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Sex differences in the hemodynamic responses to mental stress: Effect of caffeine consumption

**NOHA H. FARAG^a, ANDREA S. VINCENT^{a,b}, BARBARA S. MCKEY^b, MUSTAFA AL'ABSI^d,
THOMAS L. WHITSETT^c, and WILLIAM R. LOVALLO^{a,b}**

*a*Department of Psychiatry and Behavioral Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

*b*Veterans Affairs Medical Center, Oklahoma City, Oklahoma, USA

*c*Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

*d*University of Minnesota Medical School, Duluth, Minnesota, USA

Abstract

The effect of caffeine on stress responses was compared in 25 men and 22 women in a 2-week placebo-controlled, double-blind, randomized crossover trial. On each week, participants abstained from all dietary sources of caffeine before undergoing a 6-h laboratory protocol under placebo or caffeine exposure followed by a 30-min mental stressor with blood pressure (BP) and cardiovascular hemodynamic assessments. On the placebo session, men and women showed a significant BP increase to stress, although women had significant cardiac responses whereas men had vascular responses. Caffeine ingestion before stress caused both men and women to have enhanced hemodynamic responses to the stressor associated with an increase in cardiac index and a drop in the peripheral resistance index. Caffeine enhances the cardiovascular fight-or-flight response pattern to stress in men and women.

Descriptors

Sex; Stress; Hemodynamics; Blood pressure; Caffeine

Exaggerated cardiovascular reactivity to stress has been prospectively linked to subsequent development of hypertension and cardiovascular disease (CVD; Matthews, Zhu, Tucker, & Whooley, 2006). Hemodynamic response patterns to mental stress differ between men and women. Reactivity studies have described men as vascular reactors and women as myocardial reactors to mental stress (Allen, Stoney, Owens, & Matthews, 1993; Girdler, Turner, Sherwood, & Light, 1990; Hartley, Lovallo, & Whitsett, 2004). This sex difference may be due to differences in sensitivity and/or density of peripheral adrenergic receptors (Freedman, Sabharwal, & Desai, 1987). However, there is little information on the effect of caffeine on the cardiovascular hemodynamic responses to stress in men and women.

Caffeine is a widely used pharmacologic substance capable of interacting with all levels of the stress axis. Caffeine's primary mode of action is through blockade of adenosine receptors (Fredholm, 1995), thereby acting as a central nervous system stimulant (Rainnie, Grunze, McCarley, & Greene, 1994), affecting cardiovascular (Hartley, Lovallo, Whitsett, Sung, & Wilson, 2001), and endocrine functions (Lovallo, al'Absi, Blick, Whitsett, & Wilson, 1996).

Studies of the cardiovascular effects of caffeine at rest in men have demonstrated that caffeine exerts a pressor effect by increasing peripheral resistance (Pincomb et al., 1985). Consumption of caffeine increases during periods of stress in daily life (Conway, Vickers, & Ward, 1979), and it exerts an additive effect on blood pressure (BP) responses during stress (Lane, 1983; Shepard, al'Absi, Whitsett, Passey, & Lovallo, 2000; Sung, Lovallo, Pincomb, & Wilson, 1990). We know very little about the combined effects of caffeine and stress in women. With few exceptions (Hartley et al., 2004; James & Gregg, 2004), prior studies have been conducted in men (Myers, Shapiro, McClure, & Daims, 1989; Pincomb et al., 1985) or have focused on BP and heart rate (HR) responses to stress and caffeine (France & Ditto, 1989; James, 1994; Strickland, Myers, & Lahey, 1989), leaving the underlying cardiac dynamics unexplored.

We have ample evidence of the cardiovascular effects of caffeine on stress responses in men but we know much less in women. Because men and women have different cardiovascular response patterns during mental stress (Girdler et al., 1990), we cannot assume that the effects of caffeine during mental stress will be the same for both groups. Therefore the purpose of this study was to explore the effect of caffeine on hemodynamic responses to stress in healthy young men and women.

