Role of Adenosine in Pathogenesis of Anginal Pain

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The intravenous infusion of adenosine provokes anginalike chest pain. To establish its origin, an intracoronary infusion of increasing adenosine concentrations was given in 22 patients with stable angina pectoris. During adenosine infusion, 20 patients had chest pain without electrocardiographic signs of ischemia. They all reported that the chest pain was similar to their usual anginal pain. In 10 of the 22 patients adenosine was also infused into the right atrium, but it never produced symptoms at the doses that had provoked chest pain during intracoronary infusion. In seven other patients, the intracoronary adenosine infusion was repeated after intravenous administration of aminophylline, an antagonist of adenosine P1-receptors. Aminophylline decreased the severity of adenosine-induced chest pain (assessed with a visual analog scale) from 42±22 to 23±17 mm (p<0.001). In the remaining five of the 22 patients, monitoring of blood oxygen saturation in the coronary sinus during intracoronary adenosine administration showed that maximum coronary vasodilation was achieved at doses lower than those responsible for chest pain. A single-blind, placebo-controlled, randomized trial of the effect of aminophylline on exercise-induced chest pain was also performed in 20 other patients with stable angina. Aminophylline, compared with placebo, decreased the severity of chest pain at peak exercise from 67±21 to 51±23 mm (p<0.02), despite the achievement of a similar degree of ST-segment depression. Finally, the effect of intravenous adenosine was compared in 10 patients with predominantly painful myocardial ischemia and in 10 patients with predominantly silent ischemia. The latter tolerated a longer period of adenosine infusion and developed significantly less severe chest pain than patients with painful ischemia (18±3.6 vs. 14.4±3.6 minutes, p<0.05 and 26±28 vs. 63±23 mm, p<0.02, respectively). Thus, intracoronary adenosine administration provokes chest pain similar to the anginal pain at doses that do not produce symptoms during intra-atrial infusion. Furthermore, aminophylline, an adenosine P1-receptor antagonist, significantly reduces the severity of both adenosine and exercise-induced chest pain. These findings indicate that adenosine is a stimulus adequate to produce cardiac pain and could be partially responsible for the anginal pain during myocardial ischemia. This effect does not seem to be related to adenosine-induced coronary dilation and appears predominantly mediated by P1-receptor stimulation. The fact that the severity of chest pain provoked by intravenous adenosine is less in patients with silent ischemia, although difficult to interpret because of the systemic algogenic effects of this substance, further supports the hypothesis that adenosine may play an important role in the production of the anginal pain. (Circulation 1990;81:164–172)

After the initial description of angina pectoris by Heberden in 1772,1 many attempts have been made to identify its mechanisms and its relation with myocardial ischemia. Although it was proposed many decades ago that stretching of the ventricular wall2 and local release of chemical substances3 might be the stimuli responsible for the anginal pain, there has been no conclusive evidence in favor of or against either of these hypotheses. More recently, Sylven et al.4 on the basis of the observation that the intravenous infusion of adenosine provokes anginalike chest pain, have proposed that endogenous adenosine, released in the coronary circulation during myocardial ischemia,5 could be responsible for the anginal pain. This hypothesis, however, lacks objective support because 1) it is not

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known whether the chest pain produced by the intravenous administration of adenosine originates from the heart and 2) it is not known whether endogenous adenosine has the same effect as exogenous adenosine.

To better understand the relations between adenosine and the anginal pain, we performed three different, but interrelated, studies in patients with stable effort angina pectoris aimed at assessing 1) the origin of the chest pain provoked by exogenous adenosine, 2) the role of endogenous adenosine in the production of exercise-induced anginal pain, and 3) the effect of adenosine in patients with predominantly silent and in those with predominantly painful myocardial ischemia.

Methods

Patients

Sixty-two patients with chronic stable angina pectoris (symptom duration ranging from 6 months to 12 years; mean, 3.8 years), positive exercise test for myocardial ischemia (horizontal or down-sloping ST-segment depression >1.5 mm), and documented coronary artery disease (internal diameter reduction >70% of at least one major branch) participated in this study. Nineteen patients had suffered a previous myocardial infarction more than 3 months before the study.

