Effects of Coffee on Cardiovascular Responses to Stress: A 14-Week Controlled Trial

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We studied the cardiovascular responses to orthostatic and mental stress of 43 healthy subjects who daily received six cups of boiled or filtered coffee and of 21 healthy subjects who abstained from caffeine-containing beverages. All 64 subjects first received six cups of filtered coffee/day for 2 weeks. Then blood pressure (BP) and heart rate (HR) were recorded before, during, and after a "stand upright" test and a mental arithmetic test. Subjects were then randomized to either complete abstinence from caffeine-containing beverages ($n = 21$), or consumption of six cups of filtered coffee ($n = 21$), or consumption of six cups of boiled coffee/day ($n = 22$). The stress tests were repeated after subjects had been on these regimens for 8 weeks. Abstinence from coffee did not affect the responses of BP or HR to orthostatic stress, or the response of BP to mental stress. The increase in HR caused by mental stress was five beats/min less ($p = 0.02$) in the no-coffee group than in the filtered- (95% confidence interval − 8.8 to −1.2) or boiled- (95% confidence interval −8.4 to −0.8) coffee group. It is concluded that elimination of caffeine decreases the HR response to mental stress.

INTRODUCTION

Caffeine ingestion produces transient increases in blood pressure (BP) in subjects who have abstained from caffeine for 11 to 18 hours (1–10). Mental or physical stress also acutely increases blood pressure (11, 12). Since in daily life subjects often consume caffeine-containing beverages during periods of stress, researchers have focused on the possibility of additive or synergistic effects of stress and caffeine. Some studies have shown that caffeine and mental stress produce additive increments in blood pressure (1–5, 7, 8, 13) or heart rate (4) in both caffeine users and nonusers, while others have reported synergistic effects on blood pressure, heart rate, forearm blood flow or neuroendocrine variables (2, 3, 6, 14–17).

Most previous studies in both abstainers and regular users looked at combined effects of a single acute dose of caffeine and stress after an overnight period of abstinence (1–8, 14–17). This corresponds to taking measurements at the time of the day when the pressor effect of caffeine is at its maximum. In regular users caffeine sensitivity is a function of the plasma level of caffeine at the time of dosing (10, 18). During the day, when plasma caffeine levels are already high in regular coffee users, the further consumption of caffeine

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TABLE 1. Baseline Characteristics (Mean ± SD) of the Three Study Groups

Characteristic	Boiled Coffee $N = 22$	Filtered Coffee $N = 21$	No Coffee $N = 21$
Sex (male/female)	11/11	11/10	11/10
Age (years)	39 ± 6	39 ± 9	39 ± 8
Body mass index (kg/m²)	23 ± 2	24 ± 3	22 ± 2
Blood pressure (mm Hg)			
Systolic	121 ± 16	121 ± 15	123 ± 14
Diastolic	77 ± 10	78 ± 7	80 ± 9
Heart rate (beats/min)	67 ± 10	75 ± 12	73 ± 12

Baseline blood pressures were measured with a regular sphygmomanometer.

produces smaller (16, 18–20), or negligible (21, 22) changes in blood pressure. We have now looked at the combined effects of caffeine and stress in regular coffee users at a time of the day (the afternoon) when serum caffeine levels were high, and in nonusers who had abstained from caffeine for a period of 8 weeks. Our main interest was whether prior consumption of caffeine would elicit greater cardiovascular responses to stress, after controlling for cardiovascular effects produced by caffeine alone. The present data were obtained during a study on the effects of boiled coffee, boiled coffee that has been filtered through paper, and no coffee on blood pressure (23) and serum lipids (24).

METHODS

Subjects

The subjects were recruited through advertisements in local newspapers. Out of 167 applicants, 66 met all criteria for eligibility: aged 17 to 57 years, apparently healthy, blood pressure systolic <160 mm Hg and diastolic <95 mm Hg, serum cholesterol <7.0 mmol/liter, body mass index <30 kg/m², abstinence from smoking for at least 1 year, no use of medication, not on a prescribed diet, no use of oral contraceptives, not pregnant, not working night shifts, and a habitual consumption of four to seven cups of regular drip filter coffee a day. Two women withdrew from the study during the pretreatment baseline, one for medical and one for personal reasons. Thus, data from 64 subjects were analyzed. Table 1 provides their baseline characteristics.

The protocol for the study, which had been approved by the local Ethic Committee, was explained to the volunteers, and all subjects gave their written informed consent. The subjects were asked to maintain their usual pattern of activity and to keep up a stable body weight.

