Dietary Caffeine Does Not Affect Adenosine Myocardial Perfusion Imaging Interpretation

Dietary Caffeine and Adenosine MPI [Running title; 34 characters, limit 45]

Abstract: [296 words, limit 300]

Objectives

This prospective study investigated the effects of caffeine ingestion on the extent of perfusion abnormalities inducible by adenosine during myocardial perfusion imaging (MPI).

Background

Current recommendations for prolonged abstinence from caffeine and related methylxanthines before adenosine MPI are based on limited and conflicting studies. Contravention of this requirement is the most common reason for postponement or cancellation of adenosine MPI and results in delays in clinical care and economic losses.

Methods

Thirty patients with inducible perfusion abnormalities in at least two myocardial segments on standard (caffeine-abstinent) adenosine MPI underwent repeat testing with supplementary coffee intake. On both occasions, a blood sample was taken 60 seconds before the commencement of the adenosine infusion for measurement of plasma levels of caffeine and metabolites. Baseline and test MPIs were assessed by standard commercial software for stress percent defect, rest percent defect and percent defect reversibility.

Results

Despite significant increases in caffeine and metabolite concentrations over a wide range, there was no statistically significant change in stress percent defect, rest percent defect or percent defect reversibility between the baseline and test scans. Plasma caffeine concentration increased from 268 ± 428 at baseline to 3374 ± 1855 μg/L at the test scan (mean difference 3106 μg/L ([95% CI: 2460, 3752 μg/L; $p < 0.001$]). Likewise, there were statistically significant increases in the concentrations of the three metabolites. The increase in caffeine concentration between the baseline and test phases had little effect on the percent defect reversibility (average decrease of 0.003 for a 100 μg/L increase; 95% CI –0.17, 0.16; $p= 0.97$).

Conclusion

There was no significant relationship between the extent of adenosine-induced coronary flow heterogeneity and serum concentration of caffeine or its principal metabolites. Hence, the stringent requirements for prolonged abstinence from caffeine before adenosine MPI do not appear necessary.

Condensed abstract: [90 words, limit 100]

This prospective investigation evaluated the requirement for abstinence from caffeine prior to myocardial perfusion imaging (MPI) – a requirement based on conclusions of case observations over 20 years old. Subsequent data have been conflicting and studied only at a narrow range of caffeine intake. This study compared MPI findings for patients with known adenosine-induced perfusion abnormalities, with and without caffeine restriction. There was no relationship between the extent of adenosine-induced coronary flow heterogeneity and serum concentration of caffeine or its principal metabolites. Hence, prolonged abstinence from caffeine does not appear necessary before adenosine MPI.

Keywords:

Myocardial perfusion imaging, adenosine, caffeine

Abbreviations:

CI – confidence interval

MPI – myocardial perfusion imaging

SDS – summed difference score

SRS – summed rest score

SSS – summed rest score

Introduction:

Adenosine is a potent coronary arteriolar vasodilator which activates the A2A receptor to increase myocardial blood flow 3.5 – 4-fold {Henzlova}, and is therefore used for pharmacologic stress myocardial perfusion imaging (MPI). {Nishimura} Methylxanthines (caffeine, theophylline, and theobromine) are non-selective, competitive inhibitors of adenosine action {Daly}, and abstinence from caffeine is recommended for 12 – 24 hours prior to adenosine stress MPI {ACC/ASNC - Miyamoto, Henzlova; ESC – Hesse}. This recommendation is based on observational reports – more than 20 years old – of false-negative thallium MPI results with dipyridamole in the presence of caffeine {Smits 1989, 1991}, and subsequent supportive evidence for it has been limited and conflicting. {Zoghbi, Reyes}

Caffeine and related methylxanthines are present not only in coffee but also in several commonly available products including tea, cola and "energy" drinks, and chocolate {Barone, McCusker, Kovacs, McCusker2}. Thus, the embargo on caffeine before adenosine stress remains a frequent logistical problem when scheduling patients, particularly for urgent studies. The aim of this study was to compare the effects of *ad libitum* caffeine intake *vs* 24-hour abstinence from caffeine on the extent and severity of adenosine-induced perfusion abnormalities, supported by quantification of plasma levels of caffeine and its principal metabolites.

Methods:

We used a prospective (single-center) study to investigate the association between caffeine and the scans during normal conditions, and when patients had deliberately elevated levels of caffeine. The study was approved by the institutional ethics committee and district research governance, and was conducted in full conformity with the current Declaration of Helsinki and applicable local laws and regulations.

