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Original article

# Comparison of Hemodynamic Effects and Negative Predictive Value of Normal Adenosine Gated Myocardial Perfusion Scan With or Without Caffeine Abstinence

**Maseeh uz Zaman[1,2], Nosheen Fatima[2,3], Areeba Zaman[4], Unaiza Zaman[4], Rabia Tahseen[4]**

[1]Department of Radiology, The Aga Khan University Hospital, [2]Department of Nuclear Cardiology, Karachi Institute of Heart Diseases, [3]Department of Nuclear Medicine, Dr. Ziauddin Medical University, [4]Dow University of Health Sciences, Karachi, Pakistan

## Abstract

For vasodilator stress, myocardial perfusion imaging (MPI) with at least 12-h caffeine abstinence is recommended, as it attenuates cardiovascular hyperemic response of adenosine and dipyridamole. However, many published conflicting results have shown no significant effect upon perfusion abnormalities in MPI performed without caffeine abstinence. The aim of this study was to compare the hemodynamic changes and negative predictive value (NPV) of normal MPIs with adenosine stress performed with or without caffeine abstinence. This was a prospective study that accrued 50 patients from May 2013 till September 2013 and followed till November 2014. These patients had a normal adenosine-gated MPI (GMPI) with technetium-99m methoxy isobutyl isonitrile ($^{99m}$Tc-MIBI) after 12-h caffeine abstinence (no-caffeine). Next day, all patients had a repeat adenosine stress within 60 min after ingestion of a cup of coffee (about 80 mg of caffeine) followed by no MPI in 30 patients due to concern about radiation dose (prior-caffeine adenosine—no MPI; group A). Twenty patients opted for a repeat MPI (prior-caffeine adenosine—MPI; group B). Adenosine-induced hemodynamic response and NPV of the normal MPI with no-caffeine and prior-caffeine protocols were compared. The mean age of the study cohort was 57 ± 9 years with a male-to-female ratio of 76:24% and mean body mass index (BMI) of 26.915 ± 4.121 kg/m$^2$. Prevalence of hypertension, diabetes, dyslipidemia, and positive family history were 76%, 20%, 22%, and 17%, respectively. Comparison of group A with group B revealed no significant difference in demographic parameters, hemodynamic or electrocardiography (ECG) parameters, or left ventricular (LV) function parameters during adenosine intervention with prior-caffeine and no-caffeine protocols. During the follow-up, no fatal myocardial infarction (MI) was reported but 6 nonfatal MIs were reported based upon the history of short hospitalization for chest pain but without biochemical or ECG criteria for infarction (3/30 in group A and 3/20 group B). Event-free survival (EFS) for fatal MI was 100% for both the groups while EFS for nonfatal MI was 90% for group A and 85% for group B (nonsignificant *P* values). Kaplan–Meier survival plot also depicted nonsignificant EFS for nonfatal MI. This study did not find any significant attenuation effect upon adenosine-induced hemodynamic response and similar NPV of a normal GMPI in patients with or without caffeine abstinence. We assume that better designed prospective studies are required to validate findings of our study and provide justification for revision of guidelines about caffeine abstinence.

**Keywords:** Adenosine, caffeine, gated MPI, hyperemia, negative predictive value

**Address for correspondence:**
Dr. Maseeh uz Zaman,
Department of Radiology, The Aga Khan University Hospital,
Karachi, Pakistan.
E-mail: maseeh.uzzaman@aku.edu

