Diagnosis of Coronary Artery Disease by Controlled Coronary Vasodilation With Adenosine and Thallium-201 Scintigraphy in Patients Unable to Exercise

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Pharmacological coronary vasodilation induced by dipyridamole is often used in association with thallium-201 myocardial scintigraphy to evaluate the presence and prognostic significance of coronary artery disease. Because dipyridamole acts by blocking the cellular uptake of adenosine, we investigated the usefulness of direct intravenous administration of adenosine, a physiological substance with an exceedingly short (<2 seconds) plasma half-life, to induce maximal controlled coronary vasodilation in conjunction with $^{201}$TI scintigraphy. We studied 89 patients (44 men and 45 women; mean age, 64±10 years [SD]) who were unable to perform an exercise test and were referred for evaluation of suspected coronary artery disease. The intravenous infusion of adenosine began at an initial rate of 50 μg/kg/min and was increased by stepwise increments every minute to a maximal rate of 140 μg/kg/min. $^{201}$TI was injected intravenously after 1 minute at the highest infusion rate, followed by immediate and delayed (4 hour) tomographic imaging. At the highest infusion rate, adenosine induced a significant ($p<0.001$) decrease in systolic (8.7±19.3 mm Hg) and diastolic (6.7±9.4 mm Hg) blood pressures as well as a significant ($p=0.0001$) increase in heart rate (14.5±11.0 beats/min). Side effects occurred in 83% of the patients but resolved spontaneously within 1 or 2 minutes after discontinuing the adenosine infusion. Chest, throat, or jaw pain were the most frequent symptoms and occurred in 57% of the patients. Headache (35%) and flush (29%) were also common. Ischemic electrocardiographic changes occurred in 12% of the patients, and transient first-degree atrioventricular block occurred in 10%. The overall sensitivity and specificity for coronary artery disease detection were 83% and 94%, respectively. Most false-negative studies occurred in patients with one-vessel coronary artery disease. We conclude that maximal controlled pharmacological coronary vasodilation with adenosine, in combination with $^{201}$TI scintigraphy, appears to be a safe and potentially useful test for the diagnosis of coronary artery disease in patients unable to exercise. (Circulation 1990;82:80–87)

Pharmacological vasodilation with intravenous or oral dipyridamole in combination with standard thallium-201 scintigraphy is a recently developed innovative approach to the noninvasive diag-

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for developing coronary arterial restenosis after successful coronary angioplasty.

The mechanism by which dipyridamole induces coronary vasodilation is thought to be through the blockade of cellular adenosine uptake, leading to a subsequent increase in both myocardial and arterial
wall adenosine concentrations. According to this hypothesis, dipyridamole has only an indirect vasodilatory effect, whereas endogenous adenosine would be a direct mediator of coronary dilation.18–20

The potent vasodilation produced by adenosine has been used successfully to induce controlled hypotension in patients undergoing surgical correction of intracranial aneurysms, without significant untoward effects.21 The short half-life of adenosine, determined to be less than 10 seconds by Klabunde22 and, more recently, less than 2 seconds by Moser et al,23 affords a high degree of safety because its effects disappear promptly on discontinuing the drug infusion, unlike dipyridamole, which has a longer duration of action.

Adenosine has been previously used in combination with 201TI scintigraphy to demonstrate regional perfusion differences in dogs with experimental coronary stenoses.24

In this study, we sought to assess the feasibility, safety, and diagnostic accuracy of controlled pharmacological coronary vasodilation with adenosine in combination with 201TI scintigraphy for diagnosing coronary artery disease in patients unable to perform an exercise test.

**Methods**

**Patient Selection**

Eighty-nine patients (44 men and 45 women; mean age, 64±10 years; range, 38–86 years) participated in this research protocol, which was approved by the Institutional Review Boards for Human Research of Baylor College of Medicine and The Methodist Hospital. All patients gave signed informed consent. All eligible patients were referred to the Nuclear Cardiology Laboratory for evaluation of possible coronary artery disease by 201TI single-photon emission computed tomography during pharmacological coronary vasodilation. These patients were considered by their physicians to be physically unable to perform a conventional exercise stress test. Fifty-five patients had either stable angina (n=24), a remote myocardial infarction more than 3 months before the study (n=22), or both angina and a remote infarction (n=9). Twelve patients had received prior coronary artery bypass graft surgery. The remaining 34 patients had no direct evidence of coronary artery disease but were being investigated because of atypical chest pain or for risk assessment in anticipation of major abdominal, thoracic, or vascular surgery. Sixty-seven patients (75%) were using long-acting nitrates (n=32), β-blockers (n=24), calcium antagonists (n=44), or a combination thereof (n=27).