Subjects

Eligible subjects were recruited from patients referred for adenosine MPI after abstinence from caffeine (and related products) for at least 24 hours. Exclusion criteria were: any contraindication to adenosine {Henzlova}; age less than 55 years; current therapy with rifampin, cimetidine or estrogens {Lapeyre}; liver failure {Lapeyre}; and severe medical illness. Although it is known that tobacco smoking can affect caffeine metabolism {Kroon, Butler}, smoking was not defined as an exclusion criterion given the high prevalence of cigarette smoking among patients at risk for coronary artery disease (CAD). Consenting patients had a venous blood sample taken one minute before the start of the adenosine infusion for measurement of plasma levels of caffeine and its three main metabolites (theophylline, theobromine and paraxanthine).

MPI

Initial rest/adenosine stress MPI was performed using either a two-day or a one-day rest/stress protocol. The total activity of Tc-99m sestamibi (Cardiolite®, Lantheus, North Billerica, MA) was 1395 ± 75 MBq (mean ± SD). Adenosine (Adenoscan, Astellas Pharma, Deerfield, IL) was administered as a continuous infusion of 140 μg/kg/minute over four minutes with 12-lead ECG and blood pressure monitoring. Single-photon emission computed tomograhic (SPECT) sestamibi images were acquired over a 180 degree arc from right anterior oblique to left posterior oblique using a dual-head, large-field-of-view gamma camera (Symbia T-6, Siemens, Knoxville, TN) fitted with low-energy, parallel-hole, high-resolution collimators; a low-dose, non-contrast X-ray computed tomographic (CT) scan encompassing the heart was sequentially obtained for attenuation correction. Post-stress sestamibi images were acquired with ECG gating (eight frames per cycle). Attenuation-corrected and non-corrected images were reconstructed using an iterative algorithm (Flash-3D® [Siemens]: stress phase 6 iterations, 5 subsets; rest phases 5 iterations, 5 subsets) and a Gaussian filter. Reconstructed images were displayed on a dedicated nuclear medicine workstation.

Patients who were assessed visually to have reversible perfusion defects on initial MPI in at least two segments of the ACC/ASNC 17-segment model {Cerqueria 2002} were enrolled in the study, and attended on a separate day for a repeat adenosine stress SPECT-CT examination after caffeine administration (see below), using a mean (± SD) sestamibi activity of 595 (± 64) MBq. This adenosine stress study was paired with the subject's original rest study. No interventions or changes in medication were permitted between the original and the second examination. Blood was again collected one minute prior to the start of the adenosine infusion.

Caffeine administration

For the second phase of the study, subjects were instructed to resume their usual coffee or tea consumption. In addition, each subject was given an extra cup of coffee 60 minutes before the

repeat adenosine stress test. The strength of the coffee was determined according to a random number generator to be one-half, one or two teaspoons of instant coffee to mimic a range of caffeine use. The interval of 60 minutes between coffee ingestion and MPI was chosen based on published data on peak blood concentration. {Liguori}

Methylxanthine assay

Assays were performed with a validated, multi-calibrator, ultrahigh performance liquid chromatography/tandem mass spectrometry method with isotopically-labelled internal standards and protein precipitation with acetonitrile, very similar to a previously published method. {Stewart} Assay performance was monitored using diluted Clinchek Antiasthmatics Plasma Control Level 1 (Recipe, Munich, Germany). The limits of quantification and detection for methylxanthines were 25 μg/L and 5 μg/L, respectively. The intra-assay coefficient of variation (CV) was less than 5% and the inter-assay CV less than 6%.

MPI interpretation

The rest/stress scan pairs were de-identified and numbered randomly. All scans were quantified for rest percent defect, stress percent defect and percent defect reversibility against a gender-specific reference database through a standard commercial software package (Corridor 4DM-SPECT, INVIA, Ann Arbor, MI). {Xu}

As a secondary, semi-quantitative measure of perfusion defect extent and severity, stress and rest perfusion data were also scored visually by two experienced nuclear medicine physicians to yield a summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS = SSS – SRS){Samuels} for the 17 myocardial segments (theoretical range of scores: 0 [normal] – 68 [absent myocardial perfusion]).

Statistical Analyses

Linear regression was used to investigate the relationship between the percent defect reversibility (and SDS as a secondary outcome) and the serum concentration of caffeine and metabolites. A logarithmic transformation was applied to the concentrations of caffeine and metabolites due to the strong positive skew of both. To examine the effect of caffeine administration on the percent defect reversibility or the SDS, an analysis of covariance was used with the percent defect reversibility (or SDS) for the test scan as the dependent variable, and the baseline percent defect reversibility (or SDS) as an independent variable. This reduced the potential problem of regression to the mean. {Barnett}

The Bland–Altman method was used to verify consistency between the calculated rest percent defects on the first and second scan assessments.

