Cardiac Imaging

High-Dose Adenosine Overcomes the Attenuation of Myocardial Perfusion Reserve Caused by Caffeine

Eliana Reyes, MD,*† Chee Y. Loong, MRCP,*† Mark Harbinson, MD, MRCP,†
Jackie Donovan, MSc, DipRCPath,‡ Constantinos Anagnostopoulos, MD, PhD, FRCP, FRCR, FESC,†
S. Richard Underwood, MD, FRCP, FRCR, FESC, FACC*†

London, United Kingdom

Objectives   We studied whether an increase in adenosine dose overcomes caffeine antagonism on adenosine-mediated coronary vasodilation.

Background   Caffeine is a competitive antagonist at the adenosine receptors, but it is unclear whether caffeine in coffee alters the actions of exogenous adenosine, and whether the antagonism can be surmounted by increasing the adenosine dose.

Methods   Myocardial perfusion scintigraphy (MPS) was used to assess adenosine-induced hyperemia in 30 patients before (baseline) and after coffee ingestion (caffeine). At baseline, patients received 140 μg/kg/min of adenosine combined with low-level exercise. For the caffeine study, 12 patients received 140 μg/kg/min of adenosine (standard) and 18 patients received 210 μg/kg/min (high dose) after caffeine intake (200 mg). Myocardial perfusion was assessed semiquantitatively and quantitatively, and perfusion defect was characterized according to the presence of reversibility.

Results   Caffeine reduced the magnitude of perfusion abnormality induced by standard adenosine as measured by the summed difference score (SDS) (12.0 $\pm$ 4.4 at baseline vs. 4.1 $\pm$ 2.1 after caffeine, p < 0.001) as well as defect size (18% [3% to 38%] vs. 8% [0% to 22%], p < 0.01), whereas it had no effect on the abnormalities caused by high-dose adenosine (SDS, 7.7 $\pm$ 4.0 at baseline vs. 7.8 $\pm$ 4.2 after caffeine, p = 0.7). There was good agreement between baseline and caffeine studies for segmental defect category (kappa = 0.72, 95% confidence interval: 0.65 to 0.79) in the high-dose group. An increase in adenosine after caffeine intake was well tolerated.

Conclusions   Caffeine in coffee attenuates adenosine-induced coronary hyperemia and, consequently, the detection of perfusion abnormality by adenosine MPS. This can be overcome by increasing the adenosine dose without compromising test tolerability.   (J Am Coll Cardiol 2008;52:2008–16) © 2008 by the American College of Cardiology Foundation

Adenosine is a potent coronary vasodilator that increases myocardial blood flow up to 4-fold and provokes flow heterogeneity and even ischemia in territories served by stenosed epicardial coronary arteries (1). According to experimental data (2,3), methylxanthines can attenuate the coronary hyperemic response to adenosine through the blockade of arteriolar A_{2A} adenosine receptors, thereby potentially halting the detection of flow-limiting coronary artery disease (CAD) by adenosine myocardial perfusion scintigraphy (MPS). A limited body of evidence indicates that caffeine, a 1,3,7-trimethylxanthine that binds to the

ubiquitous adenosine receptors in a competitive manner (4), can abolish myocardial blood flow heterogeneity induced by dipyridamole, a vasodilator agent that acts by augmenting the concentration of endogenous adenosine (5,6). On this basis, it might be expected that caffeine would also inhibit hyperemia by exogenous adenosine. However, recent studies have shown that caffeine does not modify the coronary vasodilator response to adenosine and have suggested that at the doses given, adenosine results in greater concentrations of adenosine molecules than dipyridamole to compete with caffeine for receptor occupancy (7,8). Other factors such as variations in study methodology, subject population, and caffeine dose could also account for these discrepant results.

The effect of caffeine on adenosine MPS remains unclear. Furthermore, adenosine stress testing is increasingly performed with supplemental exercise yet the effect of caffeine on

this modality of stress is unknown. Because of the competitive interaction between adenosine and caffeine, receptor blockade by caffeine could be surmounted by increasing the adenosine dose; however, the effectiveness of this measure has not been examined. Thus, we hypothesized that caffeine in coffee would reduce the magnitude of the reversibility of a perfusion abnormality demonstrated by adenosine MPS, and that an increase in adenosine would overcome caffeine antagonism and provoke the same perfusion abnormality in the presence of caffeine compared with the abnormality using a standard protocol after caffeine abstention.

Methods

Study design and subject selection. This was a prospective single-center study. Patients were eligible if they had suspected or known CAD (i.e., previous myocardial infarction, revascularization, or documented angiographically significant coronary artery stenosis) and were scheduled for adenosine MPS (baseline procedure) for the clinical assessment of anginal symptoms. Patients were enrolled if they had refrained from caffeine-containing products for at least 12 h before stress testing and had unequivocal reversible myocardial perfusion abnormality at baseline. Patients who fulfilled the entry criteria returned for repeat adenosine MPS after caffeine intake. Exclusion criteria were as follows: 1) contraindication to adenosine, intolerable symptoms, or adverse reaction during baseline procedure; 2) left bundle branch block or paced rhythm on resting electrocardiogram; 3) serum caffeine concentration ≥ 2 mg/l at baseline; 4) reversibility involving $<10\%$ of total left ventricular myocardium or, in other words, <2 of 17 myocardial segments on baseline MPS; and 5) change in symptoms, medication, or documented acute ischemic event or coronary intervention between the 2 MPS procedures. A total of 30 patients were enrolled in the study. The Royal Brompton and Harefield Research Ethics Committee approved the study, and written informed consent was obtained from all patients.