Methods

Healthy volunteers (25 men and 22 women) ages 21–35 years were recruited from the community (Table 1). All participants were normotensive (BP<135/85) at screening, nonsmokers, nonobese (BMI<30), and in good health by self-report and routine physical exam. Participants were excluded if they had current or past evidence of heart disease, liver or renal disease, diabetes, severe asthma, or cerebrovascular disease. All participants regularly consumed 50–700 mg/day of caffeine by structured report and indicated no intolerance to caffeine. Participants were free of nonprescription medication during the time they were enrolled in the study. Women were free from oral contraceptives and were not pregnant, as determined by urine pregnancy test (One Step Pregnancy Test, Inverness Medical Ltd., Beachwood Park, North Inverness, Scotland). All participants signed a consent form approved by the Institutional Review Board of the Veterans Affairs Medical Center and the University of Oklahoma Health Sciences Center and were paid for their participation.

Study Design

The primary study design was a 4-week randomized, placebo-controlled, double-blind, crossover trial of caffeine versus placebo effects on cardiovascular and endocrine function. The crossover conditions were counterbalanced. Two of the study weeks began with 5 days of home self-administration of placebo (0 mg/day) and two began with caffeine (300 mg/day or 600 mg/day taken in three equal doses). Each of these periods was followed by a laboratory test day during which the subject received placebo on 1 week ($3 \times 0 \text{ mg} = 0 \text{ mg}$) and caffeine on the other 3 weeks ($3 \times 250 \text{ mg} = 750 \text{ mg}$). Weeks were separated by a crossover day (caffeine = 100, 0, and 0 mg) to buffer sudden changes in caffeine intake. The development of tolerance and its effect on cardiovascular hemodynamics have been reported elsewhere (Farag, Vincent, McKey, Whitsett, & Lovallo, 2005; Lovallo et al., 2004).

Data reported here examine the effect of caffeine (250 mg) versus placebo on the responses to mental stress following 5 days of placebo home maintenance. This allowed us to compare stress responses following acute administration of placebo versus caffeine after 5 days of caffeine washout.

Caffeine Dosing and Compliance

Home maintenance placebo was supplied in bottles of identical gelatin capsules (College of Pharmacy, University of Oklahoma, Oklahoma City) containing lactose. Test-day challenge doses were supplied in identical-appearing capsules containing either lactose or lactose mixed with 250 mg of USP caffeine (Gallipot, St. Paul, MN). The 250 mg challenge dose is equivalent to 2.5 (6-ounce) cups of coffee. This dose is sufficient to produce reliable cardiovascular and neuroendocrine effects, is within the range persons normally consume in their daily lives, and is within the dose range used in other studies (James, 1991; Pincomb et al., 1985).

Compliance with home dosing of placebo was assessed by capsule counts, by caffeine assay of saliva specimens collected at home each day at 7:00 p.m. (Salivette[®], Starstedt, Germany), and from a saliva specimen collected on testing days upon entering the laboratory. Caffeine concentrations in saliva were measured by high performance liquid chromatography (Waters Corp., Milford, MA), following precipitation of proteins, using a methanol and water mobile phase and ultraviolet detection (Christensen & Whitsett, 1979; Scott, Chakraborty, & Marks, 1984). The 5 maintenance days with placebo administration at home allows an effective washout period from the effects of dietary caffeine, thereby removing this as a confounder in the analysis. The average half-life for elimination of caffeine from plasma is 3.5 h (ranges from 2 to 10 h; Magkos & Kavouras, 2005). Therefore, the 5 days of placebo washout prior to the days of testing were 12–60 times the half-lives for elimination of caffeine and were therefore adequate to clear caffeine from the system. This was further validated by saliva samples collected at 7:00 p.m. each day and predrug on the morning of testing days. Participants found to be noncompliant by any of these criteria were dropped and replaced ($n = 3$).

