CASE REPORT

Myocardial infarction related atrial fibrillation: role of endogenous adenosine

Barry D Bertolet, James A Hill, Richard A Kerensky, Luiz Belardinelli

Abstract

Exogenous administration of adenosine induces atrial fibrillation in up to 7·0% of patients. Animal studies affirm endogenous adenosine released in response to tissue hypoxia may play a mechanistic role in arrhythmias associated with myocardial ischaemia or hypoxia. Therefore, atrial fibrillation occurring early after the acute phase of myocardial infarction involving atrial tissue may be secondary to an excessive accumulation of adenosine that leads to a shortening of atrial refractory period. Early in the course of acute inferior myocardial infarction, two patients (males aged 45 and 68) suffered new onset sustained atrial fibrillation that was abrupt in onset and complicated their clinical management. They were administered 250 mg theophylline as a slow intravenous injection at a rate of 100 mg/min or until conversion to normal sinus rhythm occurred. Both patients converted to normal sinus rhythm within five minutes of the administration of theophylline. In up to 52 hours of continuous ECG monitoring after the theophylline administration the atrial fibrillation did not recur. Neither patient experienced any adverse outcome from theophylline administration. These observations are the first reported in humans or laboratory animals to suggest that atrial fibrillation, presumably due to elevated interstitial atrial concentration of adenosine caused by myocardial ischaemia, can be terminated with an adenosine receptor antagonist. However, the hypothesis that excessive accumulation of endogenous adenosine in atrial tissue may induce atrial fibrillation is well substantiated by other investigators. Thus, A_1 adenosine receptor antagonists may prove to be valuable in the management of ischaemia related atrial fibrillation.

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Keywords: adenosine; atrial fibrillation; theophylline; aminophylline; myocardial infarction

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It is now well accepted that intravenous administration of adenosine in both laboratory animals,[1] and humans,[2 3] may induce atrial fibrillation. Clinical trials evaluating the efficacy of intravenous bolus injections of adenosine for the termination of supraventricular tachycardia, and during continuous intravenous infusion of adenosine for cardiac stress testing, report the induction of atrial fibrillation in 1·5–7·0% of patients.[4–6] The cellular basis for atrial fibrillation and flutter induced by adenosine is the shortening of the atrial action potential and refractory period,[1] both resulting from activation of the inwardly rectifying K^+ current I_{KADO}.[7] Moreover, there are substantial data from studies with in vitro and in situ heart preparations[8 9] affirming that endogenous adenosine released in response to tissue hypoxia may play a mechanistic role in arrhythmias associated with myocardial ischaemia and hypoxia. Based on these observations, it is reasonable to postulate that atrial fibrillation occurring early after the acute phase of myocardial infarction involving atrial tissue is secondary to an excessive accumulation of adenosine that leads to a shortening of atrial refractory period predisposing to atrial fibrillation. To test this hypothesis, we administered 250 mg of theophylline, an adenosine receptor antagonist, to two patients with new onset, sustained atrial fibrillation early in the course of acute inferior myocardial infarction.

Case reports

Two men, aged 45 and 68, who were admitted to the Gainesville Veterans Affairs Hospital in Florida, USA with the diagnosis of acute inferior myocardial infarction developed sustained atrial fibrillation within four hours of admission. The initial ECG rhythm in both patients was normal sinus rhythm, and neither had a previous history of cardiac dysrhythmias. Both patients were treated with oral aspirin (325 mg), intravenous heparin, and nitroglycerin, and one received thrombolytic therapy with recombinant tissue plasminogen activator. In both patients, the onset of atrial fibrillation was abrupt and complicated their clinical management. The first patient, despite treat-