Study protocol. All patients made 2 visits. For each visit, patients were asked to refrain from caffeinated products for a minimum of 12 h before the test. Medications were not altered. For the baseline procedure (visit 1), stress testing was performed with adenosine infused at the standard dose of 140 μg/kg/min for 6 min combined with low-level exercise on a bicycle ergometer. Patients unable to cycle performed isometric exercise with handgrip. A blood sample was drawn immediately before the start of the adenosine infusion to measure caffeine concentration. Within 6 weeks of the baseline procedure (visit 2), repeat stress testing was performed 60 min after ingestion of coffee to allow plasma caffeine level to reach its maximum (9). To determine the effect of caffeine on adenosine MPS, 12 patients received adenosine at 140 μg/kg/min for 6 min combined with exercise as for the baseline study (standard adenosine group). To demonstrate the efficacy of high-dose adenosine,

18 patients received 210 μg/kg/min of adenosine for 6 min with supplemental exercise performed in identical way as baseline (high-dose adenosine group). As for the baseline study, blood was drawn before the start of the adenosine infusion to measure caffeine concentration.

The electrocardiographic rhythm was monitored throughout each stress procedure, and blood pressure and heart rate recorded every 2 min. Symptoms were recorded as reported by the patient, who was also questioned directly about symptoms every 2 min until completion of the test. Patient symptoms were graded at the time of test using a symptom-severity score from 0 (none) to 3 (severe). A summed score was obtained by addition of the score for each symptom. Safety was assessed by collection of vital signs, electrocardiographic data, and adverse events during each procedure. Detailed information on daily caffeine consumption, smoking habit, medications, and co-morbidities including history of hepatic or renal disease was collected by a questionnaire. Dietary caffeine intake was estimated according to previously published data (10,11).

Caffeine administration. Coffee was prepared on-site using a 15-bar pump pressure espresso machine. Patients were given 2 large shots of espresso, which, according to previous reports, would provide $\approx$200 mg of caffeine (10), the total caffeine content in 2 standard cups of coffee or in a 355-ml (12-fl oz) serving of brewed coffee from specialty shops (10). The dosage was chosen to reach a serum caffeine concentration ≥ 2 mg/l, which is known to inhibit the hemodynamic response to intravenous adenosine (12).

Serum caffeine. Blood samples were taken from a vein cannula, and total serum concentration of caffeine (protein bound and unbound) was measured by a commercially available homogenous enzyme immunoassay technique (Emit Assay, Dade Behring Ltd., Milton Keynes, United Kingdom).

Image processing. For the baseline procedure, 80 to 120 MBq (2.2 to 3.2 mCi) of thallium-201 was injected 3 min into the adenosine infusion and stress image acquisition started within 10 min of thallium-201 injection. Rest images were acquired 3 to 4 h later after an additional injection of 40 MBq (1.1 mCi) of thallium-201. For the repeat MPS procedure, stress images were acquired in an identical way as for baseline. Rest imaging was not conducted to minimize radiation exposure to the patient. Emission tomographic imaging was performed using a dual-headed gamma camera (Optima, IGE Medical Systems, Milwaukee, Wisconsin) equipped with a low-energy all-purpose collimator. Patients were supine, and 64 projections were acquired over a semicircular 180° arc from 45°

Abbreviations and Acronyms

CAD = coronary artery disease

MI = myocardial infarction

MPS = myocardial perfusion scintigraphy

SDS = summed difference score

SSS = summed stress score

TID = transient ischemic dilation

right anterior oblique to 45° left posterior oblique. A 20% symmetrical energy window was used at 72 and 167 keV. Transverse tomograms of the left ventricle were reconstructed using a Hanning pre-filter with a cutoff frequency of 0.75 cycles/cm and a ramp filter during back-projection. Transaxial slices were reoriented according to current recommendations (13). No attenuation correction was applied.
Image interpretation. Unprocessed planar images were displayed in the cine format to assess quality and to exclude significant patient motion or attenuation. The tomographic slices were divided into 17 segments, and tracer uptake was graded semiquantitatively for each segment by 2 experienced nuclear cardiologists without knowledge of clinical data or caffeine status. In case of disagreement, the segment was assigned to a category by a third reader. Scores were attributed on a 5-point system by taking into account the severity of the perfusion defect: 0 = normal uptake (tracer activity ≥70% of maximal myocardial activity); 1 = mild reduction (50% to 69%); 2 = moderate reduction (30% to 49%); 3 = severe reduction (10% to 29%); and 4 = absent uptake (tracer activity 0% to 9% of maximum). For each patient, the summed stress score (SSS) and summed rest score (SRS) were obtained by addition of the perfusion score for each segment. The summed difference score (SDS) was estimated by subtracting the SSS from the SRS, and this measure was used to define the extent and depth of reversibility.