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## Introduction

Pharmacological stress using either adenosine or dipyridamole is used in about 50% of all myocardial perfusion imaging (MPI) performed in the United States and Europe.[1,2] Adenosine, dipyridamole, and regadenoson augment the coronary blood flow by 3.5–4 folds by stimulating the adenosine $A_{2A}$ receptors.[3] Caffeine and other methylxanthine derivatives are nonspecific antagonists of all adenosine receptors subtypes ($A_1$, $A_{2A}$, $A_{2B}$, $A_3$)[4] and may obliterate the adenosine-induced coronary hyperemia resulting in reduced sensitivity of stress MPI.[5] A few earlier studies have shown either false negative or reduced ischemia burden of $^{201}$thallium MPI performed with dipyridamole in the presence of caffeine[6,7] and a recent study also revealed reduced severity of reversible ischemia with standard dose of adenosine 1 h after receiving about 200 mg of caffeine.[8] Based on results of these observations, the current American Society of Nuclear Cardiology (ASNC) imaging guidelines recommend abstinence from caffeine and other methylxanthines (such as aminophylline and theobromine) for at least 12 h and consider it a contraindication for performing the procedure.[3] However, the results of subsequent studies are contradictory showing no significant impact of caffeine on adenosine-induced hyperemia assessed by fractional flow reserve (FFR) during the angiography[9] or with MPI.[10,11]

Based on the recent evidence based data, some institutes instead of cancelling or rescheduling the test of patients who have ingested one cup of coffee, they either proceed for adenosine stress study or follow a rest-adenosine stress protocol if caffeine is taken more than or less than 1 hour, respectively.[5] We assume that practicing this strategy, validity of normal adenosine stress MPI would be a major concern and no study has been performed so far to validate the negative predictive value (NPV) of a normal MPI in patients who ingested caffeine within 1 hour of adenosine stress.

The aim of this study was to compare the hemodynamic changes and NPV of normal MPIs with adenosine stress performed with or without caffeine abstinence.

## Materials and Methods

### Study design and demographic

This was a prospective study conducted at the Nuclear Cardiology Department of Karachi Institute of Heart Diseases (KIHD), Karachi, Pakistan. Patients were accrued from May 2013 till September 2013 and followed till November 2014. The study was duly approved by the Ethical Committee of Institute. Inclusion criteria were patients who were referred for an adenosine stress MPI for evaluation of typical or atypical chest pain, having at least 12 h abstinence for caffeine, not taking beta or calcium blocker and nitrate for 24 h and had a normal adenosine stress gated MPI (GMPI). Written consent was also obtained from these patients. Fifty-seven patients were selected for the study but 7 could not complete the follow-up and were excluded from the study population. Remaining 50 patients with normal no-caffeine adenosine stress MPI (who also completed follow-up) constitute the study population. They consented to participate for the second-day study with adenosine stress within 1 h after consumption of a cup of coffee but without MPI (30/50 due to concerns of radiation dose; group A: Prior-caffeine adenosine stress—no MPI) while 20/50 patients consented for MPI as well (prior-caffeine adenosine stress MPI, group B). Adenosine stress was selected by their primary cardiologists due to either limited effort tolerance or inability to walk due to musculoskeletal problem (41/50) or left bundle branch block (LBBB) on resting electrocardiography (ECG) (9/50). The patients with history of coronary artery disease (CAD) or revascularization or positive MPI were excluded from the study. Rest of the patients were followed for a period of 12–18 months for any major cardiac events such as fatal or nonfatal myocardial infarctions (MIs).

### Stress protocol

For no-caffeine study, the patients were asked to maintain caffeine abstinence (i.e. tea/coffee/caffeinated drink or xanthine derivatives) for at least 12 h, and adenosine intervention was performed at 0.142 μm/kg/min intravenously for 6 min and radiotracer [259–370 MBq of technetium-99m methoxy isobutyl isonitrile ($^{99m}$Tc-MIBI)] was intravenously injected on the 4$^{th}$ min of infusion from the contralateral arm. For prior-caffeine study (on other day), all patients were given one cup of coffee (8 ounce with 1.5 teaspoon of instant coffee powder having about 80 mg caffeine) and within 60 min (45–60 min) similar adenosine infusion protocol was given without $^{99m}$Tc-MIBI injection in 30 patients (group A: Prior-caffeine adenosine stress but no MPI) and with $^{99m}$Tc-MIBI injection also in 20 (group B: Prior-caffeine adenosine stress MPI). Heart rate and blood pressure were measured during the adenosine infusions. Rise in heart rate (≥10) (from baseline) or drop of ≥10 mmHg of systolic blood pressure with or without symptoms or ST changes on ECG were considered as adequate response to adenosine.

