The feasibility and safety of graded adenosine stress test for myocardial perfusion in asthmatic and/or COPD patients

Vandana K Dhingra[1] DNB, Prasanta K Pradhan[2] MD, Navin Garg[3] MD, DM, Sandip Basu[4] DNB

1. Department of Nuclear Medicine, AIIMS, Rishikesh Uttarakhand India
2. Department of Nuclear Medicine, SGPGIMS, Lucknow, Uttar Pradesh, India.
3. Department of Cardiology, SGPGIMS, Lucknow, Uttar Pradesh, India.
4. Radiation Medicine Centre (BARC) Parel, Mumbai, India

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Corresponding author:
Dr. P K Pradhan MD
Department of Nuclear Medicine, SGPGIMS, Lucknow,
Uttar Pradesh, India
pkp9918@gmail.com

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Abstract

Subjects and Methods: A total of 40 patients (M/F: 26/14, age range: 37-84yrs; mean: 64.1yrs) with known chronic obstructive pulmonary disease (COPD) (ranging from mild to severe), referred for a stress myocardial perfusion study, were included in this study over a period of one year. All patients underwent adenosine stress in a titrated protocol and pre-infusion of short acting bronchodilators albutamol 2 puffs few minutes prior to start adenosine infusion. In a fraction of 26 patients, pulmonary function tests (PFT) were performed and used in addition to clinical examination to classify the severity of pulmonary obstruction. On the basis of forced expiratory volume in one second (FEV1) on PFT, 4 patients had a mild disease (FEV1 60%-80%) and n=17 had a moderate obstructive disease (FEV1 41%-59%) and 4 had severe COPD/asthma (FEV1 <40%) while 2 patients had normal >95% FEV1. Post-stress questionnaire to assess subjective tolerance and symptoms were undertaken for all patients. **Results:** The results demonstrated an excellent tolerance to adenosine infusion in this group of patients, with adequate stress achieved in all. None had complaints of severe dyspnoea or respiratory distress requiring medical intervention. Thirteen patients had mild to moderate degree dyspnoea during infusion. The study included a significant number of 23 patients of elderly patients (>65 years), who showed better tolerance than the younger patients. **Conclusion:** In this pilot study in patients with COPD who referred for myocardial perfusion scintigraphy, the feasibility and safety of adenosine in a graded protocol along with a good pre-stress assessment and a short acting bronchodilator treatment was documented.

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Introduction

Despite advances in the understanding of the pathophysiology of atherosclerosis and a significant reduction in cardiovascular mortality from coronary artery disease (CAD) over the last decade, this continues to be an important cause of mortality and morbidity in the world, with a rising incidence predicted in developing nations like India. While primary prevention of CAD is a priority for modern medicine, so is the need for development of non-invasive techniques for appropriate imaging of myocardial ischemia. Stress myocardial perfusion scintigraphy occupies a central position within the cardiac imaging portfolio[1]. Myocardial perfusion imaging (MPI) today has an established role in the non-invasive diagnosis and prognostication of coronary artery disease.

Stress in MPI can be performed by exercise (i.e physical stress) or pharmacological stressors viz. adenosine, dobutamine or dipyridamole. Adenosine, which is a purine agonist, acts on the adenosine receptors by direct action [2]. This is the only stress agent that is also endogenously produced [3]. There are 4 known adenosine receptors viz. A_1, A_{2A}, A_{2B} and A_3 receptors [2]. The pharmacologic effect of adenosine is extremely rapid, which acts by increasing endogenous adenosine concentrations (by blocking the reuptake mechanism). A_1 receptors have an overall effect of bradycardia, A_{2a} receptors cause vasodilatation and protection against ischemic damage, A_{2b} receptors cause relaxation of smooth muscle in vasculature, inhibition of monocyte-macrophage function, stimulation of mast cell mediator release. A_3 receptors cause enhancement of mediator release from mast cells. Dyspnoea, a common side effect of adenosine infusion (like dipyridamole), is thought to be due to the effect of bronchoconstriction of adenosine [4]. Owing to this effect, adenosine is generally contraindicated in patients with asthma or chronic obstructive pulmonary disease(COPD) and not used for this group of patients in most nuclear cardiology laboratories. Asthma and COPD are both disorders of chronic inflam-

