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

Maseeh uz Zaman¹,², Nosheen Fatima³,³, Areeba Zaman⁴, Unaiza Zaman⁴, Rabia Tahseen⁴

¹Department of Radiology, The Aga Khan University Hospital, ²Department of Nuclear Cardiology, Karachi Institute of Heart Diseases, ³Department of Nuclear Medicine, Dr. Ziauddin Medical University, ⁴Dow 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 (⁹⁹mTc-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-cafèine adenosine—no MPI; group A). Twenty patients opted for a repeat MPI (prior-cafèine adenosine—MPI; group B). Adenosine-induced hemodynamic response and NPV of the normal MPI with no-cafèine and prior-cafèine 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/m². 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-cafèine and no-cafèine 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

Access this article online

Quick Response Code:
Website: www.wjnm.org
DOI:
10.4103/1450-1147.176887

How to cite this article: uz Zaman M, Fatima N, Zaman A, Zaman U, Tahseen R. Comparison of hemodynamic effects and negative predictive value of normal adenosine gated myocardial perfusion scan with or without caffeine abstinence. World J Nucl Med 2016;15:190-5.
**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.\(^\text{[1,2]}\) Adenosine, dipyridamole, and regadenoson augment the coronary blood flow by 3.5–4 folds by stimulating the adenosine A\(_{2A}\) receptors.\(^\text{[3]}\) Caffeine and other methylxanthine derivatives are nonspecific antagonists of all adenosine receptors subtypes (A\(_1\), A\(_{2A}\), A\(_{2B}\), A\(_{3}\))\(^\text{[4]}\) and may obliterate the adenosine-induced coronary hyperemia resulting in reduced sensitivity of stress MPI.\(^\text{[5]}\) 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\(^\text{[6-7]}\) 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.\(^\text{[8]}\) 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.\(^\text{[9]}\) 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\(^\text{[9]}\) or with MPI.\(^\text{[10,11]}\)

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.\(^\text{[9]}\) 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 \(\mu\)g/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 in 20 patients (group B: Prior-caffeine adenosine stress MPI). Heart rate and blood pressure were measured during the adenosine infusions. Rise in heart rate (\(\geq10\)) (from baseline) or drop of \(\geq10\) 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 χ²-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/m². 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].

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

| Variables                | N=50 |
|--------------------------|------|
| Age in years (mean±SD)   | 57±9 |
| BMI (kg/m²)              | 26.915±4.121 |
| Male:female              | 38:12 |
| Hypertension             | 38 (76%) |
| Diabetes mellitus        | 20 (40%) |
| Dyslipidemia             | 22 (44%) |
| F/H of CAD               | 17 (34%) |
| Smoking                  | 12 (24%) |
| 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
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. However, in last couple of years a few studies have been published with conflicting findings. Human studies have shown that caffeine attenuated the adenosine-induced hypotension and tachycardia. 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. and Lee et al. 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. As per the ASNC guidelines, 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 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 and vasodilators. However, the finding

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 | P values* |
|----------------------------|---------------------------------------------------|---------------------------------------------------|------------|-----------|
| Age in years (mean±SD)     | 58±9                                              | 54±9                                              | -1.540     | 0.130     |
| BMI (kg/m²)                | 27.213±5.035                                      | 26.467±4.178                                      | -0.548     | 0.586     |
| Male:female                | 22:08                                             | 16:04                                             | 0.052      | 0.818     |
| Hypertension               | 73% (27%)                                         | 80% (20%)                                         | 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 (23%)                                           | 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%)                                           | 0 (0%)                                            | 0.029      | 0.881     |
| AV block (2nd 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     |
| Post adenosine 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 (2nd 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.
having a normal GMPI with vasodilator stress than with physical exercise.\textsuperscript{[15,16]} Various explanations have been postulated such as increased age and higher rate of comorbidity in these patients,\textsuperscript{[16]} although other studies have ruled out these explanations.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[17]} In another study, a detectable level of caffeine was found in 74% of the participants after 12 h abstinence.\textsuperscript{[18]} Pakistan is the fifth among the 10 countries with high tea and coffee consumption\textsuperscript{[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.\textsuperscript{[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

of our study is in accordance with other previously published studies revealing higher event rate in patients...
findings of our study and provide justification for revision of guidelines about caffeine abstinence.