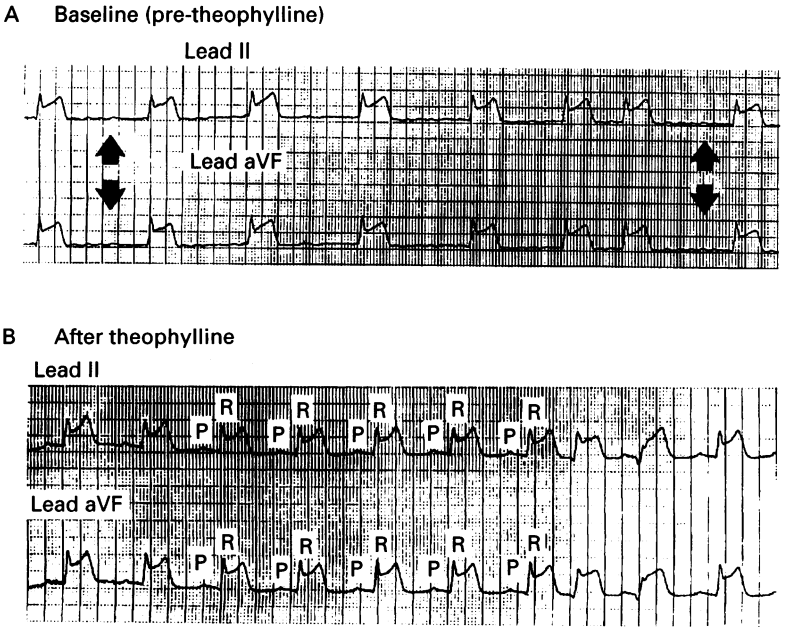

Figure 1 Conversion of atrial fibrillation to normal sinus rhythm by theophylline. (A) ECG recording from a patient who developed atrial fibrillation and slow ventricular response associated with systemic hypotension following an acute inferior wall myocardial infarction. The arrows highlight the coarse fibrillatory waves. (B) After intravenous administration of 200 mg theophylline, the patient converted to normal sinus rhythm. After conversion, the PR segment is elevated compared with the TP interval suggesting the presence of atrial infarction.

ment with intravenous digoxin (0·5 mg), esmolol (100 μg/kg/min), and diltiazem (10 mg/h) remained in atrial fibrillation with a rapid ventricular response (110–170 beats/min). The second patient had a slow ventricular response (45 beats/min) associated with systemic hypotension (80/50 mm Hg). Each patient received 250 mg theophylline as a slow intravenous injection at a rate of 100 mg/min, or until conversion to normal sinus rhythm occurred. Both patients converted to normal sinus rhythm within five minutes of the administration of theophylline. Figure 1A illustrates the ECG recording from patient 2 who converted to normal sinus rhythm (fig 1B) within two minutes of the administration of 200 mg of theophylline, and remained in sinus rhythm with 1:1 AV conduction during 52 hours of observation. Coincident with the return to normal sinus rhythm, blood pressure rose to 110/65 mm Hg. Moreover, after conversion, the PR segment was elevated compared with the TP interval suggesting the presence of atrial infarction.

Discussion

These observations are the first, to our knowledge, in humans or laboratory animals, to suggest that atrial fibrillation (presumably resulting from elevated interstitial atrial concentration of adenosine caused by myocardial