Laboratory Protocol

The laboratory protocol included the following activities: breakfast, instrumentation for impedance cardiography measures (60 min), a rest period (20 min), predrug impedance and BP baseline (10 min), capsule, postdrug response (60 min), mental stress (30 min), and recovery (40 min). The mental stressor consisted of a reaction time task in alternation with mental arithmetic. BP was measured every 3 min during screenings and test sessions using a Dinamap 845 oscillometric vital signs monitor (Criticon, Talahassee, FL).

Impedance Cardiography

Thoracic impedance measurements were carried out using a commercial impedance cardiograph system (Minnesota Impedance Cardiograph Model 304B, Minneapolis, MN) and a microcomputer; it is a technique familiar to this laboratory. Impedance cardiography is a noninvasive, unobtrusive technique for cardiac measurements that is appropriate for behavioral research (Sherwood et al., 1990), and it is reliable for within-day and between-day repeated measurements (Pincomb et al., 1985). The impedance system recorded the thoracic impedance waveform (ΔZ) using a standard tetrapolar electrode configuration. The first derivative (dZ/dt) was extracted to yield systolic time intervals of pre-ejection period (PEP) and left ventricular ejection time (LVET), as well as the peak of the dZ/dt (in ohms per second), using previously described methods (Sherwood et al., 1990). Impedance waveforms and electrocardiograms were ensemble averaged and data were extracted by proprietary software (Waveshell Software, Center for Biomedical Engineering, Research Triangle Institute, Research Triangle Park, NC) on an IBM-compatible computer. Validation of ensemble averaging and automated extraction of parameters have been demonstrated against hand scoring and editing of raw waveforms (Everson, Lovallo, Pincomb, Kizakevich, & Wilson, 1991; Kelsey et al., 1998).

The following dependent variables were then derived for further analysis: systolic BP, diastolic BP in millimeters of mercury, HR in beats per minute, and stroke volume in milliliters, using

the equation of Kubicek (Kubicek et al., 1970). The following variables were then calculated: cardiac output = stroke volume $\times$ heart rate in liters per minute, and total peripheral resistance = mean arterial pressure $\times$ 80/cardiac output) in dyne-s-cm⁻⁵. To account for differences in body size, body surface area was used to calculate stroke index (SI; stroke index = stroke volume/body surface area), cardiac index (CI; cardiac index = cardiac output/body surface area), and total peripheral resistance index (TPRI; total peripheral resistance index = mean arterial pressure/cardiac index) $\times$ 80; Devereux et al., 1984), which were used in the analysis.

Menstrual Cycle Assessment

For women, we recorded the first day of their previous menstrual cycle and a cycle they started during the protocol. We used this information to determine their menstrual cycle phase on testing weeks. The follicular phase was defined as days 2–12, and the luteal phase was defined as days 18–25 of their menstrual cycle. Using these criteria, we had complete menstrual cycle data on 17 of the 22 women in the study.

Data Reduction and Statistical Analysis

Ensemble averaged impedance waveforms were taken over 1-min intervals during all periods of the protocol. These values were then averaged across the 10-min baseline, 40–60 min after caffeine response, 30 min stress, and 40 min recovery. Blood pressures were averaged over the same time periods.

The data were analyzed in three stages. First we compared BP and hemodynamic indices of men and women at rest. Then we examined sex differences in response to caffeine. Finally, we compared stress responses in men and women during placebo versus caffeine exposure conditions. Data were analyzed using multivariate repeated measures analysis of variance (MANOVA), Student's *t* test, and Pearson's *r*. Significant interactions from the MANOVA were followed by simple effects tests. All tests were two-tailed, and statistical significance was set at $\alpha = .05$. Effect sizes were taken as small, partial $\eta^2 = .2$, medium, partial $\eta^2 = .5$, and large, partial $\eta^2 = .8$ (Cohen, 1988). The data were analyzed using SPSS (SPSS for Windows, rel. 10.1.0, SPSS Chicago, IL).

Results

Saliva caffeine levels taken at home on placebo maintenance days and from morning samples in the laboratory were all near 0 $\mu\text{g/ml}$ on the 2 study weeks, indicating compliance with dietary caffeine restrictions for all participants included in the final data set. Saliva caffeine levels after 250 mg caffeine in the laboratory ranged from 3.5 to 5.8 $\mu\text{g/ml}$, indicating expected concentrations for this dose and verifying accuracy of administration on the caffeine test day.

