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Effect of Adenosine Antagonism on Metabolically Mediated Coronary Vasodilation in Humans

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Objectives. This study was performed to assess the importance of adenosine in mediating metabolic coronary vasodilation during atrial pacing stress in humans.

Background. Numerous animal studies have examined the role of adenosine in the regulation of coronary blood flow, with inconsistent results.

Methods. The effect of the adenosine antagonist aminophylline (6 mg/kg body weight intravenously) on coronary functional hyperemia during rapid atrial pacing was determined in 12 patients. The extent of inhibition of adenosine vasodilation was assessed using graded intracoronary adenosine infusions before and after aminophylline administration in seven patients. Coronary blood flow changes were measured with a 3F intracoronary Doppler catheter.

Results. After aminophylline administration, the increase in coronary flow velocity during adenosine infusions was reduced from 84 ± 48% (mean ± SD) to 21 ± 31% above control values ($p < 0.001$) at 10 μg/min and from 130 ± 39% to 59 ± 51% above control values ($p < 0.001$) at 40 μg/min. During rapid atrial pacing under control conditions, coronary blood flow velocity increased by 26 ± 16%. The flow increment during paced tachycardia after aminophylline (23 ± 10%) was unchanged from the control value, despite substantial antagonism of adenosine coronary dilation by aminophylline.

Conclusions. These data suggest that adenosine does not play an important role in the regulation of coronary blood flow in response to rapid atrial pacing in humans.

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Although coronary blood flow is closely controlled to meet myocardial metabolic demands under normal conditions, the mechanism, or mechanisms, responsible for metabolic coronary vasoregulation remains uncertain (1). Adenosine has been widely investigated as a potential regulator of coronary flow. Theophylline and other methylxanthines are known to antagonize adenosine-induced vasodilation in the coronary circulation of animals (2,3) and in the human forearm (4). Numerous animal studies have examined coronary flow responses after adenosine antagonism with methylxanthines or destruction of adenosine by adenosine deaminase, with inconsistent results. Some studies demonstrate that adenosine plays a significant role in regulation of coronary flow during reactive hyperemia (5,6), pacing-induced hyperemia (7,8), inotropic stimulation with dobutamine (9) and behaviorally induced coronary flow increases (10). In contrast, other studies indicate no change in basal myocardial blood flow (11,12), metabolic regulation (13), coronary vasodilation during exercise (14) and coronary autoregulation (15) after pharmacologic reduction of adenosine activity.

Few data are available with regard to the role of adenosine in coronary vasoregulation in humans. Also, the efficacy of aminophylline in inhibiting adenosine-induced coronary vasodilation in humans is unknown. Accordingly, the purpose of this study was to assess the importance of adenosine in mediating the coronary vasodilation that occurs with atrial pacing stress. Aminophylline was used to produce pharmacologic antagonism of adenosine-induced coronary vasodilation, and the extent of this effect was assessed using graded intracoronary adenosine infusions before and after aminophylline.

Methods

Patients undergoing elective coronary arteriography for the evaluation of chest pain were considered for study if angiography revealed a nonstenotic coronary artery that was anatomically suitable for placement of a coronary Doppler catheter and there was no evidence of left ventricular dysfunction. The research protocol was approved by the University of Iowa Institutional Review Board, and written informed consent was obtained from each patient before cardiac catheterization.

Coronary flow velocity measurement. Changes in coronary blood flow were assessed using intracoronary Doppler catheter measurement of coronary flow velocity according to

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the method of Wilson et al. (16). A 7F or 8F coronary angioplasty guide catheter was positioned at the coronary ostium, and a 0.014-in. coronary angioplasty guide wire was advanced into the coronary artery to be studied. A 3F 20-MHz coronary Doppler catheter with an infusion lumen at its tip (NuMed Inc.) was advanced over the guide wire into the proximal vessel and positioned to obtain a high quality phasic signal of blood flow velocity. The pulsed Doppler meter (Bioengineering Department, University of Iowa Hospitals and Clinics) was range gated to maximize the amplitude of the mean coronary blood flow velocity signal. Phasic and mean coronary blood flow velocity (kHz shift), mean arterial pressure (mm Hg) obtained from the guiding catheter, heart rate (beats/min) and surface electrocardiogram were continuously recorded on a multichannel recorder. Alterations in coronary blood flow velocity were expressed as percent change from the rest value. An index of change in coronary vascular resistance was also calculated as the quotient of mean aortic pressure (mm Hg)/blood flow velocity (kHz shift) after an intervention and mean aortic pressure/blood flow velocity at control conditions.

