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Cardiac Imaging

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

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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

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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.

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

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 ≈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°