Caffeine Affects Cardiovascular and Neuroendocrine Activation at Work and Home

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Objective: This study investigated the effects of moderate doses of caffeine on ambulatory blood pressure and heart rate, urinary excretion of epinephrine, norepinephrine, and cortisol, and subjective measures of stress during normal activities at work and at home in the evening. **Methods:** Healthy, nonsmoking, habitual coffee drinkers ($N = 47$) participated in 3 days of ambulatory study. After a day of ad lib caffeine consumption, caffeine (500 mg) and placebo were administered double-blind in counter-balanced order on separate workdays. Ambulatory blood pressure and heart rate were monitored from the start of the workday until bedtime. Urinary excretion of catecholamines and cortisol was assessed during the workday and evening. **Results:** Caffeine administration significantly raised average ambulatory blood pressure during the workday and evening by 4/3 mm Hg and reduced average heart rate by 2 bpm. Caffeine also increased by 32% the levels of free epinephrine excreted during the workday and the evening. In addition, caffeine amplified the increases in blood pressure and heart rate associated with higher levels of self-reported stress during the activities of the day. Effects were undiminished through the evening until bedtime. **Conclusions:** Caffeine has significant hemodynamic and humoral effects in habitual coffee drinkers that persist for many hours during the activities of everyday life. Furthermore, caffeine may exaggerate sympathetic adrenal-medullary responses to the stressful events of normal daily life. Repeated daily blood pressure elevations and increases in stress reactivity caused by caffeine consumption could contribute to an increased risk of coronary heart disease in the adult population. **Key words:** caffeine, ambulatory monitoring, blood pressure, catecholamines, cortisol, occupational stress.

DASH = Dietary Approaches to Stop Hypertension; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

INTRODUCTION

Caffeine is consumed daily by an estimated 85% of adults in the United States in coffee, tea, and soft drinks (1). This widespread consumption persists despite accumulating evidence that caffeine has potent stimulatory effects on the cardiovascular and neuroendocrine systems that could have implications for health and disease (2).

Laboratory studies over the last 20 years have consistently demonstrated that a caffeine dose equivalent to 2 to 3 cups of brewed coffee will raise resting blood pressure by 7 to 10 mm Hg when administered either to "caffeine-naive" individuals or to habitual coffee drinkers after overnight abstinence (3–14). The observed blood pressure elevations reach a maximum 30 to 60 minutes after caffeine administration and persist for several hours. A smaller number of experimental studies have shown that caffeine can raise plasma levels of the major stress hormones, including the catecholamines epinephrine and norepinephrine (3, 8) and cortisol (8, 15). These humoral effects indicate the activation of both the sympathetic adrenal-medullary and the hypothalamic pituitary adrenal-cortical components of neuroendocrine stress responses. The stimulatory effects of caffeine are similar to the physiological responses that are associated with the experience of stress, and the experimental evidence suggests that caffeine itself might act like a stressor when coffee and other caffeinated beverages are consumed in everyday life (4). In addition, the laboratory studies have also demonstrated that caffeine can intensify both cardiovascular and humoral responses to experimental stressors, amplifying the increases in cardiac output and skeletal muscle blood flow and the increases in plasma levels of epinephrine and cortisol elicited by challenging or threatening tasks (5, 6, 8, 10). These results suggest that caffeine consumption may exaggerate the deleterious effects of stress in daily life and aggravate the damage to health that stress can cause.

The laboratory studies have clearly demonstrated the kinds of effects that caffeine can have, but they have generally been limited to relatively short periods of data collection under well-controlled laboratory conditions. As such, these studies are less conclusive about the effects of caffeine in the natural environment of everyday life, where it is so widely consumed in coffee, tea, and other caffeinated beverages.

Ambulatory studies provide the opportunity for ecological validation of the hemodynamic and neuroendocrine effects observed in the laboratory. Several studies have investigated how caffeine affects ambulatory mea-

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sures of blood pressure and heart rate in healthy habitual coffee drinkers (16–20). These studies have found that both ad lib caffeine consumption and administration of fixed caffeine doses approximating moderate coffee drinking raise average daytime blood pressures by 4 to 5 mm Hg compared with a caffeine-abstinence control condition. The pressor effects of caffeine in the natural environment may be limited to the waking hours, because effects were not observed when blood pressure was recorded during sleep (18). Our study of 21 habitual coffee drinkers compared high- and low-caffeine doses and found that average workday systolic and diastolic blood pressures were higher by 4/3 mm Hg when we administered 250 mg of caffeine in the morning and at midday compared with 50 mg at the same times (16). Less attention has been paid to the effects of caffeine on neuroendocrine measures of stress in the natural environment. However, we observed in one study that a 300-mg dose of caffeine raised urinary epinephrine excretion during the morning hours at work by 37% compared with placebo (21). Similarly, others reported that caffeine elevated cortisol levels during the stress of medical school examinations (22, 23). Thus, caffeine may stimulate hemodynamic and humoral stress reactivity during everyday activities, as it does in the laboratory.