A one sample t-test was used to examine the difference between baseline and test scans for the concentrations of caffeine and metabolites (after verifying that the difference was roughly normally distributed). These tests were used to show the change in average caffeine levels.

The R statistical program was used for all analyses (version 2.12.2, http://www.r-project.org).

Sample size was determined using a linear regression model: 30 subjects were required in order to detect a change in percent defect reversibility of 5 units for a one unit change in standardized caffeine concentration with 90% power and two-sided statistical significance of 5%. The assumed standard deviation in the difference in percent defect reversibility was 8.

Results:

The baseline patient characteristics are in Table 1. Twenty-five (83%) of the subjects were known to have coronary disease, of whom 16 had prior revascularisation, either by percutaneous (11) or surgical (11) intervention (6 had undergone both). None of the women was taking estrogen replacement therapy or oral contraceptives.

Table 1. Patient characteristics (n=30). Statistics are number (%) or mean ± standard deviation.

Demographics		
	Male	21 (70%)
	Age (years)	70 ± 8
	Weight (kg)	86 ± 19
	Height (cm)	168 ± 9
Medical history		
	Smoking (active or previous)	17 (57%)
	Diabetes mellitus	10 (33%) Type 1 – 2 (7%) Type 2 – 8 (26%)
	Hypertension	20 (67%)
	Dyslipidemia	26 (87%)
	Peripheral vascular disease	2 (7%)
	Previous myocardial infarction	6 (20%)
	Previous coronary artery bypass graft surgery	10 (33%)
	Previous percutaneous coronary intervention	9 (30%)
	Pacemaker	1 (3%)
	Left bundle branch block	0 (0%)
Referral diagnosis		
	Chest pain	25 (83%)
	Dyspnea	4 (14%)
	Pre-operative evaluation (non-cardiac surgery)	1 (3%)
Medications		

	Angiotensin-converting enzyme inhibitor	12 (40%)
	Angiotensin receptor blocker	5 (17%)
	Beta-blocker	17 (57%)
	Calcium channel blocker	11 (37%)
	Nitrate	19 (63%)
	Lipid lowering agent	24 (80%)

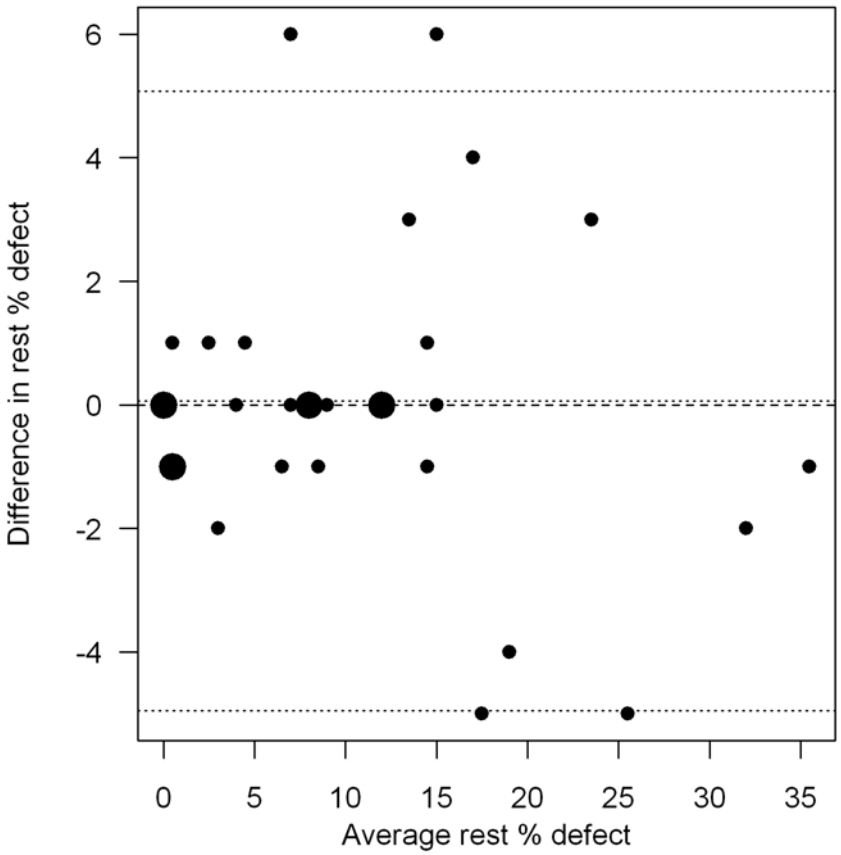
Serum caffeine levels were available for all patients. The means and ranges of concentrations of caffeine and caffeine metabolites during baseline and test conditions (i.e. after sanctioned caffeine consumption) are shown in Table 2. The difference in the caffeine concentrations between baseline and test scans was statistically significant, increasing by a mean of 3106 μg/L (95% CI: 2460, 3752 μg/L; $p < 0.001$). Likewise, there was a significant increase in the mean for each of the measured metabolites between the baseline and test samples.