Design

The study lasted 14 weeks, from September 11 to December 15, 1989. During a pretreatment baseline of 17 days all subjects consumed six 5-ounce cups (0.9 liter) of filtered coffee per day. After having been matched for sex, blood pressure, and age, the subjects were randomly allocated to receive during the next 79 days either 0.9 liter per day of boiled coffee (cf. "Coffee Preparation," below), 0.9 liter of filtered coffee, or no coffee at all.

All subjects received two cups of herbal tea (Kneipp (Würzburg, FRG) and Salus Haus (Bruckmühl, FRG)) during the full study period as a source of fluid free from caffeine and other methylxanthines. Subjects who were on the no-coffee regimen received one glass of orange or apple juice, one glass of mineral water, and two additional cups of herbal tea per day. Only nonmedicinal herbal teas that complied with the strict safety regulations of the

Federal Republic of Germany were used. The coffee, the paper filters, coffee milk, herbal tea, juices, and mineral water were provided by us. Consumption of tea and other caffeine-containing products and preparations was prohibited for all subjects, with the exception of chocolate, which was allowed in amounts up to 15 g providing up to 15 mg of caffeine per day. Throughout the trial subjects met once a week with a dietitian who checked food intake by a 24-hour dietary recall, weighed the subject, gave out packages for the next week, and collected empty packages from the previous week. Subjects were further instructed to record any signs of illness and any deviation from the protocol in their diaries.

All subjects underwent a stand-up test and a mental arithmetic test 7 days prior to the trial so as to habituate them to the experimental procedure. The tests were then repeated on days 14 (pretreatment baseline) and 75 (treatment period) of the trial. The room, the investigator, the time and day of the week, and the temperature of the room were identical in the pretreatment baseline and treatment period. All tests were carried out in the afternoon; at that time subjects in the coffee groups had consumed three cups of coffee before noon and none thereafter. The delay between the third cup of coffee and the time of testing differed from 1 to 4 hours, but was always the same for one subject in the initial baseline and treatment period. On arrival at the hospital outpatient clinic, the subjects were asked to empty their bladder. A blood pressure cuff of a semiautomatic blood pressure monitor (Arteriosonde 1225; Roche, Medical Electronic Division, Orangeburg, NJ) was attached to the nondominant arm. Heart rate (HR) was calculated from the last 10 intervals between the R-waves of an electrocardiographic registration. After a supine rest of 16 minutes, three blood pressure and heart rate readings were taken at 2-minute intervals. Then the subject was asked to stand up and the measurements were repeated at the first, third, and fifth minute of standing upright. During the tests, conversation with the subjects was avoided as much as possible. After another supine rest period of 16 minutes, the BP and HR measurements were repeated. Subsequently, the subject carried out a forced mental arithmetic test by counting backwards from a four-digit number in steps of 17 (e.g., 2050, 2033, 2016 . . .) as quickly as possible for 5 minutes while being paced by a metronome. Subjects remained supine throughout this test. Subjects had to perform the calculations aloud, and mistakes were pointed out immediately. Blood pressure and heart rate were measured at the first, third, and fifth minute of the arithmetic test. After the mental arithmetic test had been completed, blood pressure and heart rate were recorded after 2, 4, and 6 minutes of rest.

Coffee Preparation

The subjects were instructed to prepare and drink 0.9 liter or 6 cups of coffee brew a day. In view of our interest in coffee and lipids (24), two different brewing methods were used. So-called "boiled" coffee was prepared by pouring 0.5 liter of boiling water onto 25 g of coarsely ground coffee (Roodmerk, Douwe Egberts, Utrecht, the Netherlands) in a 0.5 liter Thermos® flask. Ten minutes later the liquid was decanted into a second Thermos flask in which the coffee beverage was stored, and from which it was poured out into a cup before consumption. The contents of one bottle were usually consumed within half a day, after which another bottle was prepared. Filtered coffee was prepared like the boiled coffee, but now the liquid was poured into the second Thermos flask through a white Melitta paper filter (Melitta Nederland, Veenendaal, The Netherlands, 1*4. No. 4006508 200016) in a conical plastic filter holder. Subjects in both groups were allowed to dilute the brew in the second Thermos bottle with hot water if they found it too strong for their taste.

The mean (±SD) caffeine content was 860 ± 13 mg per liter (130 mg per cup) for the boiled, and 887 ± 6 mg per liter (133 mg per cup) for the filtered coffee.