Sex Differences at Rest

The screening and demographic data for the 47 participants are shown in Table 1. Student's *t* test demonstrated no significant differences between men and women in any of the hemodynamic indices at rest either on placebo or caffeine days, with the exception that men had higher resting systolic BP than women on placebo, $t(45) = -5.29$, $p < .0001$, and caffeine days, $t = -3.60$, $p = .001$. Men and women did not differ in habitual caffeine consumption, $t(45) = .05$, $p = .9$.

Effect of Caffeine

We previously reported in this group of participants that, at rest, there were no sex differences in the hemodynamic responses to caffeine consumption (Farag et al., 2005). To summarize that report, a 2 (Period: baseline, postdrug) $\times$ 2 (Week: placebo, caffeine) $\times$ 2 (Sex) MANOVA

demonstrated that caffeine resulted in an increase in systolic (Week $\times$ Period: Wilk's $\lambda = .68$, $F[1,47] = 22$, $\eta^2 = .32$, $p < .0001$) and diastolic BP (Week $\times$ Period: Wilk's $\lambda = .64$, $F[1,47] = 26$, $\eta^2 = .36$, $p < .0001$) and TPRI (Week $\times$ Period: Wilk's $\lambda = .83$, $F[1,44] = 9.1$, $\eta^2 = .17$, $p = .004$). There were no significant Week $\times$ Sex or Period $\times$ Sex interactions, indicating that these caffeine effects were similar in men and women.

To determine the hemodynamic mechanisms underlying the BP increase to caffeine, we used Pearson's correlations between the changes in systolic and diastolic BP from baseline to post-caffeine with the changes in the hemodynamic variables at that time. The diastolic BP rise to caffeine was positively correlated with the increase in TPRI change to caffeine, $r = .4$, $p = .004$, in the sample as a whole. This correlation was weaker in women, $r = .4$, $p = .06$, than in men, $r = .5$, $p = .01$. In women, neither of the other hemodynamic variables (CI and SI) approached a significant correlation with systolic or diastolic BPs, $r_s = .01-.2$. In men, SI was negatively correlated with diastolic BP change to caffeine, $r = -.5$, $p = .02$. Thus, the larger increase in TPRI in men was balanced by a drop in SI, resulting in a net diastolic BP increase that was equivalent in men and women.

Effect of Psychological Stress and Modifying Effects of Caffeine

To test for sex differences in stress responses following caffeine versus placebo, we performed a 2 (Week: placebo, caffeine) $\times$ 2 (Period: pre-, poststress) $\times$ 2 (Sex) MANOVA. In this case, the prestress (baseline) value was taken as the postdrug measurement, allowing the stress response to be separated from the acute effect of caffeine at rest. Results of the MANOVA are described in Table 2, and the mean values are shown in Table 3. There were significant effects of week and period on systolic and diastolic BPs, indicating that stress increased BP under placebo and caffeine conditions. There were significant Period $\times$ Sex interactions for TPRI and CI. During stress, women showed a drop in TPRI after both caffeine and placebo, whereas men showed an increase during placebo and a drop after caffeine. The CI during stress increased on both caffeine and placebo weeks, but this increase was larger for women (Figure 1). The MANOVA also revealed significant Week $\times$ Period interactions for HR, TPRI, CI, and SI, indicating an effect of caffeine on both cardiac and vascular responses during stress (Table 2).

Although we did not obtain significant Sex $\times$ Week interactions, the Sex $\times$ Period and Week $\times$ Period interactions encouraged us to undertake exploratory analyses based on separate Sex $\times$ Period MANOVAs for the placebo and caffeine weeks to gain an appreciation for sex differences in hemodynamic responses to psychological stress following placebo and caffeine consumption.