Table 2. Values and differences of concentrations of caffeine and caffeine metabolites in baseline and test phases.

	Baseline		Test		Difference		
	Range	Mean	Range	Mean	Range	Mean	p-value
Caffeine (μg/L)	25–1790	268	706–10430	3374	+440 to +8640	3106	<0.001
Theophylline (μg/L)	25–427	76	25–779	180	–133 to +352	104	<0.001
Theobromine (μg/L)	25–909	236	83–2430	491	–252 to +1567	255	<0.001
Paraxanthine (μg/L)	25–2060	293	192–4540	1111	–565 to +2480	818	<0.001

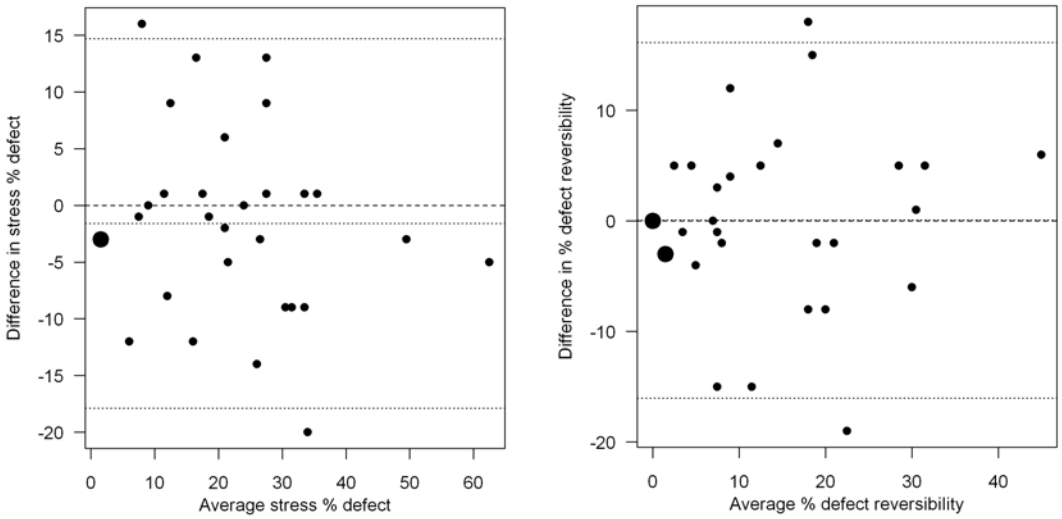
As the same rest examination was used for both the baseline and test studies, there should have been no significant difference in rest percent defect between the two datasets (Figure 1). The limits of agreement were –5.1 to +5.0 (mean difference 0.1, $p = 0.89$).

Figure 1. Bland–Altman plot of change in rest % defect between baseline and test studies. The sizes of the dots are proportional to the number of observations. The horizontal dotted lines show the mean difference and the limits of agreement (–5.1 to +5.0). The dashed horizontal line at zero shows perfect agreement.



There was no statistically significant change in stress percent defect or percent defect reversibility between the baseline and test scans (Figure 2). For stress percent defect, the limits of agreement were –17.9 to +14.7 (mean difference –1.6, p = 0.30). For percent defect reversibility, the limits of agreement were –16.1 to +16.0 (mean difference 0.1, p = 0.96).

Figure 2. Bland–Altman plots of changes in (a) stress percent defect; and (b) percent defect reversibility. The sizes of the dots are proportional to the number of observations. The horizontal dotted lines show the mean difference and the limits of agreement. The dashed horizontal line at zero shows perfect agreement.



The relationship between the change in percent defect reversibility and caffeine concentration was evaluated, for both baseline and test settings (Figure 3). Log caffeine concentration was not a statistically significant predictor of percent defect reversibility. In the baseline phase, for every unit increase in log caffeine concentration, percent defect reversibility decreased by 0.38 (95% CI –2.67, 1.92; p = 0.75). In the test phase, for every unit increase in log caffeine concentration, percent defect reversibility increased by 0.69 (95% CI –5.36, 6.74; p = 0.83). The within-subject increase in caffeine concentration between baseline and test phases had little effect on the percent defect reversibility (mean change –0.003 for every 100 μg/L increase in caffeine; 95% CI –0.17, 0.16; p= 0.97) (Figure 4).

