Caffeine Consumption Decreases the Response to Bronchoprovocation Challenge with Dry Gas Hyperventilation*

CPT Patrick Duffy, M.D.; and LTC Yancy Y. Phillips, M.D., F.C.C.P.

Objective: To determine whether caffeine consumption affects bronchoprovocation challenge (BPC).

Design: A prospective, double-blind, placebo-controlled, randomized, crossover trial.

Patients: Eleven nonsmoking men, aged 18 to 42 years, with normal baseline spirometry and evidence of exercise-induced bronchospasm.

Intervention: On three separate test days, each individual received, in random order, either placebo, 5 mg/kg caffeine, or 10 mg/kg caffeine, and then underwent BPC with eucapnic voluntary hyperventilation (EVH).

Results: Caffeine (10 mg/kg) significantly reduced bronchoconstriction compared to placebo (p = 0.02). The reduction in bronchoconstriction correlated with the serum level of caffeine (p = 0.014).

Conclusions: Caffeine decreases bronchoconstriction due to EVH. Caffeine should be eliminated from diet prior to BPC.

AHR = airway hyperresponsiveness; BPC = bronchoprovocation challenge; EVH = eucapnic voluntary hyperventilation; %FEV = percentage fall in FEV, as a result of BPC; CI = confidence interval

The cardinal physiologic feature of asthma is widespread, reversible narrowing of the airways.1 In the setting of normal spirometry, bronchoprovocation challenge is commonly employed to make a diagnosis of asthma by demonstrating an increase in airway reactivity.2,3 Administration of increasing concentrations of pharmacologic agents—notably methacholine and histamine—is the most common method of BPC.2,4 Physiologic stimuli, such as nonisotonic aerosols and exercise, are also known to induce airflow obstruction in many, if not all, asthmatics.3,5-7 These nonpharmacologic challenges can be used for both research and clinical purposes.

Eucapnic voluntary hyperventilation of cold or dry air or both, induces epithelial loss of heat and water, thereby duplicating the critical stimuli of exercise-induced bronchospasm and giving an equivalent degree of airway narrowing without the requirement for exhaustive exercise.5,7,8 Both exercise and EVH have been compared to other provocation tests and have been shown to be reliable, reproducible means to assess airway reactivity in asthmatic subjects.7,9-11

A number of factors can influence BPC results, and individuals are routinely instructed to avoid or report circumstances or pharmacologic agents which might alter bronchial reactivity.4,12 For example, airway responsiveness may be enhanced after cigarette smoking or an upper respiratory viral infection. Conversely, a number of pharmaceutical agents can lessen airway responsiveness either for hours (beta-adrenergic agents, anticholinergics, and theophylline) or for days or weeks (chromolyn and glucocorticoids).

Caffeine (1,3,7-trimethylxanthine), a nearly ubiquitous dietary substance related to theophylline, has been shown to have a dose-related bronchodilator effect on basal airway function13-15 and on the degree of exercise-induced bronchospasm.16 Despite these reports, caffeine is generally not specifically prescribed before BPC.1,12

We hypothesized that dietary quantities of caffeine would blunt the response to a physiologic bronchial challenge by EVH. If this was the case, caffeine consumption might prove to be an important source of day-to-day variability in clinically evident airway reactivity and would be an important variable to control in any BPC.

Materials and Methods

Study Population

We recruited adults of either gender who either responded to an advertisement or were being followed in a clinic for exercise-induced asthma. Volunteers had to demonstrate both normal baseline spirometry—as defined by FVC and FEV1, greater than 80 percent of predicted normal,17 and significant airway reactivity with at least a 10 percent fall in FEV1 in response to EVH bronchoprovocation. Normal values for Afro-American subjects were taken as 0.85 of the predictions from Knudson et al.17

Reasons for exclusion included the following: daily medication for control of asthma, an upper respiratory infection or influenza vaccination within six weeks before testing, an episode of asthma requiring hospitalization or steroids within the previous six weeks, pregnancy, or cardiorespiratory disease other than asthma. Eleven nonsmoking men, aged 19 to 42 years, completed the study. Informed consent was obtained from all subjects. The study protocol

*From the Department of Medicine, Walter Reed Army Medical Center, Washington, DC.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Reprint requests: Dr. Phillips, Pulmonary Research, Walter Reed Army Medical Center, Washington, DC 20307-5000

1374 Caffeine and Bronchoprovocation Challenge (Duffy, Phillips)
was reviewed and approved by the Human Use Committee Institutional Review Board of the Walter Reed Army Medical Center.