**Financial support and sponsorship**
Nil.

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

**References**

1. Reyes E, Wiener S, Underwood SR; European Council of Nuclear Cardiology. Myocardial perfusion scintigraphy in Europe 2007: A survey of the European Council of Nuclear Cardiology. Eur J Nucl Med Mol Imaging 2012;39:160-4.

2. Lapeyre AC 3rd, Goraya TY, Jhonston DL, Gibbons RJ. The impact of caffeine on vasodilator stress perfusion studies. J Nucl Cardiol 2004;12:506-11.

3. Henzlova MJ, Cerqueira MD, Hansen CL, Taillefer R, Yao SS. ASNC Imaging Guidelines for Nuclear Cardiology Procedures: Stress Protocols and Tracer. J Nucl Cardiol 2009;16:325-6.

4. Daly JW, Hide I, Muller CE, Shamim M. Caffeine analogs: Structure-activity relationships at adenosine receptors. Pharmacology 1991;42:309-21.

5. Hage FG, Iskandrian AE. The effect of caffeine on adenosine myocardial perfusion imaging: Time to reassess? J Nucl Cardiol 2012;19:415-9.

6. Smits P, Aengevaeren WR, Corstens FH, Thien T. Caffeine reduced dipyridamole-induced myocardial ischemia. J Nucl Med 1989;30:1723-6.

7. Smits P, Corsten FH, Aengevaeren WR, Wacker FJ, Thien T. False-negative dipyridamole-thallium-201 myocardial imaging after caffeine infusion. J Nucl Med 1991;32:1538-41.

8. Reyes E, Loong CY, Harbinson M, Donovan J, Anagnostopoulos C, Underwood SR. High dose adenosine overcomes the attenuation of myocardial perfusion reserve caused by caffeine. J Am Coll Cardiol 2008;52:2008-16.

9. Aqel RA, Zoghbi GJ, Trim Jr, Baldwin SA, Iskandrian AE. Effect of caffeine administered intravenously on intracoronary-administered adenosine-induced coronary hemodynamics in patients with coronary artery disease. Am J Cardiol 2004;93:343-6.

10. Zoghbi GJ, Hay T, Aqel R, Blackmon L, Heo J, Iskandrian AE. Effect of caffeine on ischemia detection by adenosine single-photon emission computed tomography perfusion imaging. J Am Coll Cardiol 2006;47:2296-302.

11. Lee JC, Fraser JF, Barnett AG, Johnson LP, Wilson MG, McHenry CM, et al. Effect of caffeine on adenosine-induced reversible perfusion defects assessed by automated analysis. J Nucl Cardiol 2012;19:474-81.

12. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: A meta-analysis. J Am Coll Cardiol 2007;49:227-37.

13. Zaman MU, Usmani S, Niaz K, Fatima N, Kamal S, Hameed A. Validation of prognostic and negative predictive values of normal cardiac perfusion study in then local population. Pak J Radiol 2009;17:999-1008.

14. Rozanski A, Gransar H, Hayes SW, Friedman JD, Hachamovitch R, Berman DS. Comparison of long-term mortality risk following normal exercise vs adenosine myocardial perfusion SPECT. J Nucl Cardiol 2010;17:999-1008.

15. Fatima N, Uz Zaman M, Ishaq M, Rasheed SZ, Baloch DJ, Wali A, et al. Higher events rate in patients with a normal gated myocardial perfusion imaging with dipyridamole than exercise: “Run for reliability”. Indian J Nucl Med 2012;27:172-5.

16. Navare SM, Mather JF, Shaw LJ, Fowler MS, Heller GV. Comparison of risk stratification with pharmacologic and exercise stress myocardial perfusion imaging: A meta-analysis. J Nucl Cardiol 2004;11:551-61.

17. Jacobson AE, Cerqueira MD, Raisys V, Shattuck S. Serum caffeine levels after 24 hours of caffeine abstinence: Observations on clinical patients undergoing myocardial perfusion imaging with dipyridamole or adenosine. Eur J Nucl Med 1994;21:23-6.

18. Majd-Ardekani J, Clowes P, Menash-Bonsu V, Nunan TO. Time for abstention from caffeine before an adenosine myocardial perfusion scan. Nucl Med Commun 2000;21:361-4.

19. Memon NA. Tea: A common man’s drink. Pak Food J 2013;8:20.

20. Böttcher M, Czernin J, Sun KT, Phelps ME, Schelbert HR. Effect of caffeine on myocardial blood flow at rest and during pharmacological vasodilatation. J Nucl Med 1995;36:2016-21.