Blood Sampling and Analysis

Nonfasting blood samples were collected on days 32, 58, and 82 in the afternoon in order to allow us to check the concentration of C-reactive protein in cases of suspected intercurrent illness, which later appeared to be unnecessary. Serum was obtained by low-speed centrifugation within 1.5 hours and stored at −80°C. Serum caffeine was measured in these samples, by reversed phase high-performance liquid chromatography (25). Subjects were not aware of the latter determination.

Statistical Analysis

To examine the absolute effects of the stress tests as such, analysis of variance (General Linear Models

(GLM) procedure) (26) was performed on all data obtained during the pretreatment baseline, when all subjects were receiving filtered coffee. The independent variables in that analysis were sex, test procedure (i.e., supine rest 1, standing upright, supine rest 2, mental arithmetic test, supine rest 3), and sex* test procedure. In the treatment period, differences among the three groups in absolute levels of blood pressure and heart rate during all test conditions (rest 1 to rest 3) were examined by analysis of variance (using GLM procedure after correction for corresponding levels during pretreatment baseline).

Our hypothesis was that long-term elimination of coffee, tea, and other sources of caffeine would decrease cardiovascular responses to stress when compared with chronic consumption of caffeine-containing (filtered or boiled) coffee. Responses in pretreatment and treatment period were calculated as the mean of the measurements obtained during a stress test minus the mean of the corresponding measurements taken during the preceding final 5 minutes of supine rest. Power calculations showed that the minimum reductions in cardiovascular responses that our study could detect with a power of 80% ($p < 0.05$) were (expressed as a percentage of the baseline stress response), respectively, 100, 36, and 37 for systolic and diastolic blood pressure and heart rate during physical stress, and, respectively, 32, 34, and 32 during mental stress. As the response of systolic blood pressure to standing turned out to have poor reproducibility, we do not present these results. The effect of treatment on the response of blood pressure and heart rate to stress was calculated for each subject as the change in response from the pretreatment baseline to the treatment period (within-subject comparison). Differences in stress response between the three groups were then examined by analysis of covariance, with group as independent variable and the initial level (supine rest 1 during pretreatment baseline) as covariate. The effect of sex within each group was examined by *t* test. All *p* values are two-tailed.

Compliance

Ninety-eight percent of all 20,866 packages distributed were returned empty by the subjects. During the treatment period the mean serum caffeine level (±SD) was 4.9 ± 2.2 mg/liter (range, 2.2 to 11.1) in the boiled-coffee group, 4.7 ± 2.4 mg/liter (range, 1.2 to 9.4) in the filtered-coffee group, and 0.4 ± 1.1 mg/liter (range, 0.1 to 5.2) in the group that drank no coffee. The single high value in this group was due to one woman who had a mean serum caffeine level of 5.2 ± 0.9 mg/liter (range, 4.4 to 6.2). If her data were eliminated, the mean serum caffeine level in the no-coffee group was 0.1 ± 0.1 mg/liter (range, 0.1 to 0.3). In the filtered-coffee group, one man had employed a faulty method to prepare the coffee, and one woman was admitted to a hospital directly after the trial had ended because of a poor physical and mental condition. All analyses were performed both with and without the data of these three subjects.

The mean change in body weight (±SD) from the end of the pretreatment baseline to the end of the treatment period was 0.4 ± 1.0 kg (range, −1.9 to 2.5) in the boiled-coffee group, 0.2 ± 1.8 kg (range, −6.3 to 3.0) in the filtered-coffee group, and 0.6 ± 1.7 kg (range, −2.9 to 5.6) in the no-coffee group. The changes in body weight did not differ significantly among groups.

RESULTS

Both stress tests produced significant cardiovascular effects (analysis of variance, $p < 0.001$). In the pretreatment baseline, during which all subjects consumed filtered coffee, mean diastolic blood pressure increased by 14 mm Hg, and heart rate by 14 beats/minute during the stand-up test relative to the preceding period of supine rest. During the mental arithmetic test, mean systolic blood pressure increased by 19 mm Hg, diastolic blood pressure by 11 mm Hg, and heart rate by 14 beats/minute. All responses to both stress tests were similar for men and women.