Each myocardial segment was classified further as showing a fixed, reversible, or partially reversible (mixed) defect, or as normal. Segments were also assigned to 1 of the following territories: left anterior descending artery (segments 1, 2, 7, 8, 13, 14, and 17), left circumflex artery (segments 5, 6, 11, 12, and 16), and right coronary artery (segments 3, 4, 9, 10, and 15) (13). Each territory was characterized using the same segmental classification. Defect size was quantified as a percentage of the myocardium involved in the left anterior descending, left circumflex, or right coronary artery territory. Quantitative defect size, transient ischemic dilation (TID [stress/rest left ventricular volumes ratio ≥1.22]) and lung thallium-201 uptake (lung/heart counts ratio ≥0.45) were calculated using a commercially available program (Quantitative Perfusion SPECT [single-positron emission computed tomography], Cedars-Sinai Medical Center, Los Angeles, California).
Statistical analysis. Results were summarized as mean (± SD) or median (interquartile range). Histogram plots and the Shapiro-Wilk W test were used to test for normality. When this was the case, comparisons within the groups were performed using the *t* test for paired observations. Non-normally distributed data were analyzed using the Wilcoxon signed-rank test. Comparison between groups was performed with the 2-sample *t* test. Categorical differences were examined with the chi-square test or with the McNemar test for paired observations. Pearson correlation was used to assess the variation in SDS according to serum caffeine concentration.

The primary outcome measures were SDS and segmental defect classification at baseline and after caffeine intake. A reduction in baseline SDS of at least 40% after caffeine was considered to be clinically relevant. A sample of 12 patients gives 90% power to detect such difference (2-sided significance at alpha = 0.05). Agreement for segmental defect classification between baseline and caffeine studies was examined to determine whether high-dose adenosine would provoke the same defect in the presence of caffeine compared with the defect at baseline. Because agreement is likely to be better than that expected by chance, the value in the null hypothesis was set at 0.40. A total of 308 myocardial segments gives 90% power to detect a kappa value of 0.70 (2-sided significance at alpha = 0.05), which is indicative of good agreement (14). Differences were considered statistically significant at p values <0.05 (2-sided). Analysis was performed using SPSS version 14.0 (SPSS Inc., Chicago, Illinois).

Results

Patient characteristics. Patient characteristics are summarized in Table 1. Both adenosine MPS procedures were completed at a median interval of 12 days (range 6 to 21 days). All patients were habitual caffeine consumers with a median daily consumption of 5 cups (range 1 to 10 cups) of tea or coffee, or both, which represents a median caffeine intake of 300 mg/day (range 60 to 600 mg/day). None of the patients had a history of hepatic or renal impairment.
Serum caffeine concentration. At baseline, caffeine was undetectable in 17 patients (serum caffeine concentration ≤0.1 mg/l) and ranged from 0.2 to 1.3 mg/l in 13 patients after abstention from caffeinated products for a median 18 h (range 12 to 41 h) (Table 2). Sixty minutes after ingestion of coffee, serum caffeine concentration increased significantly (Fig. 1).
Baseline. At baseline, adenosine stress provoked a significant increase in heart rate and rate pressure product in both the standard and high-dose adenosine groups, whereas there was no change in systolic or diastolic blood pressure (Table 3). There was no difference between groups for any of the hemodynamic measures (p > 0.05 for all comparisons).
Caffeine. Resting heart rate, blood pressure, and rate pressure product did not change significantly after caffeine intake (Table 3). Similarly, caffeine had no effect on the hemodynamic response to either standard or high-dose adenosine. No statistically significant difference was found between groups for any of the hemodynamic parameters (p > 0.05 for all comparisons).

Effect of Caffeine on Adenosine MPS

Standard adenosine. Mean SDS decreased by 65% (95% CI: 58% to 73%) after caffeine intake (12.0 ± 4.4 at baseline vs. 4.1 ± 2.1 after caffeine, p < 0.001). Individual SDS is shown in Figure 2. The mean difference in SSS and SDS

| Table 1 | Patient Characteristics by Stress Protocol |

	All Patients	Standard Adenosine	High-Dose Adenosine	p Value
n	30	12	18	—
Age, yrs	65 ± 7	66 ± 6	64 ± 7	0.4
Weight, kg	82 ± 23	83 ± 32	81 ± 14	0.8
Body mass index, kg/m²	28 ± 3	29 ± 4	27 ± 3	0.1
Hypertension, n (%)	15 (50)	8 (67)	7 (39)	0.1
Hypercholesterolemia, n (%)	20 (67)	7 (58)	13 (72)	0.4
Smoking, n (%)	12 (40)	4 (33)	8 (44)	0.7
Diabetes mellitus, n (%)	10 (33)	6 (50)	4 (22)	0.1
Symptoms, n (%)				
Chest pain	25 (83)	10 (83)	15 (83)	>0.9
Exertional dyspnea	21 (70)	10 (83)	11 (61)	0.2
Known CAD, n (%)	24 (80)	9 (75)	15 (83)	0.5
Previous MI, n (%)	14 (47)	4 (33)	10 (56)	0.2
Previous revascularization, n (%)				
PCI	10 (33)	5 (42)	5 (28)	0.4
CABG	10 (33)	3 (25)	7 (39)	0.4
Medication, n (%)				
Beta-blocker	20 (67)	7 (58)	13 (72)	0.4
Calcium antagonist	8 (27)	3 (25)	5 (28)	0.8
Nitrates	6 (20)	3 (25)	3 (17)	0.5
Nicorandil	9 (30)	4 (33)	5 (28)	0.7
Aspirin	24 (80)	10 (83)	14 (78)	0.7
Statin	19 (63)	7 (58)	12 (67)	0.6

Values are mean ± SD where appropriate.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

between baseline and caffeine studies was −7.9 ± 3.0 and −7.8 ± 3.2, respectively (Fig. 3). Representative images are shown in Figure 4.

