Clinical Investigation

Effects of Adenosine on Human Coronary Arterial Circulation

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Adenosine is a potent vasodilator used extensively to study the coronary circulation of animals. Its use in humans, however, has been hampered by lack of knowledge about its effects on the human coronary circulation and by concern about its safety. We investigated in humans the effects of adenosine, administered by intracoronary bolus (2–16 μg), intracoronary infusion (10–240 μg/min), or intravenous infusion (35–140 μg/kg/min) on coronary and systemic hemodynamics and the electrocardiogram. Coronary blood flow velocity (CBFV) was measured with a 3F coronary Doppler catheter. The maximal CBFV was determined with intracoronary papaverine (4.5±0.2 · resting CBFV). In normal left coronary arteries (n=20), 16-μg boluses of adenosine caused coronary hyperemia similar to that caused by papaverine (4.6±0.7 · resting CBFV). In the right coronary artery (n=5), 12-μg boluses caused maximal hyperemia (4.4±1.0 · resting CBFV). Intracoronary boluses caused a small, brief decrease in arterial pressure (similar to that caused by papaverine) and no changes in heart rate or in the electrocardiogram. The duration of hyperemia was much shorter after adenosine than after papaverine administration. Intracoronary infusions of 80 μg/min or more into the left coronary artery (n=6) also caused maximal hyperemia (4.4±0.1 · resting CBFV), and doses up to 240 μg/min caused a minimal decrease in arterial pressure (−6±2 mm Hg) and no significant change in heart rate or in electrocardiographic variables. Intravenous infusions in normal patients (n=25) at 140 μg/kg/min caused coronary vasodilation similar to that caused by papaverine in 84% of patients (4.4±0.9 · resting CBFV). At submaximal infusion rates, however, CBFV often fluctuated widely. During the 140-μg/kg/min infusion, arterial pressure decreased 6±7 mm Hg, and heart rate increased 24±14 beats/min. One patient developed 1 cycle of 2:1 atrioventricular block, but otherwise, the electrocardiogram did not change. In eight patients with microvascular vasodilator dysfunction (ΔCBFV, <3.5 peak/resting velocity after a maximally vasodilating dose of intracoronary papaverine), the dose-response characteristics to intracoronary boluses and intravenous infusions of adenosine were similar to those found in normal patients. These studies suggest that maximal coronary vasodilation can be achieved safely with intracoronary adenosine administration and that intravenous infusions at a rate of 140 μg/kg/min cause near-maximal coronary hyperemia in most patients. (Circulation 1990;82:1595–1606)

Many studies of the coronary circulation require the use of drugs that can safely and reliably produce maximal coronary hyperemia of brief duration (for example, for measurement of coronary flow reserve, thallium-201 scintigraphy, and echocardiographic imaging).1-6 An ideal agent for these studies would cause maximal coronary vasodilation, would be effective when given systemically or by the intracoronary route, would be quickly reversible, and would have no significant effects on systemic hemodynamics or on electrocardiographic variables.

The two drugs currently available for producing maximal coronary hyperemia in humans have undesirable characteristics.7-10 Papaverine, given by the intracoronary route, causes relatively brief (15–30 seconds) maximal coronary hyperemia, but the total dose that can be given is limited by its relatively slow systemic excretion (half-life, 3–6 hours).11 Consequently, intravenous or prolonged intracoronary
infusions cannot be given without incurring systemic hypotension. In addition, intracoronary papaverine prolongs the QT interval and can cause polymorphic ventricular tachycardia. Intravenous dipyr-ridamole also elicits maximal coronary hyperemia, but its duration of action is quite long (>30 minutes) and, therefore, precludes repeated measurements during the same study. Even though the vasodilator effects can be attenuated by methylxanthesines, prolonged ischemia, presumably due to coronary steal, has been reported. Because dipyriramol causes coronary vasodilation by increasing interstitial adenosine concentration and because adenosine is rapidly metabolized, adenosine itself may be a safer, more practical agent for producing coronary hyperemia. These studies were undertaken to evaluate the usefulness of adenosine for studies of the coronary circulation of humans.

Since the identification of nucleoside adenosine in the myocardium in 1929, many investigators have shown that it is synthesized in the myocardium and that interstitial adenosine concentration rises in response to increased metabolic oxygen requirements and ischemia. Although the physiological role of adenosine in regulating coronary blood flow is uncertain, exogenously administered adenosine is known to cause profound microvascular coronary dilation mediated by an adenosine receptor on the cell membrane of resistance vessel myocytes. Three properties of adenosine have led to its extensive use in animal studies designed to assess the effects of pathological states (hypertrophy, infarction, and cardiomyopathy) on minimal total coronary resistance. First, intravenous or intracoronary adenosine can reliably increase coronary conductance to maximal levels (that is, at or exceeding that produced by transient ischemia). Second, the duration of action of adenosine is very brief (5–30 seconds). Third, at high doses, adenosine produces transmural vasodilation.

Despite the widespread use of adenosine in animal studies, concern over adenosine-induced hypoten- sion and heart block have hampered its use in humans. In dogs, intravenous doses sufficient to produce maximal coronary dilation also results in a significant fall in systemic arterial blood pressure. In addition, large doses of adenosine increase the refractory period of the sinoatrial and atrioventricu- lar nodes and can result in heart block. A preliminary study using intracoronary adenosine in humans revealed a strikingly high incidence of adenosine-induced conduction block in the atrioventricular node.

The purpose of this study was to examine the dose-response kinetics of intravenous and intracorono- nary adenosine administration in humans.

