

The effect of caffeine on adenosine myocardial perfusion imaging: Time to reassess?

Fadi G. Hage, MD, FACC,^{a,b} and Ami E. Iskandrian, MD, MACC^a

See related article in this issue by Lee, et. al. Readers online can view the article at doi:10.1007/s12350-012-9517-x.

“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—based on limited studies—appears ill-founded.” These were the conclusions of the study by Lee et al¹ in this issue of the Journal. The interest, confusion, and the clinical relevance of the interaction (or lack of it) between adenosine and caffeine prompted this editorial viewpoint. This discussion will focus on adenosine; important differences between adenosine and dipyridamole (used in much earlier reports) suggest caution in mixing the old and the newer data but unfortunately the current practice guidelines for “vasodilator stress testing” of “prolonged abstinence” referred to above were based on the older data.

Caffeine, a methylxanthine alkaloid derivative, is widely quoted to be the most common psychoactive substance used by humans; the vast majority of adults in the United States report using some caffeine on a daily basis.² Caffeine is abundant in coffee, tea, chocolate, soft drinks, over-the-counter drugs, and other widely used products (Table 1). An online search for the term caffeine yields 11,800,000 hits with Google (accessed on December 26, 2011). Caffeine is a nonspecific competitive antagonist of all the adenosine receptor subtypes.³ Adenosine, dipyridamole, and regadenoson induce coronary hyperemia by stimulating the adenosine

receptor A_{2A}.⁴ It is therefore hypothesized that caffeine intake may interfere with adenosine-induced coronary hyperemia and myocardial perfusion imaging (MPI). The current American Society of Nuclear Cardiology (ASNC) imaging guidelines⁵ recommend that caffeine and other methylxanthines (such as aminophylline or theobromine) be withheld for at least 12 hours prior to vasodilator stress MPI and list this as a contraindication for performing the test.

Animal studies have demonstrated that there is a large A_{2A} receptor reserve in the coronary circulation such that an A_{2A} antagonist must block >70% of the receptors before a maximal response to adenosine is attenuated and >95% to reduce coronary vasodilation in response to adenosine by one-half.⁶ Indeed, an intravenous caffeine infusion (1-10 mg/kg) did not lower regadenoson-induced maximum increase in coronary blood flow in conscious dogs (although the duration of increased flow was reduced it remained ≥ 2 -fold baseline levels for ≥ 3 min in the presence of 1, 2, and 4 mg/kg caffeine).⁷ This is in contrast to the small reserve in the A₁ receptor (which mediates AV block and chest pain). Thus, intravenous theophylline (5 mg/kg), a more potent adenosine receptor antagonist than caffeine, in patients with angiographically normal coronary arteries abolished the prolongation of the A-H interval in response to adenosine but had minimal effect on the increase in coronary blood flow.⁸ Heller et al⁹ also noted that pretreatment with theophylline did not affect the adenosine-induced thallium-201 imaging results.

DOES CAFFEINE AFFECT ADENOSINE-INDUCED CHANGES IN MYOCARDIAL BLOOD FLOW?

Positron emission tomography studies have shown that caffeine impairs myocardial blood flow response to physical exercise,^{10,11} dipyridamole,^{12,13} and adenosine triphosphate¹³ but not regadenoson.¹⁴ The effect of caffeine administration on adenosine-induced myocardial blood flow response has not been studied using positron emission tomography but intravenous caffeine (4 mg/kg resulting in serum caffeine range of 2-8 with a mean of 3.7 mg/L) infusion had no effect on adenosine-induced myocardial hyperemia as assessed by fractional flow reserve using a pressure wire in subjects with angiographic evidence of coronary stenosis.¹⁵ Although

From the Division of Cardiovascular Diseases,^a University of Alabama at Birmingham, Birmingham, AL; and Section of Cardiology,^b Birmingham Veteran's Administration Medical Center, Birmingham, AL.

Reprint requests: Fadi G. Hage, MD, FACC, Division of Cardiovascular Diseases, University of Alabama at Birmingham, Zeigler Research Building 1024, 1530 3rd AVE S, Birmingham, AL 35294-0006; fadihage@uab.edu.

