Original Article

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IMPACT AND OUTCOME OF MAXIMUM BICYCLE ERGOMETER EXERCISE ON ADENOSINE TC-99M SESTAMIBI MYOCARDIAL PERFUSION IMAGING IN CORONARY ARTERY DISEASE

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ABSTRACT

Objective: To determine the effects of combining maximum physical stress with adenosine infusion by using bicycle ergometer in sestamibi myocardial perfusion imaging and its impact on adenosine induced adverse effects, image quality, detection of ischemia and patient's compliances.

Study Design: Prospective randomized controlled trial.

Place and Duration of Study: Department of Nuclear Cardiology, Armed Forces Institute of Cardiology / National Institute of Heart Diseases; Rawalpindi: Pakistan from 1st July 2014 to 31st Oct 2015.

Material and Methods: Total study population eight hundred and twenty-eight patients age ranging from twenty-six to eighty-four years included four hundred fifty males and three hundred seventy-eight females. In three hundred and eight patients exercise was contraindicated due to physical or technical reason so they were included in adenosine only group while remaining five hundred and twenty patients were included in adenosine exercise group. These patients underwent resting first adenosine Tc-99m sestamibi gated cardiac single photon emission computed tomography with or without exercise supplementation protocols.

Results: The stress induced heart rate, systolic blood pressure and pulse pressure in adenoEx and adeno groups were 126.6 ± 19.0 vs 89.6 ± 15.2 $p<.0001$; 160.0 ± 20.4 vs 127.0 ± 21.2 $p<.0001$ and 75 ± 19.5 vs 50 ± 17.2 $p<.0001$ respectively. In adenoEx group the ischemic ST-segment depression occurred more often than with adeno alone group (40% vs 12%; $p=0.006$). The combined incidence of ischemic chest pain or ST depression (or both) was also higher 48% vs 24%; $p=0.015$) with adenoEx than with adeno. Other effects like atypical chest pain, shortness of breath, flushing and one or more adverse effects were more common in adeno group. The heart to lung, heart to liver and heart to splanchnic uptake ratios were higher in AdenEx group as compared to the Adeno group.

Conclusion: Physical stress with adenosine Tc-99m sestamibi myocardial perfusion imaging not only reduces adenosine induced side effects but also enhances image quality, and reduces artifacts. Maximum bearable stress should be combined with adenosine stress myocardial perfusion studies whenever indicated and possible.

Keywords: Bicycle ergometer, Sestamibi, Subdiaphragmatic activity, Adenosine, Myocardial perfusion, Scintigraphy, Electrocardiogram.

INTRODUCTION

Myocardial perfusion imaging (MPI) is one of the best non-invasive procedure utilized by clinicians for diagnostic, therapeutic and prognostic assessments of myocardium. Stress either physical or pharmacological is integral part of this procedure[1]. All those patients who could not perform exercise tolerance test, the pharmacological stress with adenosine, dobutamine, dipyridamole or regadenoson is the best alternative choice[2]. Pharmacological stress alone or in combination with some physical stress is in practice and various protocols are being utilized to maximize the outcome[3-5]. Adenosine is utilized as a stress agent in all over the world because it has short half-life, rapid onset and termination of its effects and shorter duration adverse effects. The adenosine hyperemic stress alone leads to high background activity in liver, lungs and splanchnic vasculature overlapping the myocardium and interfering its evaluation[6-8]. To overcome these effects, we added physical stress with bicycle ergometer with adenosine

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infusion. In standard adenosine stress protocol, the radiopharmaceutical is usually administered at midway of the infusion. In this study we modified the protocol by addition of physical stress before the start of infusion. This combination new protocol provides the opportunity to improve image quality and reduce the negative chronotropic and dromotropic effects of adenosine.

MATERIAL AND METHODS

The study population consisted of 828 patients, to undergo requested pharmacologic stress MPI, between 1st July 2014 to 31st Oct 2015. Patients population included 450 men and 378 women, ranging in age from 26 to 84 years. Whole procedure was explained to each patient and all required information recorded on designed sheet. Informed consent was obtained. I/V line with three-way catheter was secured at dorsum of hand or forearm. In 520 patients' adenosine exercise (adenoEx) resting first protocol was implemented (fig-1) and in remaining 308 patients who could not perform physical stress; adenosine (Adeno) resting first protocol was utilized (fig-2). 8-12 mCi Tc-99m sestamibi was injected and patient was encouraged to drink one cup of full cream milk

Table-1: Baseline characteristics in both groups.