**Methods**

**Patient Selection**

Thirty-nine patients undergoing coronary angiography for the diagnosis of a chest pain syndrome were studied. Two groups were studied. Thirty-one patients had chest pain atypical for angina pectoris, normal or mildly stenotic (<50% diameter stenosis, visual inspection) epicardial coronary arteries, normal left ventricular function (contrast ventriculogram ejection fraction, ≥50%), and normal coronary flow reserve (≥3.5 peak/resting velocity ratio after a maximally vasodilating dose of papaverine at a resting heart rate of ≤80 beats/min). Each of these patients also underwent M-mode and cross-sectional echocardiography and had normal left ventricular wall thickness (≤11 mm septal and posterior wall diastolic thickness) and function. In addition, they had no other known condition that could have altered coronary microvascular tone or function, for example, collagen vascular disease, anemia (hemoglobin, <11 g/dl), or prior myocardial infarction. Of these patients, eight received calcium channel antagonists, and 11 received aspirin within 24 hours of study.

Eight additional patients had microcirculatory abnormalities (coronary flow reserve, ≤3.5 peak/resting blood flow velocity ratio after papaverine administration) associated with ventricular hypertrophy (n=5) or of uncertain etiology (n=3). Of these patients, one was taking β-adrenergic receptor antagonists, two were taking calcium channel antagonists, and two received aspirin within 24 hours of study. All patients were studied after informed consent was obtained, and all studies were approved by the Institutional Review Board of the University of Minnesota.

**Catheterization Protocol**

Cardioactive medications were continued until the time of catheterization. Patients were brought to the catheterization laboratory in a fasting state after premedication with diazepam (5–10 mg, orally). After vascular access was obtained, sodium heparin was given intravenously in doses sufficient to prolong the activated clotting time to more than 300 seconds. After diagnostic coronary and left ventricular angiography, a 20-MHz 3F coronary Doppler catheter (NuMed Inc., Hopkinton, N.Y.) was advanced through an 8F guiding catheter into the midportion of a coronary artery. The coronary artery studied was randomly assigned, but nondominant right coronary vessels were not studied. The catheter position and range gate were adjusted to obtain an adequate signal of coronary blood flow velocity within the vessel. The technique has been described elsewhere. Mean and phasic signals of coronary blood flow velocity, arterial pressure obtained by the guide catheter, and heart rate were continuously monitored. The arterial waveform obtained from the guide catheter was damped by the presence of the coronary Doppler catheter, consequently, only mean arterial pressure could be accurately monitored.

**Intracoronary papaverine.** After measurement of resting blood flow velocity, 6–12 mg papaverine (2 mg/ml 0.9% saline) was injected through the guide catheter into the coronary ostium, and the resultant increase in coronary blood flow velocity was recorded. To confirm that any dose of papaverine produced maximal coronary hyperemia, an addi-
functional, larger dose was administered, and the resultant hyperemic response was recorded. Blood flow velocity was allowed to return to baseline levels between doses of papaverine. In 31 patients, the left coronary artery was studied. In the remaining eight patients, blood flow velocity was measured in the right coronary artery. The mean dose needed to produce maximal hyperemia was 10±2 mg.

Intracoronary boluses of adenosine. After coronary blood flow velocity had returned to basal levels, sequentially greater boluses of adenosine (2 μg/ml 0.9% saline, MedCo Research, Los Angeles) were injected through the guide catheter into the coronary ostium. In the left coronary artery (n=25; 20 with normal coronary flow reserve), boluses of 2, 4, 8, 12, and 16 μg were given. In the right coronary artery (n=8; five with normal coronary flow reserve), doses of 2, 4, 8, and 12 μg were administered. Care was taken to inject at a rate that would not cause reflux of the adenosine solution into the aorta. Immediately before and at peak response after adenosine administration, the electrocardiogram was recorded at a fast paper speed (100 mm/sec) to assess adenosine-related changes in the PR, QRS, and QT intervals.

Intracoronary infusions of adenosine. The dose-response characteristics of intracoronary infusions of adenosine were determined in the left coronary artery of six patients with normal coronary flow reserve. Once coronary blood flow velocity had returned to normal after the papaverine dose-response study, the guiding catheter was filled with an adenosine solution, and adenosine was continuously infused into the left coronary at six doses: 10, 20, 40, 80, 120, and 240 μg/kg/min. Infusions were performed with an infusion pump (Harvard Apparatus). Adenosine, prepared at 5.2, 20.8, 62.8, and 81.2 μg/ml 0.9% saline, was infused at 1.91 or 3.82 ml/min to achieve the desired drug infusion rate. All infusions were continued for 2 minutes, and data were obtained during the last 30 seconds of infusion. To limit the total study time, additional studies with intracoronary boluses or intravenous infusions were not performed in these six patients.

Intravenous infusions of adenosine. After coronary blood flow velocity returned to baseline, adenosine (1.0 mg/ml 0.9% saline) was infused into the femoral vein (n=5) or peripheral arm vein (n=25) at 70 μg/kg/min by a high-flow infusion pump. Twenty-five patients had normal coronary flow reserve; five had reduced reserve. Two minutes later, the infusion was increased to 100 μg/kg/min, and 2 minutes later, it was increased to 140 μg/kg/min. In addition, an initial dose of 35 μg/kg/min was given to 17 patients. During the infusions, coronary blood flow velocity, mean arterial pressure, and heart rate were continuously recorded. Near the end of each infusion, an electrocardiogram was recorded at 100 mm/sec paper speed to assess changes in the electrocardiographic intervals. All infusions were continued for at least 2 minutes, and measurements were obtained during the last 30 seconds of the infusion.