There was no association between caffeine and the secondary outcome of segmental scoring system. A one-unit increase in log caffeine concentration in the baseline phase reduced SDS by an average of 0.20 (95% CI: 1.68, 1.28; p = 0.79). In the test phase, a one-unit increase in log caffeine concentration corresponded with an average SDS reduction of 3.96 (95% CI: –8.59, 0.68; p = 0.10). For every 100 μg/L increase in caffeine concentration between baseline and test phases, the change in SDS decreased by 0.09 (95% CI –0.19, 0.01; p= 0.08).

Figure 3. Relationship between percent defect reversibility and caffeine concentration at (a) baseline and (b) test phases. (Caffeine concentration is plotted on a log scale because of its strong positive skew.)

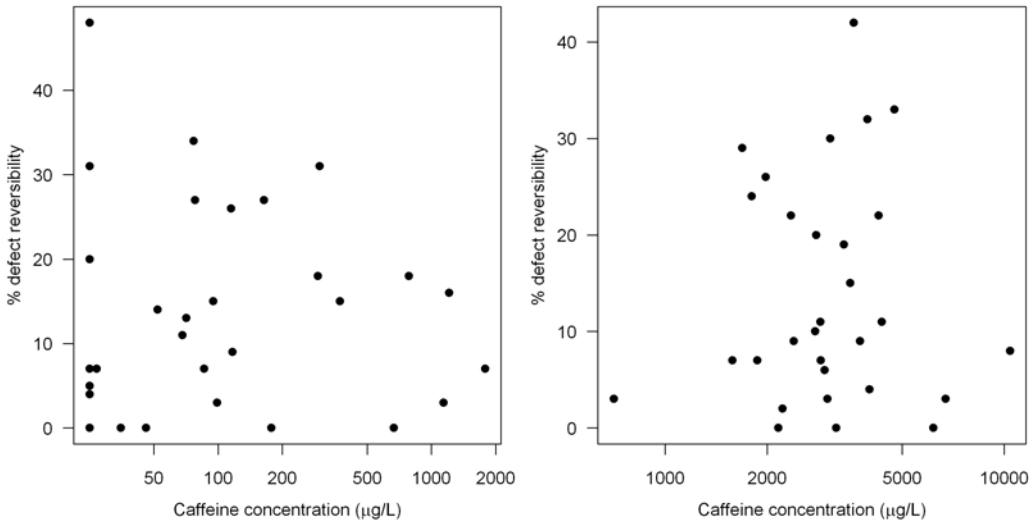
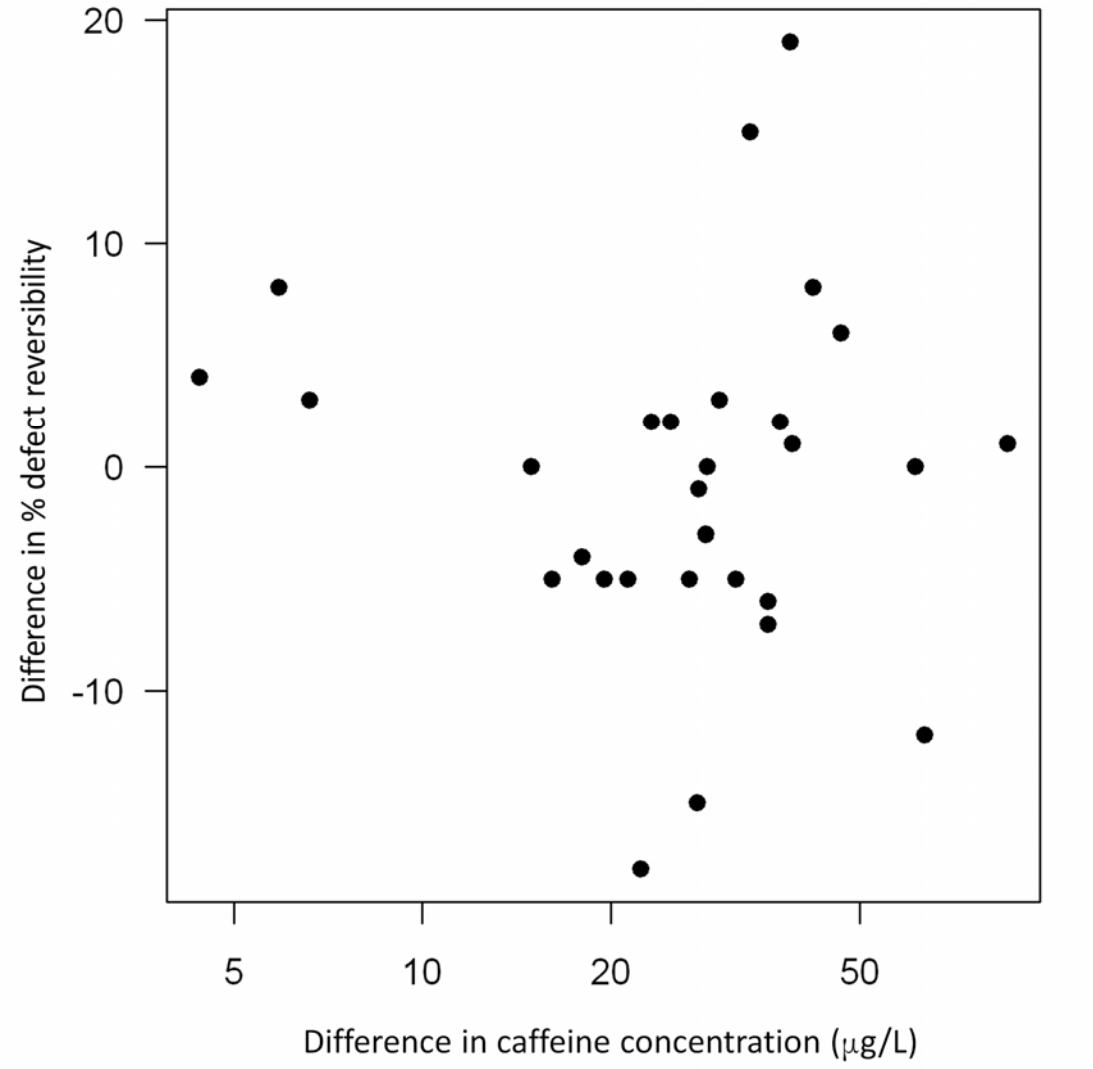