J Nucl Cardiol
1071-3581/\$34.00

Copyright © 2012 American Society of Nuclear Cardiology.
doi:10.1007/s12350-012-9519-8

Table 1. Caffeine content of various foods and drugs

Product	Serving size	Caffeine (mg)
Coffees		
Coffee, generic brewed	8 oz	133 (range 102-200)
Starbucks brewed coffee, Grande	16 oz	320
Dunkin' Donuts regular coffee	16 oz	206
Starbucks vanilla latte, Grande	16 oz	150
Coffee, generic instant	8 oz	93 (range 27-173)
Coffee, generic decaffeinated	8 oz	5 (range 3-12)
Teas		
Tea, brewed	8 oz	53 (range 40-120)
Starbucks Tazo Chai Tea Latte, Grande	16 oz	100
Snapple, peach lemon or raspberry	16 oz	42
Arizona Iced Tea, black	16 oz	32
Arizona Iced Tea, green	16 oz	15
Soft drinks		
Coca cola, classic	12 oz	35
Diet Coke	12 oz	47
Coke zero	12 oz	35
Pepsi	12 oz	38
Diet Pepsi	12 oz	36
Dr Pepper	12 oz	41
Mountain Dew, regular or diet	12 oz	54
Jolt Cola	12 oz	72
Mountain Dew MDX, regular or diet	12 oz	71
Sprite, regular or diet	12 oz	0
Sierra Mist, regular or free	12 oz	0
7-Up, regular or diet	12 oz	0
Energy drinks		
Spike Shooter	8.4 oz	300
Monster Energy	16 oz	160
Full Throttle	16 oz	144
Red Bull	8.3 oz	80
Amp	8.4 oz	74
Frozen desserts		
Ben & Jerry's Coffee Heath Bar Crunch	8 fl oz	84
Haagen-Dazs Coffee Ice Cream	8 fl oz	58
Chocolates/candies		
Hershey's Special Dark Chocolate Bar	1.45 oz	31
Hot Cocoa	8 oz	9 (range 3-13)
OTC drugs		
NoDoz (maximum strength)	1 tablet	200
Vivarin	1 tablet	200
Excedrin (extra strength)	2 tablets	130
Anacin (maximum strength)	2 tablets	64

Table modified from Center for Science in the Public Interest www.cspinet.org/reports/caffeine.pdf. Accessed on December 13, 2011.

these agents all ultimately work by activating adenosine A_{2A} receptors in the coronary circulation, it cannot be stressed enough that they induce variable effects on myocardial blood flow depending on the interstitial

availability of adenosine or its receptor agonist (regadenoson) locally. Further, it is unclear whether a modest decrease in the myocardial blood flow reserve with caffeine to the level detected in these studies will affect

myocardial perfusion by MPI since nuclear tracer extraction plateaus at myocardial blood flow lower than that seen after caffeine supplementation in these studies. For example, in the study by Bottcher et al¹² dipyridamole-induced myocardial blood flow reserve decreased from 3.35 ± 0.75 to 2.3 ± 0.75 after caffeine administration (one or two cups of coffee 1-4 hours prior to MPI). The authors concluded that since the flow reserve was above 2 in the majority of subjects even after caffeine, “the diagnostic accuracy of pharmacological stress testing might not be altered” by caffeine intake.

DOES CAFFEINE AFFECT ADENOSINE MPI?