The pattern of significant BP and hemodynamic responses for men and women during stress on placebo and caffeine weeks is summarized in Table 4. On placebo week, SBP, DBP, and HR all increased in response to psychological stress and did so in both sexes, indicated by significant effects of Period (SBP: Wilk's $\lambda = .25$, $F[1,47] = 144$, $\eta^2 = .75$, $p < .0001$; DBP: Wilk's $\lambda = .35$, $F[1,47] = 89$, $\eta^2 = .65$, $p < .0001$; HR: Wilk's $\lambda = .29$, $F[1,47] = 114$, $\eta^2 = .71$, $p < .0001$) and an absence of Sex $\times$ Period interactions. However, there were significant Sex $\times$ Period terms for the hemodynamic variables underlying the BP responses to stress. The women showed a drop during placebo in TPRI (Period $\times$ Sex: Wilk's $\lambda = .87$, $F[1,45] = 6.5$, $\eta^2 = .13$, $p = .02$) and an increase in CI (Period $\times$ Sex: Wilk's $\lambda = .89$, $F[1,45] = 5.6$, $\eta^2 = .35$, $p = .02$), and SI (Period $\times$ Sex: Wilk's $\lambda = .94$, $F[1,45] = 3.1$, $\eta^2 = .06$, $p = .09$), indicating that their BPs increased due to cardiac activation and not peripheral resistance responses. This pattern of responses is characteristic of the classic fight-or-flight response. The fight-or-flight response describes a state of sympathetic nervous system stimulation in response to stress (Cannon, 1929). This involves an increase in CI and a decrease in TPRI analogous to an exercise response (Lovallo, 2005). Conversely, men responded to stress during placebo by an increase in TPRI, a decline in SI, and a modest increase in CI (see Figure 1).

On the other hand, there were no sex differences in the pattern of stress responses on the caffeine week. Psychological stress presented 1 h after ingestion of caffeine resulted in significant Period effects seen as increases in systolic (Wilk's $\lambda = .28$, $F[1,47] = 119$, $\eta^2 = .72$, $p < .0001$) and diastolic BP (Wilk's $\lambda = .54$, $F[1,47] = 39.4$, $\eta^2 = .46$, $p < .0001$), as well as in HR (Wilk's $\lambda = .34$, $F[1,45] = 4.4$, $\eta^2 = .66$, $p < .0001$) and CI (Wilk's $\lambda = .61$, $F[1,45] = 28.3$, $\eta^2 = .39$, $p = .003$). These increases were accompanied by a drop in TPRI (Wilk's $\lambda = .79$, $F[1,45] = 12.3$, $\eta^2 = .22$, $p = .001$). There was also a trend toward an increase in SI (Period: Wilk's $\lambda = .93$, $F[1,45] = 3.3$, $\eta^2 = .07$, $p = .08$). Thus, caffeine ingestion prior to stress induced a fight-or-flight reaction in men and maintained women's fight-or-flight response.

To gain additional insight into the hemodynamic contributions underlying BP responses to stress in men and women, we conducted Pearson's correlations between BP and hemodynamic changes to stress. On the placebo week, men's diastolic BP change correlated positively with TPRI change, $r(23) = .4$, $p = .04$. In women, the diastolic BP change was correlated positively with change in TPRI, $r(20) = .6$, $p = .007$, and negatively with the change in SI, $r(23) = -.5$, $p < .02$. Systolic BP change in women was marginally positively correlated with change in CI, $r(20) = .4$, $p = .07$. This pattern of correlations indicated that men increased their BP primarily by vascular mechanisms whereas women relied on a combination of vascular and cardiac factors. Changes in HR were positively correlated with CI change to stress only in women, $r(20) = .6$, $p = .007$.

On the caffeine week, systolic BP change was positively correlated with CI change in women, $r(20) = .6$, $p = .001$, and marginally so in men, $r(23) = .4$, $p = .06$. Diastolic BP change was positively correlated with TPRI change to stress in men, $r(23) = .5$, $p = .01$, and women, $r(20) = .5$, $p = .02$, and negatively correlated with SI changes in men, $r(23) = -.5$, $p = .03$. HR change to stress was positively correlated with CI change to stress in men, $r(23) = .6$, $p = .005$, and women, $r(20) = .8$, $p < .0001$.