Data Analysis

Intracoronary bolus studies. The maximal change in coronary blood flow velocity after a bolus of intracoronary papaverine or adenosine was expressed as the ratio of the maximal coronary blood flow velocity (after adenosine or papaverine administration) to the resting blood flow velocity (ΔCBFV). An index of the change in total coronary resistance (ΔTCRI) was calculated as the quotient of the peak hyperemic coronary blood flow velocity (kHz) shift divided by mean arterial pressure at peak hyperemia (in mm Hg) and (coronary blood flow velocity at rest divided by arterial pressure at rest).

The time course of the increase in coronary blood flow velocity after intracoronary vasodilator administration was characterized by three parameters. T90% was defined as the time from the onset of injection to until coronary blood flow velocity reached 90% of the eventual maximal increase in velocity. Tmax was defined as the time during which blood flow velocity remained 90% or more of the peak flow velocity. T10% was defined as the time from the onset of injection until flow velocity returned to within 10% of basal flow velocity.

Intracoronary infusion studies. The change in coronary blood flow velocity during each infusion was calculated as the quotient of the mean coronary blood flow velocity (kHz shift) from 110–120 seconds after the onset of the infusion (when a steady state had been achieved) and the basal coronary blood flow velocity. The changes in heart rate, arterial pressure, and an index of total coronary resistance (calculated as described above) were also assessed during the last 10 seconds of the infusion.

Intravenous infusion studies. The change in coronary blood flow velocity during each intravenous adenosine infusion was calculated as the quotient of the peak mean blood flow velocity (kHz shift) during the infusion and the basal blood flow velocity. In cases where the blood flow velocity had marked cyclical variation during adenosine infusion (that is, ≥20% fluctuation in total coronary resistance index at "steady state"), the existence of cyclic variations was noted, but the average change in blood flow velocity during the last 10 seconds of the infusion was recorded. The changes in heart rate, arterial pressure, and total coronary resistance were also assessed at the peak change in coronary blood flow velocity.

Statistical Analysis

Differences between group means were tested by analysis of variance. Paired differences were analyzed with a paired t test. Linear correlation was assessed with the least-squares method. Except where noted, all data are expressed as mean±SD. Statistical significance was defined as a p value of 0.05 or less.

Results

Intracoronary Adenosine Boluses

Coronary blood flow velocity and resistance. Intracoronary boluses of adenosine produced a dose-
TABLE 1. Intracoronary Adenosine Boluses: Dose-Response Characteristics in Arteries With Normal Flow Reserve

<table>
<thead>
<tr>
<th></th>
<th>ΔCBFV (x resting)</th>
<th>ΔTCRI (x resting)</th>
<th>ΔMAP (mm Hg)</th>
<th>ΔHR (beats/min)</th>
<th>Percent maximal</th>
<th>T90% (sec)</th>
<th>Tmax_dur (sec)</th>
<th>ΔPR (msec)</th>
<th>ΔQRS (msec)</th>
<th>ΔQT (msec)</th>
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</tr>
<tr>
<td>2</td>
<td>3.3±0.9*†</td>
<td>0.32±0.09*†</td>
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<td>0</td>
<td>11±3†</td>
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<td>50</td>
<td>14±3†</td>
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<td>37±7†</td>
<td>5±8</td>
<td>-1±3</td>
<td>-6±30†</td>
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<td><strong>Right coronary artery (n=5)</strong></td>
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<td>Adenosine (µg)</td>
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</tr>
<tr>
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<td>3.4±1.3*†</td>
<td>0.29±0.11*†</td>
<td>-10±10*</td>
<td>4±6</td>
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<td>27±13†</td>
<td>10±8</td>
<td>0±3</td>
<td>-25±7*</td>
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<td>4</td>
<td>4.1±1.4*</td>
<td>0.24±0.09*</td>
<td>-13±4*†</td>
<td>3±5</td>
<td>40</td>
<td>11±1†</td>
<td>33±11†</td>
<td>-10±8</td>
<td>-5±4</td>
<td>-10±11</td>
</tr>
<tr>
<td>8</td>
<td>4.4±1.0*</td>
<td>0.21±0.04*</td>
<td>-10±9*†</td>
<td>0±1</td>
<td>80</td>
<td>12±3†</td>
<td>13±5†</td>
<td>40±26†</td>
<td>-7±13</td>
<td>-2±3</td>
</tr>
<tr>
<td>12</td>
<td>4.1±1.0*</td>
<td>0.20±0.01*</td>
<td>-17±13*†</td>
<td>0±1</td>
<td>100</td>
<td>11±1†</td>
<td>16±11†</td>
<td>52±32†</td>
<td>-3±18</td>
<td>-5±7</td>
</tr>
</tbody>
</table>

Values are mean±SD.
CBFV, coronary blood flow velocity; TCRI, total coronary resistance index; MAP, mean arterial pressure; HR, heart rate; percent maximal, percent of patients with ΔTCRI within 10% of papaverine; T90%, time for CBFV to reach 90% of the maximum; Tmax_dur, duration of ≥90% maximal CBFV; T90%, time for CBFV to return to within 10% of basal value.

*p<0.05 vs. basal condition; †p<0.05 vs. papaverine; ‡p<0.05 vs. left coronary.