The present study was conducted to investigate the effects of typical patterns of caffeine consumption on ambulatory measures of cardiovascular and stress-related humoral activity during the day at work and at home in the evening. Ambulatory measurements of blood pressure, heart rate, and humoral activity were collected from habitual coffee drinkers on three different days in which caffeine was either consumed ad lib, administered in a moderate fixed dose of 500 mg, or withheld by substitution of a placebo. Comparisons of the fixed dose and placebo provided the opportunity to determine how caffeine affected levels of blood pressure and heart rate and the release of epinephrine, norepinephrine, and cortisol during everyday activities in the natural environment. Based on the results of laboratory studies, stimulatory effects were predicted, with increases in blood pressure and excretion of stress hormones. In addition, an interaction between caffeine and stress was predicted, in which the physiological effects of stressful events would be exaggerated on the day that caffeine was ingested.

METHODS

Subjects

Forty-seven healthy male and female employees of Duke University and surrounding businesses participated in the study, which was approved by the Institutional Review Board. They were recruited by advertisements placed in campus newspapers and handbills posted throughout the medical center and campus. All volunteers were normotensive (blood pressure <140/90 mm Hg) adults who worked in relatively sedentary office and laboratory positions. All were habitual coffee drinkers (2–7 cups daily). Coffee consumption was initially assessed by retrospective self-report and confirmed by completion of a 7-day diary of caffeinated beverage consumption. Women who used oral contraceptive steroids were excluded because these drugs are known to slow the metabolism and elimination of caffeine, increasing the half-life three-fold (24, 25). Cigarette smokers were excluded from the study because smoking is known to decrease the elimination half-life of caffeine by half (26) and because nicotine is known to affect blood pressure, heart rate, and the release of catecholamines and cortisol.

The sample included both male ($N = 27$) and female ($N = 20$) volunteers and had a diverse racial composition (34 white, 9 black, 3 Asian, and 1 Hispanic). Ages ranged from 22 to 45 years, with mean ± SD = 33.4 ± 7.2 years. Self-reported daily caffeine intake from all sources (based on standard values for caffeine content) averaged 574 ± 236 mg, equivalent to about four cups of brewed coffee.

Experimental Design and Treatments

The study used a double-blind, placebo-controlled crossover design, in which a controlled dose of caffeine and a placebo were administered in single-day trials to each participant. The experimental caffeine and placebo treatments were presented in randomized counter-balanced order. A fixed dose of 500 mg of caffeine per day was chosen to represent moderate adult caffeine consumption, roughly equivalent to 32 oz. (950 ml) of brewed coffee. The Duke University Medical Center Pharmacy prepared identical #2 hard-gelatin capsules that contained 250 mg of caffeine plus dextrose filler or dextrose filler alone. The participant swallowed the first capsule in the laboratory before the start of monitoring (0730–0830 hours) and the second capsule roughly 4 hours later at midday. All caffeine was consumed before 1300 hours. This approach of fixed doses and times was judged to be superior to ad lib consumption of caffeinated beverages. Standard dosing with capsules eliminated variations in total daily caffeine dose that would have occurred with ad lib consumption. Furthermore, capsules provided the opportunity for double-blind presentation to control for potential expectation effects. The standardized dosing schedule was intended to simulate the expected patterns of caffeine ingestion in moderate coffee drinkers. Evaluation of diaries confirmed that the majority of daily caffeine was consumed before lunchtime.

Experimental Protocol

Enrollment and orientation. Participants received detailed information on the study in an orientation appointment at the laboratory. All experimental procedures were explained in detail, and informed consent for the study was obtained from the subject. Seated resting blood pressure was measured three or more times with an automated monitor (Dinamap Vital Signs Monitor, Critikon, Tampa, FL) to confirm the normotensive status of each volunteer. Volunteers completed a battery of questionnaires that gathered demographic and health history information and a retrospective self-report measure of their typical daily consumption of coffee, tea, and other caffeinated beverages. Subjects selected for the study completed a 7-day diary of caffeinated beverage consumption by recording the time and quantity of each serving of coffee, tea, or caffeinated soft drink when it was consumed. Diary information was used to confirm total daily caffeine intake.

