JACC Vol. 8, No. 5
November 1986:1232–4

Mechanism of Atropine-Resistant Atrioventricular Block During Inferior Myocardial Infarction: Possible Role of Adenosine

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Mechanisms responsible for atrioventricular (AV) block during acute inferior myocardial infarction are only partially understood. Increased parasympathetic tone is the factor usually postulated; however, persistence of AV block after atropine administration is frequently observed. Adenosine, an endogenous ischemic metabolite, has well established depressant effects on AV node conduction. In this report, an episode of atropine-resistant AV block was reversed by aminophylline, a competitive adenosine antagonist, in a patient with an acute inferior myocardial infarction. This observation suggests a role for adenosine in the mediation of ischemia-induced AV node block.

(J Am Coll Cardiol 1986;8:1232–4)

Second and third degree atrioventricular (AV) block has been observed in 10 to 33% of patients with acute inferior infarctions (1–4). These conduction abnormalities are associated with a normal QRS complex in conducted or junctional escape beats, suggesting that the site of block is the AV node (5). The genesis of ischemia-induced AV node block has been attributed to a transient increase in parasympathetic activity (6–8). However, atropine is often unsuccessful in abolishing heart block during acute inferior infarction (1,7).

An alternative mechanism to account for ischemia-induced AV node block is the production of ischemic metabolites with negative dromotropic effects (9). Adenosine, an endogenous metabolite that accumulates in the interstitium during hypoxia and ischemia (10–12), mediates the depressant effects of hypoxia and ischemia on AV node conduction in experimental preparations (13–15). Recently, adenosine has also been shown to depress AV node conduction in humans (16,17). The negative dromotropic effect of adenosine is mediated through an extracellular receptor site (18). For example, AV node block, induced by occlusion of the canine AV node artery and potentiated by inhibition of extracellular adenosine uptake, can be completely reversed through competitive antagonism of the adenosine receptor (13).

In this report, we demonstrate the reversal of atropine-resistant AV node block during inferior infarction with aminophylline, a competitive adenosine antagonist. This observation suggests a role for adenosine in the mediation of ischemia-induced AV node block in humans.

Case Report

A 62 year old black woman with a history of insulin-dependent diabetes mellitus and well controlled hypertension was admitted 3 days after the onset of light-headedness, weakness and fatigue unaccompanied by chest pain, nausea, flushing or diaphoresis. An electrocardiogram at the time of admission revealed a new Q wave in lead III, ST elevation in leads III and aVF and complete heart block (narrow QRS complex) with a junctional escape rate of 50 beats/min. Metoprolol, 50 mg orally four times a day, had been discontinued by the patient 3 days before admission. Serum creatine kinase rose to 472 U/liter (normal 0 to 204 U/liter) with an MB fraction of 6%. On day 1, atropine, 2 mg intravenously was administered without any effect on AV node conduction.

Response to aminophylline. On day 3, the patient continued to exhibit third degree and 2:1 second degree AV

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Manuscript received February 10, 1986; revised manuscript received April 1, 1986, accepted April 4, 1986.

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0735-1097/86/$3.50

node block. Aminophylline, 400 mg intravenously administered over 30 minutes, led to complete resolution of AV block (that is, 1:1 AV conduction) (Fig. 1). A serum theophylline level obtained at the resolution of AV block was 14.3 μg/ml. High grade AV block, however, recurred 10 hours after its initial resolution with a theophylline level of 8.5 μg/ml.

By day 5, high grade AV node block had continued unabated. Atropine, 2 mg intravenously, again failed to resolve AV block (Fig. 2). Over the course of day 6, the level of AV block progressively diminished (that is, higher ratios of Wenckebach block) with complete spontaneous resolution by day 7.

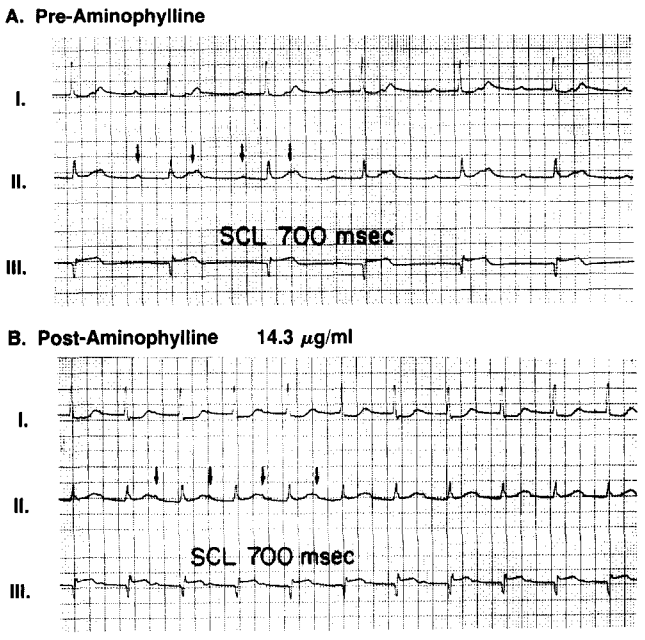
Discussion

The findings in this study demonstrate that aminophylline, a competitive adenosine antagonist, can reverse atropine-resistant AV block that accompanies acute inferior infarction. Several observations support the hypothesis that endogenous adenosine rather than enhanced parasympathetic tone mediates AV block in this setting. Signs of excessive parasympathetic activity, such as nausea, flushing and diaphoresis, were absent at the time of AV block. Most importantly, atropine failed to reverse AV block, strongly suggesting that the block was not parasympathetically mediated.