Exclusion criteria for the protocol were severe hypertension (>200 mm Hg systolic and >110 mm Hg diastolic blood pressures), hypotension (<90 mm Hg systolic blood pressure), history of asthma or severe chronic obstructive pulmonary disease requiring the administration of bronchodilators or steroids, presence of wheezing during the physical examination immediately before the test, severe congestive heart failure (New York Heart Association class III or IV), second- or third-degree atrioventricular block, or acute myocardial infarction (within 5 days of the study). All studies were performed after approximately 12 hours of fasting. Patients who were using dipyridamole had this drug discontinued at least 24 hours before the test. Caffeine ingestion was not allowed for at least 12 hours preceding the test.

**Adenosine Administration**

Adenosine (Adenoscan®) was supplied by Medco Research, Los Angeles, California, 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. Adenosine was infused through 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/min, followed by 75, 100, and then 140 μg/kg/min. An infusion rate of up to 217 μg/kg/min has been found to be safe in patients undergoing neurosurgery. However, because the safety of adenosine by intravenous infusion in patients with coronary artery disease is unknown, we elected to titrate the dose cautiously. In patients who could not tolerate the 140 μg/kg/min dose, the infusion rate was decreased to the previous highest tolerated infusion rate. After 1 minute at the highest dose, 3 mCi 201TI were injected as a bolus in a contralateral vein and rapidly flushed with 10 ml of normal saline. The adenosine infusion was then maintained at the highest dose for 3 additional minutes after the thallium injection.

Vital signs and a 12-lead electrocardiogram were obtained immediately before, at every minute during, and for the first 5 minutes after the adenosine infusion. Subsequently, vital signs and an electrocardiogram were recorded every 10 minutes for 30 minutes.

**201TI Scintigraphy**

201TI myocardial perfusion scintigraphy was performed as previously reported from our laboratory. Images were acquired with a large field-of-view rotating gamma camera (ARC 3000, ADAC Laboratories, Milpitas, California) equipped with a low-energy, high-resolution collimator and interfaced to a computer (ADAC 3300). Thirty-two images were obtained over an 180° arc, from the left posterior oblique to the right anterior oblique position, at 6° intervals, for 40 seconds per image. The data were stored on a 64×64×8 byte matrix. Imaging commenced 5 minutes after completion of the infusion and was repeated 4 hours later.

Transaxial reconstruction of the raw tomographic data used a back projection technique and a Butterworth (order, 5) high-pass filter, low-pass window at a 50% cutoff. The reconstructed tomographic slices of 6 mm thickness (120,000–218,000 counts per slice) were then reoriented in the short, horizontal long, and vertical long axes and displayed on a large color monitor.
Interpretation of Tomographic Images

The myocardial segments and the coronary arteries were matched as previously reported from our laboratory; the septal and anterior segments corresponded to the left anterior descending, inferior and posterior segments to the right, and lateral segments to the left circumflex coronary arteries. The apex did not define any particular vessel distribution. An image was considered abnormal if there was a decrease, by visual inspection, of radioactivity in any myocardial segment. Perfusion defects were graded on a four-point scale: 3, normal uptake; 2, mildly diminished uptake; 1, moderately diminished uptake; and 0, severely diminished uptake. The presence or absence of redistribution was visually noted in the 4-hour images. All images were interpreted by the same experienced investigator without knowledge of the electrocardiogram or coronary arteriographic findings.

The myocardial uptake of $^{201}$TI was also quantified using two-dimensional polar plots depicting the three-dimensional thallium distribution, as previously reported for our laboratory. The polar plots obtained for each individual patient were statistically compared with a data bank derived from 27 normal subjects who underwent adenosine $^{201}$TI tomography in our laboratory. Myocardial pixels with counts below 2.5 SDs from the mean values of the corresponding pixels in the normal data bank were considered abnormal and coded as such by the computer program. Focal defects involving 3% or more of the total left ventricular pixels were considered indicative of significant coronary stenosis.