All patients were normotensive, in sinus rhythm, and without evidence of heart failure, cardiomyopathy, or valvular disease. No patient had evidence of left ventricular hypertrophy or conduction defects on the electrocardiogram that could interfere with the interpretation of ST-segment changes, and no patient was taking digitalis. Patients were requested to abstain from xanthine-containing food and drinks for at least 12 hours before study. Nitrate preparations, other than sublingual nitroglycerin and calcium entry-blocking agents, were withdrawn 2 days before the study; β-blocking agents were withdrawn 4 days before. Only sublingual nitroglycerin was used during the latter period, and a minimum of 6 hours was allowed to elapse before testing was begun if this drug was used.

All patients gave written informed consent for participation in the study.

Adenosine Preparation

Adenosine (adenosine base, Fluorochem, Derby, UK) was dissolved in 0.9% NaCl and prepared for intravenous human use by the Pharmacy, Hammersmith Hospital, London, England, in a concentration of 5 mg/ml.

Assessment of Chest Pain

At the beginning of each test, patients were informed that they could develop chest pain or other unpleasant symptoms. They were instructed to promptly report the onset of chest pain or of any other discomfort. The severity of chest pain was assessed by use of a visual analog scale, a well-accepted method for the assessment of pain. The 10-cm scale was marked from no symptoms to severe symptoms. The scale was measured from 0 to the subject's mark in millimeters. Patients were also asked to report the distribution, radiation, and type of chest pain and the presence of any other symptom.

Intracoronary Adenosine Administration

Twenty-two patients were studied (20 men and two women, aged 45–68 years; mean, 58 years). During exercise testing, all patients developed chest pain. ST-segment depression at the onset of chest pain was 0.9±0.3 mm (ranging from 0.6 to 1.5 mm). Coronary angiography showed one-vessel disease in 10 patients, two-vessel disease in 11 patients, and three-vessel disease in one patient. After routine diagnostic coronary angiography (Judkins technique), a 7F catheter was advanced through an 8F femoral sheath to the left coronary ostium. Adenosine was then infused at a rate of 1 ml/min into the left coronary ostium at increasing concentrations of 10−8, 10−7, 10−6, 10−5, 10−4, 10−3, 2.5×10−3, and 4×10−3 M for periods of 2 minutes each. Two electrocardiographic leads (V5 and aVF) and arterial pressure (obtained through the side port of the femoral sheath) were continuously monitored and recorded on paper and on magnetic tape throughout the whole study. The infusion was stopped in the presence of 1) intolerable symptoms, 2) increase in heart rate greater than 30 beats/min, and 3) ST-segment depression greater than 1.5 mm.

These 22 patients were also submitted, during the same cardiac catheterization, to one of the following three protocols: 1) In 10 patients, adenosine was also infused through a 7F catheter positioned into the right atrium. The same protocol as that for the intracoronary infusion was used, but doses of adenosine were 20 times greater. 2) In seven other patients, the intracoronary adenosine infusion with the same doses given during the first intracoronary infusion, was repeated after the intravenous administration of aminophylline (7 mg/kg over a period of 10 minutes). 3) In the remaining five patients, a 5F fiberoptic catheter was advanced through the left subclavian vein and into the great cardiac vein before intracoronary adenosine infusion. The proximal end of the catheter was coupled to a reflectometer (model IVH3, Schwarzer) to obtain a continuous in vivo measurement of oxygen blood saturation in the great cardiac vein by applying the reflection spectrophotometry principle. The second infusion of adenosine was always stopped at the onset of chest pain.

