the production of inositol phosphates, which breaks down inositol triphosphate, a second messenger mediating intracellular calcium release and smooth muscle contraction. The effect of adenosine is antagonized by aminophylline by means of direct competitive inhibition. Aminophylline competes directly with adenosine at the receptor level. Therefore, plasma adenosine levels tend to increase after administration of aminophylline as adenosine is displaced from the receptors by aminophylline (12). Furthermore, adenosine has also been shown to depress sinoatrial and AV node activity (12). Clinical studies (13) indicate that adenosine is a safe, effective and reliable means of terminating supraventricular tachycardia and it has recently been approved for this indication. In ventricular myocardium, adenosine has no direct effect; its indirect negative inotropic effect can only be demonstrated when cyclic adenosine monophosphate is elevated by beta-adrenergic agents (12).*

**Mechanism of perfusion abnormalities with adenosine or dipyridamole.** The mechanism by which coronary vasodilation leads to perfusion defects in patients with coronary

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**Table 6. Comparison of Adenosine and Exercise Testing in 30 Patients**

<table>
<thead>
<tr>
<th></th>
<th>Adenosine</th>
<th>Exercise</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak heart rate (beats/min)</td>
<td>90 ± 20</td>
<td>139 ± 21</td>
<td>0.0001</td>
</tr>
<tr>
<td>Δ Heart rate (beats/min)</td>
<td>20 ± 16</td>
<td>67 ± 22</td>
<td>0.0001</td>
</tr>
<tr>
<td>Peak systolic BP (mm Hg)</td>
<td>135 ± 22</td>
<td>170 ± 22</td>
<td>0.0001</td>
</tr>
<tr>
<td>Δ Systolic BP (mm Hg)</td>
<td>2 ± 19</td>
<td>4 ± 19</td>
<td>0.0001</td>
</tr>
<tr>
<td>Peak rate-pressure product (beats/min × mm Hg × 10²)</td>
<td>11.9 ± 2.8</td>
<td>23.8 ± 5.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Δ Rate-pressure product (beats/min × mm Hg × 10²)</td>
<td>2.7 ± 2.0</td>
<td>14.7 ± 5.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Chest pain during test</td>
<td>7 (23%)</td>
<td>9 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive ECG response</td>
<td>10 (33%)</td>
<td>10 (33%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Exercise time (min)</td>
<td>0</td>
<td>7.0 ± 3.0</td>
<td></td>
</tr>
<tr>
<td>Exercise work load (METs)</td>
<td>8.9 ± 2.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses represent percent. BP = blood pressure; Δ = change from baseline values to peak effect. ECG = electrocardiographic.

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**Table 7. Comparison of Exercise and Adenosine SPECT Thallium Imaging Results in 30 Patients**

<table>
<thead>
<tr>
<th></th>
<th>Exercise Thallium</th>
<th>Adenosine Thallium</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>75% (55%-90%)</td>
<td>88% (68%-97%)</td>
<td>NS</td>
</tr>
<tr>
<td>Specificity</td>
<td>100% (85%-100%)</td>
<td>100% (85%-100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>100% (82%-100%)</td>
<td>100% (85%-100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>45% (10%-79%)</td>
<td>63% (20%-99%)</td>
<td>NS</td>
</tr>
<tr>
<td>Predictive accuracy</td>
<td>80% (61%-92%)</td>
<td>90% (72%-97%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent the 95% confidence intervals.
artery disease is complex. Perfusion abnormalities may be seen in the absence of chest pain, ischemic ST segment changes and wall motion abnormalities. These defects are probably caused by disparities in regional myocardial perfusion induced by dipyridamole and adenosine, which produce a three- to fivefold increase in flow in normal vessels but little or no increase in flow in stenotic vessels, whose reserve is nearly exhausted at baseline study (1,2,14). True myocardial ischemia does not need to be present in these situations: this is supported by our results showing that most of our patients had a reversible perfusion defect in the absence of ST depression or wall motion abnormality. However, in some patients with severe coronary artery disease, myocardial ischemia caused by coronary steal or a modest increase in rate-pressure product may also occur. Coronary arteriolar dilation will result in an increased pressure gradient across the stenosis and a decrease in distal perfusion pressure, with a consequent reduction in subendocardial flow despite an increase in epicardial flow. This intracoronary or transmural steal may occur in the absence of collateral vessels. In the rest state with severe coronary stenosis, subendocardial blood flow is reduced enough to cause maximal subendocardial arteriolar dilation and nearly exhaust its maximal vasodilatory reserve. Dipyridamole and adenosine then induce significantly greater vasodilation in subepicardial regions than in subendocardial regions, which leads to an absolute decrease in subendocardial perfusion because of a greater increase in subepicardial flow (15,16).

Another mechanism has been evoked to explain perfusion defects in presence of collateral vessels. In the rest state, myocardial beds distal to a severe stenosis receive most of their blood supply through collateral channels from a normal or less severely diseased vessel. The collateral flow may be sufficient to prevent ischemia under rest conditions. Dipyridamole and adenosine dilate the vascular bed of the donor artery, decreasing the perfusion pressure at the origin of collateral vessels and causing a decrease in collateral flow. There is no true steal or backward flow through the collateral channel to the normal vascular bed. The absolute collateral flow is decreased during arteriolar dilation below levels at rest, thereby producing ischemia (16,17).