Before the first experimental condition, participants completed a

practice day of ambulatory monitoring. This initial day provided for habituation to the novelty of ambulatory monitoring procedures. In addition, it ensured that each participant was able to comply with instructions for data collection and that valid measurements could be obtained. During this practice day, participants consumed caffeinated beverages ad lib, but recorded the time of day, the type of beverage, and the serving size consumed on each occasion.

Ambulatory Monitoring

Study days were scheduled with at least 1 day intervening. All ambulatory studies were scheduled for workdays from Monday to Thursday to maintain consistency in evening home activities. Subjects were asked to choose typical days that they expected would be similar in work activity and stress and to avoid days that they knew would be significantly more or less demanding than usual. Vigorous physical exercise was banned on study days. Otherwise, participants were instructed to pursue their usual activities at work and at home and not to change their behaviors to accommodate the monitoring procedures.

Each ambulatory study began in the early morning after overnight abstinence from all sources of caffeine. Instrumentation and instruction in the laboratory began at least 30 minutes before the start of the workday. The Accutracker II monitor (Suntech Medical Instruments, Raleigh, NC) was used for ambulatory blood pressure and heart rate measurements. This programmable, automated device performs auscultatory measurements using a pressure cuff on the nondominant arm, an electronic microphone for detection of Korotkoff sounds, and EKG electrodes for the detection of heart rate and temporal gating of sound detection. The validity of this device for the measurement of blood pressure and heart rate has been established (27–29), and it has been shown to meet Association for Advancement of Medical Instrumentation standards for blood pressure monitors (29). During the instrumentation of each participant, blood pressure readings from the monitor were compared with simultaneous auscultatory readings taken by the study technician. Valid monitor operation was assumed when the averages of five readings by each method agreed within 5 mm Hg. The Accutracker monitor was programmed to collect measurements four times each hour, with random variation in timing, and to repeat measurements when artifacts were detected. Study participants wore the monitor until bedtime or at least 10 PM, then turned it off and removed the cuff, microphone, and electrodes when preparing for bed. Ambulatory measurements were not collected overnight to reduce the potential disruptions of sleep associated with cuff inflation and deflation.

Study participants were instructed to complete a brief "diary" entry at the conclusion of each blood pressure measurement. They recorded the time of measurement (as displayed on the monitor), entered single-letter codes to designate their current location (work, home, travel, or other) and their posture (sitting, standing, lying down, or walking), and made numerical ratings of their physical activity and perceived stress during the minutes before the measurement. These numerical ratings were made on a one to five numerical scale anchored at the lower and upper limits of the individual's usual experience. Entries were made on a single preprinted 4- by 6-inch index card that included sufficient space for the entire day's measurements.

Urine collection was performed for the measurement of catecholamine and cortisol excretion, which provided an assessment of activity in the sympathoadrenal-medullary and hypothalamic pituitary adrenal-cortical components of neuroendocrine stress reactivity (30, 31). One sample was collected during the workday, from the start of ambulatory measurements until the end of the workday. A second sample was collected during the evening at home, beginning at the end of the workday and continuing until bedtime. Samples were collected into 1-liter plastic containers that were kept cold in an insulated bag. Participants were instructed to begin each collection period with an empty bladder, to collect all urine excreted during each of the three time periods, and to completely empty the bladder into the container at the conclusion of each sample interval. They were also instructed to increase caffeine-free fluid consumption throughout the day to ensure adequate urine production.

Before the start of work the following morning, participants returned the ambulatory monitor, urine samples, and completed diary cards to the laboratory. Records and samples were inspected, and the participant was debriefed about the experience. Ambulatory BP and HR data were downloaded from the monitor and saved on a personal computer. Diary entries were matched with corresponding BP and HR values and combined in data files for later analysis. The volumes of urine samples were recorded, and small aliquots were frozen at −20°C until assays were performed.

Ambulatory BP and HR measurements were independently inspected by two investigators (JDL and CFP), and readings were deleted by consensus when error codes indicated significant artifacts in the measurement. When a programmed measurement was deleted, the retry value was used if possible. However, if the suspect measurement was judged satisfactory, the retry value was deleted from the data file to prevent oversampling of that time point.

Urinary-free catecholamines were measured by high-performance liquid chromatography using electrochemical detection (32). Urinary-free cortisol was measured using radioimmunoassay and a commercial kit. Urinary creatinine was measured using the Jaffe method as modified by Slot (33). Values of catecholamines and cortisol were adjusted for the creatinine content of each urine sample. Because the urinary output of creatinine is generally thought to be constant over time, adjustments for creatinine levels provide a means to control for variations in the duration of sampling intervals and the volume of urine (34, 35).