Each subject was instructed to abstain from caffeine and methylxanthine-containing substances (including medications) for 12 hours prior to testing. All were asked to abstain from food and cigarettes for 4 hours before testing. Testing was performed at approximately the same time on three separate days. After baseline pulmonary function tests, caffeine was given in a randomized, crossover, double-blind fashion. Gelatin capsules were administered (time = 0) which contained either 0 mg, 5 mg/kg, or 10 mg/kg caffeine. Venous blood was sampled after 45 min for the measurement of caffeine and theophylline levels. At 90 min, spirometry was repeated, and bronchoprovocation with EVH was performed.

Lung function was measured by forced expiratory spirometry with a computerized pneumotachometer-based pulmonary function testing system. At each testing interval, at least three successive forced vital capacity maneuvers were measured. The value selected as representative of lung function at that time was the effort in which the sum of FVC and FEV1 was greatest.

Caffeine and theophylline levels were measured by high pressure liquid chromatography.

Bronchoprovocation was carried out 90 min after ingestion of the caffeine/placebo capsules. The challenge was to respiratory heat and water loss by the technique of EVH as previously described. Room temperature dry gas containing 5 percent CO2 (to prevent hypocapnia) in air was delivered to the subject from a compressed gas tank at a target minute ventilation of 30 times the baseline FEV1 for 6 min. Gas flow was measured with a rotameter calibrated by timed collection into a Tissot spirometer. Forced expiratory spirometry was performed immediately, 5, 10, and 20 min after EVH. From the four postchallenge intervals, the lowest FEV1 was used to compute the change in FEV1, as a percentage of the baseline value measured prior to EVH but 90 min after capsule ingestion (%dFEV1).

Statistics

The data are presented as the mean and the 95 percent confidence interval. Analysis of variance with Scheffe's correction was used to compare caffeine dose with caffeine level, as well as caffeine dose with %dFEV1. The correlation of caffeine level with %dFEV1 was determined with unweighted least squares linear regression.

RESULTS

Of the 12 patients accepted into the study, 11 men completed the testing. One woman dropped out after one day, at the highest caffeine dose, due to side effects of nervousness and agitation presumably from the caffeine.

Prechallenge spirometry was normal with the group mean FEV1 and FVC being 92.9 percent (CI, 83.5 to 102.3) and 96.5 percent (CI, 89.4 to 103.6) of predicted normal, respectively. There was no significant difference between the three test days in FEV1 or FVC either before caffeine administration or just prior to BPC. Ninety minutes after dosing, baseline FEV1 had risen by 0.085 L for placebo (p = 0.006), 0.164 L for the lower dose (p = 0.03), and 0.100 for the higher dose (p = 0.15).

The mean serum caffeine level as shown in Figure 1 significantly increased as the dose of caffeine was raised. Mean caffeine level after placebo was 4.6 mg/L (CI, 0.4 to 0.8), after 5 mg/kg was 10.7 mg/L (CI, 6.8 to 14.6), and after 10 mg/kg was 18.8 mg/L (CI,

![Serum caffeine levels by dose](image1)

**Figure 1.** Mean serum caffeine levels (n = 11) taken 45 min after ingestion of a capsule containing 0, 5, 9 or 10 mg/kg caffeine. Bars indicate standard deviation.

12.4 to 25.2). Notably, 8 of 11 subjects had detectable caffeine levels on the day placebo was given, despite explicit instructions for avoidance of xanthine-containing products.

No subject was found to have a significant (>1 mg/dl) blood level of theophylline.