Figure 4. Relationship between the change in percent defect reversibility and change in caffeine concentration.



There were also no consistent associations between the caffeine metabolites and percent defect reversibility (Table 3).

Table 3. Linear regression coefficients between percent defect reversibility and log caffeine metabolite concentrations in baseline and test phases.

	Baseline phase	Test phase
Log theophylline	–1.50 (95% CI –5.29, 2.29; p = 0.44)	–1.44 (95% CI –5.54, 2.65; p = 0.50)
Log theobromine	–3.80 (95% CI –6.60, –0.99; p = 0.013)	–2.25 (95% CI –6.49, 2.00; p = 0.31)
Log paraxanthine	–0.99 (95% CI –3.34, 1.36; p = 0.42)	–1.93 (95% CI –6.64, 2.77; p =0.43)

Discussion:

This study used serial MPI to assess whether the ingestion of caffeine prior to adenosine stress MPI reduced the extent of adenosine-induced perfusion abnormalities. We examined both normal conditions and those with deliberately raised caffeine levels. Previous studies {Zoghbi, Reyes} have yielded conflicting results. The outcome of this study has important logistic implications for the practice of all nuclear cardiology laboratories, since the recommended prolonged abstinence from caffeine is a frequent hurdle for the performance of adenosine stress MPI.

It has previously been found that ingestion of an 8-ounce cup of coffee 1 hour before adenosine did not affect the imaging results (both total and reversible abnormalities, measured using automated quantitative methods). {Zoghbi} In that study, all subjects ingested the same quantity of coffee. A subsequent study {Reyes} — also using the same caffeine dose for all subjects — showed that caffeine decreased the size of the reversible perfusion defect on MPI. By contrast, the present study assessed adenosine-induced MPI defects over a broad range of caffeine concentrations, consistent with the recommendations of a subject review regarding trials in this subject area, {Lapeyre} and found no significant caffeine effect.

Related studies have also generated conflicting results. Flow-wire fractional flow reserve assessment of coronary stenoses with adenosine was not found to be significantly affected by the intravenous administration of caffeine {Salcedo, Aqel}, but caffeine was found to decrease myocardial flow reserve as assessed by rest/adenosine positron emission tomography. {Bottcher, Kubo, Namdar}

Additionally, intravenous aminophylline, which is known to be a more potent A2-receptor antagonist than caffeine {Stanek}, significantly attenuated adenosine-induced increases in heart rate, side-effects and ischemic ECG changes, but did not affect the size of adenosine-induced perfusion abnormalities. {Heller} The modification (or lack thereof) by caffeine of the peripheral hemodynamic effects of adenosine has been both suggested {Bottcher, Hurwitz} and rejected as a marker of the effects of caffeine on adenosine-induced coronary hyperemia. {Majd} Overall, there is insufficient evidence to support such a relationship. {Lapeyre}

Present practice is extrapolated from past case reports and case series observations. {Smits 1989, 1991} Caffeine levels (up to 9.7 mg/L) were considerably higher than those which would be achieved with reasonable dietary intakes. According to currently recommended practice, seemingly trivial and often inadvertent caffeine consumption leads to the postponement or cancellation of many inpatient and outpatient MPI procedures. Patient inconvenience and economic losses including losses of staff and time resources result. In hospitalised patients, extra costs are generated through prolonged lengths of hospital stay and delays in other potentially time-critical cardiac investigations and procedures.

