Interaction of Caffeine With Regadenoson-Induced Hyperemic Myocardial Blood Flow as Measured by Positron Emission Tomography
A Randomized, Double-Blind, Placebo-Controlled Crossover Trial

To the Editor: Regadenoson is a selective A2A adenosine receptor agonist under investigation as a pharmacologic vasodilator in nuclear stress myocardial perfusion imaging (MPI) (1). It has a higher affinity for A2A receptors than adenosine and is a more potent coronary vasodilator. It selectively dilates coronary relative to peripheral vascular beds, potentially due to the high density of coronary A2A receptors, and activation of a small percentage of these receptors evokes maximal dilation (2). The use of caffeine, a nonselective competitive A2A receptor antagonist, has been contraindicated before vasodilator MPI (3) because it attenuates the coronary hyperemia caused by the nonselective adenosine receptor agonists adenosine and dipyridamole in a dose-dependent manner (4). The objective of this study was to determine the effects of caffeine on regadenoson-induced hyperemic myocardial blood flow (MBF) response.

In this phase II, double-blind, randomized, placebo-controlled crossover study, 41 healthy volunteers (15 female) who were age 18 years or older, nonsmokers, and regular coffee drinkers received in a blinded fashion either a 200-mg caffeine capsule—a dose corresponding to 2 cups of coffee (5)—on Day 1 and placebo on Day 2 or the inverse after refraining from methylxanthine-containing products for at least 24 h.

The MBF was measured 2 h after capsule ingestion by positron emission tomography (PET) with 15O-labeled water at rest and immediately after intravenous administration of regadenoson (400 μg over 10 s). Quantitative values of global MBF in milliliters per minute per gram were obtained as reported (6). Coronary flow reserve (CFR) was calculated as the ratio of hyperemic over resting MBF.

Continuous variables summarized as mean and SD or SE were compared using analysis of variance. A value of p < 0.05 was considered significant.

Twenty-one volunteers in the placebo/caffeine sequence and 20 in the caffeine/placebo sequence completed the study. All subjects (mean age ± SD 27 ± 6 years) returned for the second study day after a washout period (2 to 14 days). Baseline caffeine levels ± SE were comparable on the 2 study days (0.36 ± 0.09 mg/l vs. 0.23 ± 0.09 mg/l) and increased significantly after caffeine, but not after placebo (4.26 ± 0.18 mg/l vs. 0.33 ± 0.18 mg/l).

All resting and hyperemic MBF as well as CFR values were comparable irrespective of the sequence (caffeine/placebo or placebo/caffeine) or period (Day 1 or 2). Thus, all data were pooled for comparison. The MBF ± SE was not significantly different between caffeine and placebo at rest (1.13 ± 0.04 ml/min/g vs. 1.06 ± 0.05 ml/min/g) and stress (2.98 ± 0.14 ml/min/g vs. 3.05 ± 0.14 ml/min/g). Consequently, the regadenoson-induced CFR was comparable with and without caffeine (2.75 ± 0.16 vs. 2.97 ± 0.16, p = NS) (Fig. 1). The data show with 1-sided 95% confidence that any CFR reduction associated with caffeine intake is <20%.

Heart rate (HR) ± SD during resting MBF was higher after caffeine as compared with placebo (65 ± 11 beats/min vs. 61 ± 9 beats/min, p < 0.05). Similarly, systolic (118 ± 11 mm Hg vs. 112 ± 10 mm Hg, p < 0.001) and diastolic (73 ± 6 mm Hg vs. 70 ± 7 mm Hg, p < 0.001) blood pressure were higher after caffeine versus placebo. The HR increase induced by regadenoson was blunted by 20 beats/min (p < 0.001) after caffeine, whereas blood pressure was not significantly affected by prior caffeine ingestion.

No serious adverse event was reported. The most frequent adverse events were dyspnea (56%), palpitations (49%), flushing (30%), headache (28%), sensation of heaviness (28%), and paresthesia (19%). Caffeine pretreatment did not change the incidence of adverse events but was associated with improved tolerability (as assessed by a questionnaire) and attenuation of adverse event severity.

Previous studies found a dose-dependent attenuation of adenosine-induced and dipyridamole-induced CFR by caffeine (4). The present study is the first to report the effect of caffeine on coronary hyperemia induced by a selective adenosine agonist in humans. It suggests that regadenoson-induced CFR was not significantly affected by prior caffeine ingestion (200 mg) and remained above 2.0 for the majority of subjects. Therefore, it seems that caffeine blunt the vasodilatory effect of adenosine but has a limited effect on regadenoson. This may be explained by the fact that regadenoson has a higher A2A receptor affinity (7) and higher receptor reserve (2) compared with adenosine, and is administered as a bolus (as opposed to a 6-min infusion for adenosine). Therefore, regadenoson may lead to a higher A2A receptor occupancy and vasodilator effect compared with adenosine.

Regadenoson increases MBF by acting on coronary A2A receptors, and it increases HR by acting on both chemosensory neurons and peripheral vascular A2A receptors. There is a higher receptor reserve for coronary A2A agonist-mediated coronary vasodilation, and 25% occupancy by regadenoson translates into 90% maximal vasodilation. The receptor reserve for regadenoson on peripheral A2A receptors and chemosensory neurons, however, is unknown and may be lower. If the effects of caffeine are inversely proportional to the receptor reserve, then the higher receptor reserve required to dilate coronary vessels than to increase HR may explain that caffeine significantly blunted the increase in HR but had a limited effect on MBF caused by regadenoson.
Overall, regadenoson was well tolerated; side effects were generally mild or moderate in severity and all self-limiting. Caffeine attenuated the severity of side effects and improved tolerability of regadenoson. The interaction of caffeine with adenosine-induced, dipyridamole-induced, and even exercise-induced MBF changes (4,6) may limit the correct detection of coronary artery disease and subsequently the proper management of the patient, leading to the general recommendation to withhold caffeine for 24 h before vasodilator stress testing (3). Because the hyperemic MBF response to regadenoson after caffeine administration lies well within the range of reported response to nonselective adenosine receptor agonists and bicycle stress (6), the present study suggests that regadenoson causes coronary hyperemia with and without prior caffeine ingestion in healthy volunteers and moderate caffeine consumption may not interfere with regadenoson stress MPI. Further study in patients with coronary artery disease and possibly at higher caffeine doses would be required before definitive conclusions could be drawn (8).

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REFERENCES


Letters to the Editor

Concerns in the SESAMI Trial

In a clinical trial aiming to evaluate the safety and effectiveness of drug-eluting stents in comparison with bare-metal stents (BMS) in acute myocardial infarction (AMI), the description of the end points should be clear and identical. As an important composite clinical end point, major adverse cardiac events (MACE) was given 3 possible full names without any definition by Menichelli et al. (1) in the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction) trial, which could cause confusion. In the Methods section,