Aminophylline and Exercise-Induced Chest Pain

Twenty men (aged 48–67 years; mean, 58 years) who consistently had anginal pain during at least two consecutive exercise tests were studied. Coronary angiography showed one-vessel disease in four patients, two-vessel disease in 10 patients, and three-vessel disease in six patients.
Fourteen of these 20 patients underwent a single-blind, placebo-controlled, randomized study. They were randomized into two groups of seven patients each. One group underwent treadmill exercise testing 2 minutes after the intravenous administration of aminophylline (7 mg/kg over a period of 20 minutes) on day 1 and after placebo on day 2. The other group received placebo on day 1 and aminophylline on day 2. Tests were performed on two consecutive days between 9:00 AM and 12:00 noon. The laboratory temperature was kept at 20–24°C. The modified Bruce protocol was used with 1.5 mm ST segment depression as the end point. A 12-lead electrocardiogram and blood pressure (cuff sphygmomanometer) were obtained before drug treatment, immediately after treatment, at 1-minute intervals during the exercise, and at 5 and 10 minutes after exercise. Three electrocardiographic leads were continuously monitored before, during, and after exercise. The level of the ST segment, 60 msec after the J point, was calculated after signal averaging by a computer-assisted system (CASE Marquette 12) in all 12 leads. The calculated values were printed out, along with the heart rate, against time in trend format. This provided measurements of the ST segment level with an accuracy of 0.1 mm. The lead showing the greatest ST-segment depression was selected for analysis.

In the remaining six patients, the same single-blind, placebo-controlled, randomized trial was repeated, but a lower dose of aminophylline (1.2 mg/kg over a period of 10 minutes) was used.

**Adenosine in Patients With Silent and Painful Ischemia**

Ten patients with predominantly silent ischemia (group 1) and 10 patients with predominantly painful ischemia (group 2) were enrolled for this study.

Group 1 consisted of 10 men (eight English and two Irish, aged 44–68 years; mean, 62 years). Coronary angiography showed one-vessel disease in two patients, two-vessel disease in four patients, and three-vessel disease in four patients. Criteria for inclusion in this group were 1) development of ST-segment depression of 2 mm or more (to avoid borderline cases) during exercise without occurrence of chest pain and 2) absence of angina for the last 3 months before study despite evidence of episodes of transient ST-segment depression during 24-hour Holter monitoring (number of episodes ranging from 1 to 6; mean, 2.6±2.2). No patient, however, was totally asymptomatic; all patients reported some, although rare, episodes of typical angina.

Group 2 consisted of 10 men (eight English, one Indian, and one Portuguese, aged 45–68 years; mean, 61 years). Coronary angiography showed one-vessel disease in one patient, two-vessel disease in five patients, and three-vessel disease in four patients. Criteria for inclusion were 1) development of chest pain at ST segment depression less than 1.5 mm during exercise testing and 2) at least one episode of angina per week for the last 3 months before study. A single-blind, placebo-controlled, randomized design was used. Adenosine was infused through an antecubital vein with a constant infusion pump beginning at 50 μg/kg/min and increasing to 100, 150, 200, 250, and 300 μg/kg/min at 4-minute intervals. The infusion was stopped in the presence of 1) increase in heart rate greater than 30 beats/min, 2) intolerable symptoms, and 3) ST-segment depression greater than 1.5 mm. Three electrocardiographic leads were monitored throughout the test; 12-lead electrocardiogram and arterial blood pressure (cuff) were taken during the control period at 2-minute intervals during the infusion and at 5 and 10 minutes during recovery.

**Statistical Analysis**

Continuous variables were compared by t test for paired and unpaired data, as appropriate. A value of \( p < 0.05 \) was considered statistically significant. Data are reported as mean±1 SD.

**Results**

**Intracoronary Adenosine Administration**

Intracoronary adenosine administration produced chest pain, without electrocardiographic signs of myocardial ischemia, in 20 of 22 patients (Figure 1). All patients tolerated the highest dose of adenosine. No patient developed electrocardiographic signs of myocardial ischemia. Four patients reported chest pain at a concentration of \( 10^{-3} \) M; 13 patients, at a concentration of \( 2.5 \times 10^{-3} \) M; and three patients, at a
concentration of $4 \times 10^{-3}$ M. All patients experienced chest pain with character, location, and radiation similar to their usual anginal pain. Both spontaneous and adenosine-induced chest pain were retrosternal without radiation in 14 patients, with radiation to the left arm in four patients, and with radiation to the neck in one patient. In the remaining patient, adenosine produced chest pain without radiation at a dose of $2.5 \times 10^{-3}$ M and chest pain with radiation to the left arm at the higher dose. This pattern was similar to that of spontaneous angina. Indeed, this patient reported that his angina was retrosternal only when it was of short duration or when it was promptly relieved by nitrates; more prolonged angina radiated to his left arm.