Dependent increase in coronary blood flow velocity such that a 16-µg bolus caused coronary hyperemia equivalent to that of papaverine (Tables 1 and 2, Figures 1–3). After a 16-µg bolus of adenosine into the left coronary artery, 18 of 20 patients developed coronary hyperemia to levels within 10% of that produced by intracoronary papaverine. In the remaining two patients, 12, 16, and 20 µg adenosine equally caused coronary resistance to decrease to 0.20 and 0.25 resting resistance, but not to within 15% of the resistance after papaverine administration (0.13 and 0.20 resting resistance, respectively). Hence, in 90% of patients, 16-µg bolus into the left coronary artery caused maximal vasodilation. In the right coronary artery, 12 µg adenosine resulted in maximal hyperemia (within 10% of that produced by papaverine) in all patients. The dose-response relation was similar in normal and abnormal arteries.

TABLE 2. Intracoronary Adenosine Boluses: Dose-Response Characteristics in Arteries With Reduced Flow Reserve

<table>
<thead>
<tr>
<th></th>
<th>ΔCBFV (x resting)</th>
<th>ΔTCRI (x resting)</th>
<th>ΔMAP (mm Hg)</th>
<th>ΔHR (beats/min)</th>
<th>Percent maximal</th>
</tr>
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<tbody>
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<td><strong>Left coronary artery (n=5)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Papaverine</td>
<td>2.8±0.6*</td>
<td>0.35±0.09*</td>
<td>-9±3*</td>
<td>1±3</td>
<td></td>
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<tr>
<td>Adenosine (µg)</td>
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<tr>
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<td>2.1±0.8</td>
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<td>60</td>
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<td>0.34±0.07</td>
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<tr>
<td>16</td>
<td>2.9±0.6</td>
<td>0.33±0.07</td>
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<td>100</td>
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<td><strong>Right coronary artery (n=3)</strong></td>
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<td>Papaverine</td>
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<tr>
<td>Adenosine (µg)</td>
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<td></td>
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<tr>
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<td>8</td>
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<tr>
<td>12</td>
<td>2.9±0.1*</td>
<td>0.30±0.01*</td>
<td>-11±6*</td>
<td>-3±4</td>
<td>100</td>
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</table>

Values are mean±SD.
CBFV, coronary blood flow velocity; TCRI, total coronary resistance index; MAP, mean arterial pressure; HR, heart rate; percent of patients with ΔTCRI within 10% of papaverine.

*p<0.05 vs. basal condition.
The correlation of the maximal change in coronary blood flow velocity after adenosine or papaverine was $r=0.90$ (SEE, ±0.46) peak/resting velocity. A bolus dose of adenosine (2–16 µg) was repeated in 12 patients ($n=15$ measurements). The change in blood flow velocity measured after the first bolus was closely correlated with the change in velocity observed after the second injection ($r=0.95$; SEE, ±0.07 peak/resting velocity).

The onset of maximal hyperemia ($T_{10\%}$) was more rapid after adenosine compared with that of papaverine. The duration of maximal hyperemia ($T_{\text{max} \text{ dura}}$) and time required for blood flow velocity to return to basal levels ($T_{10\%}$) increased with the dose of adenosine, but at any dose, both parameters were much shorter than those observed after intracoronary papaverine administration (Tables 1 and 2, Figures 1 and 2).

Systemic hemodynamics. Intracoronary boluses of adenosine produced small, brief, dose-dependent reductions in mean arterial pressure. The fall in arterial pressure after an 8-, 12-, or 16-µg bolus was similar in magnitude to that found after intracoronary papaverine (mean dose, 10±2 mg). The fall in arterial pressure for an equal dose of adenosine was significantly greater when adenosine was injected into the right compared with the left coronary artery (Tables 1 and 2). The fall in arterial pressure after a 12-µg bolus into the right coronary artery was not different from that after a 16-µg bolus into the left coronary artery, suggesting that doses with similar vasodilator effects caused similar changes in arterial pressure.

There was no significant change in heart rate after any dose of adenosine was injected into the right or left coronary artery. Intracoronary papaverine, however, caused a small, but significant, increase in heart rate.
Table 3. Intracoronary Adenosine Infusions: Dose-Response Characteristics

<table>
<thead>
<tr>
<th>Adenosine (μg/min)</th>
<th>ΔCBFV (× resting)</th>
<th>ΔTCRI (× resting)</th>
<th>ΔMAP (mm Hg)</th>
<th>ΔHR (beats/min)</th>
<th>ΔPR (msec)</th>
<th>ΔQRS (msec)</th>
<th>ΔQT (msec)</th>
<th>Percent maximal</th>
<th>Cyclic variation</th>
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<tbody>
<tr>
<td>Papaverine</td>
<td>4.0±0.2*</td>
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<td>−13±2*</td>
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<td>55±8*</td>
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<tr>
<td>10</td>
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<td>−4±3</td>
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<tr>
<td>20</td>
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<td>0.23±0.03*</td>
<td>−9±3*</td>
<td>−5±4†</td>
<td>−6±2</td>
<td>2±2</td>
<td>−6±7</td>
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<td>240</td>
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<td>−6±4†</td>
<td>−2±2</td>
<td>−2±3</td>
<td>0±6</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are mean±SD; n=6.

CBFV, coronary blood flow velocity; TCRI, coronary vascular resistance index; MAP, mean arterial pressure; HR, heart rate; percent of patients with ΔTCRI within 10% of papaverine; percent of patients exhibiting cyclic changes in CBFV (see text).

*p<0.05 vs basal conditions; †p<0.05 vs. papaverine.

rate when injected into the left (but not the right) coronary artery.