Airway reactivity as measured by the %dFEV1 (the percentage fall in FEV1 after EVH) diminished significantly between the placebo and the 10 mg/kg caffeine day (p = 0.02). The difference between the test days with placebo and 5 mg/kg caffeine tended toward significance (p = 0.12), but there was no difference between the low and high doses of caffeine (p = 0.66). The group mean data are shown in Figure 2. After placebo, mean %dFEV1 was 16.7 (CI, 2.0 to 31.4): after 5 mg/kg caffeine, mean %dFEV1 was 10.2 (CI, 4.9 to 15.5); after 10 mg/kg, mean %dFEV1 was 7.1 (CI, -1.6 to 15.8). The FVC fell by 5.7 percent after placebo (p = 0.09), 2.9 percent after 5 mg/kg (p = 0.006), and 2.2 percent after 10 mg/kg (p = 0.04).

![Change in FEV1 based on caffeine dose](image2)

**Figure 2.** Mean fall in FEV1, following BPC with EVH 90 min after ingestion of 0, 5 or 10 mg/kg of caffeine. Bars indicate standard deviation. Effect at 0 mg/kg differs from 5 mg/kg (p = 0.12) and 10 mg/kg (p = 0.02). Effect at 5 mg/kg does not differ from that at 10 mg/kg (p = 0.66).
Relative change in FEV\textsubscript{1} based on blood caffeine level

![Graph](image)

**Figure 3.** Individual data on caffeine blood level and percent fall in FEV\textsubscript{1}, following BPC with EVH. Each subject was tested on three separate days after receiving either 0, 5 or 10 mg/kg of caffeine. Note only 3 of 11 subjects ever had blood levels of zero after taking placebo despite instructions to avoid caffeine prior to testing. Serum caffeine level correlated negatively with d\%FEV\textsubscript{1} (p = 0.014).

Figure 3 displays all individual data for measured caffeine level and d\%FEV\textsubscript{1}. The response to BPC, d\%FEV\textsubscript{1}, correlated significantly with the serum caffeine level (p = 0.014). On average, each 1 mg/L increase in the serum level of caffeine reduced the d\%FEV\textsubscript{1} by 0.5 percent.

**DISCUSSION**

Dietary ingestion of caffeine, or other methylxanthines, is found in almost all of the world's cultures. It is commonly used by asthmatics as a form of conscious or unconscious selfmedication. A 1983 Italian study of over 72,000 households found that heavy coffee drinkers were much less likely to report asthmatic symptoms, suggesting that heavy caffeine intake reduced the clinical manifestations of airway hyperreactivity.

Careful study of the bronchodilator effects of caffeine have shown that it can give a dose-dependent increase in airflow similar in time course and magnitude to that seen with theophylline.\textsuperscript{13-15} Peak serum levels of caffeine were observed 45 to 60 min after oral ingestion, and peak bronchodilation occurred at about 2 hours. These data dictated the timing of blood sampling and BPC in our study. Caffeine serum half life was found to be 3.9 h as compared to 5.8 h for theophylline.\textsuperscript{15}

The effect of methyl xanthines, with theophylline as the prototype, on AHR has been reported to vary from none to potent inhibition. Koeter et al\textsuperscript{20} reported that theophylline had no effect on BPC with either histamine, acetylcholine, or propranolol. In other studies, theophylline has shown no amelioration of acute increases in AHR from inhaled platelet-activating factor\textsuperscript{22} or antigen\textsuperscript{22} and no change in response to inhaled histamine or methacholine after prolonged use.\textsuperscript{23,24} However, on balance, most investigators have demonstrated that theophylline decreases AHR to the inhalation of carbachol,\textsuperscript{25} histamine,\textsuperscript{26-28} and methacholine\textsuperscript{29,30} in a dose-dependent manner.

Caffeine has also shown contradictory responses when evaluated as a prophylactic for airway challenge. One study by Crivelli et al\textsuperscript{30} of seven asthmatic patients found that caffeine ingestion caused no "appreciable attenuation" in the response to carbachol inhalation.\textsuperscript{30} Compared to our own protocol, Crivelli et al\textsuperscript{30} enrolled fewer subjects and used a smaller dose (6 mg/kg) of caffeine. Of interest, five of seven patients in that study experienced some diminution in bronchoconstriction after caffeine, although the difference was not statistically significant.