	AdenoEx (n = 520)	Adeno (n = 308	*p*-value
Age	56 ± 12.4	58 ± 9.5	NS
Male patients	280	170	NS
Female patients	240	138	NS
Heart rate	74 ± 15.4	76 ± 13.2	NS
Systolic blood pressure	126 ± 18.4	130 ± 20.5	NS
Diastolic Blood pressure	85 ± 15.8	88 ± 16.4	NS

Table-2: Hemodynamic responses.

	AdenoEx (n = 520)	Adeno (n = 308	*p*-value
Heart rate at 3rd min of cycling before adenosine infusion	105 ± 18.3		
Maximum heart rate (beats/min)	126.6 ± 19.0	89.6 ± 15.2	<.0001
Percent maximum heart rate (%)	79.6 ± 15.4	51.7 ± 9.4	<.0001
Change in heart rate (beats/min)	50.5 ± 12.3	13.5 ± 10.9	<.0001
Maximum systolic blood pressure (mmHg)	160.0 ± 20.4	127.0 ± 21.2	<.0001
Diastolic Blood pressure (mmHg)	80 ± 22.8	90 ± 16.4	NS
Maximum Pulse pressure (mmHg)	75 ± 19.5	50 ± 17.2	<.0001

Table-3: Adverse effects (number of patients) in both groups.

Adverse effect	AdenoEx	Adeno	*p*-value
ST Dep	38	12	<0.001
Angina	28	18	<0.1
ST Dep / Angina	54	24	<0.001
Atyp CP	8	26	<0.001
SOB	29	36	<0.04
flushing	12	70	<0.001
1 or more adverse	59	82	<0.001

ST-segment depression (ST Dep), atypical chest pain (Atyp CP), shortness of breath (SOB)

Table-4: Heart to lung, liver and sub-diaphragmatic uptake ratios.

	AdenoEx (n = 200)	Adeno (n = 150)	*p*-value
Heart to liver uptake ratio	1.65 ± 0.59	1.38 ± 0.50	<0.01
Heart to lung uptake ratio	2.64 ± 0.55	2.46 ± 0.62	<0.1
Heart to splanchnic uptake ratio	2.85 ± 0.62	2.46 ± 0.64	<0.01

after 20 minutes of injection. Gated single photon emission computed tomography (SPECT) study was acquired at 30 minutes' post injection. After 2 to 2.5 hours of resting study stress study was acquired in both groups as follow.

Patients were made to sit on a comfortable sofa chair. All necessary gadgets like 12 lead ECG and BP apparatus were attached. All baseline data was recorded. A specially designed bicycle ergometer was placed at adjustable distance and patient was asked to start cycling while sitting on sofa chair. Workload of the ergometer was adjusted 2 minutes' warm-up at 25 watts, 2 minutes submaximal at 50 watts 2 minutes intermediate at 75 watts and 3 minutes maximal at 100 watts. At completion of third min or on achievement of 70% of target heart rate (220 - age of the patient), adenosine infusion at a dose of 140 microgram/kg/min for 6 minutes was started. Cycling was continued and at completion of 3rd minute of infusion 20-30 mCi of Tc-99m sestamibi was injected through the similar IV line (fig-1). On the other hand, in Adeno group only adenosine (140 microgram/kg/min) was given for 6 minutes and radiotracer was injected at midway of the infusion (fig-2). All parameters like, heart rate, blood pressure, ECG changes, any symptom described by the patient was recorded at every minute in both groups.

Imaging: Images were acquired on randomly selected two dual head cardiac dedicated gamma cameras Philips Adac CardioMD and Positron/IS2 Pulse CDC equipped with a high resolution, parallel-hole collimator. Our acquisition parameters were based on guidelines and recommendations published by the American Society of Nuclear Cardiology[9]. A window of 20% centered on the 140-keV photopeak was used. We acquired mages in a step-and-shoot mode, using a non-circular orbit of 180°, starting at a 45° right anterior oblique angle and ending at a 45° left posterior oblique orientation for a total of 32 projections, each of 40 seconds' duration. Images were stored in 64x64 matrix and processed by means of a Butterworth filter with a frequency cutoff of 0.47 cycles/pixel and an order of 7.5 for image reconstruction. The tomographic slices were analyzed systematically. The diagnosis of ischemia was based on qualitative and quantitative analysis and defects were described in relation to their extent and severity. Reversibility was classified as

Figure-1: Resting first adenosine exercise protocol.