Electrocardiographic changes. Intracoronary boluses of adenosine did not significantly change the PR, QRS, or QT intervals on the electrocardiogram, even when the injected dose was sufficient to cause maximal coronary hyperemia or when the drug was injected directly into the right coronary artery. Hence, there was no evidence of significant sinoatrial or atrioventricular node dysfunction after administration of intracoronary boluses of adenosine. Papaverine caused significant prolongation of the QT interval but did not change the other electrocardiographic parameters.

Intracoronary Adenosine Infusion

Coronary blood flow and resistance. There was a dose-dependent increase in coronary blood flow velocity during the intracoronary infusion of adenosine into the left coronary artery (Table 3). All patients had increased blood flow velocity maximally (equivalent to that achieved with intracoronary papaverine) at infusion rates of 80 μg/min or less. Cyclic variations in blood flow velocity at submaximal infusion rates (see below) were not observed.

The time from the onset of a 240-μg/kg/min infusion until blood flow velocity was within 90% of the eventual peak was 47±31 seconds. The time from the offset of the infusion until blood flow velocity was within 10% of basal values was 143±75 seconds.

Systemic hemodynamics. The heart rate was not significantly changed during the intracoronary infusions (Table 3), even at infusion rates fourfold higher than those needed to cause maximal hyperemia (that is, 240 μg/min). Mean arterial blood pressure fell minimally, but significantly, during the 120- and 240-μg/min infusions (mean change, −9±7 and −6±5 mm Hg, respectively).

Electrocardiographic changes. None of the electrocardiographic intervals changed during the intracoronary infusions of adenosine (Table 3).

Intravenous Adenosine Infusion

Coronary blood flow velocity and resistance. Intravenous adenosine infusions resulted in a dose-dependent increase in coronary blood flow velocity and decrease in total coronary resistance such that minimal total coronary resistance during the 140-μg/kg/min infusion was not significantly different from that elicited by papaverine (Table 4, Figures 4 and 5). In 11 normal patients (44%), an infusion rate of 100 μg/kg/min was sufficient to decrease total coronary resistance to within 10% of the minimal resistance after papaverine. In 10 of the remaining patients, an infusion rate of 140 μg/kg/min was needed to reduce resistance to within 10% of the papaverine-induced minimal resistance. Four patients, however, failed to achieve maximal vasodilation with an infusion rate of 140 μg/kg/min. In two, the 140-μg/kg/min infusion reduced coronary resistance to 0.22–0.27 resting resistance, but that was at least 10–30% greater than the minimal resistance caused by papaverine. In the remaining two, the infusion failed even to decrease coronary resistance to within 30% of the papaverine-induced minimal resistance. An increase in the infusion rate to 180–200 μg/kg/min failed to elicit any greater vasodilation. Hence, 84% of normal patients achieved maximal vasodilation at an infusion rate of 140 μg/kg/min or less, 92% achieved near-maximal hyperemia, but 8% failed to develop hyperemia within 30% of that produced by papaverine. The dose-response relation was similar in a smaller group of patients with microvascular dysfunction.

At the lower infusion rates (70–100 μg/kg/min), coronary blood flow velocity often rose and fell in a cyclic pattern with a cycle length of about 30 seconds (Table 4, Figure 5). Two factors suggest that the cyclic variation in coronary conductance resulted from a cyclical variation in adenosine concentration in the blood perfusing the myocardium. First, when the coronary infusion rate was increased, hyperemia became sustained at the maximal level. Second, intracoronary bolus injections of adenosine at the time when coronary blood flow velocity had receded, resulted in a prompt increase in blood flow velocity. To further investigate the mechanism of this cyclic phenomena, we changed the infusion site from the peripheral vein to the femoral vein in three patients; the pattern did not change. There was no difference
Arteries with normal flow reserve (n=25)

<table>
<thead>
<tr>
<th>Arteries with normal flow reserve (n=25)</th>
<th>( \Delta \text{CBFV} ) (X resting)</th>
<th>( \Delta \text{TCRI} ) (X resting)</th>
<th>( \Delta \text{MAP} ) (mm Hg)</th>
<th>( \Delta \text{HR} ) (beats/min)</th>
<th>( \Delta \text{PR} ) (msec)</th>
<th>( \Delta \text{QRS} ) (msec)</th>
<th>( \Delta \text{QT} ) (msec)</th>
<th>Percent maximal</th>
<th>Cyclic variation</th>
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<tr>
<td>Papaverine</td>
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<td>74±13*</td>
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Arteries with abnormal flow reserve (n=5)

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<th>Arteries with abnormal flow reserve (n=5)</th>
<th>( \Delta \text{CBFV} ) (X resting)</th>
<th>( \Delta \text{TCRI} ) (X resting)</th>
<th>( \Delta \text{MAP} ) (mm Hg)</th>
<th>( \Delta \text{HR} ) (beats/min)</th>
<th>( \Delta \text{PR} ) (msec)</th>
<th>( \Delta \text{QRS} ) (msec)</th>
<th>( \Delta \text{QT} ) (msec)</th>
<th>Percent maximal</th>
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</table>

Values are mean±SD.

CBFV, coronary blood flow velocity; TCRI, coronary vascular resistance index; MAP, mean arterial pressure; HR, heart rate; percent of patients with \( \Delta \text{TCRI} \) within 10% of papaverine; percent of patients exhibiting cyclic changes in CBFV (see text).

\[ p<0.05 \text{ vs. basal conditions; } \ddagger p<0.05 \text{ vs. papaverine.} \]

Table 4. Intravenous Adenosine Infusions: Dose-Response Characteristics

in the frequency of cyclic hyperemia in patients who did and did not receive aspirin and in those with normal and abnormal coronary vessels.