Myocardial segments with diminished uptake and complete redistribution were considered ischemic. The presence of redistribution was determined by visual analysis of the tomographic slices. This was necessary because the accuracy of the redistribution polar plots in depicting filling-in of perfusion defects is still indeterminate. Segments with partial redistribution (defined as any amount of defect improvement without complete normalization) were considered to have both ischemia and scar. Defects without redistribution were defined as scar, although such a definition probably underestimates the presence of ischemia because delayed myocardial redistribution (more than 4 hours) is now considered common in areas that show only partial or no redistribution at 4 hours.

Coronary Angiography and Clinical Correlates

Coronary angiography was performed in 57 patients within 3 months of adenosine $^{201}$TI scintigraphy. In most cases, the angiographic and scintigraphic studies were obtained during the same hospitalization. No patient had myocardial infarction or revascularization procedures between the scintigrams and the coronary angiograms. All angiograms were reviewed by an independent expert who had no knowledge of the adenosine scintigraphic results. The severity of coronary stenosis was assessed by caliper measurements and expressed as percent luminal diameter stenosis. Stenoses of more than 50% of the normal luminal diameter were considered significant. The inaccuracy of the angiographically determined stenosis severity in predicting the functional significance of a given coronary stenosis is well recognized.

Statistical Analysis

Paired t tests and the Wilcoxon signed-rank test were used to analyze variables with and without normal distribution, respectively. A $p$ value of less than 0.05 was considered significant. Sensitivity and specificity were calculated using SDs. Values are given as mean±SD.

Results

Hemodynamic Effects of Adenosine

At a rate of 140 $\mu$g/kg/min, the adenosine infusion led to a significant ($p<0.001$) decrease in systolic (8.7±19.3 mmHg) and diastolic (6.7±9.4 mmHg) blood pressures (Figure 1). At all other infusion rates, the changes in blood pressure were variable and insignificant. The lowest measured systolic blood pressure was 94 mmHg. Systolic and diastolic blood pressures returned to within 10 mm Hg of baseline values in most patients by 2 minutes after discontinuation of the adenosine infusion (78% and 91%, respectively).

The heart rate increased during stepwise increments in the adenosine infusion rate. This increase was not significant at the lowest dose (50 $\mu$g/kg/min) but was significant at all subsequent higher infusion rates. At the infusion rate of 140 $\mu$g/kg/min, a highly significant ($p=0.0001$) increase of 14.5±11.0 beats/min occurred. The highest heart rate achieved was 133 beats/min. The largest increase in heart rate was 37 beats/min. Six patients had a paradoxical decrease in heart rate (-5.2±2.8; range, -3 to -6 beats/min).
Table 1. Side Effects in 89 Patients During Adenosine 201Tl SPECT

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Patients (n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td>Headache</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Flushing</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Ischemic electrocardiographic changes</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>First-degree atrioventricular block</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

Side Effects of Adenosine Infusion

Most patients (74 of 89) experienced side effects during the adenosine infusion (Table 1). Chest, throat, or jaw pain were the most frequent symptoms, occurring in 51 of 89 patients (57%). These pains were variously described as having a pressure, burning, or squeezing quality, usually started during the two highest infusion rates and disappeared within 1 or 2 minutes after discontinuing the infusion. Aminophylline was not administered in any of the patients in this series. Only half (25 of 51) of the patients with chest pain had abnormal 201Tl tomograms, which demonstrated ischemia in 17 of these 25 patients. In the 26 patients with chest pain but without perfusion abnormalities, 16 had cardiac catheterization showing no evidence of coronary artery disease in 10, one-vessel disease in four patients, two-vessel disease in one, and three-vessel disease in one.