mation and pulmonary limitation. COPD affects the pulmonary and parenchyma while asthma affects only the pulmonary. Small pulmonary airways are involved in both emphysema and asthma, while irreversible destructive, parenchymal disease is observed in COPD but not in asthma.

The generalized contraindication of adenosine in patients with asthma or COPD is not well understood. Furthermore, the safety profile of adenosine in these patients is not well-documented barring a few studies documenting the feasibility [5,6]. We examined the feasibility and safety of a graded adenosine infusion protocol (along with premedication with salbutamol), in patients with asthma and COPD with an aim to study the tolerability of adenosine stress in this group. This is of significance as adenosine is one of the most easily available agents and has an overall excellent safety profile for patients undergoing cardiac stress. This is one of the few original studies performed to confirm the feasibility of adenosine in this setting.

Subjects and Methods

In this study, patients with history of obstructive pulmonary disease (COPD and bronchial asthma), referred for a stress myocardial perfusion scintigraphy, were included. These patients were diagnosed with the COPD previously by the referring physician or another physician. The spectrum of disease ranged from mild to severe asthma/COPD.These patients were unfit for any other kind of stress (exercise or dobutamine) but were selected for this protocol.

The general indications and contraindications for adenosine stress were maintained as per the recommended guidelines [7]. A detailed informed consent was taken from all patients with statements of the adverse effects of adenosine and the theoretical risk of precipitation of symptoms related to bronchoconstriction during adenosine infusion.

A detailed clinical history was taken for all patients, and the patients were carefully assessed by one or two specialist nuclear medicine physicians who assessed the baseline condition of the patient and the clinical severity of his disease. The relevant past history of smoking, allergy, occupational history, medications, exacerbations, drugs, requirement of bronchodilators was included for assessment of overall status of the obstructive pulmonary disease. Investigations including, 2D echocardiography (2D ECG) and angiography (where available) were noted as part of the routine stress MPI protocol for pre-test cardiac assessment. Pulmonary function tests/spirometry was undertaken to confirm and understand the severity of the obstruction. Prior to appointment, the patients were also clinically assessed to for active wheeze or other signs of severe COPD.

The standard procedure of adenosine MPI was followed: the patients came overnight fasting with no caffeine containing beverages or medications for at least 12 hours prior to the stress procedure.

Adenosine stress protocol

All patients were given a short acting bronchodilator (salbutamol) 2 puffs just few minutes prior to start of adenosine infusion. A titrated dose of adenosine starting with 70microgram/kg/minute for 1 minute, increased to 100micrograms/kg/minute for 2nd and then to 140micrograms/kg/minute for next 4 minutes. Three hundred and thirty three Mbq of radiotracer technetium-99m (^{99m}Tc) sestamibi (MIBI) was injected at end of 4th minute, followed by another 2 minutes of infusion.

Chest auscultation was performed every minute to look for signs of bronchoconstriction (wheeze), along with continuous assessment of patient symptoms and comfort by communication throughout the infusion. Electrocardiogram and blood pressure were recorded every minute during the infusion.

Continuous communication was ensured with the patient for any dyspnoea or other difficulty to assess the tolerability of adenosine. The adenosine infusion was deemed to be stopped early under the following signs/symptoms [7]: continuous wheezing, with patient's complaints of dyspnoea or any respiratory discomfort, severe hypotension (systolic blood pressure <80mm Hg), development of symptomatic, persistent second degree or complete heart block, severe chest pain (associated with ST depression of 2mm or greater), signs of poor perfusion (pallor, cyanosis, cold skin).