The courses of the blood pressure and heart rate levels in the three groups during the pretreatment baseline and treatment (test) period are shown in Figure 1. During all test conditions (rest 1 to rest 3) in the treatment period, the absolute levels of systolic and diastolic blood pressure and heart rate (corrected for corresponding levels during pretreatment baseline) differed significantly among the three groups (*p* values, respectively, 0.0001, 0.025, and 0.036). In the boiled-coffee group, the overall level of systolic blood pressure was 3.7 mm Hg higher (95% CI, 1.2 to 6.3) compared with the filtered-coffee group, and 6.3 mm Hg (95% CI, 3.7 to 8.9) compared with the no-coffee group. Also, in the boiled-coffee group, diastolic blood pressure and heart rate increased by 2.4 mm Hg (95% CI, 0.3 to 4.4) and 2.6 beats/minute (95% CI, 0.1 to 5.2), respectively, rela-

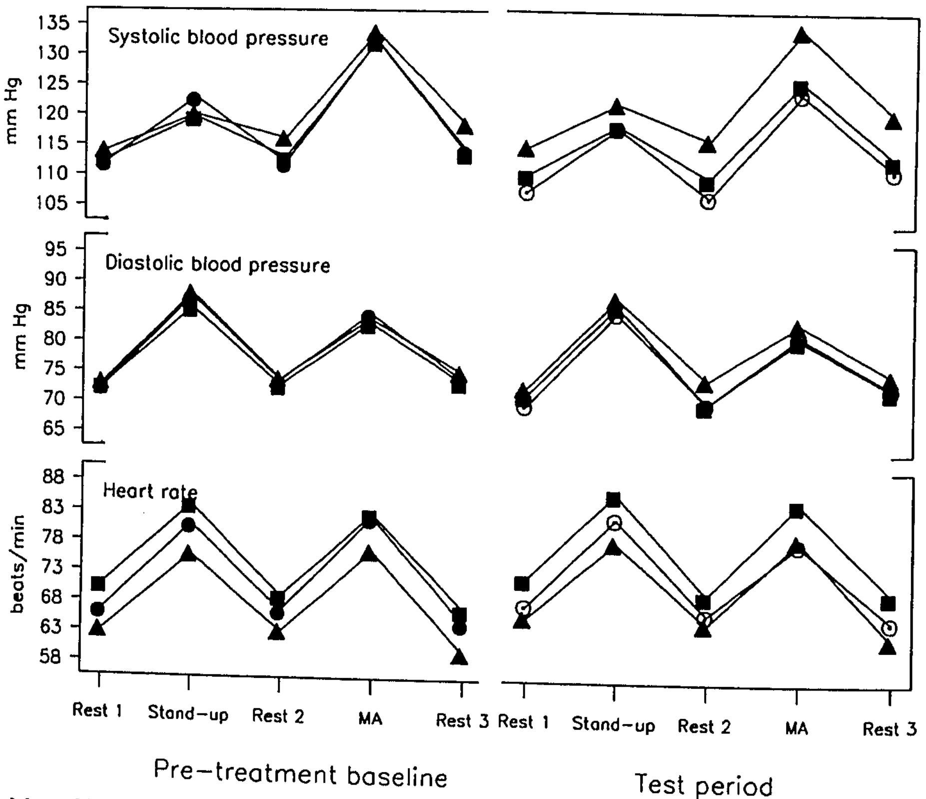

Fig. 1. Mean blood pressure and heart rate values during the test procedure on the 14th day of the pretreatment baseline and on the 58th day of the treatment (test) period. Values were recorded after a 16-minute supine rest (Rest 1), and again while standing up-right (Stand-up), after another 16-minute supine rest (Rest 2), during a 5-minute mental arithmetic test (MA) and after a 4-minute recovery (Rest 3).

All subjects drank six cups of filtered coffee during the pretreatment baseline (■, n = 21; ▲, n = 22; ●, n = 21). During the test period 21 subjects continued the consumption of filtered coffee (■) 22 subjects consumed six cups of boiled coffee/day (▲), and 21 subjects abstained from caffeine-containing beverages (O).

tive to the group who abstained from caffeine. None of the overall levels in the filtered-coffee group differed significantly from those in the no-coffee group.