The present prospective study found that there was no consistent relationship between the percent defect reversibility or SDS (measures of adenosine-induced myocardial perfusion heterogeneity) and serum concentration of caffeine or its principal metabolites. This was well-illustrated with scatterplots of the relationship between percent defect reversibility and caffeine concentration at baseline and test phases appearing random with no clear pattern.

The strengths of this study were: firstly, all subjects had unequivocal reversible ischemia on the baseline MPI scan; secondly, all subjects acted as their own controls when we examined the effect of the change in caffeine concentration; thirdly, the study simulated a realistic range of caffeine ingestion. Given the considerable variation in the caffeine content of foodstuffs {Barone} and in inter-individual rates of caffeine consumption and metabolism, {Balogh, Tiffin, Mahmarian – ADVANCE 2} caffeine doses were deliberately not controlled. On the contrary, it was considered more relevant to achieve a range of serum concentrations of caffeine (and of its principal

metabolites) to correlate with the MPI findings. Indeed, the lack of published data on the effects of variable caffeine levels has been criticised in the literature. {Lapeyre}

The study is limited by its small subject population. Although the sample size was adequately powered to address the clinical scenario intended, it was inadequate for time- or dose-ranging studies. It also could not address possible differences in caffeine effects among smokers and regular caffeine consumers: both of these groups are common in the population at risk of coronary artery disease. However, the rate of caffeine metabolism is likely to be higher in these groups, so they are likely to have lower plasma caffeine levels after any given dose of caffeine, and therefore there should be less effect related to supplementary caffeine.

Adenosine remains the most commonly used direct coronary vasodilator for MPI worldwide. The findings of this study are likely to be applicable to the use of adenosine as a coronary vasodilator for MPI using other modalities, such as positron-emission tomography, contrast echocardiography, magnetic-resonance imaging and X-ray computed tomography. The use of regadenoson, a relatively selective A2A receptor agonist, as an alternative to adenosine for MPI has increased recently. It has been validated for MPI {ADVANCE, ADVANCE 2} and the effect of caffeine on regadenoson MPI is the subject of an ongoing multicenter study {Tejani}.

Conclusion:

There was no relationship between the extent of adenosine-induced coronary flow heterogeneity and serum concentration of caffeine or its principal metabolites. Hence, ingestion of caffeine a few hours before adenosine MPI is unlikely to result in significant underestimation of the extent of flow-limiting coronary disease. This calls into question the policy of prolonged abstinence from caffeine required by most nuclear cardiology services in preparation for adenosine MPI; certainly, minor infractions of this policy should not cause the postponement or cancellation of adenosine MPI studies. The required duration, if any, of abstinence from caffeine for optimal adenosine MPI remains to be determined through time- and dose-ranging studies.

References:

Henzlova MJ, Cerqueira MD, Hansen CL, Taillefer R, Yao S-S. ASNC imaging guidelines for nuclear cardiology procedures: Stress protocols and tracers. J Nucl Cardiol 2009; doi:10.1007/s12350-009-9062-4.

Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Equivalence between adenosine and exercise thallium-201 myocardial tomography: A multicenter, prospective, crossover trial. J Am Coll Cardiol 1992;20:265-75.

Daly JW, Hide I, Muller CE, et al. Caffeine analogs: structure-activity relationships at adenosine receptors. Pharmacology 1991;42:309-21.

Miyamoto MI, Vernotico SL, Majmundar H, Thomas GS. Pharmacologic stress myocardial perfusion imaging: a practical approach. J Nucl Cardiol 2007;14:250-5.

Hesse B, Tägil K, Cuocolo A et al. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. Eur J Nucl Med Mol Imaging 2005;32:855-97.

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

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

Zoghbi GJ, Htay 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.

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.

Barone JJ, Roberts HR. Caffeine consumption. Food Chem Toxicol 1996;34:119-29.

McCusker RR, Goldberger BA, Cone EJ. Caffeine content of specialty coffees. J Anal Toxicol 2003;27:520-2.