Intra-atrial infusion of adenosine provoked chest pain in all 10 patients in whom it was given at a concentration of $5 \times 10^{-2}$ M. No patient developed electrocardiographic signs of myocardial ischemia. In eight of these 10 patients who also had chest pain during intracoronary administration of adenosine, the ratio between the intravenous and intracoronary adenosine dose producing chest pain was 12.5 in one patient, 20 in six patients, and 50 in one patient (Figure 2). During intra-atrial adenosine administration, chest pain was similar to the usual anginal pain in only five patients. It was retrosternal without radiation in eight patients; two patients experienced radiation to both arms. Three patients had abdominal pain. Six patients experienced facial flushing. Five patients complained of difficulty in breathing accompanied by a feeling of anxiety (Figure 1).

Aminophylline decreased the severity of chest pain provoked by intracoronary adenosine in all seven patients who underwent this protocol. Before aminophylline, adenosine administration provoked chest pain at a concentration of $10^{-3}$ M in two patients, $2.5 \times 10^{-3}$ M in four patients, and $4 \times 10^{-3}$ M in one patient. The severity of chest pain provoked by adenosine administration was $42 \pm 22$ mm before aminophylline. After aminophylline, the severity of chest pain, at the same doses of adenosine, was significantly less ($23 \pm 17$ mm, $p<0.002$) (Figure 3). Furthermore, after aminophylline, two patients were able to tolerate a higher dose (one level higher) of adenosine before the onset of chest pain than they were able to tolerate before aminophylline.

In all five patients in whom blood oxygen saturation was monitored in the great cardiac vein, it progressively increased during increasing doses of intracoronary adenosine. The maximum value of oxygen saturation (80 ± 9%, ranging from 68% to 93%) was achieved at a concentration of $10^{-3}$ M in one patient, $2.5 \times 10^{-3}$ M in three patients, and $4 \times 10^{-3}$ M in the remaining patient. All five patients had chest pain. Oxygen saturation at the adenosine dose immediately before the development of chest pain was already $74 \pm 7\%$, ranging from 63% to 87% (Figure 4).

During intracoronary adenosine infusion, blood pressure and heart rate did not change for doses that did not produce symptoms. At doses that provoked chest pain, a modest, but significant, increase of systolic blood pressure was noted (8 ± 6 mm Hg, $p<0.05$); diastolic blood pressure and heart rate did not change significantly. During intra-atrial adenosine infusion, a significant increase of heart rate (23 ± 9 beats/min, $p<0.001$) was observed. Blood pressure, on the average, did not change. However, an increase was observed in six patients; a reduction was observed in five patients; and a reduction followed by an increase occurred in three patients.

**Aminophylline and Exercise-Induced Chest Pain**

All patients had exercise-induced chest pain after both aminophylline and placebo. However, after the higher dose of aminophylline (7 mg/kg), the severity
of chest pain, compared with placebo, decreased both at its onset (from 29±20 to 18±16 mm, \( p<0.02 \)) (Figure 5) and at peak exercise (from 67±21 to 51±23 mm, \( p<0.02 \)) (Figure 6). Aminophylline did not delay the onset of chest pain; the interval between onset of pain and onset of myocardial ischemia was similar to that after placebo (0.5±1.2 vs. 0.6±1.6 minutes, \( p=NS \)). Peak ST-segment depression after aminophylline infusion was similar to that after placebo (1.6±0.1 vs. 1.5±0.1 mm, \( p=NS \)) (Figure 6). In each patient the difference of ST-segment depression between the two tests never exceeded 0.2 mm. Aminophylline administration at this higher dose, however, did increase both exercise duration (from 8.3±3.2 to 10.7±3.2 minutes, \( p<0.001 \)) and peak heart rate–blood pressure product (from 175±37 to 206±46 beats/min-mm Hg\(^{10-3} \), \( p<0.001 \)).

The administration of the lower dose of aminophylline (1.2 mg/kg), compared with placebo, decreased the maximum severity of chest pain (from 64±28 to 43±27 mm, \( p<0.05 \)), but it did not delay the onset of chest pain (time to chest pain, 6±2.6 vs. 6.7±3.4 minutes, \( p=NS \)). Peak ST segment depression after aminophylline infusion was similar to that after placebo (1.6±0.1 vs. 1.6±0.1 mm, \( p=NS \)); in each patient the difference of ST-segment depression between the two tests never exceeded 0.2 mm. Aminophylline administration at this lower dose, compared with placebo, did not affect the exercise duration (8.4±1.9 vs. 8.3±3.1 minutes, \( p=NS \)) nor the peak heart rate–blood pressure product (163±37 vs. 154±28 beats/min-mm Hg\(^{10-3} \), \( p=NS \)).