Figure-2: Resting first adenosine protocol.

completely reversible, partially reversible, or nonreversible (fixed). For comparisons with the ECG, all completely or partially reversible defects described in the conclusion of the study were considered ischemic results.

Heart to liver, heart to gut and heart to lung activity ratios: Background-to-target ratios were used as a surrogate for image quality. Of the 32 images acquired for each patient, the eighth image was selected to quantify cardiac, gut and liver activity. Images were quantified for counts in the myocardium, lung, liver, and gut in randomly selected 350 patients. Of the evaluated patients, 200 were in the adenoEx group and 150 in the adeno group. Background-to-target ratios were determined for each parameter and compared between the 2 groups. The regions of interest that were used to assess these parameters were the entire left ventricle, mid-left lung, right upper lobe of the liver, and the gut consisting of 5x5 pixels irregular in outlined areas.

Data Collection: All resting, during stress and post stress parameters like hemodynamic responses, unwanted effects and ECG printouts were retrospectively analyzed.

Statistical Analysis: All the collected data presented as mean ± standard deviation or frequency, when appropriate. Comparisons between group means were determined by utilizing unpaired Student t test, except for the comparison of the frequency of adverse reactions in which a 2-sample proportional Student t test was used. All calculations were

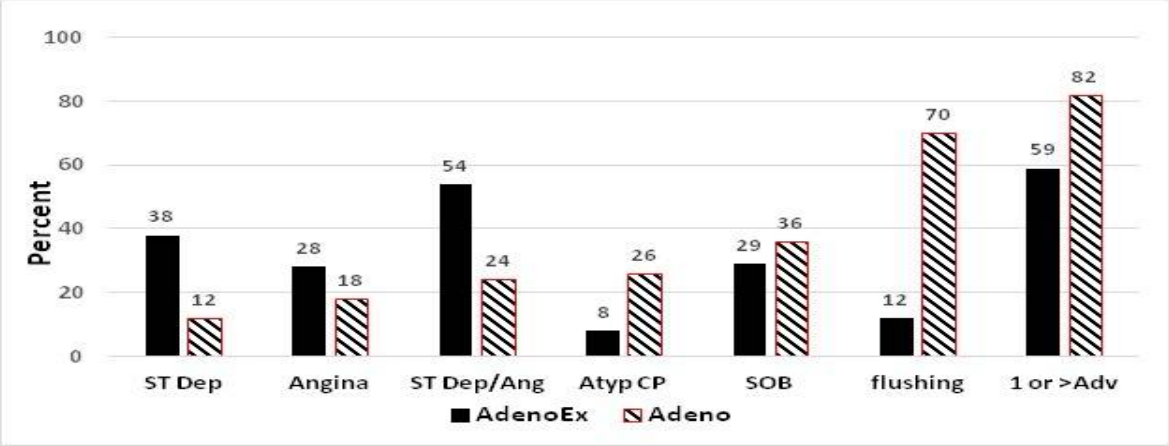

Figure-3: Adverse effects in number of patients both groups ST-segment depression (ST Dep), angina (Ang), ST depression and/or angina (ST Dep/Ang), atypical chest pain (Atyp CP), shortness of breath (SOB), flushing, and 1 or more adverse effect (1 or >adv).