Experimental protocol. Subjects were brought to the cardiac catheterization laboratory in a fasting state. Prescribed medications were continued on the day of the research study. Diazepam (5–10 mg intravenously or orally) was given for sedation. No patient received atropine premedication. The study was performed during intravenous infusion of nitroglycerin at 8 μg/min to prevent catheter-induced coronary artery spasm and to avoid changes in coronary artery caliber that would influence the relation between changes in coronary flow velocity and coronary blood flow. No patient received medications containing methylxanthines or dipyridamole. Beverages containing methylxanthines were withheld for at least 12 h before the procedure.

Effect of aminophylline on adenosine-induced coronary vasodilation. The effect of acute administration of intravenous aminophylline on the coronary vasodilator actions of intracoronary adenosine was studied in two female and five male patients with a mean (±SD) age of 58 ± 12 years. Coronary flow velocity was measured in the left anterior descending coronary artery in all patients. Single-vessel coronary artery disease (diameter stenosis >50%) was present in one patient, and minor lumen irregularities were seen in three patients. Medications included calcium channel blocking agents in four patients. No patients were receiving beta-adrenergic blocking agents.

A 6F bipolar pacemaker was positioned at the high right atrium, and atrial pacing was performed at 15 beats/min above the rest rate throughout the protocol to prevent changes in coronary flow related to aminophylline-induced increases in heart rate. Adenosine (Adenocard, Fujisawa Pharmaceutical Company) in normal saline solution was infused through the infusion lumen of the intracoronary Doppler catheter at 10 and 40 μg/min for 2 min each. All adenosine infusions were performed at a volume infusion rate of 3 ml/min with a piston pump, and hemodynamic variables were allowed to return to baseline between infusions. Aminophylline (Abbott Laboratories) was then infused intravenously at the dose of 6 mg/kg over 10 min. The adenosine infusions were repeated, and blood was drawn for measurement of serum theophylline level 5 to 10 min after completion of the aminophylline infusion.

Effect of aminophylline on metabolically mediated coronary vasodilation. The effect of adenosine antagonism with aminophylline on the coronary blood flow response to rapid atrial pacing stress was assessed in 15 patients. In three patients, marked changes in the mean flow velocity signal were observed after aminophylline administration, suggesting movement of the Doppler catheter during the protocol; these studies were discarded. In the remaining six female and six male patients (mean age 54 ± 11 years), single-vessel coronary artery disease (diameter stenosis >50%) was present in one, and minor lumen irregularities were seen in five. Coronary flow velocity was measured in the left anterior descending coronary artery in nine patients, in the left circumflex coronary artery in two patients and in the left main coronary artery in one patient. Medications taken included beta-blockers in one patient and calcium channel blockers in six patients. The intracoronary adenosine protocol was also performed in two of these patients.

A 6F bipolar pacemaker was positioned at the high right atrium, and atrial pacing was performed at 15 beats/min above the rest sinus rate to prevent changes in coronary flow related to aminophylline-induced increases in heart rate. Myocardial metabolic demands were increased by gradually increasing the heart rate over 2 min with atrial pacing to the highest rate attainable without atrioventricular block; this rate was maintained for 2 min. After a 5-min recovery period, aminophylline was infused intravenously at the dose of 6 mg/kg body weight over 10 min. The rapid atrial pacing protocol was repeated, and blood was drawn for measurement of the serum theophylline level 5 to 10 min after completion of the aminophylline infusion.

Data analysis. Group data in the text are presented as mean value ± SD. Changes in study variables were compared using the Student *t* test or two-way analysis of variance for repeated measures, with assessment of intergroup differences using the Scheffé F test. Differences were considered significant at the $p \leq 0.05$ level.

Results

Effect of aminophylline on adenosine-induced coronary vasodilation. *Systemic hemodynamic status.* Throughout the study heart rate was maintained at 89 ± 10 beats/min by atrial pacing. Mean arterial pressure averaged 109 ± 11 mm Hg under control conditions and was unchanged during the intracoronary adenosine infusions and the intravenous aminophylline infusion (Table 1). After aminophylline infusion, the serum theophylline level averaged 10.3 ± 1.9 ng/ml.