All other symptoms were well tolerated and short lived. The one exception was a patient who developed posterior thoracic chest pain and ischemic electrocardiographic alterations at the 100 μg/kg/min infusion rate, which persisted for 30 minutes after discontinuing the infusion, despite two doses of 0.4 mg of sublingual nitroglycerin. At the onset of chest pain, there was no change in the patient’s blood pressure, although the heart rate was 24 beats/min slower than at baseline. At the 140 μg/kg/min infusion rate, there was a 32 mm Hg reduction in systolic blood pressure and a 27 beats/min increase in heart rate compared with baseline measurements. This patient had large, multiple perfusion defects on the initial thallium tomograms that completely redistributed 4 hours later (Figure 2, top). At coronary angiography the next day, this patient was found to have severe left main and three-vessel coronary artery disease, for which he underwent coronary artery bypass graft surgery. He had repeat adenosine scintigraphy 6 days after an uneventful postoperative course. During this study, the patient had no symptoms, no electrocardiographic alterations, and only minimal changes in blood pressure and heart rate. The thallium tomograms were completely normal (Figure 2, bottom).

Electrocardiographic Alterations

Ischemic electrocardiographic alterations (>1 mm horizontal or downsloping ST segment depression measured 0.08 seconds after the J point) occurred in 11 of 89 patients (12.0%), 10 of whom also had chest pain during the adenosine infusion. Nine of the 11 patients with ischemic ST alterations had abnormal 201Tl tomograms; in eight patients, the defects underwent total or partial redistribution and thus were indicative of ischemia. All 11 patients with ischemic electrocardiographic alterations had significant coronary artery disease documented by coronary angiography.

A significant, albeit minimal, increase in the PR interval (172±27 versus 179±30 msec, p<0.001) and QRS duration (87±21 versus 93±43 msec, p<0.05) occurred from baseline to the maximal adenosine infusion rate, respectively. No change in QT interval was observed. Transient prolongation of the PR interval occurred in 30 of 85 (37%) patients, with nine developing first-degree atrioventricular block (PR >200 msec). However, four of five patients with baseline first-degree block by electrocardiography had no further prolongation of the PR interval after adenosine. One patient developed transient second-degree atrioventricular block with only one nonconducted P wave at the 100 μg/kg/min infusion rate. The infusion rate was decreased from 100 to 75 μg/kg/min, and the patient remained in sinus rhythm, without further problems.

Correlation Between 201Tl Tomography and Coronary Angiography

In all 89 patients, the tomographic images were of good or excellent quality. In the 57 patients with coronary angiography, 41 had coronary artery disease, and 16 had normal coronary arteries. Twelve patients with prior coronary artery bypass graft surgery were excluded from this analysis. The 201Tl tomograms were abnormal in 24 of the 29 remaining patients with coronary artery disease by computer quantification and in 21 of 29 patients by visual analysis (sensitivities, 83% and 73%, respectively). The perfusion defects were classified according to the degree of redistribution as pure ischemia in 52%, scar and ischemia in 29%, and pure scar in only 19%. The sensitivity, assessed by quantitative tomography, was 73% (11 of 15 patients) for patients with one-vessel, 90% (nine of 10 patients) for those with two-vessel, and 100% (four of four patients) for patients with three-vessel coronary involvement. Only one of the 16 patients with normal coronary arteries had an abnormal tomogram (specificity, 94%).

Discussion

This study is the first to use intravenous adenosine as a pharmacological stress agent for evaluating patients with suspected coronary artery disease in conjunction with 201Tl emission computed tomography. Our data clearly demonstrate the safety of adenosine and its potential diagnostic use for diagnosing coronary artery disease through controlled pharmacological coronary vasodilation.

The total duration of the adenosine infusion in this investigation was 7 minutes due to our cautious titration of this drug, which had not previously been
FIGURE 2. Top panel: Adenosine $^{201}$TI single-photon emission computed tomography (SPECT) images in a patient with three-vessel coronary artery disease before coronary bypass surgery (prebypass). Representative initial tomographic slices (top row) demonstrate perfusion defects in the anterior wall and septum (short axis); apex and septum (horizontal long axis); and anterior wall, apex and posterior wall (vertical long axis). Tomographic slices 4 hours later (bottom row) show complete redistribution indicating myocardial ischemia. Notice the presence of left ventricular dilation in the initial tomograms. Bottom panel: Adenosine $^{201}$TI SPECT images in the same patient after three-vessel coronary artery bypass surgery (postbypass). The images are displayed in a format identical to those in top panel. No perfusion defects are seen in the initial (top row) or 4-hour redistribution (bottom row) tomographic slices.
used to evaluate patients with potentially severe coronary artery disease. Given the remarkable safety of our protocol, however, it may be feasible to administer a constant infusion at 140 μg/kg/min for a total of 4 minutes, thus shortening the procedure time and duration of side effects.

