



Adenosine: A Cause of Angina

Jadhav Ajit^{1*} and Hardas Suhas²

¹Department of Cardiology, Baroda Heart Institute and Research Centre, India

²Department of Cardiology, Poona Hospital and Research Centre, India

Abstract

Adenosine has a critical role in the non-invasive and invasive assessment of myocardial perfusion as well as having therapeutic efficacy in patients with no-reflow. It has an important role in both the diagnosis and treatment of a range of arrhythmias. Although side effects are frequently reported, they are seldom troublesome and due to the short half-life of the drug, are transient. Commonly reported side effects included flushing, dyspnoea, chest pain, gastrointestinal discomfort, nausea, vomiting, headache, AV block and arrhythmias. We report one of our patient while undergoing fractional flow reserve measurement for functional significance of the moderate epicardial coronary luminal narrowing (70%) experienced similar angina what he used to experience while exertion. In Such clinical scenario, revascularization Vs deferral of such lesions can still be safely considered or not.

Keywords: Adenosine; Angina; FFR

Introduction

Adenosine is an extracellular signaling molecule with essential functions in human physiology. Due to the widespread expression of adenosine receptors, it has many effects across different organ systems. It has been extensively studied for both its therapeutic and diagnostic abilities due to its prominent role in cardiovascular system.

An important target of adenosine is the coronary microcirculation where adenosine acts as a prominent vasodilator with many of the beneficial effects of adenosine reflected in its capacity to affect the micro vessels and acts as a coronary hyperemic agent during vasodilator stress testing. Adenosine also has an important role in the pre-conditioned state and also in the attenuation of ischemia-reperfusion injury [1].

Case Presentation

A 57 year old male, with family history of Ischemic heart disease, presented with typical exertional retrosternal squeezing type of chest pain radiating to jaw, lasting for a minute or two, which promptly used to relieve with rest. ECG showed T inversions in anterior precordial leads. He had two such episodes in the preceding month.

Exercise stress test was strongly positive at 7 METs with significant ST depressions at peak exercise as well as during recovery. He was subjected to coronary angiogram which revealed moderate 70% stenosis in the mid segment of the LAD. Rests of the arteries were normal. He was subjected to FFR evaluation for objective assessment of inducible ischemia in the LAD territory prior to decision of revascularisation.

FFR was done with institutional study protocol and incremental doses IC Adenosine 150 ug, 180 ug injections were given and FFR values were obtained. FFR in the lesion was noted to be 0.81. However patient experienced similar chest heaviness and squeezing type of retrosternal pain after every injection of hyperaemic agent what he use to experience prior. Chest heaviness relieved on its own within 2 min to 5 min and was not associated with any ST segment deviations on the ECG and sinus rhythm was seen during entire procedure. Patient was discharged and being managed on anti-anginal medications with Nitrates, Beta blocker, Aspirin and Statin. Patient will be followed up for next one year as per institutional study protocol.

Now here one question which needs to be addressed is what will the clinical implications of the FFR value which approaches to borderline (0.75 to 0.80) when there is reproduction of similar clinical angina during IC adenosine. Whether such lesion needs to be revascularized or not? Or whether we need to lower the threshold for revascularization of such lesions.

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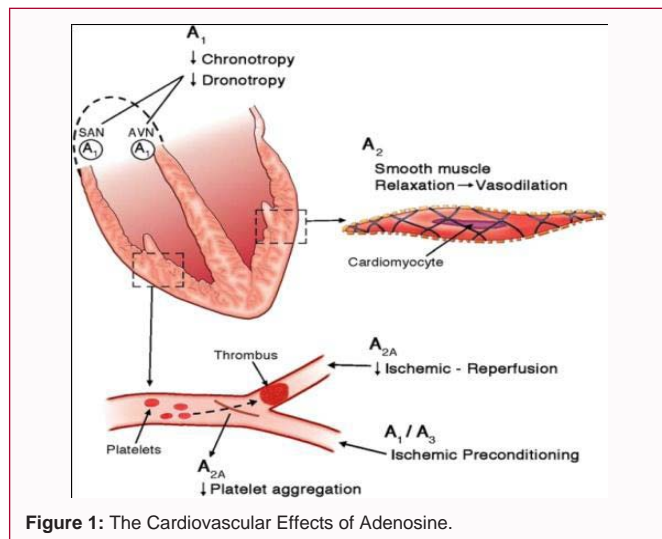
*Correspondence:

Jadhav Ajit, Department of Cardiology,
Baroda Heart Institute and Research
Centre, 102, Wingsville appt. 41
Arunodaya Society, Alkapuri, Vadodara,
Gujarat, 390007, India, Tel: 91-
9028898494;
E-mail: ajit92698@gmail.com
Received Date: 21 Jun 2018
Accepted Date: 03 Aug 2018
Published Date: 10 Aug 2018

Citation:

Ajit J, Suhas H. Adenosine: A Cause of
Angina. *Ann Cardiol Cardiovasc Med*.
2018; 2(2): 1017.

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Discussion

Adenosine binds with 4 evolutionary well-conserved receptor subtypes that are ubiquitously expressed: A₁, A_{2A}, A_{2B}, and A₃ [2,3]. Activation of cardiac A₁ receptors has a myocardial depressant effect with negative chronotropic and dromotropic effects, inhibition of Atrio Ventricular (AV) node conduction and prolongation of the refractory period (Figure 1) [4].

Activation of A_{2A} and A_{2B} adenosine receptors produces potent vasodilation of most vascular beds including the coronary circulation, resulting in an increase in myocardial blood flow. A_{2B} receptors are thought to produce mast cell degranulation and bronchial constriction [5]. A₃ receptors are mainly peripherally located but are thought to play a role in mediating pre-conditioning. Adenosine causes a sensation of dyspnea in healthy patients but has not been shown to objectively produce bronchospasm. This dyspnoegenic property has been proposed to be a result of direct stimulation of pulmonary C fibers by adenosine [6].

Intracoronary adenosine administration provokes chest pain similar to the angina at doses used for hyperemia testing. Aminophylline, an adenosine A₁-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 (mediated mainly by A_{2a} and A_{2b} receptors) and appears predominantly mediated by A₁-receptor stimulation. Typical angina pain during pharmacological vasodilator stress may reflect regional myocardial ischemia based on coronary steal. Chest pain may occur with patients with normal myocardial perfusion studies because of the involvement of adenosine A₁ receptors in the nociceptive pathway influencing the

sensation of chest pain [8]. 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 [8]. According to ACC/AHA/SCAI AUC for cardiac catheterisation, FFR measurements <0.75 are associated with ischemia on exercise testing and adjunct imaging (echo or nuclear) with high sensitivity (88%), specificity (100%), and overall accuracy (93%). FFR measurements >0.80 are associated with negative ischemic results with a predictive accuracy of 95% [9]. According to 2013 ESC guidelines on the management of stable coronary artery disease it's a class IB indication to revascularize the stenoses with FFR<0.80 in patients with angina symptoms or positive stress test [10]. In such lesions deferral of revascularization could still be safely considered.

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