Table 1. Effect of Intravenous Aminophylline and Intracoronary Adenosine Infusions on Mean Arterial Pressure

	Control	Adenosine (10 μg/min)	Control 2	Adenosine (40 μg/min)
Rest MAP (mm Hg)	109 ± 11	110 ± 10	112 ± 7	113 ± 8
MAP after aminophylline infusion (mm Hg)	108 ± 7	109 ± 6	108 ± 7	107 ± 7

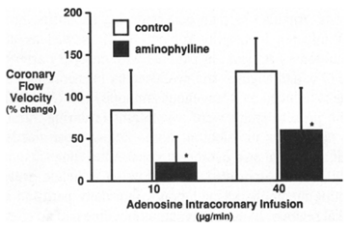
Data are group mean value ± SD. MAP = mean arterial pressure.

Coronary blood flow velocity. Intracoronary infusion of adenosine at 10 μg/min before aminophylline administration resulted in an 84 ± 48% increase in coronary blood flow velocity (Fig. 1). Adenosine infusion at 40 μg/min resulted in an increase in coronary flow velocity of 130 ± 39%. The coronary blood flow response to adenosine was markedly blunted by aminophylline. After aminophylline administration, the adenosine-induced increase in coronary blood flow was attenuated to 21 ± 31% ($p < 0.001$ vs. control values) and 59 ± 51% ($p < 0.001$ vs. control values) for infusions at 10 and 40 μg/min, respectively (Fig. 1).

Coronary vascular resistance index. Intracoronary infusion of adenosine under control conditions resulted in a decrease in coronary vascular resistance index to 0.57 ± 0.11 during the 10-μg/min infusion and 0.45 ± 0.06 during the 40-μg/min infusion. After aminophylline administration, the adenosine-induced decrease in coronary vascular resistance index was attenuated to 0.86 ± 0.15 ($p < 0.01$ vs. control values) and 0.67 ± 0.17 ($p < 0.01$ vs. control values) for infusions at 10 and 40 μg/min, respectively. Thus, the coronary vasodilator effect of intracoronary adenosine infusions producing submaximal coronary hyperemia was substantially reduced by aminophylline.

Effect of aminophylline on metabolically mediated coronary vasodilation. *Systemic hemodynamic status.* Control and peak paced heart rates (78 ± 8 and 123 ± 9 beats/min, respectively) were identical before and after aminophylline administration. Aminophylline infusion resulted in a decrease in mean arterial pressure from 102 ± 12 to 94 ± 9 mm Hg ($p < 0.05$) (Fig. 2). During paced tachycardia, mean arterial pressure was unchanged from the respective control values (Fig. 2). After aminophylline infusion, the serum theophylline level averaged 12.1 ± 3.0 ng/ml.

Figure 1. Effect of intravenous aminophylline on the coronary blood flow velocity response to intracoronary infusions of adenosine. Data are group mean value ± SD. *p < 0.001 versus control conditions.



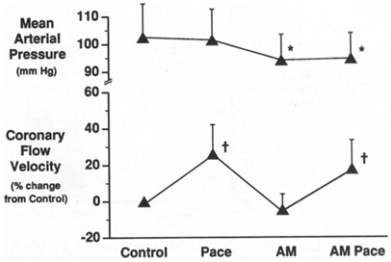


Figure 2. Effect of intravenous aminophylline (AM) on mean arterial pressure and coronary blood flow velocity during increases in myocardial metabolic demand resulting from paced tachycardia (PACE). During control periods, heart rate was maintained at 15 beats/min above the initial rest rate. Coronary blood flow velocity is expressed as percent change from the initial control flow velocity. Data are group mean value ± SD. *p < 0.05 versus control conditions and rapid atrial pacing. †p < 0.01 versus control conditions and after aminophylline.

Coronary blood flow velocity. Coronary blood flow velocity increased by 26 ± 16% during paced tachycardia before aminophylline administration ($p < 0.01$) (Fig. 2). Control flow velocity was not significantly affected by aminophylline (−5 ± 9% change from the initial control flow velocity). During paced tachycardia after aminophylline administration, coronary flow velocity increased by 23 ± 10% over the aminophylline control values ($p < 0.01$), which was similar to that observed before aminophylline administration. Thus, the increase in flow velocity during pacing tachycardia was not attenuated by adenosine antagonism with aminophylline.

Coronary vascular resistance index. Aminophylline had no effect on the coronary vascular resistance index during paced tachycardia (0.80 ± 0.10 before, 0.82 ± 0.06 after aminophylline) (Fig. 3).