**Mechanism of Action of Adenosine**

Adenosine is a potent vasodilator in most vascular beds, with the exception of the kidney, and is thought to exert its pharmacological effects through activation of purine receptors (A₁ and A₂ membrane adenosine receptors). The mechanisms by which adenosine receptor activation relaxes vascular smooth muscle may be either an inhibition of the slow inward calcium current, reducing calcium uptake, or an activation of adenylate cyclase through A₂ receptors in smooth muscle cells. Adenosine may also lessen vascular tone by modulating sympathetic neurotransmission. Regardless of the mechanism, the adenosine concentration in the interstitial fluid must increase for vasodilation to occur because once adenosine penetrates the cells, it is rapidly phosphorylated to adenosine monophosphate by adenosine kinase or deaminated by adenosine deaminase.

Although adenosine has been considered a modulator of coronary autoregulation and vasodilation after hypoxia, its specific physiological role in regulating coronary blood flow remains controversial. All of the adenosine effects can be blocked by A₂ receptor antagonists (e.g., methylxanthines).

Recently, Wilson et al. compared the effects of intracoronary papaverine with those of intracoronary and intravenous adenosine on coronary flow reserve in the same patients. The mean duration of maximal hyperemia was 10 seconds with intravenous adenosine compared with 29 seconds with papaverine, and the time to normalization of coronary blood flow velocity was only 37 seconds with adenosine compared with 118 seconds with papaverine. At a dose of 100 μg/kg/min intravenously, Wilson et al found a mean 4.4-fold increase in coronary blood flow velocity, which was maximal at 123 seconds after the onset of the intravenous infusion and returned to basal levels 113 seconds after discontinuing the adenosine infusion. Even at lower infusion rates (70 μg/kg/min), there was a 2.9-fold increase in coronary blood flow velocity.

The principal mechanism of adenosine infusion is probably a perfusion mismatch between vascular territories supplied by normal coronary arteries and those perfused by stenotic arteries—a mechanism that does not necessarily invoke the presence of ischemia. However, adenosine, like dipyridamole, may lead to a myocardial steal phenomenon and thus induce ischemia, as evidenced by angina or ischemic electrocardiographic alterations.

**Side-Effect Profile**

Side effects, especially chest discomfort, were frequent during the adenosine infusion but were well tolerated and usually disappeared within 1 or 2 minutes of discontinuation of the infusion. No serious acute or lasting complications, such as severe hypotension or life-threatening arrhythmias, resulted from adenosine. The PR and QRS intervals were significantly—although only minimally—prolonged, and no patient developed high-grade atrioventricular block.

The frequency of chest pain appears to be higher with adenosine than dipyridamole, possibly due to the greater potency of the former. In fact, the occurrence of chest pain during an adenosine infusion is dose dependent. Sylven et al demonstrated that all of six healthy volunteers developed “angina pectoris-like” chest pain after a high-dose intravenous bolus of adenosine (8.0–15.9 mg). At these very high doses, first- and second-degree atrioventricular block were also frequent and preceded the onset of chest pain. The mechanism of chest pain after adenosine or dipyridamole in normal subjects is unknown.

Intravenous adenosine may not be safe in patients with bronchospastic pulmonary diseases or in those with arterial hypotension. We anticipate that in patients with reactive airway disease, adenosine could induce severe bronchospasm because this complication has been reported to occur after dipyridamole administration. Aerosolized adenosine may induce bronchospasm in asthmatics but not in normal volunteers.

Adenosine may also be contraindicated in patients with sick sinus syndrome because adenosine may cause symptomatic bradyarrhythmias in the latter. Finally, adenosine administration should be avoided in patients already taking oral dipyridamole, because the latter may markedly potentiate the effects of adenosine and precipitate severe hypotension and advanced atrioventricular block.

**Potential Clinical Usefulness**

In this initial series of patients, good sensitivity (83%) and specificity (94%) for detecting coronary artery disease were found combining adenosine with 201T1 tomography. These sensitivity and specificity values are similar to those currently obtained with 201T1 tomography during dipyridamole or exercise stress. Although adenosine is associated with a slightly higher incidence of side effects than dipyridamole, the very short half-life of adenosine reduces the duration of side effects.

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