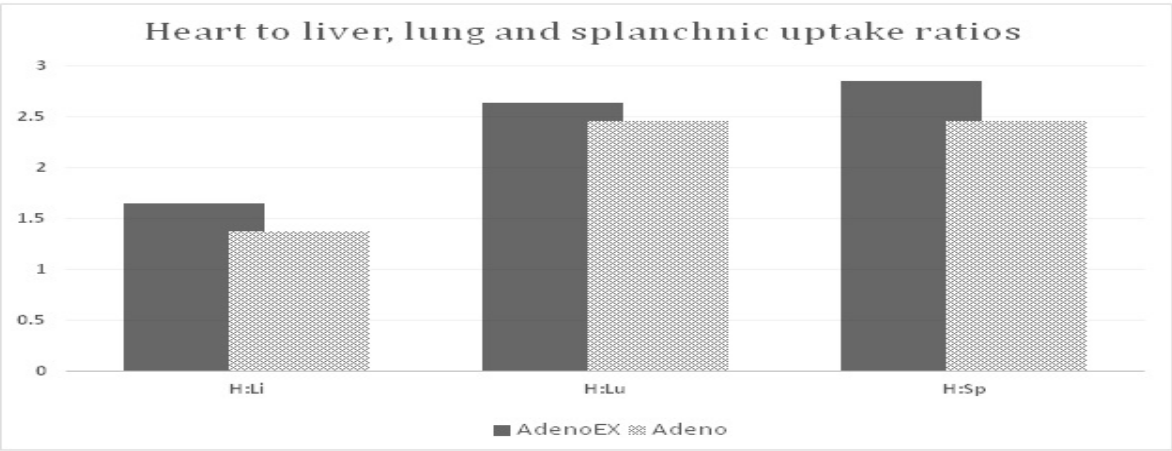

Figure-4: Heart to lung, liver and sub-diaphragmatic uptake ratios.
Heart to liver (H:Li), Heart to lungs (H:Lu) and Heart to splanchnic (H:Sp)

made with the help of software SPSS version 16. A *p* value<.05 was considered statistically significant.

RESULTS

Baseline characteristics, mean age, sex, mean heart rate, systolic and diastolic blood pressures are summarized in table-1. Hemodynamic responses in both the groups are displayed in table-2. Mean peak heart rate, systolic blood pressure and pulse pressures were significantly higher in the adenoEx group as compared to adeno group. There was no significant difference in diastolic blood pressure at peak systolic blood pressure. The adenosine group had the mean lowest systolic blood pressure recorded during infusion. AdenoEx combination (3+6 minutes) was tolerated well by most of the patients. Fewer patients had single or multiple unwanted effects like flushing, atypical chest pain, shortness of breath, nausea, dizziness, and leg pain during adenoEx than during adenosine only group (table-3 and fig-3).

Electrocardiographic Changes: In adenoEx group the ischemic ST-segment depression occurred more often than with adenosine (40% vs 12%; *p*=0.006). The combined incidence of ischemic chest pain or ST depression (or both) was also higher 48% vs 24%; *P*=0.015) with adenoEx than with adenosine.

Quantitation and interpretation of images

The heart to lung, heart to liver and heart to splanchnic ratios were higher in AdenEx group as compared the Adeno groups (table-4 and fig-4). The image quality of AdenoEx group was better than the adeno group. Ninety-two percent of adenoEx images were classified as excellent or fair versus 66% with adeno (*p* <0.003). 4.5% of studies with adenosine only were not interpretable as compared to only 1.3% studies with adenoEx group.

DISCUSSION

Combination of physical exercise with adenosine infusion for MPI is safe, feasible, significantly enhances image quality, reduces unfavorable side effects, reduces artifacts and greater detection of ischemia as compared with adenosine alone[1-5]. Whatever stress combination with adenosine is there; the radiopharmaceutical has to be injected at the end of 2 or 3 minutes of infusion in four/six minutes' protocol. In any case if both physical exercise and adenosine are being started together than the total physical stress is either 2 or 3 minutes before radiotracer injection[9-11]. In all reported studies adenosine and bicycle treadmill were started simultaneously and isotope was administered at midway of the infusion[2,3, 12-15].

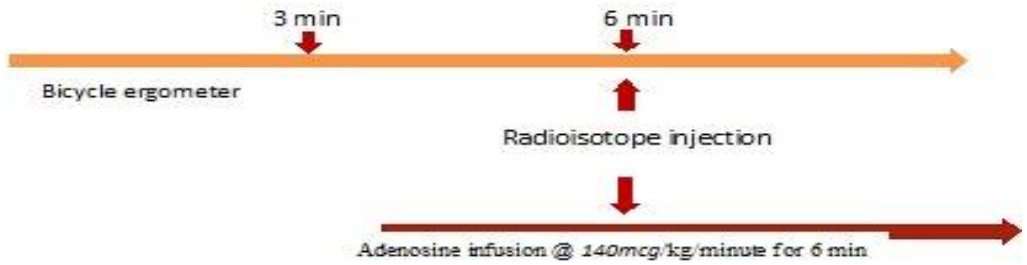

Figure-5: Modified AdenoEx protocol.