Discussion

This study demonstrates that coronary blood flow responses to intracoronary infusions of adenosine, producing submaximal vasodilation, are substantially reduced by administration of intravenous aminophylline in humans. This effect is consistent with antagonism by theophylline of adenosine receptors that mediate coronary vasodilation and was observed with a dose of aminophylline commonly used in clinical practice. Although aminophylline markedly attenuated the coronary vasodilator effect of adenosine, it did not influence coronary vasodilation related to increased myocar-

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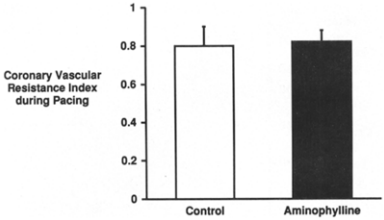

Figure 3. Effect of intravenous aminophylline on the coronary vascular resistance index during paced tachycardia. Data are group mean value ± SD.

dial metabolic demands produced by rapid atrial pacing stress. These data suggest that adenosine does not play an important role in the regulation of coronary blood flow in response to atrial pacing in humans.

Effect of aminophylline on adenosine coronary vasodilation. Methylxanthines are known to selectively inhibit adenosine-induced vasodilation in the coronary circulation of animals (2,3). In humans, aminophylline and caffeine attenuate adenosine-induced increases in forearm blood flow (4,17) and systemic hemodynamic changes (18,19). The effect of methylxanthines on adenosine-induced coronary vasodilation in humans has been assessed indirectly by demonstration of the elimination of dipyridamole-induced coronary sinus flow increases by aminophylline (20) and abnormalities in myocardial perfusion scans by theophylline (21). The present study is the first to directly demonstrate attenuation of the coronary vasodilator effect of adenosine by methylxanthines in humans.

The adenosine hypothesis. The close association between myocardial oxygen demand and perfusion suggests that products of myocardial metabolism act as messengers in the control of coronary blood flow. Although several potential chemical regulators have been proposed and studied, the mechanisms of metabolic coronary vasoregulation remain uncertain (1). A role for adenosine in the control of coronary flow was suggested by Berne (22), and studies in animals demonstrate that adenosine fulfills several criteria for this purpose. Adenosine elicits coronary vasodilation at very low concentrations (23). It is released from the heart during inotropic stimulation (24), exercise (25) and conditions in which myocardial oxygen supply is insufficient to meet demands, such as hypoxia (22). However, studies using pharmacologic reduction in adenosine activity to attenuate coronary vasomotor responses have been inconclusive (26). A number of studies support the "adenosine hypothesis." In anesthetized dogs, intravenous aminophylline resulted in a reduction in the increment in coronary flow during atrial pacing and an increase in the transcardiac arteriovenous oxygen difference (7,8). Coronary vasodilation in response to inotropic stimulation with dobutamine was blunted by 8-*p*-sulfophenyltheophylline in anesthetized dogs (9). Reactive hyperemia after brief coronary occlusion was reduced by intracoronary adenosine deaminase or theophylline in anesthetized dogs (27) and by intravenous aminophylline in conscious dogs (6). Increases in coronary blood flow related to aversive stress were attenuated by intravenous aminophylline in conscious dogs (10).

The results of other studies appear to be inconsistent with the adenosine hypothesis. Intracoronary adenosine deaminase produced minor or no changes in basal myocardial blood flow in sedated pigs and anesthetized dogs (11,12). No change in myocardial reactive hyperemia was observed after intravenous aminophylline (28). Aminophylline did not reduce functional hyperemia resulting from intracoronary norepinephrine infusion in anesthetized dogs (29), and neither the potent adenosine antagonist 8-phenyltheophylline nor adenosine deaminase reduced hyperemia in exercising dogs (14). Coronary autoregulation was unaffected by intracoronary adenosine deaminase (15) and by topical adenosine deaminase and 8-phenyltheophylline (30) in anesthetized dogs. It is likely that different mechanisms are involved in coronary blood flow regulation during the multitude of flow perturbations used in studies of the adenosine hypothesis, and some mechanisms may not be pertinent to the regulation of coronary blood flow in response to increased oxygen demand.

Information with regard to the role of adenosine in the regulation of coronary blood flow in humans is limited. Edlund et al. (20) assessed the effect of intravenous aminophylline on coronary hemodynamic status during supine cycling in normal subjects. After aminophylline administration, coronary vascular resistance and myocardial oxygen extraction during exercise were increased compared with control values, although coronary sinus thermodilution flow was not changed significantly.