Smits et al¹⁶ were the first to evaluate the effect of caffeine on vasodilator MPI. In a study on 8 patients with perfusion abnormalities on dipyridamole MPI, intravenous caffeine administration (4 mg/kg, serum caffeine 9.7 ± 1.3 mg/L) resulted in negative tests in 6 of the 8 patients with the other 2 showing near-complete redistribution in *more* segments after caffeine but lower number of segments with mild redistribution. On a semi-quantitative score (15 segments; 0 = no, 1 = mild, and 2 = near complete redistribution), caffeine administration resulted in a decrease from 9.0 ± 0.9 to 2.0 ± 1.1 . Zoghbi et al¹⁷ studied 30 subject with known or high likelihood of coronary artery disease who had evidence of reversible defect on a clinically indicated adenosine MPI. A second adenosine MPI was performed 1 hour after the subjects drank an 8 oz cup of brewed coffee prepared similarly for all the subjects who abstained from caffeine for 24 hours prior to both MPIs. The caffeine study was performed using the same protocol and tracer as the initial study. Caffeine administration (serum caffeine range of 1-7, mean 3.1 mg/L) did not affect automated quantitative perfusion defect size (12.6 ± 10.1 vs 12.4 ± 10.4 , $P = .6$). The summed stress (SSS), summed rest (SRS), and summed difference (SDS) scores were similarly unaffected by caffeine administration on blinded side-by-side interpretation. The SDS with and without caffeine administration were highly correlated ($r = 0.88$, $P < .0001$) and there was no difference in the defect size with and without caffeine when the subjects were stratified by caffeine blood levels. Reyes et al¹⁸ also studied 30 subjects with known or suspected coronary artery disease who underwent clinically indicated adenosine MPI and had unequivocal reversible perfusion defect at baseline. Subjects were asked to abstain from caffeine for 12 hours before MPI. 1 hour after receiving 2 large shots of espresso coffee (~ 200 mg caffeine, serum caffeine range of 2.9-12.3 mg/L), 12 subjects underwent a repeat adenosine MPI using the standard adenosine dose of 140 $\mu\text{g}/\text{kg}/\text{min}$ for 6 min), while 18 subjects received a higher

adenosine dose of 210 $\mu\text{g}/\text{kg}/\text{min}$ for 6 min. All the groups performed supplemental exercise in addition to adenosine. SSS, SRS, and SDS were determined by 2 blinded readers and a third reader was involved in case of disagreement. SDS decreased from 12.0 ± 4.4 at baseline to 4.1 ± 2.1 after caffeine when the standard adenosine dose was used but did not significantly change with the high adenosine dose, 7.7 ± 4.0 at baseline to 7.8 ± 4.2 with high-dose adenosine, $P = .7$. It is important to mention that even in this study, there was no relationship between the change in SDS from baseline to caffeine study and serum caffeine concentration ($r = -0.26$, $P = .4$). The higher dose of adenosine is not approved for use in the United States in imaging. Further, Wilson et al¹⁹ more than 2 decades ago, showed that the standard dose of adenosine produces near-maximal coronary hyperemia.

In an observational study of 86 patients who underwent adenosine or dipyridamole MPI and reported that they abstained from caffeine products for >24 hours, serum caffeine levels were detectable in 40% (range 0.1-5 mg/L) of subjects and the frequency of thallium redistribution was similar among those with undetectable (22 of 52 patients, 42%), low caffeine levels 0.1-0.9 mg/L (8 of 29 patients 28%), and high caffeine levels >1.0 mg/L (2 of 5 patients 40%).²⁰

The study by Lee et al¹ adds to this literature by assessing the extent and reversibility of the stress perfusion defect with and without caffeine supplementation in 30 patients who have inducible perfusion abnormalities on standard adenosine MPI. Consistent with previous studies, subjects had detectable levels of caffeine despite being instructed to abstain from any caffeine intake (range 0.025-1.790 with a mean of 0.268 mg/L). In addition to resumption of their usual caffeine consumption, subjects received an extra cup of coffee (containing 0.5, 1, or 2 teaspoons of instant coffee) 1 hour prior to the repeat adenosine MPI. Not surprisingly, caffeine levels increased in these subjects (range 0.706-10.430 with a mean of 3.374 mg/L, $P < .001$). There was no change in the stress percent defect or percent defect reversibility on automated or on visual semi-quantitative scoring between the 2 adenosine MPIs. Granted there is substantial variation between the 2 stress scans with regards to percent defect before and after caffeine supplementation (see Figure 2 in Lee et al¹) but this has to be considered in context of the variability in reprocessing the same set of rest images twice (see Figure 1 in Lee et al¹) and the lack of a clear association between the direction of change of percent defect size and caffeine supplementation. This study is also unique in supplementing subjects with a random dose of caffeine (in addition to the variable usual consumption) which resulted in a wide range of caffeine levels. The caffeine concentration (at baseline or after

supplementation) was not associated with percent defect reversibility and the change in caffeine concentration from baseline to supplementation had no effect on percent defect reversibility (mean change -0.003 for every $100 \mu\text{g/L}$, $P = .97$).

DOES CAFFEINE AFFECT ADENOSINE-INDUCED CHANGES IN HEART RATE?