### Gated SPECT myocardial perfusion imaging

On both days, 30–45 min after $^{99m}$Tc-MIBI injection during adenosine infusion, gated single-photon emission computed tomography (SPECT) MPI acquisitions were

performed using dedicated cardiac gamma camera (Cardio MD, Philips) fitted with low energy all purpose (LEAP) collimators, 32 projections around a 180 degree arc, a 64 × 64 matrix, and 16 frames per cardiac cycle. Image reconstruction and left ventricular (LV) functional parameters [ejection fraction (EF), end diastolic volume (EDV), end systolic volume (ESV), and wall motion (WM)] were contemplated by using commercially available Astonish® and Autoquan® software packages (Holland Philips), respectively. An EF ≥50%, ESV ≤70 mL, and WM score of 0 (in a 17-segment model) were considered normal as per department protocol, to ensure optimal quality of scan, fatty meal with a glass of water prior the imaging was used to minimize subdiaphragmatic activity and use of gated images (partial volume effect and wall motion) to rule out attenuation artifacts. We did not use any attenuation correction methodology.

### Follow-up

All patients/family were interviewed on telephone (median follow-up: 14 months; range: 12–18 months) regarding overall death and fatal or nonfatal MI. These events were confirmed by hospital records for those who were managed at our institute and by reviewing the discharge notes for those who were managed at other health-care facilities. Cardiac death was defined as death caused by MI, significant cardiac arrhythmias, refractory congestive heart failure, or unexplained sudden death.

### Statistical analysis

Comparisons between patient groups were performed using Student's *t*-test for continuous variables and the $\chi^2$-test for categorical variables. Continuous variables were described by mean ± standard deviation (SD). Kaplan–Meier cumulative survival analysis for MACE such as fatal and nonfatal MIs was performed, and survival curves were compared by the Logrank (Mantel-Cox) test. Statistical significance was defined as $P < 0.05$. Commercially available software packages Medcalc® (MedCalc Software bvba, Belgium) and Statistical Package for the Social Sciences (SPSS 17®) (SPSS-Inc., Chicago, IL) were used.

## Results

The mean age of the study cohort was 57 ± 9 years with a male-to-female ratio of 76:24% and mean body mass index (BMI) of 26.915 ± 4.121 kg/m$^2$. Prevalence of hypertension, diabetes, dyslipidemia, and positive family history were 76%, 20%, 22%, and 17%, respectively. Twelve participants (12/50; 24%) were smokers (defined as current or left smoking less than 5 years). Table 1 also shows overall mean heart rate and blood pressures before and after adenosine interventions on no-caffeine and prior-caffeine days, and mean LV function parameters of no-caffeine adenosine MPI. Comparison of group A (30 patients with prior-caffeine adenosine stress but no MPI) with group B (20 patients with prior-caffeine adenosine stress MPI) revealed no significant difference in demographic parameters and no significant change in hemodynamic and ECG parameters during adenosine intervention with prior-caffeine and no-caffeine protocols [Table 2 and Figure 1]. Similarly, no significant difference was observed in LV function parameters prior-caffeine and no-caffeine MPIs in group B [Table 2 and Figure 2].

**Table 1: Patients' demographics**

| Variables | *N*=50 |
|---|---|
| Age in years (mean±SD) | 57±9 |
| BMI (kg/m$^2$) | 26.915±4.121 |
| Male:female | 38:12 |
| | (76%:24%) |
| Hypertension | 38 (76%) |
| Diabetes mellitus | 20 (40%) |
| Dyslipidemia | 22 (44%) |
| F/H of CAD | 17 (34%) |
| Smoking | 12 (24%) |
| No-caffeine | |
| Baseline HR | 74±10/min |
| Postadenosine HR | 86±11/min |
| Baseline BP | 128±19/85±10 |
| Postadenosine HR | 117±19/80±10 |
| Prior-caffeine | |
| Baseline HR | 75±10/min |
| Postadenosine HR | 82±10/min |
| Baseline BP | 126±19/85±10 |
| Postadenosine HR | 118±19/80±10 |
| LV function | |
| LVEF% | 68±08 |
| EDV (mL) | 80±22 |
| ESV (mL) | 28±12 |