Exploring Possible Confounders

We explored the effects of habitual caffeine consumption levels and menstrual cycle phase to determine possible modifying effects on caffeine and stress responses. There were no sex differences in the habitual caffeine consumption levels, $t(45) = .05$, $p = .96$. Including habitual caffeine consumption level as a covariate in all the previously described MANOVAs did not affect the results.

We had complete menstrual cycle data on 17 women for which a series of $2 (\text{Week}) \times 2 (\text{Period}) \times 2 (\text{Menstrual Cycle Group})$ MANOVAs were performed on the independent variables. There was a significant Week $\times$ Menstrual Cycle Group interaction for HR (Wilk's $\lambda = .43$, $F[1,15] = 18.9$, $\eta^2 = .56$, $p = .001$). Otherwise, there were no significant main effects or interactions of Menstrual Cycle Group for any of the other variables. Follow-up t tests indicated that the only significant difference was on caffeine week, where postcaffeine HR levels were lower in the follicular phase, $t(15) = -3.4$, $p = .004$. However, there were no significant differences in HR change to caffeine or stress. It is worth noting that there were only 5 women in the follicular phase compared to 12 women in the luteal phase on caffeine week.

Discussion

In this study we compared the effect of caffeine on the cardiovascular responses to mental stress in men and women during placebo exposure. Systolic BP, diastolic BP, and HR increased in response to stress in men and women on placebo day; however, the hemodynamic mechanisms underlying this pressor effect varied significantly. The BP response in males had a predominantly vascular contribution, so that the BP increase was accompanied by an increase in peripheral vascular resistance. On the other hand, BP responses to stress in women had a

predominantly cardiac component, as evidenced by an increase in CI. This finding replicates those of previous studies documenting a predominant cardiac reactivity in females versus vascular reactivity in males (Girdler et al., 1990).

Sex differences in peripheral vascular adrenergic receptors may be responsible for this difference in reactivity. Freedman et al. (1987) observed a dose-dependent vasoconstriction during phenylephrine infusion and dose-dependent vasodilation during isoproterenol infusion in men but not in women, thus leading to the conclusion that the sensitivity or density of peripheral vascular adrenergic receptors is lower in women than men. Another possibility for the differences in the hemodynamic response to stress in women could reflect vascular hormonal effects. Estrogen influences the relaxation of vascular smooth muscle either directly through estrogen receptors on endothelial cells or indirectly through increasing circulating levels of endothelial derived relaxing factors (Sarrel, 1990; Wren, 1992). The pattern of responses characterized by an increase in cardiac activation and a drop in peripheral resistance is distinctive of the classic fight-or-flight response to stress and is analogous to an exercise response (Lovallo, 2005). Under the placebo condition, only women exhibited cardiovascular responses characteristic of the fight-or-flight response to stress.

Caffeine ingestion prior to stress resulted in equivalent increases in BP in men and women. These BP responses to caffeine were associated with increases in TPRI that were similar in men and women (Farag et al., 2005). Sex differences in the stress response seen on the placebo day were altered in the presence of caffeine. Exposure to psychological stress following caffeine resulted in a decrease in peripheral resistance compared to the pretask baseline in both sexes. Based on previous observations that caffeine increased forearm blood flow and decreased forearm vascular resistance during performance of mental arithmetic, it is possible that caffeine actively enhances vasodilation during mental stress (Lane & Williams, 1985; Pincomb et al., 1985). Additionally, caffeine led to an enhancement of stress-related increases in CI. It is important to note that, in this study, the average level of peripheral resistance reached during the task was similar on both caffeine and placebo days. Therefore, caffeine did not produce a net vasodilation, but, rather, the previous increase in vascular resistance seen at rest was eliminated during the task, particularly in males. In females, the drop in TPRI during stress was in excess of the pretask (postcaffeine) levels (Table 3). As seen in Table 3, the vascular resistance levels rose to pretask (postcaffeine) levels during recovery. The combination of caffeine and stress induced a fight-or-flight reaction in men and maintained the fight-or-flight response seen in women on the placebo day.