Adenosine, by activating A_{2A} receptors, is known to increase heart rate via a direct effect on the sympathetic nervous system.^{21,22} In the original case report on the effect of caffeine on dipyridamole MPI in 1989, Smits et al²³ reported on a 46-year-old man who underwent dipyridamole MPI after sustaining a myocardial infarction. Dipyridamole infusion after a 36-hour caffeine abstinence period resulted in an impressive 6-mm ST depression on the electrocardiogram and a reversible perfusion defect on MPI. The heart rate increased from 74 to 102 beats/min. One week later the study was repeated 30 minutes after an infusion of 4 mg/kg intravenous caffeine. The heart rate increased from 79 to 88 beats/min consistent with the antagonistic effect of caffeine on the adenosine receptors. The ST changes were not seen on ECG and the reversible defect on MPI was much smaller. In the subsequent study by the same group on 8 patients described in the previous section, a lower increase in HR was again evident after caffeine administration (heart rate increased from a mean of 70 to 73 beats/min, $P = \text{NS}$ after caffeine vs 71 to 86 beats/min with caffeine abstinence, $P < .001$).¹⁶ In the report by Bottcher et al,¹² the heart rate response to dipyridamole was again blunted by caffeine and it was inversely related to serum caffeine levels. The studies by Zoghbi et al¹⁷ and Reyes et al¹⁸ showed that the heart rate response to adenosine was similar with and without caffeine. Since the effects of caffeine on the heart rate response to adenosine and dipyridamole are not consistent with its effect on MPI, and since the change in heart rate is a poor predictor of the change in myocardial blood flow,²⁴ it is unlikely that the original thesis first proposed by Bottcher et al¹² that the effect of caffeine on dipyridamole MPI is mediated via blunting of the heart rate response and thus the rate-pressure product is true. In a study on conscious dogs, increasing doses of intravenous caffeine (1-10 mg/kg) significantly attenuated regadenoson-induced rise in heart rate but not the peak increase in coronary blood flow.⁷ In the current report by Lee et al¹ the heart rate response to adenosine was lower after caffeine administration despite no change in the percent perfusion defect. The reason why the heart rate response was affected by caffeine in this study but not in the previous 2 studies is not clear. Since the change in heart rate response to adenosine

carries prognostic significance independent from imaging,²⁵ it will be important to settle this discrepancy and determine in future studies whether caffeine obscures the effect of the cardiac autonomic system on the heart rate response to adenosine (and regadenoson).

WHAT SHOULD WE DO NOW: TIME TO REASSESS?

Although we believe that it is reasonable to ask patients reporting for adenosine MPI to abstain from caffeinated products the morning of the test, we anticipate that a significant proportion will not comply with this strict requirement. Rather than cancelling and/or rescheduling the test to another day which will place unnecessary burden on the nuclear laboratory and delay the diagnostic and prognostic information from the referring physician, we believe that the weight of the evidence presented here justifies the performance of adenosine MPI in patients who have ingested one cup of coffee (acknowledging the variability of caffeine concentration in each cup) more than 1 hour prior to the test (which we submit to be the usual scenario) without jeopardizing the test results. In patients suspected of ingesting larger quantities of caffeine (or within 1 hour of the test), a reasonable alternative is to proceed with the rest MPI to allow for serum caffeine levels to fall followed by the adenosine portion of the test. Our recommendation is consistent with that by Salcedo and Kern²⁶ that "the adenosine study, however, should not be delayed or cancelled if the patient has ingested one cup of coffee more than 1 hr before the test. Additionally, several cups of coffee may even be permissible depending on how long prior to the scheduled start time the last cup was consumed, keeping in mind that the half-life of caffeine is around 2.5-4.5 hr." It is time to revise the practice guidelines to allow for more flexibility in performing vasodilator stress tests in patients who have inadvertently ingested a reasonable quantity of caffeine.

Acknowledgement

The authors are thankful for the insightful comments provided by Dr Luiz Belardinelli during the preparation of this manuscript.

References

1. 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. doi:10.1007/s12350-012-9517-x.
2. Lovett R. Coffee: The demon drink? *New Scientist* 2005;38-41.
3. Daly JW, Hide I, Müller CE, Shamim M. Caffeine analogs: Structure-activity relationships at adenosine receptors. *Pharmacology* 1991;42:309-21.