**Adenosine in Patients With Painful and Silent Myocardial Ischemia**

Placebo administration did not produce symptoms in any of the patients. Adenosine infusion produced chest pain in 19 of the 20 patients. Only one patient in group 1 (who had a history of asymptomatic myocardial infarction) did not develop any pain; in this patient, the test was interrupted after 14.3 minutes because of nausea. Time to onset of chest pain was greater in group 1 than in group 2 (13.3±5.9 vs. 9.5±2.2 minutes), although this difference did not achieve statistical significance (\( p=0.07 \)) (Figure 7). The severity of chest pain, both at the onset and at peak, was significantly less in group 1 than in group 2 (10±9 vs. 24±12 mm, \( p<0.02 \) and 26±28 vs. 63±23 mm, \( p<0.02 \), respectively) (Figure 8). No patient had ST-segment depression at the onset of chest pain; however, seven patients in each group subsequently developed ST-segment depression greater than 1 mm during the test. Only three patients in group 1 and five in group 2 reported that adenosine-induced chest pain...
pain was similar in character and location to their angina pain; six of these patients developed ST segment depression greater than 1 mm during the test (three in group 1 and three in group 2). The pain was located in the center of the chest without radiation in five patients in group 1 and in four patients in group 2; in the remaining patients, it radiated to either the jaws (two in group 1 and four in group 2) or to the arms (two in group 1 and one in group 2). Eight patients (three in each group) complained of difficulty in breathing accompanied by a feeling of anxiety. Two patients (one in each group) had severe nausea.

The total duration of the test was greater in group 1 than in group 2 (18±3.6 vs. 14.4±3.6 minutes, p<0.05) (Figure 7). Seven patients in group 1 but only two in group 2 tolerated a dose of 250 μg/kg/min or more (Figure 9). The test was interrupted because of chest pain in one patient in group 1 and in four in group 2, because of ST-segment depression in three patients in each group, because of tachycardia or frequent ventricular extrasystoles in four patients in group 1 and in three patients in group 2, and because of nausea in one patient in group 1. In the remaining patient in group 1, the maximum dose of adenosine was achieved.

Placebo administration did not produce hemodynamic changes in any of the patients. The hemodynamic response to adenosine administration was similar in the two groups. Heart rate increased by 21±16 beats/min (p<0.001) in group 1 and by 20±12 beats/min (p<0.001) in group 2. Blood pressure did not change significantly in either group.

**Discussion**

*Origin of Adenosine-Induced Chest Pain*

Our study shows that in patients with stable angina pectoris, the intracoronary administration of adenosine causes chest pain without electrocardiographic signs of myocardial ischemia. The character, location, and radiation of adenosine-induced chest pain are remarkably similar to those of the anginal pain experienced by the patients during their daily life.

Because the half-life of adenosine in blood is 10 seconds and the transit time in the coronary circulation is about 6–8 seconds, the amount of adenosine reaching the right atrium during intracoronary administration was considerably less than that infused. However, even though it was assumed that no substantial degradation occurred due to the decreased transit time caused by adenosine-induced coronary dilation, the recirculating adenosine was inadequate to produce pain because the dose that caused chest pain during intra-atrial infusion was, in the majority of patients, 20 times greater than the dose causing symptoms during intracoronary administration. It is reasonable to assume, therefore, that the chest pain provoked by intracoronary adenosine infusion was

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**Figure 7.** Bar graphs of effect of intravenous administration of increasing doses of adenosine in patients with silent (S) and painful (P) myocardial ischemia. Time to pain and total duration of the test were longer in patients with silent ischemia.

**Figure 8.** Plot of effect of intravenous administration of increasing doses of adenosine in patients with silent and painful myocardial ischemia. The severity of chest pain at its onset and at the time the test was terminated was significantly less in patients with silent ischemia. It is worth noting that, despite a statistically significant difference between patients with silent and those with painful ischemia, the overlapping of results between the two groups is considerable.