The average time from the onset of infusion until the maximal response was achieved was 84±46 seconds (range, 23–125 seconds). The time from offset of infusion (140 \( \mu \text{g/kg/min} \)) until coronary blood flow velocity returned to basal levels was 145±67 seconds (range, 54–310 seconds).

Systemic hemodynamics. Intravenous infusions of adenosine produced a dose-dependent fall in mean arterial blood pressure and a rise in heart rate (Table 2, Figure 6). At 140 \( \mu \text{g/kg/min} \) in normal patients, the heart rate rose 24±14 beats/min, and mean arterial pressure fell 6±7 mm Hg. In all patients, the mean arterial pressure during the 140-\( \mu \text{g/kg/min} \) infusion remained more than 50 mm Hg.

Electrocardiographic changes. The PR, QRS, and QT intervals did not significantly change during the infusions. Of importance, however, one normal patient developed 2 cycles of 2:1 narrow-complex heart block during the 140-\( \mu \text{g/kg/min} \) infusion. The infusion was continued without further arrhythmia, and the PR interval did not change just before the termination of the infusion. The patient had received diltiazem and a \( \beta \)-adrenergic receptor antagonist continuously before catheterization.

Safety

Other than the one, brief episode of atrioventricular block during intravenous adenosine infusion, no patient developed arrhythmias, systemic hypotension (systolic blood pressure <90 mm Hg, diastolic blood pressure <40 mm Hg), or electrocardiographic changes suggestive of ischemia (>0.1 mV ST segment depression 80 msec after the "J" point). Many patients developed a vague sensation of chest warmth or flushing during the intravenous infusion.

Discussion

These data demonstrate in humans that adenosine, given by the intracoronary or intravenous route, can cause near-maximal coronary vasodilation, equivalent in magnitude to that generated by intracoronary papaverine, without causing clinically important changes in systemic hemodynamics or on the electrocardiogram. In the left coronary artery, boluses of 16 \( \mu \text{g} \) or more (12 \( \mu \text{g} \) in the right coronary artery) or a continuous intracoronary infusion of 80 \( \mu \text{g/kg/min} \) or more were needed to reliably cause maximal coronary vasodilation. Most, but not all, patients developed maximal vasodilation during intravenous infusions of 140 \( \mu \text{g/kg/min} \). The advantages of adenosine over papaverine or dipyridamole are its very short duration
of action, the absence of QT interval prolongation on the electrocardiogram, and its efficacy when given by the intravenous or intracoronary routes.

Potential Methodological Problems

There are several potential problems that should be considered when interpreting these data. Those related to measurement of coronary blood flow using a coronary Doppler catheter have been discussed in detail elsewhere. Of importance, all patients received intracoronary nitroglycerin to maximally dilate the vessel containing the Doppler catheter, and the guide catheter was withdrawn from the coronary ostium at peak hyperemia to ensure that maximal blood flow into the ostium was not impeded by the catheter.

A second potential problem is that we purposely did not control heart rate, arterial pressure, or left ventricular preload during these studies. In this study, we administered two drugs that change both arterial pressure and heart rate. We have recently shown in humans that increases in heart rate augment resting coronary blood flow without altering maximal hyperemic flow (reducing the peak/resting velocity ratio), whereas increases in arterial blood pressure cause proportionately equal increases in resting and hyperemic blood flow (preserving the peak/resting velocity ratio). We were careful, however, to compare the changes in blood flow velocity elicited by adenosine and papaverine to a single basal coronary blood flow velocity that was measured before any drug was given. To compensate for changes in arterial pressure, we expressed the vasodilation caused by each agent as the fractional change in resting coronary resistance (total coronary resistance index). Hence, changes in systemic hemodynamics should not have affected comparisons between different doses of adenosine or between adenosine and papaverine.

A third potential limitation is that we primarily studied patients with normal or moderately narrowed coronary arteries and normal ventricular function. Although not supported by prior studies in animals, the vasodilator response to adenosine may be selectively impaired by certain cardiomyopathies (for example, viral or hypertrophic cardiomyopathy), by severe coronary obstructions, or by other acquired abnormalities. We observed a reduced vasodilator response to adenosine (but not papaverine) in two apparently normal humans. Other investigators have also reported sporadic instances of reduced response to adenosine in animals, the mechanism of which is unknown. Moreover, other patients have been shown to have reduced sensitivity to dipyridamole, which causes vasodilation indirectly by increasing interstitial adenosine concentrations. The lack of a response to adenosine with an intact response to papaverine may signify a specific defect in the microcirculation that could have clinical significance. In addition, the intracoronary dose of adenosine

Figure 5. Record obtained from the same patient presented in Figure 2. Top two panels: Phasic and mean coronary blood flow velocity (CBFV) in the left anterior descending coronary artery. Bottom three panels: Aortic blood pressure, intracoronary blood pressure (from the Doppler catheter), and electrocardiogram (ECG). Intravenous infusion of adenosine at 35 μg/kg/min failed to significantly alter CBFV. When the infusion was increased to 70 μg/kg/min, CBFV rose and fell in a cyclical pattern. When the infusion was further increased to 100 and 140 μg/kg/min, CBFV stabilized at a level similar to that achieved with a maximally vasodilating dose of intracoronary papaverine.