McCusker RR, Goldberger BA, Cone EJ. Caffeine content of energy drinks, carbonated sodas, and other beverages. J Anal Toxicol 2006;30:112-4.

Kovacs D, Pivonka R, Khosla PG, Khosla S. Effect of caffeine on myocardial perfusion imaging using single photon emission computed tomography during adenosine pharmacologic stress. Am J Ther 2008;15:431-4.

Lapeyre AC III, Goraya TY, Johnston DL, Gibbons RJ. The impact of caffeine on vasodilator stress perfusion studies. J Nucl Cardiol 2004;11:506-11.

Kroon LA. Drug interactions with smoking. Am J Health Syst Pharm 2007;64:1917-21.

Butler MA, Iwasaki M, Guengerich FP, Kadluber FF. Human cytochrome P-450PA (P-450IA2), the phenacetin O-deethylase, is primarily responsible for the hepatic 3-demethylation of caffeine and N-oxidation of carcinogenic arylamines. Proc Natl Acad Sci USA 1989;86:7696-700.

Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. J Nucl Cardiol 2002;9:240-5.

Liguori A, Hughes JR, Grass JA. Absorption and subjective effects of caffeine from coffee, cola and capsules. Pharmacol Biochemistry Behav 1997;58:721–6.

Stewart NA, Buch SC, Conrads TP, Branch RA. A UPLC-MS/MS assay of the “Pittsburgh cocktail”: six CYP probe-drug/metabolites from human plasma and urine using stable isotope dilution. Analyst 2011;7:505-12.

Xu Y, Hayes S, Ali I et al. Automatic and visual reproducibility of perfusion and function measures for myocardial perfusion SPECT. J Nucl Cardiol 2010;17:1050-7.

Samuels B, Kiat H, Friedman JD, Berman DS. Adenosine pharmacologic stress myocardial perfusion tomographic imaging in patients with significant aortic stenosis. Diagnostic efficacy and comparison of clinical, hemodynamic and electrocardiographic variables with 100 age-matched control subjects. J Am Coll Cardiol. 1995;25:99-106.

Barnett AG, van der Pols J, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol 2005;34:215–20.

Salcedo J, Kern MJ. Effects of caffeine and theophylline on coronary hyperemia induced by adenosine or dipyridamole. Catheter Cardiovasc Interv 2009;74:598-605.

Aqel RA, Zoghbi GJ, Trimm 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.

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

Kubo S, Tadamura E, Toyoda H, et al. Effect of caffeine intake on myocardial hyperaemic flow induced by adenosine triphosphate and dipyridamole. J Nucl Med 2004;45:730-8.

Namdar M, Koepfi P, Grathwohl R, et al. Caffeine decreases exercise-induced myocardial flow reserve. J Am Coll Cadiol 2006;47:405-10.

Stanek EJ, Melko GP, Charland SL. Xanthine interference with dipyridamole-thallium-201 myocardial imaging. Ann Pharmacother 1995;29:425–7.

Heller G, Dweik R, Barbour M, et al. Pretreatment with theophylline does not affect adenosine-induced thallium-201 myocardial imaging. Am Heart J 1993;126:1077-83.

Hurwitz R, Lyons K, Taketa R. Adenosine challenge and boost protocols: new tools for myocardial perfusion imaging. Clin Nucl Med 1999;24:92-3.

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.

Balogh A, Harder S, Vollandt R, Staib AH. Intra-individual variability of caffeine elimination in healthy subjects [published erratum appears in Int J Clin Pharmacol Ther Toxicol 1993;31:208]. Int J Clin Pharmacol Ther Toxicol 1992;30:383-7.

Tiffin P, Ashton H, Marsh R, Kamali F. Pharmacokinetic and pharmacodynamic responses to caffeine in poor and normal sleepers. Psychopharmacology 1995;121:494-502.

Iskandrian AE, Bateman TM, Belardinelli L, et al. Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: Results of the ADVANCE phase 3 multicenter international trial. J Nucl Cardiol 2007;14:645-58.

Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE. Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A2A agonist regadenoson versus adenosine in myocardial perfusion imaging. J Am Coll Cardiol Imaging 2008;1:307-16.

Mahmarian JJ, Cerqueira MD, Iskandrian AE, et al. Regadenoson induces comparable left ventricular perfusion effects as adenosine: A quantitative analysis from the ADVANCE MPI 2 trial. J Am Coll Cardiol Imaging 2009;2:959-68.

Tejani F, Thompson RC, Iskandrian AE, McNutt BE, Franks B. Effect of caffeine on SPECT myocardial perfusion imaging during regadenoson pharmacologic stress: Rational and design of a prospective, randomized, multicentre study. J Nucl Cardiol 2011;18:73-81.