4. Zoghbi GJ, Iskandrian AE. Selective adenosine agonists and myocardial perfusion imaging. *J Nucl Cardiol* 2011. doi:[10.1007/s12350-011-9474-9](https://doi.org/10.1007/s12350-011-9474-9).
5. Henzlova MJ, Cerqueira MD, Hansen CL, Taillefer R, Yao S. ASNC imaging guidelines for nuclear cardiology procedures: Stress protocols and tracers. *J Nucl Cardiol* 2009. doi:[10.1007/s12350-009-9062-4](https://doi.org/10.1007/s12350-009-9062-4).
6. Shryock JC, Snowdy S, Baraldi PG, Cacciari B, Spalluto G, Monopoli A, et al. A2A-adenosine receptor reserve for coronary vasodilation. *Circulation* 1998;98:711-8.
7. Zhao G, Messina E, Xu X, Ochoa M, Sun HL, Leung K, et al. Caffeine attenuates the duration of coronary vasodilation and changes in hemodynamics induced by regadenoson (CVT-3146), a novel adenosine A2A receptor agonist. *J Cardiovasc Pharmacol* 2007;49:369-75.
8. Bertolet BD, Belardinelli L, Avasarala K, Calhoun WB, Franco EA, Nichols WW, et al. Differential antagonism of cardiac actions of adenosine by theophylline. *Cardiovasc Res* 1996;32:839-45.
9. Heller GV, Dweik RB, Barbour MM, Garber CE, Cloutier DJ, Messenger DE, et al. Pretreatment with theophylline does not affect adenosine-induced thallium-201 myocardial imaging. *Am Heart J* 1993;126:1077-83.
10. Namdar M, Koepfli P, Grathwohl R, Siegrist PT, Klainguti M, Schepis T, et al. Caffeine decreases exercise-induced myocardial flow reserve. *J Am Coll Cardiol* 2006;47:405-10.
11. Namdar M, Schepis T, Koepfli P, Gaemperli O, Siegrist PT, Grathwohl R, et al. Caffeine impairs myocardial blood flow response to physical exercise in patients with coronary artery disease as well as in age-matched controls. *PLoS One* 2009;4:e5665.
12. Botcher 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.
13. Kubo S, Tadamura E, Toyoda H, Mamede M, Yamamuro M, Magata Y, et al. Effect of caffeine intake on myocardial hyperemic flow induced by adenosine triphosphate and dipyridamole. *J Nucl Med* 2004;45:730-8.
14. Gaemperli O, Schepis T, Koepfli P, Siegrist PT, Fleischman S, Nguyen P, et al. Interaction of caffeine with regadenoson-induced hyperemic myocardial blood flow as measured by positron emission tomography: A randomized, double-blind, placebo-controlled crossover trial. *J Am Coll Cardiol* 2008;51:328-9.
15. 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.
16. 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.
17. 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.
18. 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.
19. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. *Circulation* 1990;82:1595-606.
20. Jacobson AF, Cerqueira MD, Raisys V, Shattuc 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.
21. Hage FG, Iskandrian AE. Cardiac autonomic denervation in diabetes mellitus. *Circ Cardiovasc Imaging* 2011;4:79-81.
22. Biaggioni I, Killian TJ, Mosqueda-Garcia R, Robertson RM, Robertson D. Adenosine increases sympathetic nerve traffic in humans. *Circulation* 1991;83:1668-75.
23. Smits P, Aengevaeren WR, Corstens FH, Thien T. Caffeine reduces dipyridamole-induced myocardial ischemia. *J Nucl Med* 1989;30:1723-6.
24. Mishra RK, Dorbala S, Logsetty G, Hassan A, Heinonen T, Schelbert HR, et al. Quantitative relation between hemodynamic changes during intravenous adenosine infusion and the magnitude of coronary hyperemia: Implications for myocardial perfusion imaging. *J Am Coll Cardiol* 2005;45:553-8.
25. Hage FG, Dean P, Bhatia V, Iqbal F, Heo J, Iskandrian AE. The prognostic value of the heart rate response to adenosine in relation to diabetes mellitus and chronic kidney disease. *Am Heart J* 2011;162:356-62.
26. Salcedo J, Kern MJ. Effects of caffeine and theophylline on coronary hyperemia induced by adenosine or dipyridamole. *Catheter Cardiovasc Interv* 2009;74:598-605.