The responses to the stand-up and mental arithmetic test (unadjusted for possible influences of initial level) in the pretreatment baseline and treatment period are presented in Table 2. Although the caffeine abstainers appear to have somewhat larger responses during the pretreatment baseline for all three cardiovascular measures, none of the group differences were significant. The changes from the pretreatment baseline to the treatment period of the diastolic blood pressure and heart rate responses to the stand-up test did not differ among the three groups. Likewise, changes in the systolic and diastolic blood pressure response to mental stress were not significantly different. However, the change from pretreatment baseline to treatment period of the heart rate response to mental stress differed significantly among groups (analysis of covariance, p = 0.02). In the no-coffee group, the mean increase in heart rate during mental stress (adjusted for possible influence of initial level) was five beats/minute (95% CI, −8.8 to −1.2) less than in the filtered-coffee group, and 4.6 beats/minute (95% CI, −8.4 to −0.8) less than in the boiled-coffee group. This treatment

TABLE 2. Mean Effects (±SD) of Long-Term Consumption of Caffeine-Containing Boiled or Filtered Coffee or no Coffee on Cardiovascular Responses to Physical and Mental Stress in 64 Healthy Volunteers

Variables	Boiled Coffee $N = 22$	Filtered Coffee $N = 21$	No Coffee $N = 21$
Physical stress: standing upright			
Diastolic blood pressure response (mm Hg)			
Baseline period	+15.0 ± 6.7	+13.1 ± 7.2	+15.1 ± 5.5
Treatment period	+15.1 ± 6.7	+15.0 ± 6.0	+15.5 ± 3.6
Change	+0.1 ± 7.9	+1.9 ± 9.1	+0.4 ± 6.6
Heart rate response (beats/min)			
Baseline period	+12.8 ± 7.9	+13.5 ± 9.6	+14.4 ± 8.6
Treatment period	+12.6 ± 10.4	+14.2 ± 9.0	+14.5 ± 7.2
Change	−0.2 ± 7.3	+0.8 ± 6.7	+0.1 ± 6.4
Mental stress: calculating by heart under time pressure			
Systolic blood pressure response (mm Hg)			
Baseline period	+17.7 ± 6.1	+19.3 ± 9.1	+20.3 ± 9.7
Treatment period	+18.2 ± 8.6	+16.1 ± 9.8	+17.3 ± 8.0
Change	+0.6 ± 6.9	−3.2 ± 10.3	−3.0 ± 7.8
Diastolic blood pressure response (mm Hg)			
Baseline period	+10.2 ± 4.4	+10.5 ± 4.5	+11.2 ± 4.3
Treatment period	+9.4 ± 4.8	+10.9 ± 5.4	+11.4 ± 5.1
Change	−0.7 ± 4.7	+0.4 ± 5.3	+0.1 ± 4.5
Heart rate response (beats/min)			
Baseline period	+13.4 ± 7.9	+13.7 ± 7.9	+15.6 ± 8.4
Treatment period	+14.1 ± 9.2	+15.3 ± 7.8	+11.8 ± 6.6
Change	+0.6 ± 6.9	+1.6 ± 4.1	−3.8 ± 7.3[a]

[a] Denotes a significant difference with the boiled- and the filtered-coffee group, $p < 0.05$.

effect was similar for men and women in all groups. Excluding the data of the three subjects who had been ill or noncompliant did not affect the results.

SUMMARY AND DISCUSSION

The present study shows that in healthy, normotensive adults long-term elimination of the use of filtered coffee and tea reduced the response of heart rate to mental stress, which was five beats/minute or 34% smaller after long-term elimination of caffeine. In contrast, total elimination of regular coffee and tea did not affect the responses of blood pressure and heart rate to physical stress or the responses of blood pressure to mental stress. This study is unique in the literature in its evaluation of the effects of long-term changes in coffee consumption on cardiovascular responses to stressors. However, it has some limitations that need attention.

On the days of testing, the serum caffeine levels were not measured and subjects were not asked about compliance with coffee drinking. Thus, we have no guarantee of compliance on these days. However, the high percentage of empty packages that were returned by the subjects, the diaries, and frequent personal interviews suggest that the subjects were adhering to their respective caffeine conditions. Although the variance in serum caffeine level in the coffee groups was rather large, such a broad range is commonly observed in healthy subjects when blood is sampled randomly and not on a fixed time after a caffeine load (27), because elimination half-life of plasma caffeine varies between 1.5 and 9.5 hours (28). In the filtered-coffee group, three subjects had mean serum caffeine levels below 2.0 mg/liter, and thus might be suspected of bad compliance, but elimination of their data did not change the results. Finally, a blinded design of the study protocol was not possible, and consequently the results of the study must be interpreted with caution. However, as subjects were not familiar with the hypothesis, we assume that the possible influence of expectation was very small.