Kivity et al\textsuperscript{31} have recently reported that consumption of 7 mg/kg caffeine in ten subjects caused a significant amelioration of the fall in FEV\textsubscript{1}, following treadmill exercise. This effect was present even when accounting for a prechallenge bronchodilation evidenced as a 10 percent increase in FEV\textsubscript{1}. The degree of bronchodilation did not correlate with the protective effect. The mean serum caffeine level was 10.2 mg/L. A similar protective effect was noted at 3.5 mg/kg of caffeine but did not reach statistical significance. They concluded that, while efficacious, 7 mg/kg of caffeine, the amount in three or four cups of strong coffee, was impractical to ingest before exercise as a prophylactic. They did not speculate on the possibility of caffeine consumption affecting laboratory evaluation of AHR.

Our data show that caffeine consumption clearly decreases bronchial responsiveness to EVH, and that this effect is correlated with the serum level of caffeine. We were unable to show a clear effect of dose because of the considerable variability in baseline caffeine levels. In our group, 5 mg/kg of caffeine gave essentially the same blood levels as 7 mg/kg in the study of Kivity et al, and eight of our subjects had elevated blood caffeine levels on their placebo test days. This, and the normal level of baseline function in our cohort, may also account for our failure to demonstrate significant acute bronchodilation from the caffeine.

Extrapolating from the BPC studies cited above which used theophylline, it is likely that all methods of inhalation challenge would be similarly affected by caffeine consumption. This may explain some of the variability in response to BPC in the same subject between days or between different challenge methods.\textsuperscript{7,10,11} Hence, we recommend that patients avoid medications, foods, and beverages containing caffeine for 24 hours prior to any bronchoprovocation testing in our laboratory.

Caffeine was detectable in most of our subjects even after explicit instructions for dietary avoidance for at least 12 hours. A number of them were hospital-based physicians and may have found it difficult to avoid this
stimulant. In contrast, subjects studied by Kivity et al. had undetectable caffeine levels before dosing. Despite diligent attempts at dietary discretion, an individual may still unwittingly ingest caffeine in an array of foods, beverages, and pharmaceuticals. For this reason, we suggest that a blood caffeine analysis at the time of testing may be useful if BPC is negative and the clinical suspicion of AHR is high.

As a corollary to our findings, an individual with exercise-induced asthma could alleviate some bronchoconstriction by ingesting caffeine prior to exercise. In our study population, the FEV₁ after exercise would be about 10 percent greater after consuming 10 mg/kg of caffeine, about five cups of strong coffee, than when abstaining from caffeine. This is a similar degree of protection to that reported by Kivity et al. While this response would be expected to vary widely among individuals, it may, in part, explain the queues which form for coffee just before a marathon race.

We conclude that caffeine reduces the degree of bronchospasm induced by BPC with EVH in a dose-dependent manner. We recommend that caffeine and other methylxanthines be excluded from a patient’s diet for 24 hours prior to any BPC.

ACKNOWLEDGMENT: The authors gratefully appreciate the technical support of SSG Gerry Guzman and Robin S. Howard, M.A.

REFERENCES

6 Filuk RB, Serrette C, Anthonisen NR. Comparison of responses to methacholine and cold air in patients suspected of having asthma. Chest 1989; 95:948-52
9 Heaton RW, Henderson AF, Costello JF. Cold air as a bronchial provocation technique. Chest 1984; 86:810-14
11 Aquilina AR. Comparison of airway reactivity induced by histamine, methacholine, and isocapnic hyperventilation in normal and asthmatic subjects. Thorax 1983; 38:766-70
22 Cockcroft DW, Murdock KY, Gore BP, O’Byrne PM, Manning P. Theophylline does not inhibit allergen-induced increase in airway responsiveness to methacholine. J Allergy Clin Immunol 1989; 83:913-20
24 Dutoit JJ, Salome CM, Woolcock AJ. Inhaled corticosteroids reduce the severity of bronchial hyperresponsiveness in asthma but theophylline does not. Am Rev Respir Dis 1987; 136:1174-78