The number of fully or partially reversible myocardial segments detected per patient decreased significantly from 7.1 ± 1.8 at baseline to 3.7 ± 1.6 after caffeine intake (mean difference: 3.4, 95% CI: 2.4 to 4.5, p < 0.001). In addition, quantitative analysis showed a significant reduction in the median size of perfusion defect from 18% (3% to 38%) at baseline to 8% (0% to 22%) after caffeine (p < 0.01), with 9 patients demonstrating a multivessel disease distribution at baseline compared with 2 patients after caffeine intake (p = 0.02).

No statistically significant relationship was found between SDS changes from baseline to the caffeine study and serum caffeine concentration (r = −0.26, p = 0.4). With regard to nonperfusion markers of ischemia, TID was observed in 2 patients and increased thallium-201 lung

uptake in 1 patient at baseline but not after coffee ingestion (Fig. 4).

High-dose adenosine. In contrast to the standard adenosine group, mean SDS did not change significantly after caffeine intake in the high-dose group (7.7 ± 4.0 at baseline vs. 7.8 ± 4.2 after caffeine, p = 0.7) (Fig. 2). The mean difference in SSS and SDS between baseline and caffeine studies was 0.2 ± 2.3 and 0.1 ± 2.4, respectively, which was significantly smaller than the mean difference in SSS and SDS observed with standard adenosine (p < 0.001 in both cases) (Fig. 3).

There was no significant difference in the number of abnormal myocardial segments detected per patient at baseline and after caffeine intake (6.8 ± 2.9 vs. 6.7 ± 2.5, p = 0.8). The number of fully or partially reversible segments was also similar (6.0 ± 2.4 at baseline vs. 5.4 ± 2.2 after caffeine, p = 0.6). On a segmental basis, overall agreement for defect category between baseline and caffeine

| Table 2 | Serum Caffeine Concentration |

	Standard Adenosine (n = 12)	High-Dose Adenosine (n = 18)	p Value
Baseline, mg/l	0.2 ± 0.3 (0.0 to 0.8)	0.3 ± 0.4 (0.0 to 1.3)	0.2
Caffeine, mg/l	6.2 ± 2.6 (3.9 to 12.3)*	5.7 ± 2.0 (2.9 to 9.6)*	0.5
Difference between caffeine and baseline, mg/l	+5.9 ± 2.7 (+3.2 to +12.3)	+5.4 ± 2.1 (+2.0 to +9.3)	0.3

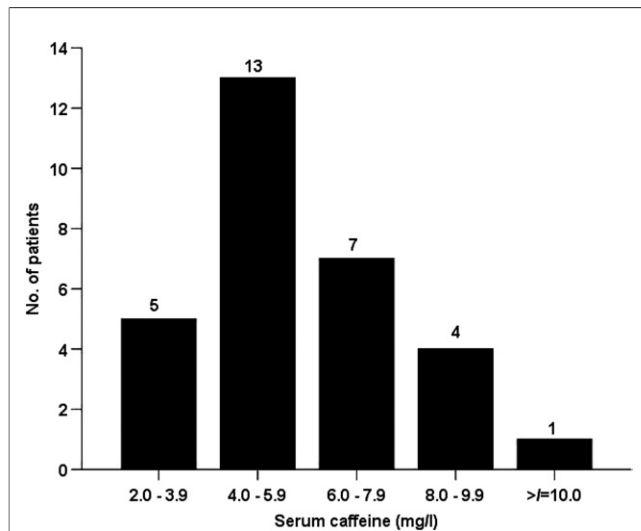Data presented as mean ± SD (range). *p < 0.01 versus baseline.

Figure 1   Serum Caffeine After Coffee Ingestion

Distribution of serum caffeine concentrations across
the study population after coffee consumption (n = 30).

studies was 84% (258 of 306 segments, kappa = 0.72, 95%
CI: 0.65 to 0.79) (Table 4). On a vascular territory basis,
agreement for defect category was 87% (47 of 54 territories,
kappa = 0.81, 95% CI: 0.69 to 0.93). Regarding nonper-
fusion markers of ischemia, TID was present in 2 patients
both at baseline and after caffeine intake. A case example is
shown in Figure 5.