Figure 6. Bar graphs of change in mean aortic blood pressure and heart rate during intravenous infusions of adenosine.
required to cause maximal hyperemia may be significantly higher in patients with increased ventricular mass. Our limited studies in patients with microvascular dysfunction, however, failed to show any difference in the dose-response relation. Further studies will be required to define the vasodilator properties and safety of adenosine in humans with other cardiovascular disease (for example, sinoatrial or atrioventricular node disease, baroreceptor dysfunction, or ventricular hypertrophy).

Comparison With Previous Studies

Aside from an assessment of the dose-response characteristics of adenosine in humans, the two major findings of this study are an apparent species difference in the response to intravenous adenosine and an observation in humans that coronary resistance fluctuates widely at submaximal adenosine infusion rates. Rembert et al reported that an intravenous adenosine infusion rate of 1,000 µg/kg/min was required to elicit maximal transmural coronary hyperemia. Lesser infusion rates caused maximal subendocardial vasodilation, but conductance of blood to the subepicardial muscle was not maximal. In humans, however, we found that an infusion of adenosine at only 140 µg/kg/min decreased coronary resistance to within 14±8% of that induced by papaverine, with a small concomitant increase in arterial blood pressure and a moderate increase in heart rate. These data suggest that humans are more sensitive than are dogs to the vasodilator properties of adenosine or that the rate of adenosine elimination is slower in humans.

Although the species differences in response to adenosine are clear, it should be emphasized that an adenosine infusion of 140 µg/kg/min in humans may not have produced absolutely maximal vasodilation in the subepicardial myocardium in all patients. In 16%, the minimal resistance during the 140-µg/kg/min infusion was more than 10% greater than that produced by papaverine. Similar intraspecies differences in adenosine responsiveness have been reported in dogs.

Although higher infusion rates may possibly cause maximal hyperemia, the safety of higher doses needs to be established. Our experience demonstrated that an infusion rate of 140 µg/kg/min significantly increased the heart rate; higher infusion rates may not be well tolerated in a significant fraction of patients.

We also found that intravenous infusion rates just less than those required to produce a maximal fall in coronary resistance frequently cause a characteristic pattern of widely fluctuating coronary resistance (that is, >20%) that has not been reported in prior studies in animals. The pattern was not affected by changes in the site or concentration of infusion and disappeared when the infusion rate was increased. We believe that this occurred in humans and not in dogs because of the short half-life of adenosine and the longer circulation time in humans that weigh 70–100 kg compared with that in dogs that weigh 20–30 kg. Initially, the adenosine was infused into a vein with relatively slow blood flow, resulting in a high concentration of adenosine. When the adenosine reached the systemic circulation, vasodilation and an increase in vein blood flow occurred. The adenosine, continuously administered at the same infusion rate, was then diluted to a lower concentration. Simultaneously, the adenosine administered at the beginning of the infusion was metabolized. The lower plasma concentration of adenosine that then reached the coronary and systemic vasculature produced less vasodilation, allowing blood flow to decrease. As venous blood flow returned to the basal level, the plasma concentration of adenosine again rose and the cycle started again. If the circulation time was faster (as in the smaller dog), then more adenosine would survive more than one circulation (particularly if the elimination rate was slower), and cyclic variations would not occur. Similarly, if the infusion rate was increased, the trough level of adenosine would still be sufficient to cause maximal vasodilation.

Two factors support this explanation. Additional intracoronary adenosine, given when blood flow velocity was decreasing, resulted in a prompt rise in flow velocity, suggesting that the fall in blood flow resulted from a lower arterial concentration of adenosine rather than decreased local effect. Second, there is inferential evidence that a fraction of the adenosine was metabolized as it passed from the venous infusion site to the myocardium. Under normal circumstances, the left coronary artery receives 2–3% of the total cardiac output. Unless there was significant metabolism, one would anticipate that the intracoronary dose needed to cause maximal hyperemia would be 2–3% of the intravenous dose. We found, however, that the intracoronary infusion rate needed to cause maximal hyperemia was less than 1% of the intravenous dose, suggesting that some adenosine was metabolized before it arrived in the coronary artery.

An additional explanation for cyclic hyperemia is that adenosine, at low doses, caused platelet activation that secondarily reduced hyperemic blood flow. This is unlikely because in vitro studies have shown that adenosine reduces platelet aggregation that secondarily reduced hyperemic blood flow. Furthermore, animal models in which platelet-mediated cyclic flow variation has been observed use severe coronary stenoses, cause cyclic reductions of resting coronary blood flow (not hyperemic flow), and tend to have a much longer periodicity. In addition, pretreatment with aspirin, a drug that abolishes cyclic variations in animal models, failed to alter the incidence of flow variations in humans.

The clinical importance of the phenomenon is that, in contrast to dogs, submaximal doses of adenosine in humans may not cause sustained submaximal hyperemia. Consequently, if adenosine is used as an adjuvant to cardiac scintigraphy, injection of thallium at the low ebb of coronary hyperemia may result in falsely normal findings. Fortunately, the vast majority of
patients achieved sustained maximal coronary hyperemia at an infusion rate of 140 μg/kg/min. These studies suggest that an infusion rate of 140 μg/kg/min should be used unless the patient develops hypotension or marked tachycardia at a lower dose.