SD: Standard deviation; BMI: Body mass index; HR: Heart rate; BP: Blood pressure; LVEF: Left ventricular ejection fraction; EDV: End diastolic volume; ESV: End systolic volume

### Follow-up analysis

During a median follow-up of 14 months (range 12–18 months), there was no fatal MI but 6 nonfatal MI based upon the history of short hospitalization for chest pain but without biochemical or ECG criteria for infarction (3/30 in group A and 3/20 in group B). Event-free survival (EFS) for fatal MI was 100% for both groups while EFS for nonfatal MI was 90% for group A and 85% for group B (nonsignificant *P* values) [Table 2]. Kaplan–Meier survival plot also depicted nonsignificant EFS for nonfatal MI [Figure 3].

## Discussion

Adenosine being the nonselective adenosine receptor agonist is the most commonly used vasodilator stress agent for MPI in the United States and Europe.[1,2] Caffeine is a potent nonselective adenosine receptors

**Table 2: Comparison of groups with or without caffeine abstinence**

| Variables | Group A (*N*=30) (prior-caffeine adenosine no-MPI) | Group B (*N*=20) (prior caffeine adenosine with MPI) | Chi-square/ *t*-test | *P* values* |
|---|---|---|---|---|
| Age in years (mean±SD) | 58±9 | 54±9 | –1.540 | 0.130 |
| BMI (kg/m$^2$) | 27.213±5.035 | 26.467±4.178 | –0.548 | 0.586 |
| Male:female | 22:08 (73%:27%) | 16:04 (80%:20%) | 0.052 | 0.818 |
| Hypertension | 23 (77%) | 15 (75%) | 0.031 | 0.860 |
| Diabetes mellitus | 12 (40%) | 7 (40%) | 0.087 | 0.768 |
| Dyslipidemia | 14 (47%) | 8 (40%) | 0.039 | 0.843 |
| F/H of CAD | 10 (33%) | 7 (35%) | 0.025 | 0.874 |
| Smoking | 7 (23%) | 5 (25%) | 0.031 | 0.860 |
| No-caffeine | | | | |
| Baseline HR | 74±10 | 74±11 | 0.000 | 1.000 |
| Postadenosine HR | 86±10 | 85±12 | –0.320 | 0.751 |
| Baseline BP | 125±20/88±8 | 131±18/89±10 | 1.081 | 0.285 |
| Post adenosine HR | 115±19/80±8 | 122±18/80±8 | 1.117 | 0.269 |
| Positive ECG | 4 (13%) | 03 (15%) | 0.029 | 0.881 |
| AV block (2$^{nd}$ degree) | 0 | 0 | - | - |
| Prior caffeine | | | | |
| Baseline HR | 75±10 | 74±10 | –0.346 | 0.731 |
| Postadenosine HR | 84±9 | 83±9 | –0.385 | 0.702 |
| Baseline BP | 126±19/89±8 | 130±18/90±10 | 0.745 | 0.460 |
| Postadenosine HR | 118±17/82±8 | 120±18/84±8 | 0.199 | 0.843 |
| Positive ECG | 4 (13%) | 3 (15%) | 0.029 | 0.881 |
| AV block (2$^{nd}$ degree) | 0 | 0 | - | - |
| No-caffeine | | | | |
| LVEF% | 69±8 | 67±8 | –0.866 | 0.391 |
| EDV (mL) | 84±23 | 74±20 | –1.585 | 0.119 |
| ESV (mL) | 29±13 | 26±11 | –0.849 | 0.400 |
| Prior-caffeine | | | | |
| LVEF% | - | 66±8 | - | - |
| EDV (mL) | | 75±20 | | |
| ESV (mL) | | 26±12 | | |
| Event-free survival | | | | |
| Fatal | 100% | 100% | 0.000 | 1 |
| Nonfatal | 90% | 85% | 0.175 | 0.656 |