Data Analysis

Data were analyzed using regression models containing both fixed and random effects, a technique labeled hierarchical regression or mixed models (36). The advantages of hierarchical models over standard repeated measures analyses for the analysis of ambulatory BP data are discussed elsewhere (37). Briefly, these models can accommodate a varying number of observations (eg, BP measurements) among the subjects in the sample and do not require deletion of subjects who have some missing data. Compound symmetry need not be assumed as in traditional repeated measures analysis of variance. Different structures for the correlations among within-subject errors, including autoregressive structures, can actually be compared, and the most appropriate error structure can be implemented. Finally, time-varying covariates are easily incorporated into the analyses. This enhances the analysis and statistical control of the effects of factors such as posture, location, or mood scores that can vary from one observation to the next and may not be equally observed in every subject.

The hierarchical regression analysis was conducted using Proc Mixed (SAS Version 8, SAS Institute, Cary, NC). Statistical significance was declared when $p \leq .05$. The hierarchical regression analysis provided estimates of means and slopes for the different fixed effects and interactions. These estimates have been used for graphical presentation of results.

RESULTS

Preliminary Analysis of Ambulatory Data

Before hypothesis testing, assumptions of normality and various error structures were examined for the residuals, and a compound symmetry structure was determined to be the most appropriate error structure. Preliminary models of the effects of the diary measures of posture, physical activity, and stress were tested to determine whether statistical control of these factors was necessary. Based on these results, tests of the effect of caffeine administration on ambulatory BP and HR included posture, activity, and stress as time-varying covariates.

Ambulatory cardiovascular readings were collected from 47 subjects at work and at home on days when they received either 500 mg of caffeine or placebo. The limited number of readings collected during traveling or in other locations and readings with missing diary information were excluded. The total number of observations remaining was 3894, with 49.8% recorded in the caffeine condition and 50.2% recorded in the placebo condition. The majority of readings (72%) were collected during the workday, with the remainder at home (28%). Seated posture was most prevalent (60%), with standing (27%), walking (9%), and lying down (4%) recorded less frequently. Ratings of physical activity were predominantly at low to moderate levels, with 39%, 37%, and 20% prevalence for ratings of one to three, respectively. Only 4% of records included ratings of four, and 0.2% had ratings of five. Similar proportions were observed for perceived stress, with 38%, 35%, and 22% for ratings of one to three and 4% and 0.2% with ratings of four and five. The average rating (mean ± SD) for activity was 1.9 ± 0.9 and for stress was also 1.9 ± 0.9.

Analysis of the time-varying covariate regression model revealed that reported posture, physical activity, and perceived stress all had robust effects on ambulatory BP and HR ($p < .0001$). Differences among the four postures reached 4.6/8.9 mm Hg for SBP/DBP and 8.5 bpm for HR. Average BP and HR levels were lowest for reclining (BP = 117/64 mm Hg, HR = 73 bpm), with higher levels for sitting (BP = 122/73 mm Hg, HR = 73 bpm), standing (BP = 123/73 mm Hg, HR = 78 bpm), and walking (BP = 123/70 mm Hg, HR = 82 bpm). Physical activity ratings (1–5 scale) were related to both BP and HR. The raw score coefficients (slopes) provided by PROC Mixed in the solution of the hierarchical regression model indicated that each unit of stress rating was associated with an increase of 1.7/0.4 mm Hg in BP and 1.8 bpm in HR. Perceived stress ratings (1–5 scale) were significantly related to BP, but not to HR. The regression coefficients indicated that an increase of one unit in perceived stress was associated with a BP increase of 1.1/0.7 mm Hg. These results confirmed the importance of statistical controls for these factors in the analyses of caffeine effects.

Effects of Caffeine on Ambulatory Cardiovascular and Neuroendocrine Activity

Blood pressure and heart rate levels. When the ambulatory readings recorded during the daytime and evening (from 0830 until 2200 hours) were analyzed, the main effect of caffeine dose was significant for all three ambulatory cardiovascular variables (Figure 1). Compared with placebo, the 500 mg dose, roughly equivalent to four cups of brewed coffee, raised average SBP through the entire day by 4 mm Hg ($F(1,44) = 70.68$, $p < .0001$) and raised average DBP by 3 mm Hg ($F(1,44) = 65.98$, $p < .0001$). In contrast, caffeine reduced average HR by 2 bpm ($F(1,44) = 14.70$, $p < .0005$).