Side effects. At baseline, 26 of 30 (87%) patients experi-
enced side effects during adenosine stress testing (Table 5).
Of 47 side effects, 44 (94%) were graded as mild. None of
the side effects was graded as severe. After caffeine intake,
the total occurrence of side effects decreased by 71% in the
standard adenosine group. The summed symptom score also
decreased from 1.6 ± 1.1 at baseline to 0.6 ± 0.7 after
caffeine (p = 0.02). In contrast, the frequency of side effects

at baseline and after caffeine was similar in the high-dose
group (Table 5). The summed symptom score was also
similar (1.4 ± 1.1 at baseline vs. 1.3 ± 1.2 after caffeine,
p > 0.9). There were no electrocardiographic changes
attributable to either caffeine intake or a high dose of
adenosine. No adverse events occurred, and no patient
needed aminophylline, dose reduction, or early termination
of the adenosine infusion either at baseline or after caffeine.

Discussion

The present study is the first to demonstrate that caffeine in
coffee attenuates the magnitude of myocardial perfusion
abnormality elicited by adenosine stress testing. According
to the study, intake of caffeine before stress may result in
significant underestimation of the extent of flow-limiting
coronary disease by adenosine MPS, which has important
implications for patient management. This observation
strengthens the hypothesis that caffeine is an effective
antagonist at the coronary adenosine receptors. The study
also shows for the first time that the inhibitory effect of
caffeine on adenosine-induced hyperemia can be sur-
mounted by increasing the adenosine dose. These results all
together provide further evidence of the competitive inter-
action between adenosine and caffeine and its potential
impact on the efficacy of vasodilator stress.

Caffeine is the most widely consumed psychoactive drug,
with a per capita consumption estimated at 280 mg/day in
the U.S. and as high as 400 mg/day in the Scandinavian
countries and in the United Kingdom (15). Coffee is the
main source of caffeine worldwide. Caffeine content in a
regular cup of coffee varies greatly depending on the variety
of coffee bean and brewing method used (10,16), and thus
caution must be exercised when relating the physiological
effects of caffeine to coffee intake rather than to actual
caffeine concentrations. In addition, caffeine levels in plasma
after coffee ingestion can vary widely owing to interindi-
vidual differences in caffeine metabolism (9,17), which is the

Table 3	**Hemodynamic Response to Adenosine Stress**			
	Standard Adenosine (n = 12)		**High-Dose Adenosine (n = 18)**	
	Baseline 140 μg/kg/min*	**Caffeine** 140 μg/kg/min	**Baseline** 140 μg/kg/min	**Caffeine** 210 μg/kg/min
Rest				
HR, beats/min	65 ± 12	65 ± 13	63 ± 9	65 ± 10
SBP, mm Hg	146 ± 18	141 ± 16	143 ± 18	144 ± 19
DBP, mm Hg	83 ± 10	86 ± 8	83 ± 12	84 ± 11
RPP, ×10^3 mm Hg · min^{-1}	9.5 ± 1.9	9.2 ± 2.0	9.1 ± 1.9	9.3 ± 2.2
Stress				
HR, beats/min	91 ± 17†	88 ± 17†	94 ± 14†	97 ± 12†
SBP, mm Hg	152 ± 20	152 ± 16	149 ± 18	143 ± 20
DBP, mm Hg	83 ± 11	87 ± 12	82 ± 14	79 ± 11
RPP, ×10^3 mm Hg · min^{-1}	13.8 ± 3.2†	13.3 ± 2.5†	14.0 ± 2.5†	13.8 ± 2.7†
Peak watts, median (range)‡	75 (15 to 75)	75 (15 to 75)	75 (25 to 75)	75 (25 to 75)

Values are mean ± SD unless indicated otherwise. *Adenosine dose. †p < 0.01 versus rest values. ‡Patients unable to cycle (n = 2) performed
isometric exercise with handgrip.

DBP = diastolic blood pressure; HR = heart rate; RPP = rate-pressure product; SBP = systolic blood pressure.
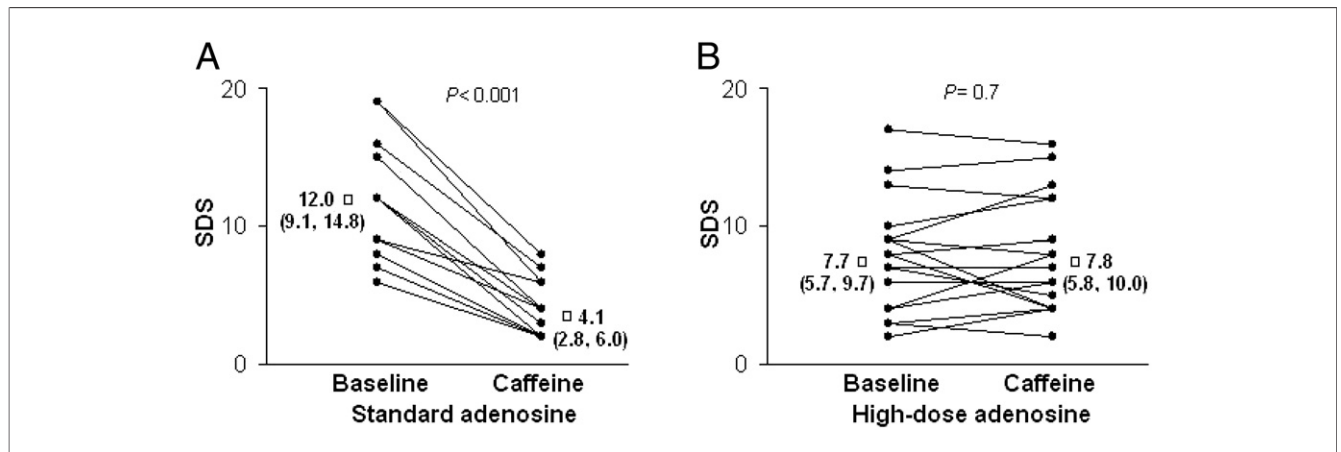
Figure 2   **SDS at Baseline and After Caffeine**