*$P$<0.05. BP: Blood pressure; SD: Standard deviation; LVEF: Left ventricular ejection fraction; BMI: Body mass index; EDV: End diastolic volume; HR: Heart rate; ESV: End systolic volume

antagonist and a few observational studies reveal that caffeine induces blunted hemodynamic response and false negative results of vasodilator MPI, ASNC has recommended an abstinence of at least 12 h for caffeine prior to vasodilator MPI.[3] However, in last couple of years a few studies have been published with conflicting findings.[9-11] Human studies have shown that caffeine attenuated the adenosine-induced hypotension and tachycardia.[10] Our study did not show any significant change in hemodynamic response or ECG abnormality during adenosine infusion with or without caffeine abstinence. Studies published by Zoghbi *et al*.[10] and Lee *et al*.[11] also revealed no significant change in hemodynamic response and ECG abnormalities during adenosine infusion with or without caffeine abstinence. The justification for using a time of 60 min (45–60 minutes) after ingesting caffeinate for adenosine stress was based on the fact that peak plasma level was achieved within 15 min after oral ingestion of 100 mg of caffeine.[10] As per the ASNC guidelines,[3] the current practice is either cancellation or rescheduling of vasodilator MPI in patients without caffeine abstinence that causes inconvenience to patients, staff, and financial impact on admitted patients. However, results of recent studies[9-11] denying any significant impact of caffeine on severity of perfusion defects in GMPI studies and this has provided a justification for some institute to perform the procedure in patients who have ingested a cup of coffee on the day of vasodilator MPI. However, to the best of our knowledge, no study has evaluated the NPV of a normal adenosine GMPI study in patients without caffeine abstinence. Our results show no significant difference in NPV of normal adenosine GMPIs done with or without caffeine abstinence. It is important to mention that NPV of our normal vasodilator GMPI in this study was significantly lower than what is established for a normal GMPI with dynamic exercise[12,13] and vasodilators.[14] However, the finding

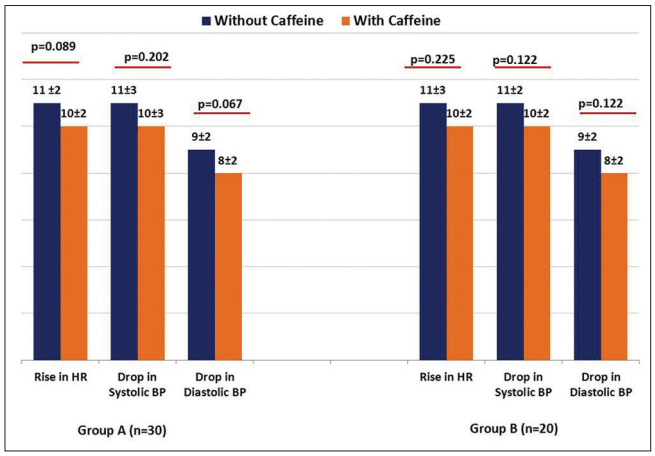


**Figure 1:** Comparative analysis of hemodynamic response in both groups with or without caffeine abstinence

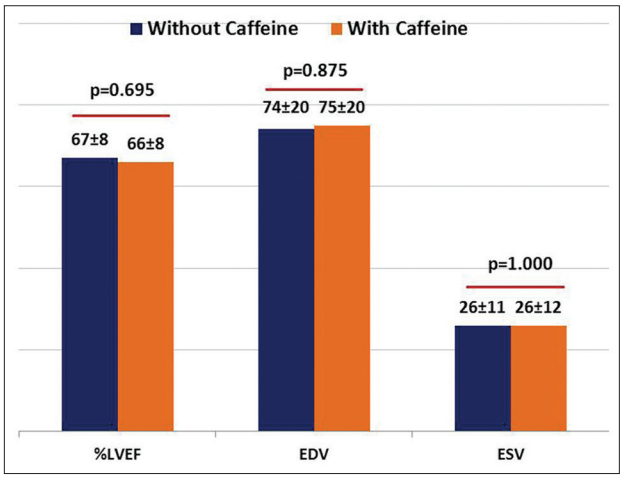


**Figure 2:** Comparative analysis of left ventricular function in group B (*N* = 20) with or without caffeine abstinence followed by gated myocardial perfusion imaging