In a previous study comparing men and women exposed to caffeine and stress, we obtained comparable results (Hartley et al., 2004). In that study, we tested separate groups of men and women that received placebo or caffeine on a single laboratory day. This was done to maximize the level of anxiety associated with the public speaking stressor. Under these conditions, caffeine and stress caused both men and women to have a decrease in peripheral resistance to stress, which provides evidence of an enhancement of the vascular dilation accompanying the fight-or-flight response. Also, caffeine modestly enhanced cardiac output change to stress in men and women similarly in both studies. Therefore, both studies reach broadly similar conclusions about the effect of caffeine on stress responses in men and women. That is, caffeine contributes to an enhanced fight-or-flight state during stress in both genders. These broad conclusions apply to a socially threatening stressor such as public speaking (Hartley et al., 2004) and to globally activating stressors such as reaction time tasks for monetary bonuses used in this study.

The effects of placebo and caffeine on stress responses to reaction time tasks and mental arithmetic in women do not appear to be a function of menstrual cycle variation. However, this study was not designed specifically to allow a fully systematic comparison of placebo versus

caffeine during luteal versus follicular phases of the cycle. Given that limitation, habitual caffeine intake and menstrual cycle do not appear to have caused the observed results. The use of a crossover design in this study allowed for within-group comparisons, thereby increasing power. However, we were interested in between-group comparisons by sex, which reduced the sample size to approximately 24 in each cell. This may have limited our power to detect moderate effect sizes in the three-way repeated measures MANOVA. Therefore, the results of this study should be replicated in a similarly rigorous study with a larger sample size.

Other studies examining gender differences in the effect of caffeine on cardiovascular stress reactivity have provided different results. James et al. documented a modest attenuating effect of caffeine on cardiac output during behavioral challenges (James & Gregg, 2004). This difference may be due to differences in methodology, including the use of different behavioral challenges as well as the lack of control for the effects of body size on cardiovascular hemodynamics in their study.

In conclusion, caffeine has additive effects on the BP responses to stress. In addition, caffeine alters the hemodynamic response to stress in men. Thus, the interpretation of stress studies in a research setting may be affected by caffeine ingestion. Namely, sex differences in hemodynamic responses to stress may be masked by caffeine intake. Restricting caffeine intake during laboratory and ambulatory monitoring studies is recommended.

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Figure 1.

Independent samples *t* test of sex differences in the stress response on placebo and caffeine. There is a significant sex difference in the response to stress on placebo week. Men increase TPRI in response to stress whereas women show a drop in TPRI in response to stress. On the other hand, women show a larger increase in CI in response to stress compared to men. Pairwise contrasts between responses to stress on placebo versus caffeine in both sexes. Men show a significant drop in TPRI and a significant increase in SI and CI in response to stress on caffeine, compared to their response on placebo.

Table 1
Characteristics of Study Participants (Mean $\pm$ SEM)

Characteristic	Men (<i>N</i> = 25)	Women (<i>N</i> = 22)
Age (years)	26 $\pm$ 0.9	31 $\pm$ 1.2
BMI (kg/m ²)	24 $\pm$ 0.5	23 $\pm$ 0.4
Race (White/African-American/Other)*	17/2/6	20/2/0
Screening systolic BP (mm Hg)	116 $\pm$ 1.4	105 $\pm$ 1.7
Screening diastolic BP (mm Hg)	66 $\pm$ 1.1	67 $\pm$ 1.4
Screening heart rate (beats/min)	67 $\pm$ 1.9	69 $\pm$ 2.3
Habitual caffeine consumption (mg/day)	458 $\pm$ 111	465 $\pm$ 81

* Significant difference by sex ($p < .0001$).