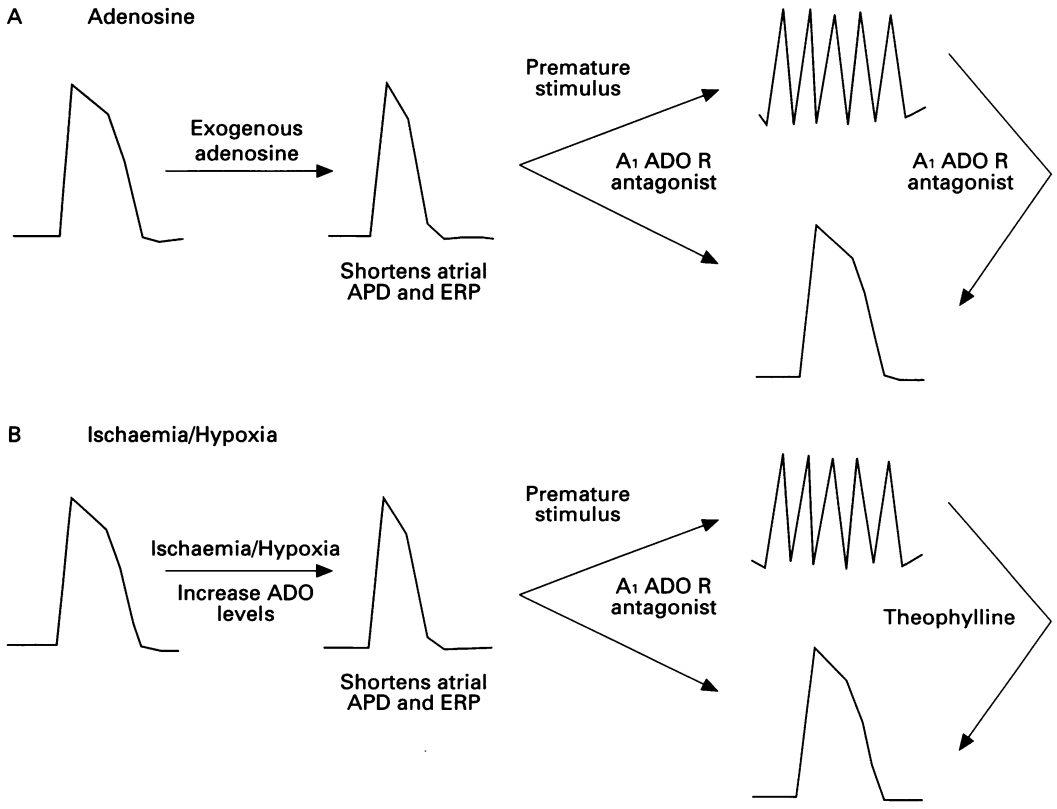

Figure 2 Changes in atrial action potential duration (APD) and effective refractory period (ERP) in response to adenosine and ischaemia/hypoxia. (A) Illustration of the shortening of atrial APD and ERP by exogenous adenosine.[12] If an atrial premature stimulus or contraction occurs when the ERP is short, atrial flutter or fibrillation may occur,[4-6 13] which can be converted to normal sinus rhythm by an A_1 adenosine receptor antagonist (A_1 ADO R antagonist).[13] Likewise, the shortening of the atrial APD caused by adenosine can be reversed by A_1 ADO R antagonists.[13] (B) Illustration of the effect of ischaemia or hypoxia, both known to increase myocardial interstitial adenosine levels,[10] to shorten the atrial APD and ERP.[11 12] Hypoxia induced shortening of the atrial APD can be reversed by an A_1 ADO R antagonist.[11 12] If an atrial premature stimulus or contraction occurs when the ERP is short, atrial flutter or fibrillation may occur. Theophylline and other A_1 ADO R antagonists may be effective in converting these atrial dysrhythmias to normal sinus rhythm.

ischaemia) can be terminated with an adenosine receptor antagonist. This interpretation and our hypothesis of the aetiological role of endogenous adenosine released from ischaemic/hypoxic atrial tissue in predisposing atrial fibrillation and atrial flutter is illustrated in figure 2. This hypothesis is consistent with the following observations.

- Atrial ischaemia has been shown to cause a threefold increase in tissue adenosine levels.[10]
- The rise in atrial adenosine concentration is expected to shorten the atrial action potential, thereby decreasing the atrial refractory period and facilitating the induction of atrial flutter or fibrillation.[1-3]
- In isolated atria, hypoxia has been shown to shorten the atrial action potential, which could be reversed with aminophylline.[11] Moreover, in in situ anaesthetised guinea pig heart preparations, shortening of the atrial action potential caused by global myocardial hypoxia can be prevented with an A_1 adenosine receptor antagonist.[12]
- Lerman *et al* observed the induction of atrial flutter concomitant with the administration of dipyridamole, an adenosine uptake blocker known to increase myocardial levels of endogenous adenosine.[13] This atrial flutter induced by dipyridamole was converted to normal sinus rhythm following the administration of intravenous aminophylline.
- Theophylline, the adenosine antagonist used in this study, is known to antagonise in humans the bradycardia and atrioventricular nodal blockade caused by exogenous adenosine,[14] as well as bradyarrhythmias associated with conditions of increased formation of myocardial adenosine such as acute myocardial infarction,[15] and cardiac transplant rejection.[16]

These studies support our hypothesis that under conditions that lead to an excessive accumulation of endogenous adenosine in atrial tissue, atrial fibrillation may be induced. Thus, A_1 adenosine receptor antagonists that are more potent, specific, and receptor subtype selective than theophylline may prove to be valuable in short and long term management of tachyarrhythmias as well as bradyarrhythmias associated with conditions of excess endogenous adenosine production such as myocardial ischaemia, sick sinus syndrome, cardiac arrest, cardiac transplant rejection, and following cardiac bypass or aortic cross-clamp.

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