Adenosine and disorders of the human coronary circulation. Several studies have reported that aminophylline possesses significant antianginal activity in patients with obstructive coronary artery disease (31,32) and syndrome X (33). This antianginal effect has been attributed to adenosine receptor blockade, with a resultant decrease in adenosine-mediated ischemic pain, or to improvement in coronary blood flow to ischemic regions. A role for adenosine in the development of anginal pain is suggested by several observations. Angina-like pain occurs during adenosine intravenous infusion in healthy subjects (34), as well as during intracoronary infusion in patients with coronary artery disease (35), and anginal pain produced by intracoronary adenosine is reduced by intravenous aminophylline (35). Patients in the present study were asymptomatic during intracoronary adenosine infusions at doses below those needed to produce anginal pain in other studies. Adenosine antagonism could lead to improved blood flow to ischemic areas by blunting metabolic vasodilation to normally perfused myocardial regions. In our study, aminophylline had no effect on

metabolic vasodilation to a nonischemic vascular bed. However, we cannot exclude the possibility that adenosine antagonism caused favorable transmural redistribution of coronary blood flow that could not be detected by Doppler catheter assessment of regional flow.

Limitations. In the present study, changes in coronary blood flow were assessed using intracoronary Doppler catheter measurements of coronary flow velocity rather than absolute measurements of coronary blood flow. However, extensive animal studies validating the coronary Doppler catheter design used in this study have been published (16).

The records of three patients were discarded because of marked alterations in coronary flow velocity (increased in two patients, decreased in one patient), suggesting movement of the Doppler catheter within the coronary artery. The results of this study are unchanged by inclusion of these patients. If all 15 patients had been analyzed, the increase in coronary flow velocity with paced tachycardia would have been 26 ± 14% under control conditions and 24 ± 10% after aminophylline administration (p = NS).

A nitroglycerin low dose (8 μg/min) intravenous infusion was used during coronary blood flow velocity measurement to prevent catheter-induced coronary artery spasm and to avoid changes in coronary artery caliber that would influence the relation between changes in coronary flow velocity and coronary blood flow. It is possible that the nitroglycerin infusion influenced the results of the study. However, our laboratory has demonstrated that nitroglycerin in much larger doses has minimal sustained effects on coronary blood flow (36). Furthermore, because the nitroglycerin infusion continued throughout the study, any effects on coronary blood flow responses would be present both at control conditions and after aminophylline infusion. The antianginal medications that some patients received might have influenced the initial hemodynamic response to atrial pacing. However, it seems unlikely that these medications altered the effect of adenosine antagonism on the coronary flow response to atrial pacing, as they have no known activity at adenosine receptors, and medication effects were present both at control conditions and after aminophylline infusion.

Although flow responses were measured in a nonstenotic coronary artery in all patients, it is uncertain whether the interrogated vessel was physiologically normal. It is possible that abnormalities in endothelial function were present in our study group, given the age of the patients and the presence of risk factors for coronary artery disease and angiographically evident coronary irregularities in many of the patients. Mechanisms of control of coronary blood flow during increased myocardial oxygen demand may differ in normal patients and in those with nonobstructive coronary atherosclerosis.

Intravenous aminophylline markedly attenuated the coronary vasodilator effect of exogenously administered adenosine but did not influence pacing-induced functional hyperemia in this study. Although these findings provide evidence against the adenosine hypothesis, other explanations are plausible. Several potential limitations relate to the use of aminophylline. In the present study, aminophylline was demonstrated to attenuate adenosine-induced coronary flow increases that were greater in magnitude than the vasodilation occurring with pacing. Because aminophylline is thought to be a competitive antagonist of adenosine receptors, equivalent attenuation of smaller degrees of vasodilation due to adenosine would be expected, but this was not demonstrated specifically in this study. It is possible that the adenosine receptors on vascular smooth muscle, rather than endothelial cell adenosine receptors, are important in coronary blood flow regulation. Whether aminophylline, which is a relatively weak antagonist of adenosine-induced vasodilation compared with agents available for use in animal studies, produces blockade of vascular smooth muscle adenosine receptors in humans is uncertain. Adenosine production during increased oxygen demand may be enhanced by adenosine antagonists (37). Increased adenosine production may largely overcome competitive receptor blockade and maintain functional hyperemia near control levels.

It is possible that several mediators may interact in the regulation of coronary blood flow, and other mediators may compensate for loss of adenosine activity to maintain physiologic responses.

Finally, the pacing protocol used in this study produced a modest increase in coronary blood flow. This small initial response makes demonstration of a reduction in the response by an intervention more difficult. Adenosine may play a greater role in metabolic coronary vasodilation at higher levels of myocardial oxygen demand than were achieved in this study.

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