Individual and mean (95% confidence interval) summed difference score (SDS) at baseline and
after caffeine intake during **(A)** standard and **(B)** high-dose adenosine myocardial perfusion scintigraphy.

most likely explanation for the observed variability in serum
caffeine concentrations despite standard brewing of the
same coffee brand.

In line with recent observations (18), coffee ingestion had
no effect on resting blood pressure or heart rate, probably
because of caffeine habituation and development of toler-
ance (19). As indicated in previous experimental studies
(20,21), our results suggest that caffeine habituation does not
modify the potency of caffeine at the adenosine receptors.

The primary mechanism of action of caffeine in humans
occurs through the blockade of adenosine receptors (2,22).
Although caffeine interacts with the receptors at low con-
centrations (2,3), it is relatively less potent than other
xanthines at the A_{2A} subtype, which is responsible for the
coronary vasodilator effect of adenosine (2). Indeed, caffeine
had no effect on myocardial blood flow heterogeneity
induced by intravenous adenosine at plasma concentrations

that were almost one-half the concentrations attained in the
present study (7). Similar concentrations of caffeine did not
modify the hyperemic response to intracoronary adenosine
as measured by the fractional flow reserve in patients with
angiographically significant coronary artery stenosis (8).
Also, comparable caffeine levels do not appear to attenuate
the peak hyperemic effect of selective A_{2A} adenosine recep-
tor agonism (23).

By contrast, administration of a high dose of caffeine was
effective at inhibiting selective A_{2A}-receptor–mediated cor-
onary vasodilation in a canine model (24). The results of the
present study extend this observation to the clinical setting
and support the notion that at a dose commonly encoun-
tered in daily life, caffeine blocks the coronary A_{2A} receptors
from adenosine, thereby attenuating its vasodilator action
and potentially reducing the sensitivity of adenosine MPS
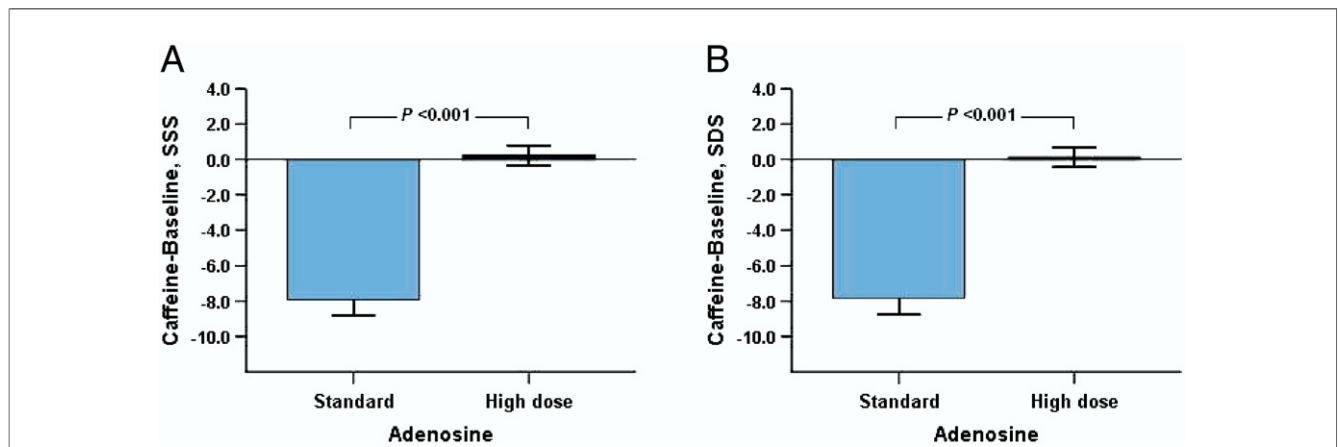for the detection of coronary stenosis. Caffeine also reduced

Figure 3   **Mean Difference in SSS and SDS Between Baseline and Caffeine Studies**