Pharmacologic actions of aminophylline. Aminophylline is a theophylline derivative with multiple pharmacologic properties and potential mechanisms of action. It competitively antagonizes the negative dromotropic action of adenosine by blocking extracellular adenosine receptors (18). In addition, it is known to inhibit phosphodiesterase activity and the release of endogenous catecholamines from sympathetic nerve terminals as well as the adrenal medulla (19–21). Thus, a sympathomimetic action of aminophylline might also contribute to the resolution of heart block. Several present and prior observations, however, suggest that the primary action of aminophylline is adenosine antagonism rather than sympathomimetic potentiation. First, in the presence of aminophylline, the sinus cycle length did not shorten at a time when AV conduction improved, suggesting the absence of catecholamine effect on the sinus node. Second, the serum concentration of theophylline associated with the resolution of AV block (14.3 μg/ml or $7.7 \times 10^{-5} M$) is below the threshold concentration required to release catecholamines or increase tissue cyclic adenosine monophosphate (cAMP) content (22). Within the concentration range observed in our patient, Sollevi et al. (23) found that plasma catecholamine levels were not changed by theophylline. Finally, aminophylline-induced reversal of the effects of exogenous adenosine, hypoxia and ischemia on AV conduction has been shown to occur in the presence of beta-adrenergic blockade (13,14,16,18).

Mechanisms of bradyarrhythmias. In addition to experimental data, the observed electrophysiologic effects of adenosine in humans are consistent with adenosine mediation of ischemia-induced intranodal block. Intravenously administered adenosine produces an intranodal block preceded by progressive prolongation of the AH interval (16,17). His bundle recordings during acute inferior wall ischemia reveal strikingly similar findings (24).

Figure 1. Reversal of atrioventricular (AV) block by aminophylline. **A,** 2:1 AV block. **B,** Restoration of normal AV conduction after aminophylline. **Arrows** denote P waves. Note that there was a 0.5 mm increase in ST segment elevation in **B** compared with **A** which was not associated with symptoms of myocardial ischemia. SCL = sinus cycle length.



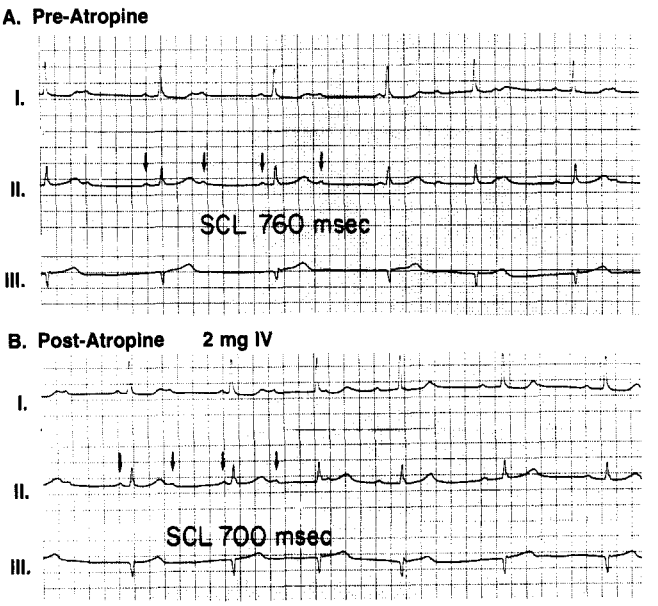


Figure 2. Failure of atropine to reverse atrioventricular (AV) block. **A,** 2:1 AV block. **B,** 2:1 AV block persists after atropine administration. **Arrows** denote P waves. SCL = sinus cycle length.

Before the present adenosine hypothesis, the origin of intranodal heart block and sinus bradycardia in acute inferior myocardial infarction was attributed to a transient increase in parasympathetic overactivity (6–8). In the first few hours after infarction, symptoms associated with enhanced parasympathetic activity such as nausea, vomiting and diaphoresis are often observed. AV block under these conditions may be mediated through activation of intramyocardial vagal afferents on the diaphragmatic wall of the heart with reflex discharge through vagal fibers around the sinoatrial and AV nodes (25,26). In the early phase of infarction, normal AV conduction can usually be restored by atropine administration, supporting a role for parasympathetic overactivity (6). However, in our patient, and in almost all patients with AV node block more than 6 hours after the onset of symptoms, atropine is ineffective, strongly suggesting an alternative mechanism (1,7).

Blood flow to the AV node is usually supplied by the right coronary artery (4). Postmortem histologic examination of the AV node in patients demonstrating AV node block after right coronary occlusion and inferior infarction has revealed minimal if any damage (9). This observation is consistent with the hypothesis that a short-term accumulation of an endogenous metabolite, such as adenosine, might mediate ischemia-induced AV node block (9).

A limitation of this study was that invasive His bundle recordings were not obtained to specifically exclude the presence of intra-Hisian block.

Conclusions. The data in our case report, in conjunction with previous experimental observations, support a role for adenosine independent of enhanced parasympathetic tone in the mediation of ischemia-induced AV node block. Moreover, the development of more potent and specific adenosine antagonists would further elucidate the extent to which adenosine underlies the genesis of these bradyarrhythmias. Such antagonists may prove to be the treatment of choice for symptomatic ischemia-induced bradyarrhythmias. Although well tolerated in our patient, aminophylline, like any agent that might increase chronotropic response, can potentially excerbate myocardial ischemia and therefore should be administered with considerable caution.

We express our gratitude to Elizabeth Howk for the preparation of the manuscript.

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