The analyses of the main effect of location revealed no consistent changes in ambulatory blood pressure and heart rate levels between daytime and evening. Only DBP differed between work and home locations ($F(1,44) = 10.94$, $p < .002$), with average DBP 1.5 mm Hg lower at home. Average SBP differed by only 0.6 mm Hg between work and home, and average HR differed by 0.2 bpm. No interactions of caffeine dose and location were observed (all p values $>.25$), which indicates that the effects of caffeine did not differ between the workday and the evening at home.

Urinary catecholamines and cortisol. When daytime and evening urine samples were analyzed, the

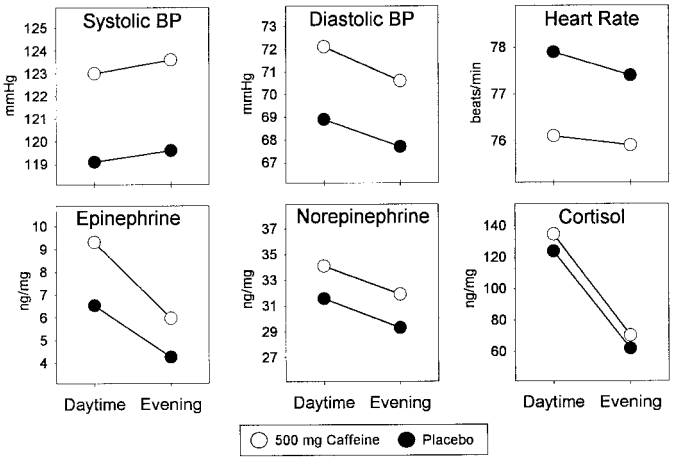

Fig. 1. Estimated values of hemodynamic and stress-related humoral measures for caffeine and placebo by time of day. Blood pressure and heart rate values are adjusted for the effects of posture, perceived stress, and physical activity. Epinephrine, norepinephrine, and cortisol are adjusted for urinary creatinine level.

main effect of caffeine dose was significant for levels of urinary-free epinephrine ($F(1,45) = 11.76$, $p = .001$), but not for norepinephrine ($F(1,45) = 1.75$, $p = .19$) or urinary-free cortisol levels ($F(1,45) = 1.63$, $p = .21$). Creatinine-adjusted levels are presented in Figure 1 by dose and time of day. Urinary-free epinephrine levels were 32% higher on the day that participants received 500 mg of caffeine compared with the day they received the placebo.

Significant location effects were observed in measures of epinephrine ($F(1,45) = 18.34$, $p < .0001$) and cortisol ($F(1,45) = 70.79$, $p < .0001$), but not in measures of norepinephrine ($F(1, 45) = 1.31$, $p = .26$). As shown in Figure 2, levels of stress hormone excretion were higher during the workday than at home in the evening. However, none of the caffeine dose by location interactions were significant (all p values $>.40$), which indicates that the effects of caffeine were consistent across the workday and the evening at home.

Stress and activity ratings. Caffeine administration had mixed effects on ratings of perceived stress collected in the ambulatory diary. Although the main effect of caffeine dose was not significant ($F(1,44) = 1.88$, $p = .18$), the caffeine dose by location interaction was significant ($F(1,42) = 12.07$, $p = .001$). Caffeine dose had no effect on stress ratings at home in the evening, with a mean rating of 1.7 on the 1 to 5 scale for both caffeine and placebo conditions. However, caffeine was associated with slightly higher ratings during the workday (2.08 vs. 1.97, on the 1–5 scale).

Ratings of physical activity demonstrated a main effect of caffeine dose and a dose by location interaction. Activity ratings were slightly higher with caffeine administration ($F(1,44) = 6.62$, $p = .01$), averaging 1.84 vs. 1.79 for placebo. However, the interaction ($F(1,42) = 8.04$, $p = .007$) revealed that caffeine increased activity ratings somewhat at work (1.99 vs. 1.89 on the 1–5 scale), but not at home (average ratings 1.69 for both conditions).

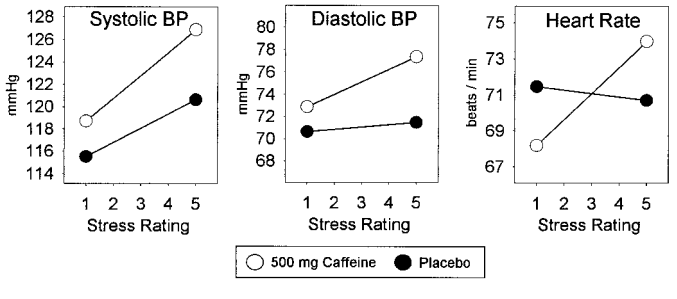

Fig. 2. Interactions of caffeine dose and perceived stress rating in the ambulatory measures of blood pressure and heart rate. Estimated values are adjusted for the effects of location (work or home), posture, and physical activity.