Prior investigators have reported that in humans much larger doses of intracoronary adenosine are required to cause maximal coronary vasodilation. Zijlstra et al. found that intracoronary boluses of 50–800 μg were required to produce maximal coronary hyperemia. The magnitude of maximal coronary blood flow obtained with papaverine or adenosine, however, was very low (1.6±0.3 peak/resting coronary blood flow velocity), suggesting that many of the patients studied had microvascular disease or other illnesses that may have altered the response to adenosine. They also reported a high incidence of transient heart block that may have been related to the large dose of adenosine administered concurrently with agents that depress atrioventricular and sinoatrial node function (for example, diltiazem, β-adrenergic receptor antagonists). Other investigators have also studied the effects of adenosine on the peripheral or coronary circulation of humans. The lack of dose-response data or problems in measurement techniques make the interpretation of their findings difficult.

**Potential Uses of Adenosine in Humans**

We studied the effects of adenosine on the coronary circulation of humans for two reasons: one related to clinical application and the other related to basic study of the coronary circulation. It was recently suggested that intravenous adenosine infusions may supplant dipyridamole in providing coronary vasodilation in conjunction with 201Tl scintigraphic studies. The ultrashort half-life of adenosine compared with that of dipyridamole may lessen the risk of prolonged coronary ischemia due to vasodilator-induced coronary “steal” and reduce the time required for redistribution of the isotope. For adenosine to replace dipyridamole, however, it must safely cause coronary hyperemia sufficient to differentiate myocardium perfused by a stenotic artery from that supplied by a normal vessel. These studies suggest that clinically tolerable doses of adenosine cause near-maximal coronary hyperemia in most, but not all, patients. Although the importance of obtaining absolutely maximal (as opposed to near-maximal) coronary vasodilation may be insignificant because epicardial coronary stenoses first cause vasodilation of the subendocardium (the layer most sensitive to the vasodilator properties of adenosine), further clinical studies will be needed to define the comparative sensitivity of 201Tl scintigraphy obtained using adenosine or dipyridamole.

The second clinical use of adenosine is in measuring coronary flow reserve in the catheterization laboratory. Intracoronary papaverine, the agent most commonly used to measure flow reserve, cannot be given as a continuous infusion (making difficult its use with measurement techniques with poor temporal resolution such as digital subtraction angiographic methods) and can cause ventricular tachycardia. Intracoronary adenosine (bolus or infusion) may be more advantageous than papaverine because it can be given as a continuous infusion without resulting in systemic accumulation, it has no important effects on the electrocardiogram at the doses tested, and it has a short half-life that reduces the potential sequelae of any toxicity (for example, heart block). Similarly, the ability to cause prolonged coronary hyperemia using continuous intracoronary infusions of adenosine should enhance many physiological studies of the coronary circulation.

Although the precise role of adenosine in regulating coronary blood flow is not certain, several aspects of its mechanism of action in causing microvascular vasodilation are known and should be considered when the drug is used in diagnostic or therapeutic studies. The myocytes of coronary resistance vessels have an adenosine receptor (A₁) on their cell membrane. When combined with adenosine, the plasma membrane-bound receptor protein causes an increase in adenylate cyclase activity and a subsequent increase in intracellular cyclic AMP. The receptor activity is inhibited by theophylline-type compounds (that is, methylxanthines), and theophylline has been shown in animals to reduce adenosine-induced hyperemia by 41–101%. Hence, patients receiving theophylline, caffeine, or other methylxanthines may not develop maximal coronary hyperemia during adenosine infusion.

A second effect of adenosine is presynaptic inhibition of norepinephrine release from sympathetic nerve terminals. Studies by Johannsen et al. and others have demonstrated that adenosine reduces, but does not fully override, coronary vasoconstriction during neural sympathetic stimulation. Studies of the effect of sympathetic neural stimulation on the coronary circulation (for example, cold pressor test) should take into account the inhibitory effect of adenosine.

**Safety**

Adenosine has two important potential side effects. Depression of sinoatrial or atrioventricular node function occurs in a dose-dependent fashion in animals and humans. The doses previously reported to cause heart block in humans were far in excess of those given in this study, and many of the patients concomitantly had received other drugs that depress atrioventricular node function (for example, diltiazem and β-adrenergic receptor antagonists). We observed one episode of 2:1 atrioventricular block (two cycles) during an intravenous infusion (140 μg/kg/min) in one patient who had previously received diltiazem and atenolol. Although the episode was clinically insignificant, more prolonged atrioventricular node block may occur during an intravenous infusion in patients with preexisting conduction system disease or in patients taking dipyridamole. To avoid important heart block, the dose of
intravenous infusions should be slowly titrated, and patients should be instructed to discontinue dipyridamole therapy. In addition, significant anemia may decrease adenosine metabolism and intensify or prolong its effect. Unlike papaverine, however, adenosine does not change the QT interval. Consequently, the 0.5% incidence of polymorphous ventricular tachycardia observed after intracoronary papaverine may be avoided by the routine use of adenosine in the measurement of flow reserve.

Intravenous infusions of adenosine can cause a significant fall in arterial blood pressure and a reflex-mediated rise in heart rate. Although these minor hemodynamic changes were well tolerated in our patients, significant hypotension may result in patients with an impaired baroreflex (and, hence, reduced reflex tachycardia) or with intravascular volume depletion, or it may result in those treated concomitantly with dipyridamole.

Finally, although these data suggest that adenosine can be safely administered to patients studied in the catheterization laboratory, we studied only 39 patients. Study in a much larger population will be required to fully ascertain the incidence and predisposing factors of any adverse effects. If more widespread use parallels our experience, adenosine should greatly facilitate studies of the coronary circulation of humans.

Acknowledgments

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