Summary of 2 (Week: Placebo, Caffeine) × 2 (Period: Pretask, Task) × 2 (Sex) Repeated Measures MANOVAs (F Values, df = 1,47)

	Variable					
	SBP	DBP	HR	TPRI	CI	SI
Week	58.6**	38.4**	0.004	0.55	5.3*	4.9*
Period	207.3**	98.3**	131.9**	4.7**	35.9**	0.28
Sex	23.4**	0.006	0.04	2.36	2.6	2.3
Period × Sex	0.24	1.2	1.7	5.2*	5.1*	2.5
Week × Period	2.03	1.8	4.4*	13.8*	9.7*	5.7*
Week × Period × Sex	0.04	0.34	0.35	1.1	0.004	0.58

* $p < .05$.
** $p < .0001$.

Table 3
Values Obtained at Baseline (Predrug), Pretask (Postdrug), Task, and during Recovery from Psychological Stress

Variable	Period	Men (N = 525)				Women (N = 522)			
		Placebo		Caffeine		Placebo		Caffeine	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
Systolic BP (mmHg)	Baseline	115	1.2	116	1.4	105	1.4	105	1.5
	Pretask	115	1.1	119	1.3	106	1.3	111	1.7
	Task	123	1.5	129	1.5	114	1.5	121	2.1
Diastolic BP (mmHg)	Recovery	116	1.1	121	1.3	109	1.3	112	1.3
	Baseline	64	1.2	64	1.4	64	1.2	63	1.2
	Pretask	63	1.4	68	1.7	64	1.4	68	1.2
Heart rate (beats/min)	Task	69	1.3	74	1.6	69	1.2	72	1.3
	Recovery	64	1.4	68	1.6	66	1.3	67	1.1
	Baseline	65	1.9	64	1.6	66	1.8	66	2.0
Peripheral resistance index (dyne-s-cm ⁻⁵ /m ²)	Pretask	64	1.9	62	1.6	62	1.7	62	2.1
	Task	71	2.2	71	2.0	71	1.8	74	2.4
	Recovery	62	1.7	62	1.8	63	1.8	64	2.0
Cardiac index (l/min/m ²)	Baseline	2464	157	2274	101	2276	175	2042	115
	Pretask	2615	159	2796	133	2545	188	2506	209
	Task	2797	189	2627	141	2377	153	2141	145
Stroke index (ml/beat/m ²)	Recovery	3136	230	2852	140	2585	184	2393	176
	Baseline	2.9	0.16	3.0	0.13	3.0	0.19	3.2	0.16
	Pretask	2.7	0.14	2.6	0.12	2.7	0.16	2.9	0.15
	Task	2.8	0.16	3.1	0.17	3.2	0.19	3.7	0.26
	Recovery	2.4	0.13	2.6	0.12	2.7	0.15	3.0	0.16
	Baseline	43.7	2.2	46.5	2.1	46.3	3.4	49.4	2.9
	Pretask	42.4	2.1	42.3	2.1	44.7	2.8	47.4	2.9
	Task	39.6	2.1	43.5	2.2	45.2	2.7	50.0	3.2
	Recovery	38.1	2.1	41.9	2.1	44.2	2.6	48.0	2.9

Table 4
Effects of Stress following Placebo and Caffeine Administration in Men and Women

	Men		Women	
	Placebo	Caffeine	Placebo	Caffeine
Systolic BP (mmHg)	↑	↑	↑	↑
Diastolic BP (mmHg)	↑	↑	↑	↑
Heart rate (beats/min)	↑	↑	↑	↑
Peripheral resistance index (dyne-s-cm ⁻⁵ /m ²)	↑ ↑	↓	↓ ↓	↓
Cardiac index (l/min/m ²)	↑	↑	↑ ↑	↑
Stroke index (ml/beat/m ²)	—	—	—	—

Significant Period effects are designated by single arrows (↑ or ↓) indicating the direction of change from pre- to poststress. Double arrows (↑ ↑) indicate a significant Period × Sex interaction. Dash indicates nonsignificant Period and/or Period × Sex effects.