Caffeine-Stress Interactions in Ambulatory Cardiovascular Activity

To determine whether caffeine amplifies the effects of stress on blood pressure and heart rate, additional analyses tested the interaction of caffeine dose and perceived stress, using the diary ratings made at the time of each ambulatory measurement. These hierarchical regression models also included the main effects of caffeine dose and perceived stress along with the time-varying covariates of location, posture, and physical activity. The interaction term tested whether the influence of perceived stress on ambulatory BP and HR values differed on caffeine and placebo days. Based on the laboratory studies, we predicted that the effect of stress would be amplified on the day that caffeine was ingested.

Caffeine dose by stress rating interactions ($df = 1,3840$) were significant for ambulatory DBP ($F = 5.78$, $p < .02$) and for HR ($F = 13.87$, $p = .0002$), and there was a trend for this interaction in SBP ($F = 2.59$, $p = .11$). Results are shown in Figure 2, using estimates from the hierarchical regression models.

The raw score coefficients (slopes) provided by PROC Mixed in the solution to the hierarchical regression equations indicated that on the day that caffeine was administered, each incremental unit of reported stress (1–5 scale) was associated with an increase in SBP of 2.0 mm Hg, which compared with 1.2 mm Hg in the placebo condition. For DBP, the relation was 1.1 mm Hg per unit of perceived stress on the caffeine day vs. 0.2 mm Hg change on the placebo day. For HR, the effect of a unit increase in stress was 1.4 bpm on the caffeine day vs. −0.2 bpm with placebo. These results, which show that the effects of stress on DBP and HR were significantly greater when caffeine was administered, support the hypothesis that caffeine can amplify the effects of stress on ambulatory hemodynamics.

DISCUSSION

The results of this ambulatory study of the effects of double-blind, placebo-controlled caffeine administration add to the growing body of evidence that everyday caffeine consumption has significant physiological effects throughout the workday and evening. Caffeine produced significant elevations in ambulatory blood pressures, as reported in earlier studies. Furthermore, caffeine amplified the effects of stress on diastolic blood pressure and heart rate. Caffeine administration also increased urinary excretion of free epinephrine during the workday and evening time periods. Taken together, the results suggest that the moderate doses of caffeine consumed every day by habitual coffee drink-

ers raise blood pressure and increase the activation of general stress reactivity systems. Such effects could have implications for blood pressure management and cardiovascular disease risk.

The observed effects of caffeine on ambulatory blood pressure levels are consistent with effects reported in earlier studies with similar protocols and similar doses of caffeine (16–20, 38, 39). These studies have all found elevations in daytime blood pressure of roughly similar magnitude, although variations in the reporting of data make direct comparisons difficult. In general, the evidence suggests that typical levels of caffeine intake are associated with increases in average blood pressure in the range of 3 to 5 mm Hg during daytime hours, although peak differences in the hours immediately after consumption may reach 7 mm Hg (eg, Refs. 18 and 19).

Larger pressor effects have been reported for caffeine administered in the laboratory. Measurements under controlled conditions find effects on resting blood pressure that range from 5 to 15 mm Hg (Ref. 2 for review). There may be a simple explanation for these larger effects. Laboratory studies have generally measured caffeine's effects on blood pressure at the time when caffeine concentrations in the blood would be expected to be their highest, 45 to 90 minutes after ingestion. Peak concentrations would be expected to yield peak effects. As the dose of caffeine is metabolized and eliminated over time, pressor effects would likely diminish. Average values over longer time intervals after caffeine ingestion would be expected to yield smaller effects. Indeed, ambulatory studies that included only 24-hr averages (40, 41) failed to detect caffeine pressor effects, most likely because no caffeine was present in the blood during much of the measurement interval.

The slightly lower average heart rate on the day of caffeine administration is not unexpected. Laboratory studies have frequently observed that moderate doses of caffeine lead to reductions in resting heart rate because of moderate blood pressure increases (eg, Refs. 4 and 8). The decrease in heart rate is generally thought to be due to vagally mediated slowing when baroreceptor reflexes are elicited by the blood pressure elevations after caffeine administration (42). Higher doses can produce heart rate acceleration, but such effects are not commonly associated with typical patterns of consumption.