Mean difference in **(A)** summed stress scores (SSS) and **(B)** summed difference scores (SDS) between baseline and
caffeine myocardial perfusion scintigraphy studies for the standard and high-dose adenosine groups. Error bars represent ± SEM.
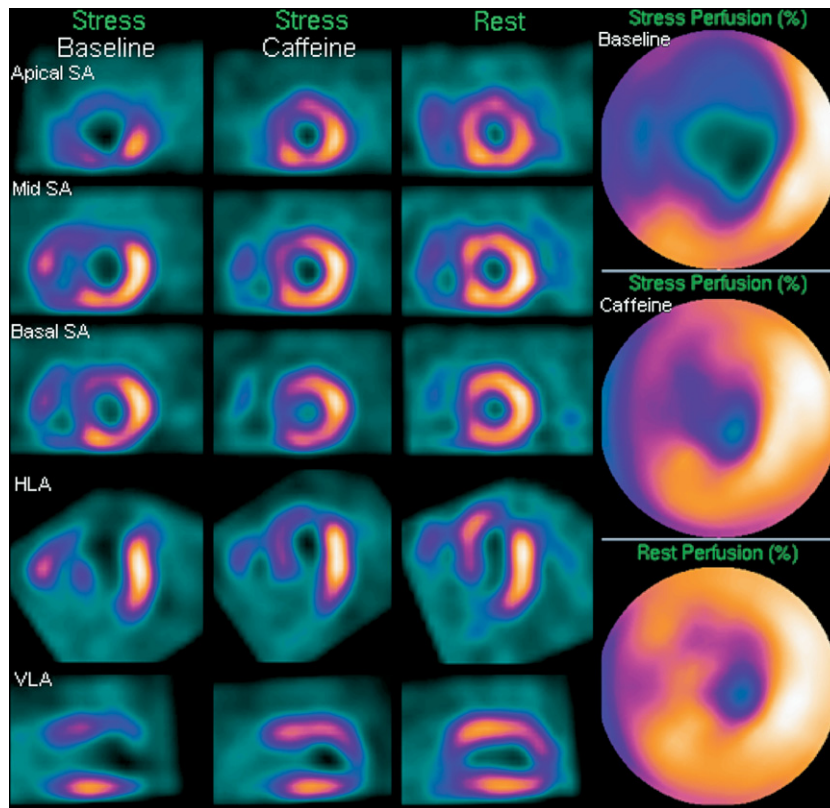
Figure 4   **MPS Images of Same Patient Illustrating Effect of Caffeine on Standard Adenosine MPS**

The baseline myocardial perfusion scintigraphy (MPS) images of a patient with a history of angina show extensive and profound apical and anteroseptal inducible perfusion abnormalities associated with transient ischemic dilation and increased right ventricular thallium-201 uptake in the stress tomograms. After coffee (serum caffeine = 12.3 mg/l), there is marked reduction in the magnitude of perfusion abnormalities. TID and abnormal right ventricular uptake are no longer present. HLA = horizontal long-axis view; SA = short-axis view; VLA = vertical long-axis view.

the frequency and severity of adenosine-related side effects, reflecting its nonselective action at the various adenosine receptors (2,3). The lack of a concentration-response effect of serum caffeine levels on the reversibility of perfusion abnormality in the present study was most likely the result of insufficient statistical power to detect such an effect.

The current study also demonstrates that, in the presence of inhibitory concentrations of caffeine, administration of 210 μg/kg/min of adenosine elicits myocardial perfusion abnormality similar to that of unantagonized adenosine.

This finding indicates that an increase in dose restores coronary responsiveness to adenosine and that, in most instances, a 50% increment would be sufficient to surmount the inhibitory effect of a relatively large intake of caffeine. Importantly, the use of a high dose of adenosine after coffee ingestion was well tolerated regardless of serum caffeine concentration.

It is not possible to determine from this study whether the observed changes of inducible perfusion abnormality are due to reduction of hyperemic perfusion or to increase in baseline perfusion. However, previous positron emission tomography studies have shown that caffeine does not increase resting perfusion (6,18); therefore, we can assume that caffeine-induced changes are due to a reduction in adenosine-induced hyperemia.

Finally, the study highlights the difficulties in standardizing the use of adenosine in patients who have consumed caffeine, and underscores the importance of screening for caffeine intake before adenosine MPS. According to our results, patients who consume caffeine within a few hours before the test could be considered for high-dose adenosine stress testing.
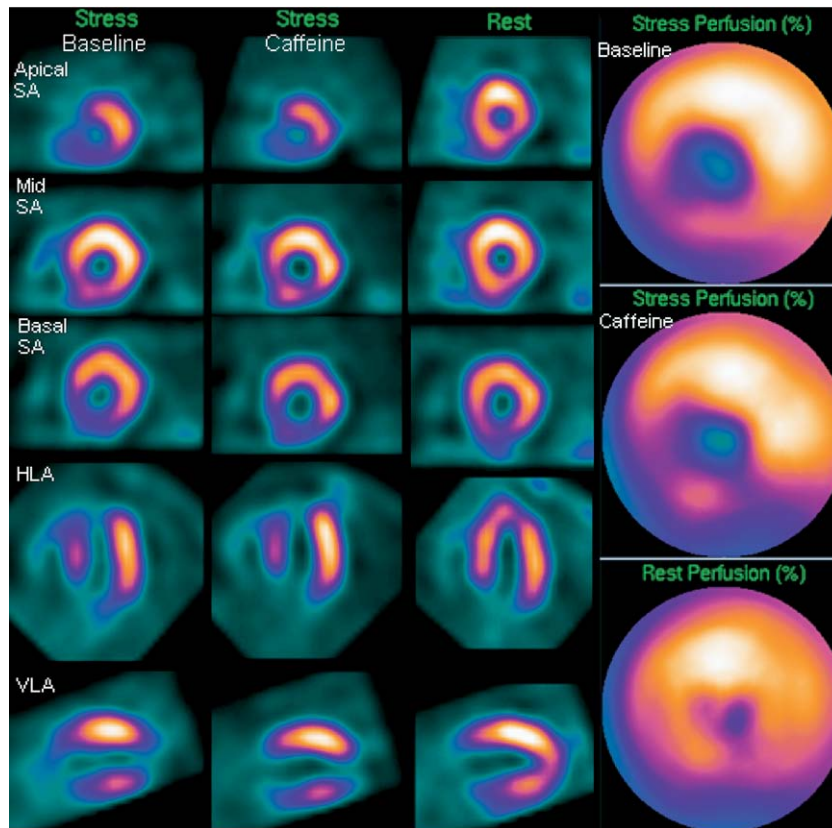
Table 4   **Segmental Agreement Between Baseline and Caffeine Studies in the High-Dose Adenosine Group According to Type of Perfusion Abnormality (n = 18)**