Adverse effects and image quality: Antidote or treatment is rarely required for minor adenosine induced side effects due to its very short half-life. However, reduction in these side effects is certainly helpful and would increase patient acceptance. Exercise-induced adrenergic activation during adenosine infusion may explain the reduction in side effects observed with the adenoEx protocol. Adenosine can induce intense flushing by activating smooth muscle cell A2b receptors and thereby vasodilating derm al vascular beds. Exercise may counteract this vasodilation by stimulating peripheral alpha-1 adrenoreceptors[16-18]. Prominent activity in subdiaphragmatic region is due to presence of radiotracer in the liver and

bowel as a result of reflux of radiopharmaceutical into the gastric lumen from the duodenum or because of uptake of free 99mTc-pertechnetate by the gastric mucosa[7-8]. The best solution is addition of low level exercise along with the pharmacologic stress resulting increased skeletal muscle blood flow and, thereby, decreasing splanchnic blood flow.

Greater detection of ischemia: The addition of exercise with adenosine infusion increases the detection of ischemia by multiple ways like appearance of ST and T-wave changes on ECG, increased pre-injection stress level, reduction of subdiaphragmatic and background activity. In our study ST-segment depression was significantly higher with the adenoEx protocol. Among the patients who had ST segment depression during stress 73% had prominent ischemia on myocardial perfusion images. Several mechanisms may potentially contribute to the greater degree of perfusion abnormalities with adenoEx protocol[19-20]. Experimental studies have shown that increasing pulse pressure while keeping the mean perfusion pressure unaltered increases coronary perfusion, despite no increase in myocardial oxygen consumption, and that administration of adenosine has a synergistic effect on pulse pressure augmented increase in myocardial perfusion compared with either intervention alone. A significantly higher pulse pressure with adenoEx compared with adenosine observed in this study may have contributed to greater augmentation of coronary perfusion and greater flow heterogeneity in the presence of CAD[21-22]. There is non-linear extraction of Tc-99m sestamibi and other myocardial perfusion agent during adenosine or dipyridamole hyperemia. At higher flow rates (2 times the baseline flow rates), there is a relative decrease in myocardial radiotracer extraction. This non-linear uptake results in underestimation of flow and can potentially result in underestimation of myocardial ischemia. Whereas a number of factors possibly contribute to this heterogeneity like decrease in blood and pulse pressure, velocity of blood flow and myocardial contractility. Combination of exercise with vasodilator infusion, counteract this heterogeneity leading to stable or increased blood pressure, increased pulse pressure and myocardial contractility may at least partly overcome this non-linear uptake phenomenon[23-24].

Protocol design: To maximize the physical stress, we introduce this protocol by adding extra three minutes before radioisotope injection, so the physical component of the stress could be maximized. This extra three minutes of stress not only gives rise to maximize the blood flow towards the skeletal muscles but also maximize the stress at the time of radioisotope injection (fig-1 and fig-5). This modification increased the sensitivity for ischemia detection from previous reported studies from 60 to 65% to > 75%. Our study showed much better beneficial effects like improvement in the target-to-background ratio reduction in arrhythmias and splanchnic activity as compared to other published studies.

CONCLUSION

Combination of physical stress with adenosine hyperemic Tc-99m sestamibi MPI significantly reduces adenosine induced undesirable side effects, enhances image quality, and reduces artifacts. In majority of the patient's physical stress not only divert the patient attention but also give rise to better hemodynamic responses and result in greater detection of ischemia. Maximum bearable stress should be combined with adenosine stress sestamibi myocardial perfusion studies whenever indicated and possible.

CONFLICT OF INTEREST

This study has no conflict of interest to declare. Abstract and results of this study were accepted and presented in an oral presentationat the International conference on Medical Education, organised by Association for Excellence in Medical Education(AEME) and held on 07th-09th March 2014 at University of Health Sciences(UHS) Lahore, Pakistan. No funding was received from any agency or institution.

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