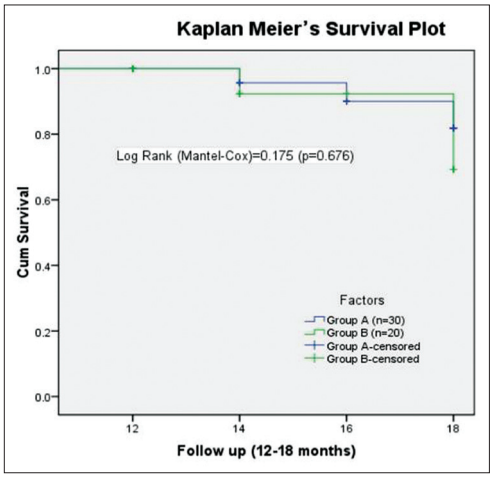


**Figure 3:** Kaplan–Meier survival plot in both groups for nonfatal cardiac events

of our study is in accordance with other previously published studies revealing higher event rate in patients having a normal GMPI with vasodilator stress than with physical exercise.[15,16] Various explanations have been postulated such as increased age and higher rate of comorbidity in these patients,[16] although other studies have ruled out these explanations.[14,15] Our results also show a similar outcome in terms of nonfatal MI in both groups. Although we did not measure serum caffeine level, the presence of adequate caffeine level at the time of adenosine MPI with caffeine abstinence could be a likely possibility. We are cognizant of the fact that the half-life of caffeine is 2.5–4 h but can be as long as 12 h as reported.[10] Similarly in an observational study, caffeine was found in detectable range in 40% of the participants who were abstained from caffeine products for more than 24 h and no significant difference in thallium-201 redistribution was seen in patients with detectable and undetectable serum caffeine levels.[17] In another study, a detectable level of caffeine was found in 74% of the participants after 12 h abstinence.[18] Pakistan is the fifth among the 10 countries with high tea and coffee consumption[19] and possibility of presence of detectable serum level of caffeine despite 12 h of abstinence needs a local prospective study to validate this assumption. Another plausible explanation for no significant difference in NPV between group A and group B could be inability of single cup of coffee to reduce coronary flow reserve (CFR) <2, which has a similar diagnostic accuracy as of CFR >3.5 because of a known trade-off phenomenon for existing MPI radiotracers at higher coronary flow.[20]

Strength of our study is that each patient acted as their own control and there was no significant difference in demographic parameters of patients in group A and group B. Furthermore, the amount of caffeine ingested in our study was compatible with usual scenarios of noncompliance of caffeine ingestion in any nuclear cardiology laboratory.

Our study has limitation of small sample size but it is adequately powered to address our clinical query. Another limitation is nonavailability of serum caffeine levels prior to the adenosine infusion in both the studies, and we cannot precisely comment upon the impact of detectable caffeine level despite abstinence in this study. Additional radiation exposure incurred by prior-caffeine MPI is another limitation despite approval by ethical committee, informed consent, and refusal of 30 patients is the sole reason for a smaller sample size of prior-caffeine-MPI group.

This study did not find any significant attenuation effect upon adenosine-induced hemodynamic response and similar NPV of a normal GMPI in patients with or without caffeine abstinence. We assume that better designed prospective studies are required to validate

findings of our study and provide justification for revision of guidelines about caffeine abstinence.

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Nil.

## Conflicts of interest
Authors do not disclose any financial or institutional conflict of interest.

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