The results reported here illustrate the importance of statistical controls for extraneous factors that could confound treatment effects in the analysis of ambulatory blood pressure. As in our earlier ambulatory study (16), posture, perceived stress, and physical activity were all found to have significant effects on individual readings of blood pressure and heart rate. By including the ambulatory diary records of these factors as time-varying covariates, the statistical analyses reduced the error variance associated with their natural fluctuations during the day and improved the precision of the estimates of caffeine effects. In addition, these analyses determined that caffeine had effects on blood pressure that were not mediated by increases in stress and activity or by changes in posture.

The results also demonstrate that this modest caffeine dose produced an amplification of the effects of stress on blood pressure and heart rate during the day. Figure 2 clearly shows that the impact of stress on blood pressure and heart rate was exaggerated on the day that caffeine was consumed compared with the placebo day. These results add support to our hypothesis that caffeine potentiates, or amplifies, the psychophysiological responses that are elicited by stressful stimuli. Earlier laboratory studies demonstrated that the increases in forearm blood flow and decreases in forearm vascular resistance that were elicited by a mental arithmetic stressor were nearly 50% larger after caffeine administration, even though caffeine did not affect resting levels of forearm blood flow (5, 6). Changes in forearm blood flow reflect changes in skeletal muscle blood flow in general, and increases during stress are an important component of the cardiovascular "fight-flight" response. Caffeine administration has also been shown to potentiate the increases in cardiac output elicited by a stressful task in the laboratory (10), even though caffeine did not affect cardiac output at rest. Caffeine can also potentiate neuroendocrine stress responses in the laboratory, as shown in an earlier study where caffeine more than doubled the size of the plasma epinephrine response and the plasma cortisol response elicited by mental arithmetic stress (8). By examining the influence of naturally occurring fluctuation in stress during the day, the present study provides the first evidence of this stress-amplifying effect of caffeine outside of the laboratory, during everyday work activities in the natural environment.

Caffeine had significant humoral effects as well in this study, significantly increasing the levels of free epinephrine excreted into the urine. These results suggest that caffeine ingestion promoted greater release of epinephrine into the bloodstream. The observation that caffeine administration increased average epinephrine levels during the workday and evening by 32% confirms our earlier report of increased epinephrine excretion after caffeine ingestion (21), where caffeine increased epinephrine during a 3-hour morning at work by 37%. Epinephrine is the major hormone of the sympathetic adrenal-medullary pathway of stress response, so increases in excreted epinephrine suggest

that caffeine increased the activation of this component of psychophysiological stress reactivity during everyday activities at work and at home.

Measures of urinary stress hormone excretion are less familiar than the more common cardiovascular measures, which makes it more difficult to judge the importance of the 32% increase in epinephrine observed in this study. By comparison, however, a recent study examined the neuroendocrine effects of job stress in registered nurses by comparing levels of free epinephrine in urine collected on days of work in the hospital and days off at home (43). Job stress in these registered nurses produced levels of epinephrine that were 24% higher than levels at home. In the present study, the effect of a moderate dose of caffeine was one-third larger than the effect of job stress in nurses. Such a comparison suggests that the elevations of epinephrine produced by caffeine are nontrivial and may be important to health. Job stress like that experienced by the nurses is commonly thought to increase risk for cardiovascular and other diseases through the mechanisms of stress reactivity. The larger effects of caffeine consumption on epinephrine could prove to be an even greater risk factor for pathogenesis and disease.

The absence of effects on cortisol excretion is consistent with our earlier ambulatory study (21). However, caffeine has increased cortisol responses to controlled laboratory stress (8), and other investigators (22, 23) have reported that caffeine increases cortisol levels during the "occupational stress" of medical students who are taking exams. The difference may lie in the nature of the daily activities. In research by Frankenhaeuser et al. (44) and Lundberg and Frankenhaeuser (45), cortisol responses are associated with a lack of control and circumstances that elicit a sense of distress or misery, which adequately describes both the laboratory and exam settings. In contrast, epinephrine responses are experimentally linked to increases in workload or subjective effort under stressful circumstances, which may be more descriptive of the everyday stresses in the workplace and at home that were part of the present study. Regardless of which type of stress and stress response are elicited during the day, the evidence of this and other studies suggests that caffeine will exaggerate the epinephrine and cortisol responses that do occur.

The persistence of caffeine effects on blood pressure and epinephrine long after ingestion is noteworthy. The second and final 250-mg dose of caffeine, equivalent to two cups of coffee, was administered at lunchtime. However, blood pressures and epinephrine levels remained significantly higher at home until recording concluded at bedtime, 10 or more hours after ingestion. The results and accompanying figures demonstrate that the effects during the evening were as large in size as the effects during the daytime, within hours of caffeine ingestion. Such persistence is not unexpected, given the known elimination half-life of caffeine, which is 3 to 5 hours in healthy adults who do not smoke or take oral contraceptive steroids (2). Although the relatively slow elimination makes it clear that caffeine can remain in the body for many hours after ingestion, the results of this study show that this continued exposure to the drug is associated with long-lasting elevations of blood pressure and epinephrine.