The infrequent findings of ischemic ECG changes (13%) and transient wall motion abnormality on two-dimensional echocardiography (10%) in our study support the contention that true myocardial ischemia is rare. So few of our patients (3 of 60) had visible collateral vessels that it is not possible to reach any conclusion about the significance of collateral supply. There was no significant difference in the rate-pressure product between patients with and those without ischemic ECG changes.

Usefulness of adenosine SPECT thallium scintigraphy. Our results suggest that this technique is feasible, safe and highly accurate in the diagnosis of coronary artery disease. Although a large percent of our patients experienced some side effects, these were transient, mild and well tolerated and disappeared within 1 min of termination of infusion. Only three patients required premature termination of infusion and reversal with aminophylline. There was a 28% increase in heart rate but no significant change in blood pressure; a decrease in systolic blood pressure is common with dipyridamole (1,2). These hemodynamic effects appear to be mediated not by the direct actions of adenosine but through an adenosine-induced reflex autonomic chemoreceptor activation (18,19).

Overall, the side effects of adenosine are comparable with those of dipyridamole, except that they are more short-lived, well tolerated and rarely require reversal with aminophylline. No patient developed prolonged chest pain or other serious complications. We observed no bronchospasm, but patients with bronchospastic disease were excluded from the study. Only 13% of our patients developed first degree AV block. The side effect profile in our patients is similar to that described by Stifring et al. (20).

Gupta et al. (21) compared intravenous adenosine thallium imaging with oral dipyridamole thallium imaging in a small group of normal subjects and patients with coronary artery disease. They reported a higher sensitivity, specificity and accuracy with adenosine than with dipyridamole for the detection of coronary artery disease, but in this comparison oral rather than intravenous dipyridamole was used. To our knowledge, there has been no published report directly
comparing intravenous adenosine and intravenous dipyridamole.

We found high levels of sensitivity (92%), specificity (100%) and predictive accuracy (93%) for adenosine SPECT thallium imaging. The high specificity in our study probably reflects the small number of patients with normal coronary arteries. It is likely that the specificity will be lower when this technique is used in a larger group of patients. Four of our patients had false negative results on adenosine SPECT thallium imaging. These four patients had one vessel disease and two of them had <60% diameter stenosis.

In a subgroup of patients who underwent both adenosine and exercise thallium imaging, we found comparable results with the two tests in the detection of coronary artery disease.

Value of adenosine two-dimensional echocardiography.
Adenosine thallium imaging and adenosine two-dimensional echocardiography have different end points: a perfusion abnormality due to heterogeneity of flow in different myocardial regions in the former procedure and a wall motion abnormality (probably a marker of myocardial ischemia suggesting coronary steal) in the latter. It should not be surprising that thallium imaging is more sensitive than two-dimensional echocardiography in the diagnosis of coronary artery disease as seen in our patients. We found an improvement in the wall motion score index with adenosine infusion. A hyperkinetic wall motion response was observed in 40% of patients, probably as a result of increased heart rate and decreased afterload (22,23). The improved systolic performance is probably linked to the increased coronary flow. It is possible that a higher dose of adenosine, a wall motion abnormality may be more frequent, as reported by others (24,25) using dipyridamole. Conversely, if the absence of hyperkinesia was considered an abnormal response as suggested by others, then the sensitivity of two-dimensional echocardiography would have increased to 60%. With use of this criterion, our adenosine protocol appears to be comparable with the high dose dipyridamole protocol (24,25) but further studies are needed to address this issue. Regional wall motion was assessed visually and subjectively in our study. It is also possible that computerized quantitative methods may detect subtle wall motion changes not discernible by subjective analysis.

Limitations. Certain limitations of our study need to be discussed. 1) The experience is still limited and safety data require a larger number of patients. 2) The patients were nonconsecutive and a possible selection bias may have affected the results. Many of our patients had other clinical indications for coronary arteriography or had previous myocardial infarction, two conditions that tend to artificially increase sensitivity. Also, there were only seven normal subjects; hence, assessment of the specificity of the technique awaits study of a much larger group of patients with normal coronary angiograms or a low pretest probability of disease. The small number of patients is also of concern in the comparison with exercise thallium scintigraphy or two-dimensional echocardiography. The patients included in this study were comparable with a much larger series of patients who had exercise SPECT thallium imaging and were reported from our laboratory (8); of these, 45% had a history of previous myocardial infarction, 49% had a history of hypertension, 15% had diabetes mellitus and most had multivessel disease.

3) We did not measure the adenosine blood level or coronary blood flow. Studies are now under way to compare the thallium kinetics during adenosine infusion with coronary blood flow measurements. 4) A quantitative technique to assess the extent of perfusion deficit based on a normal profile is needed to compare sequential studies and measure the area of myocardium at risk.

Conclusions. Our results suggest that SPECT thallium imaging with intravenous adenosine is a feasible, safe and highly accurate noninvasive technique for the detection of coronary artery disease and results are at least comparable with those of exercise thallium scintigraphy. Most reversible defects in the adenosine study are not associated with a transient wall motion abnormality.

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