**Figure 9.** Bar graph of effect of intravenous administration of increasing doses of adenosine in patients with silent (open bars) and painful (closed bars) myocardial ischemia. Seven of 10 patients with silent ischemia, but only two of 10 patients with painful ischemia, tolerated doses of adenosine that were 250 μg/kg/min or more.
entirely cardiac in origin. It is worth noting that the intracoronary infusion of substance P, a substance known to be involved in nociception, does not provoke chest pain, even with concentrations high enough to give systemic effects.10

Because the fraction of the cardiac output to the left coronary artery is about 2–3%,11 because the transit time from right atrium to left coronary artery is about 8–10 seconds,12 and because the half-life of adenosine in blood is about 10 seconds,8 the fact that the amount of adenosine causing chest pain during intracoronary adenosine administration was 5% of that during intra-atrial administration would be compatible with a cardiac origin of the pain. However, in about half of our patients the chest pain experienced was different from the usual anginal pain, and anxiety, difficulty in breathing, abdominal pain, and facial flushing were often the predominant symptoms; these facts strongly suggest that, in these cases, the symptoms did not entirely originate from the heart. This is in agreement with experimental results showing that adenosine stimulates afferent nerves in various tissues such as chemoreceptors,13 renal pelvis,14 and lung15 and with the observation in humans that the intrabrachial infusion of adenosine causes pain in the forearm.16

This study not only proves that the chest pain caused by adenosine originates from the heart, but it also sheds some light on its possible mechanisms. Indeed, the fact that aminophylline, a potent antagonist of adenosine P1-receptors,17–19 significantly decreases the severity of chest pain provoked by the intracoronary administration of adenosine appears to suggest that P1-receptors can play a key role in mediating this algogenic effect. This is in agreement with the observation that in healthy volunteers aminophylline reduces the severity of systemic symptoms caused by intravenous adenosine administration.4 On the other hand, our data appear to rule out that chest pain was due to mechanical distortion and stretching of sensory cardiac nerves located in the myocardial interstitium and in the vascular adventitia.20 In fact, a massive increase of blood oxygen saturation in the great cardiac vein, indicative of massive coronary resistive vessel dilation, was observed at doses of adenosine lower than the minimum dose able to provoke chest pain. Although Sylven et al,21 in a previous study, found that both chest pain and coronary dilation occurred at the same intravenous bolus dose of adenosine, the presence of systemic effects and the lack of an appropriate dose-escalating approach are likely to account for the inability of their study to clearly separate the algogenic and the vasoactive effects of this substance.

In theory, the intracoronary administration of adenosine can cause myocardial ischemia.22 However, it is unlikely that myocardial ischemia was the cause of chest pain in our patients. Indeed, no patient developed electrocardiographic signs of myocardial ischemia during adenosine infusion, although, during the exercise test, all patients had already developed obvious ST-segment depression before reporting chest pain. Also unlikely is the possibility that chest pain was due to a nonspecific effect of the intracoronary infusion of saline (the vehicle used to dissolve adenosine). Indeed, to minimize the risk of untoward effects from the vehicle, the increasing doses of adenosine were always given at the same infusion volume rate (1 ml/min). The fact that the chest pain never occurred at adenosine concentrations lower than 10–5 M confirms that saline was not responsible.

**Endogenous Adenosine and Chest Pain**

The demonstration that the pain provoked by exogenous adenosine originates from the heart suggests, but does not prove, that endogenous adenosine released during myocardial ischemia could have the potential to cause exercise-induced angina. To test this hypothesis we assessed the effect of aminophylline on exercise-induced chest pain in patients with stable angina pectoris. In our study, aminophylline, compared with placebo, significantly reduced the severity of exercise-induced chest pain despite the fact that patients achieved a degree of ST segment depression similar to that achieved after placebo. This was observed not only at the higher dose of aminophylline, which markedly improves exercise capacity,23,24 but also at the lower dose of this drug, which does not affect exercise capacity. It would appear, therefore, that the effect of this drug on the anginal pain is independent of the effect on exercise capacity.