A recurring issue in caffeine research concerns habituation to caffeine effects with continued daily ingestion. Several studies have suggested that caffeine pressor effects disappear after a few days (46, 47). However, the results of the present study contradict this hypothesis. The experiment was designed to match normal patterns of daily caffeine ingestion. The participants were all habitual coffee drinkers who might be expected to demonstrate tolerance to caffeine effects. They were tested after an overnight period of abstinence that was consistent with their normal patterns of daily caffeine ingestion. The fact that caffeine administration produced increases in blood pressure and epinephrine levels makes it clear that these coffee drinkers had developed at most a partial tolerance to caffeine. Despite their prior daily consumption, they still showed significant responses to the drug. Therefore, it is reasonable to conclude that caffeine produces similar effects every day that it is ingested, even in individuals who drink coffee on a daily basis. Regular use apparently provides no protection from the cardiovascular and neuroendocrine effects of caffeine.

The observed effects of caffeine consumption on blood pressure were modest in size, but even such modest increases on a daily basis could have significant implications for long-term cardiovascular disease risk and public health. Epidemiological studies have observed linear relationships between levels of blood pressure and risks for several important cardiovascular diseases. A review of nine major prospective studies of blood pressure and cardiovascular disease risk, which included data from the Framingham Study and Multiple Risk Factor Intervention Trial screening, reported that a 5-mm Hg difference in diastolic blood pressure was associated with at least a 34% difference in the incidence of stroke and a 21% difference in the incidence of coronary heart disease. These relationships were found to hold even for blood pressures in the normal range (48). Furthermore, the Hypertension Detection and Follow-up Program reported that 5-mm Hg reductions in blood pressure resulting from pharmacological treatment were associated with a 20% reduction in 5-year mortality (49). The present study and

others provide evidence that daily caffeine consumption is associated with ambulatory blood pressure elevations of this magnitude. Therefore, an assertion that the pressor effects of caffeine could meaningfully increase cardiovascular disease risk in the general population of consumers is quite plausible. The same could be said for the increases in epinephrine, which could contribute to atherogenesis by the same mechanisms as thought to occur with stress-related increases in epinephrine (50–52).

The pressor effects of caffeine observed in this study may be of special interest to hypertensive coffee drinkers, who may be able to reduce their blood pressures by quitting. Indeed, present results indicate that eliminating coffee and other sources of caffeine from the diet could be a useful adjunctive treatment for hypertension in appropriate individuals. The magnitude of potential reductions in blood pressure suggested by these results is similar to the treatment effects associated with most other nonpharmacological interventions, such as the adoption of a healthier diet. The highly regarded DASH study recently found that switching to a diet that was rich in fruits and vegetables and low-fat dairy products helped to reduce blood pressure (53, 54). However, the average benefits of the DASH diet were no larger in absolute size than the effects observed in the present study. After 8 weeks on the DASH diet, average clinic blood pressures were reduced by 5.5 mm Hg systolic and 3.0 mm Hg diastolic, and average ambulatory pressures were lower by 4.6/2.6 mm Hg. In the present study, similar reductions were observed on the first day of caffeine abstinence (the placebo condition). The long-term benefits of caffeine abstinence need further investigation, but these results suggest that caffeine abstinence might offer another nonpharmacological alternative for the treatment of high blood pressure. Certainly the elimination of a drug known to produce persistent elevations in blood pressure every day that it is ingested makes sense as an antihypertensive strategy. This treatment approach should be preferable to the lifetime administration of antihypertensive medications with their associated cost and potential for adverse effects. Coffee drinkers who have hypertension or even high-normal blood pressure levels should be advised to consider eliminating caffeine as a part of the lifestyle modifications used to control blood pressure. The benefits to each individual patient would be easy to confirm.

James (55) has argued that caffeine consumption may be an important preventable cardiovascular disease risk factor that has been overlooked by the public health community. The potential adverse effects of caffeine for health become an even greater concern given the overwhelming proportion of adults, and even children, who consume the drug on a daily basis over periods of many years. Caffeine may be the most popular drug in the world, but a growing body of evidence suggests that its adverse effects are not inconsequential. The true magnitude of caffeine's impact on health and disease remains to be determined and weighed against the perceived benefits from its use.

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