Post-stress, the patients were given a questionnaire regarding the presence of symptoms and their severity during adenosine infusion and the data was recorded. Adenosine protocol and its tolerance were assessed on a 4-point scoring system (no symptoms, mild symptom, moderate or severe symptoms) in the questionnaire. Objective parameters such as side effects, any extreme changes in heart rate or blood pressure, presence of rhonchi, requirement of bronchodilator during infusion, ability to complete infusion, intervention requirements were assessed for overall tolerability of the protocol. Stress was considered adequate if infusion was continued up to a minimum of 4 minutes, with tracer injected at 2 minutes of infusion and followed by another 2 minutes of infusion post injection.

The recorded parameters were then analyzed with other available details of patients underlying COPD/asthma: to establish the relation of disease profile with overall tolerability of the protocol for predicting the feasibility of the protocol in patients with similar profiles.

Image acquisition

Stress single photon emission tomography(SPET) images were acquired 30 minutes after stress, using a dual head Gamma camera Model Sopha DST-XL, France, with 180 degrees orbit, 6 degrees per step and 30 seconds per step. Planar images in anterior and Lateral Anterior Oblique (LAO) views were undertaken to compensate for diaphragmatic attenuation. These were followed by a rest injection of ^{99m}Tc-MIBI (999MBq) and imaging 45 minutes later with the same acquisition parameters. Raw data were reviewed for any

motion artifacts with reacquisition if needed. Data was reconstructed using Emory Cardiac Toolbox software (ECTB), and images displayed in 3 standard views (transaxial, horizontal and vertical long axis).

Results

A total of 40 patients (26 males, 14 females) were included in the study group over 18 months. The age range of the population was 37 to 84 years (mean age: 64.1 years, median age: 65 years).Twenty three patients were over 65 years commensurate with the higher incidence of COPD in the elderly male. Thirty one were diagnosed of COPD with a previous history of chronic cough with expectoration, chest tightness and wheeze. A total of 15 patients gave a history of smoking. Of these 15 smokers 6 were ex-smokers and all were heavy (chain) smokers (defined by history of more than 10 pack years). Nine patients were asthmatics with known history of episodic dyspnea and bronchospasm since many years beginning from childhood or adolescence. Most of them (n= 29) were on regular treatment with inhalers such as salbutamol (n=12), oral theophylline (n=12) or both (n=12). Eleven patients never had a history of any treatment in the recent past. None of the patients were on steroid therapy.

On clinical assessment and taking into account the patient's symptoms, examination findings and drug usage,15 patients had a mild disease and 25 had moderate disease. Baseline pulmonary function test (Spirometry-Vitalograph) data was available in 27 patients.

On the basis of spirometry results of Forced Expiratory Volume 1(FEV1)*estimated were as follows: Normal (FEV1> 95%) 2 patients, mild (FEV1 60%-80%) 4 patients, moderate (FEV1 41%-59%) 17 patients and severe (FEV1<40%) 4 patients.

A total of 12 patients had a wheeze prior to starting the infusion which disappeared post salbutamol pre-medication. Of these patients, 4 were non-smokers and 8 had history of heavy smoking. Of the patients with rhonchi on examination, 3 had bronchial asthma and were non-smokers.

Other associated risk factors like obesity i.e body mass index (BMI)>30 was seen in seven patients, diabetes mellitus (DM) was present in 10 patients and 25 had underlying hypertension. Ten patients had both DM and hypertension. As previously mentioned 15 patients were smokers, and 19 had dyslipidemia. A total of 16 patients gave a positive family history of coronary artery disease. Twenty six patients were referred for a diagnostic test to rule out coronary artery disease and remaining 14 patients had a history of known coronary artery disease, the test was indicated for evaluation of the extent of ischemia and viability i.e. prognostication of disease.