Baseline, n (%)	Caffeine, n (%)			
	Normal	Reversible	Mixed	Fixed
Normal	168 (55)	15 (5)	1 (0)	0 (0)
Reversible	19 (6)	55 (18)	0 (0)	3 (1)
Mixed	0 (0)	1 (0)	20 (7)	4 (1)
Fixed	0 (0)	0 (0)	5 (2)	15 (5)

Observed overall agreement 84% (258 of 306 segments).

Figure 5   **High-Dose Adenosine MPS After Caffeine in a Patient With Prior Myocardial Infarction and Recurrent Symptoms**

The baseline myocardial perfusion scintigraphy (MPS) images show profound apical anteroseptal and mild inferoapical and inferoseptal inducible perfusion abnormalities. After coffee ingestion (serum caffeine = 8.9 mg/l) and high-dose adenosine (210 μg/kg/min), the images are unchanged. Abbreviations as in Figure 4.

Study limitations. A potential limitation of the study is that the effect of caffeine on standard and high-dose adenosine was investigated in 2 separate groups of patients. Ideally, patients should have undergone both interventions but that would have resulted in an unacceptably high radiation burden on the patient.

Detailed angiographic data were not available for all patients, and therefore it was not possible to assess the

Table 5   **Side Effects During Adenosine Stress**

Side Effects	Standard Adenosine (n = 12)		High-Dose Adenosine (n = 18)	
	Baseline 140 μg/kg/min*	Caffeine 140 μg/kg/min	Baseline 140 μg/kg/min	Caffeine 210 μg/kg/min
Any symptom	10 (83)	5 (42)‡	16 (89)	12 (67)
Chest pain	8 (67)	2 (17)§	8 (44)	7 (39)
Dyspnea	6 (50)	4 (33)	7 (39)	8 (44)
Flushing	5 (42)	0	8 (44)	8 (44)
Headache	1 (8)	0	1 (6)	0
Dizziness	1 (8)	0	0	0
Abdominal discomfort	0	0	0	1 (6)
Other	1 (8)	0	1 (6)	1 (6)
Atrioventricular block	0	0	1 (6)	1 (6)
Ischemic ECG changes†	0	0	1 (6)	1 (6)

Data presented as n (%). *Adenosine infusion rate. †Horizontal or downsloping ST-segment depression >0.1 mV 80 ms after the J point. ‡p = 0.06 versus baseline. §p < 0.05 versus baseline.

ECG = electrocardiogram.

impact of caffeine intake on the diagnostic accuracy of adenosine MPS. Nonetheless, our results strongly suggest that moderate coffee ingestion before stress testing would significantly reduce the sensitivity of adenosine MPS for the detection of coronary stenosis.

We studied the effect of caffeine on adenosine combined with exercise rather than on adenosine only. The fact that adenosine stress testing is increasingly performed with exercise is important, because results of studies on adenosine only may not be easily extrapolated to the combined protocol. The addition of exercise could have influenced the results, although the paired design minimizes the potential confounding effect. Exercise might have blunted the peripheral effects of caffeine and adenosine, but it is unlikely that it would have potentiated caffeine antagonism. If anything, exercise might partly have offset the antagonism in some patients by eliciting active hyperemia.

Only males were recruited, and therefore our results may not be transferable to females. In women, ovarian hormones and their synthetic analogues can influence the metabolism and gastrointestinal absorption of caffeine, thus potentially altering both peak and time to peak levels of caffeine in plasma (25). This potential confounding factor warrants further investigation in female populations.

Conclusions

The present study demonstrates the competitive antagonism between adenosine and caffeine, and the impact of such interaction on myocardial perfusion imaging. Because of the relatively low affinity of adenosine receptors for caffeine, the effect of this xanthine is highly dose dependent. Moderate coffee intake attenuates adenosine-induced vasodilation in a surmountable manner, and thus an increase in adenosine dose may represent an alternative approach to the management of patients who consume caffeine before adenosine stress testing. The potential benefit of such an intervention provides a rationale to further investigate its feasibility and safety in routine clinical practice.

Reprint requests and correspondence: Dr. Eliana Reyes, Nuclear Medicine Department, Royal Brompton Hospital, Sydney Street, London SW3 6NP, United Kingdom. E-mail: e.reyes@rbht.nhs.uk.

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Key Words: caffeine ■ adenosine ■ myocardial perfusion scintigraphy ■ coronary artery disease.