It is worth noting that aminophylline did not delay the onset of angina, although it did decrease the severity of chest pain not only at peak exercise but also at its onset. These findings are not in contrast with the hypothesis that adenosine is responsible for the anginal pain, although they do indicate that other mechanisms are also important. The nature of these mechanisms can only be speculative. Interestingly, ATP, which is released in the coronary circulation by the ischemic cells25 and acts through the stimulation of P2-receptors, which are not blocked by aminophylline,26,27 has the potential to stimulate sensory nerve endings.28

**Adenosine and Silent Ischemia**

If adenosine is, at least partially, responsible for the anginal pain, it would be logical to expect a different response to adenosine in patients with painful and silent myocardial ischemia.

In our study, patients with predominantly silent ischemia had significantly less chest pain during intravenous infusion of adenosine and tolerated significantly higher doses of this substance than those with predominantly painful ischemia. Seven patients with silent ischemia but only two with painful ischemia tolerated infusion rates of 250 μg/kg/min or greater. The doses of adenosine tolerated by patients with silent ischemia were much higher than the maximum dose tolerated by healthy volunteers in previous studies in which constant rate infusions
were used. The doses tolerated by our patients with painful ischemia are comparable with those reported by Fuller et al in healthy volunteers, but they are higher than those reported by Conradson et al. The subjects enrolled in the latter study, however, had characteristics different from our patients: they had a younger age (ranging from 23 to 40 years), and there was a higher incidence of women (three out of eight).

In our study, seven patients with silent and seven patients with painful ischemia developed electrocardiographic signs of myocardial ischemia during adenosine infusion that could interfere with the interpretation of chest pain. However, because myocardial ischemia always occurred at doses higher than that causing chest pain, its severity at the onset of ischemia, which was less in patients with silent than in those with painful ischemia, was probably entirely related to the direct algogenic effect of adenosine.

Patients with silent ischemia did have chest pain during adenosine infusion in the absence of electrocardiographic signs of myocardial ischemia but not during episodes of transient severe myocardial ischemia. These findings confirm that the pain provoked by the intravenous administration of adenosine is unlikely to be entirely cardiac in origin. Therefore, the lesser severity of adenosine-induced chest pain in patients with silent ischemia than in those with painful ischemia probably reflects a generalized, rather than a local, reduced sensitivity to the algogenic effects of adenosine. Our study confirms and expands the hypothesis that in some patients a generalized defective perception of painful stimuli can play a key role in determining silent ischemia, already proposed in previous studies on the basis of the results obtained by using various painful stimuli like cold pressor, forearm ischemia, and skin or dental pulp electric stimulation. It is worth noting that in this, as in the previous studies, despite a statistically significant difference between patients with silent and those with painful ischemia, the overlapping of results between the two groups was considerable. It would appear, therefore, that although a generalized defective perception of painful stimuli may account for silent ischemia in those patients with a low sensitivity to adenosine, other mechanisms have to be invoked to explain silent ischemia in those patients who have a response to adenosine similar to that observed in patients with painful ischemia.

Although the interpretation of the different results observed in patients with silent and painful ischemia is limited by the systemic effects of adenosine, they appear to lend support to the hypothesis that adenosine plays an important role in the production of the anginal pain, or at least, they do not contradict it. Indeed, had we found that the algogenic effects of adenosine were similar in the two populations of patients, a serious shadow would have been cast on our working hypothesis.

Conclusions

In conclusion, intracoronary adenosine administration provokes chest pain with character, location, and radiation similar to the anginal pain at doses that do not produce symptoms during intra-atrial infusion. Furthermore, aminophylline, a potent antagonist of adenosine P1 receptors, reduces both adenosine and exercise-induced chest pain. These findings suggest that the stimulation of P1 receptors by adenosine could be partially responsible for the anginal pain during myocardial ischemia. The fact that the severity of chest pain provoked by intravenous adenosine is milder in patients with silent ischemia than in those with painful ischemia, although difficult to interpret because of the systemic effects of adenosine, is in agreement with this working hypothesis.

References


Crea et al: Adenosine and Anginal Pain 171


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Role of adenosine in pathogenesis of anginal pain.
F Crea, G Pupita, A R Galassi, H el-Tamimi, J C Kaski, G Davies and A Maseri

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