Adenosine infusion as per our protocol was given in all patients. All patients underwent the infusion in an upright position, these patients when asked whether they prefer a supine or sitting position and they themselves opted for a sitting position. All patients received adequate stress and completed imaging protocol with optimum studies for reporting. Stress was deferred on the first appointment in two patients. Both received oral salbutamol and antibiotics for a fortnight and revaluated for stress. Both successfully underwent the protocol at this later date with no events.

Two patients with severe disease on Spirometry (FEV1< 40) also had other classical signs of chronic COPD; like barrel chest. Despite these signs and features the fact that they were in a good general condition and no other major underlying co-morbidities, they were included for stress, and tolerated infusion well.

Post stress questionnaires revealed that headache was the commonest side effect of adenosine in our group seen in 27 and 13 patients had dyspnoea, followed by flushing in nine patients, chest pain in seven, nausea in six and dizziness in six. All the reported symptoms resolved completely after stoppage of infusion(Table 1).

Table1. *Subjective symptoms and tolerance to graded adenosine protocol.*

	None	Mild	Moderate	Severe	Total
Dyspnea	27	9	4	0	40
Headache	13	23	2	2(5)	40
Nausea	33	7	0	0	40
Chest pain	33	4	3	0	40
Dizziness	34	4	2	0	40
Flushing	31	8	1	0	40

None of the patients required intravenous aminophylline or salbutamol inhalers during or post-stress observation period. We did administer salbutamol post-stress in two patients, though the patients were comfortable. When asked regarding the repeatability of the infusion procedure, none of the patients refused. The aforementioned results suggested feasibility and high tolerability of adenosine in patients with COPD and asthmaas well as in elderly patients.

Discussion

Adenosine is considered to be a potent bronchoconstrictor and bronchoprovocatorand an indirect marker for pulmonary inflammation, which may explain the predicted difficulty and reason for avoidance for use in stress MPS in patients with COPD [8-11].

Johnston et al. (1999) [12] showed a good tolerance of adenosine infusion in patients with COPD. They did not observe a significant difference in fall of FEV1 in patients with or without COPD, patients who developed bronchospasm also resolved spontaneously and thus systematically showed that adenosine could be safely administered intravenously to selected patients with known or suspected COPD to produce coronary vasodilatation for myocardial perfusion imaging

and recommended that patients who were indicated according to the guidelines, could be safely considered for adenosine coronary vasodilatation.

Balan et al. (2001)[13] studied 122 patients undergoing stress MPI to ascertain the cause of the feeling of dyspnoea in patients undergoing adenosine infusion during MPI. 30% of their patients (n=36) had a history of COPD, though asthma was excluded from their study group. They did not observe any significant change in the spirometry parameters during and after adenosine infusion in the COPD or non-COPD group. There were no significant subjective changes in patients' symptoms in the COPD group. The authors however mentioned on inclusion of only mild COPD (FEV1 65% on an average),exerting caution on applying this protocol in more severe disease. Also their study did not include the asthmatics and thus they did not recommend use of adenosine in asthmatics. Another study by Fricke et al. (2008) had shown that the feeling of dyspnea is not significantly related to bronchospasm during adenosine infusion. This symptom is not related to respiratory resistance during adenosine infusion and may occur even in normal subjects. They also concluded that patients with mild COPD could safely undergo adenosine in their setting [14]. However, there is requirement of more convincing evidence and looking into as to what may be the possible reasons for such a smooth tolerance despite the theoretical fact of adenosine being a potent bronchoprovocator.

Other authors have shown that adenosine administration by inhalation elicits a concentration-related bronchoconstrictor in subjects with asthma and COPD [15,16] whereas the nucleoside has no discernible effect on pulmonary caliber in normal individuals. Adenosine has been suggested to play a role in inflammatory pulmonary diseases such as asthma and COPD. Elevated levels of adenosine have been measured in the pulmonary lining fluid of patients with asthma and COPD when compared to normal controls. In sensitized rabbits, high concentrations of adenosine have been reported in the lung-lavage fluid after allergen challenge, whereas in transgenic mice, adenosine-receptor transcripts are increased in association with lung inflammation and increased pulmonary hyper-responsiveness. Since these initial observations were made, considerable work has been done towards revealing the fine mechanisms of adenosine-induced bronchoconstriction; these appear to involve a selective interaction with activated mast cells, with subsequent release of preformed and newly-formed mediators [17-21]. It has been shown that many cell types that play important roles in the exacerbation of asthma and COPD, express adenosine receptors and demonstrate relevant effects through stimulation of these receptors. These include mast cells, eosinophils, lymphocytes, neutrophils, and macrophages [22-28]. Of these, the mast-cell derived mediators are largely implicated in the bronchoconstrictor response to adenosine in asthma and COPD, which is probably the result of an interaction of the nucleoside with specific mast-cell surface receptors.

Salbutamol used as a therapeutic agent for asthma and COPD has a powerful inhibitory effect on AMP-induced bronchoconstriction by serving as a functional antagonist and as a direct inhibitor of human mast cell activation-secretion coupling [29]. Salbutamol is known to have a potent anti-inflammatory action. The beta-2 agonists prevent release of the mediators from mast cells, thereby preventing inflammation [30]. Similar to a few aforementioned reports [5, 6, 12] our results also indicate an overall good tolerability of adenosine in patients with known COPD or asthma. The short term effects of the beta-2 agonists may be possible to be the reason why we did not experience any difficulty following employment of short acting beta-2 agonist (Salbutamol), just prior to the infusion in the study patients.

Reyes et al.(2007)[6] used an infusion protocol with dynamic exercise in all patients with COPD. Combining exercise with adenosine infusion has been shown to reduce the non-cardiac side effects of vasodilatation and major arrhythmias while improving redistribution and heart/background ratios [31]. The authors documented a higher incidence of dyspnea in their group than our patients which can be attributed to this exercise component. We did not use exercise in our protocol and the incidence of dyspnea was lesser in our study, 37.5% vs 53% in their group. We recommend that adenosine stress protocol in patients with asthma and COPD is best employed without dynamic exercise in order to reduce the probability of dyspnoea due to added and to increase the likelihood of completion of the protocol and avoid a suboptimal stress.

Reyes et al. (2007) [6] has attributed the dose dependent response of adenosine to be a factor in the degree of bronchoconstriction it produces [15]. It has been shown that doses ≥ 100mcg/kg/min produce bronchoconstriction while doses < 50mcg/kg do not produce significant bronchoconstriction [32, 33]. So there is a possibility that the graded adenosine protocol with gradually increasing rate of infusion for the stress i.e 70, 100 and 140mcg/kg/min used in our protocol could be more suited for these patients. The exact dose of intravenous infusion required to cause a plausible effect on pulmonary airways in this group of patients still needs to be evaluated.

The short half-life of 10 seconds of adenosine is an important factor for better tolerance. None of our patients experienced any significant dyspnoea and overall other side effects were resolved immediately after stoppage of infusion. All our patients who experienced symptoms or developed wheeze resolved spontaneously on stoppage of infusion and did not require any intervention.

Another, noteworthy aspect in our study, 65% of patients (n=26) were more than 60 years and 22.5% (n=9) were more than 70 years, may be attributed to age related changes also seen in other studies [34-37] thus implicating the feasibility of the procedure at this age group.

The titrated protocol used in our study has been used previously [6]. A standard dose of 140mcg/kg/minute is recommended [38], however lower doses of 70 and 100mcg/kg/min have not been studied extensively with respect to degree of myocardial blood flow increase for myocardial perfusion imaging but it has been shown that infusion rates of 30-50mcg/kg/ minute and above used in non-anesthetized humans without causing subjective side effects or hypotension lead to increased coronary flow.

In conclusion, the present study showed the feasibility and safety of adenosine stress protocol in patients with known obstructive pulmonary disease whether COPD or asthma.

The authors declare that they have no conflicts of interest.

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