Our results on the comparison of the overall absolute changes in blood pressure and heart rate among the three groups revealed that elimination of caffeine did not affect blood pressure or heart rate level in comparison with drinking filtered coffee. Our findings on ambulant blood pressure and heart rate (which were collected as part of the present study) showed the same results (23), as did some other long-term controlled trials on the effects of elimination of coffee (29, 30). However, comparison of absolute changes among the three groups also showed that boiled coffee significantly raised systolic blood pressure by 4 mm Hg compared with filtered coffee, and by 6 mm Hg in comparison with no coffee. The results also suggested that diastolic blood pressure and heart rate are slightly elevated on boiled coffee in comparison with no coffee. Previous data on the relation between boiled coffee and blood pressure are scarce. Recently we reported that drinking boiled versus filtered coffee raised ambulant systolic blood pressure by 3 mm Hg (23). This finding is in close agreement with the difference in absolute systolic blood pressure level reported here. The caffeine content of the boiled coffee was similar to that of the filtered coffee. Thus, there exists a possibility that boiled coffee might contain some other compound that raises systolic blood pressure, a compound that was no longer present after filtration through paper filter.

In the present study we observed a synergistic decrease in heart rate during mental stress after long-term caffeine abstinence as compared with chronic caffeine consumption. Previous studies on caffeine-stress interactions suggest that such synergistic effects would not be expected for most cardiovascular variables, and may not be observed for all stressor tasks. In one short-term study, additive effects of caffeine and stress on heart rate were observed (4). Consistent with the findings of the present study, a number of laboratory studies have reported significant synergistic increases in cardiac rate ingestion of caffeine in comparison with a placebo (6, 14, 15). MacDougall et al. (6) reported an interaction between ingestion of 200 mg of caffeine and the response of heart rate to mental stress. The increase in heart rate shown by the caffeine group was 12.6 beats/minute greater than that in the control group. Pincomb et al. (15) reported synergistic effects of stress plus caffeine on heart rate of three beats/minute after consumption of two to three cups of coffee. In females who were not regular caffeine consumers Strickland and colleagues (14) observed an average increase in heart rate of eight beats/minute during a mental arithmetic task after ingestion of 250 mg of caffeine. Thus, the tendency of caffeine alone to reduce heart rate (4, 6, 9, 10, 14, 18, 19) appears to be reversed when caffeine is consumed during active coping stress. Warren et al. (31) observed an increased heart rate response to posture during infusion of theophylline, a xanthine closely related to caffeine. According to Warren et al., the mechanism of this interaction may be related to the combination of the stress-induced increase of the production of the second messenger cyclic AMP, and the xanthine-mediated inhibition of the breakdown of cyclic AMP by phosphodiesterase. An alternative mechanism of action for the caffeine-mediated potentiation of the response to stress may be the blockade of adenosine receptors. Recent investigations in man have shown that adenosine attenuates the response to sympathetic stimuli (32). Consequently, caffeine may potentiate this response by antagonizing the effects of endogenous adenosine. Such a mode of action has been documented in man for theophylline, a xanthine closely related to caffeine (33).

The results of the present study are consistent with previous studies in men in which the blood pressure response to mental stress was not affected by prior ingestion of caffeine after 12 to 18 hours of caffeine abstinence (3–5, 7, 8, 13, 15, 17). In contrast, three studies have reported that caffeine ingestion enhanced the magnitude of the mental stress-induced systolic blood pressure response by 7 to 12 mm Hg (6, 14, 16). This discrepancy cannot be attributed to a lack of power of the present study since we were able to pick up effects of the systolic blood pressure response to mental stress of 6 mm Hg or more. A major difference with the present study, however, constitutes the prior consumption of caffeine. Subjects in the three above mentioned studies were regular caffeine consumers who had abstained from caffeine for 8 to 18 hours before the start of the experiment (6, 16), or were relatively caffeine-naive (14), while in the present study frequent caffeine consumers who had ingested caffeine some hours before the experiment were compared with subjects who had abstained from caffeine for a period of 8 weeks. We assume that the present data more closely approach caffeine's effects in daily life.

Cardiovascular responses to mental and physical stress were similar for men and women. This is in agreement with findings of previous studies on mental stress (6, 34).

In conclusion, total elimination of caffeine-containing beverages decreases the heart response to mental stress, but does not appear to attenuate systolic and diastolic blood pressure responses to mental stress or heart rate and diastolic blood pressure responses to orthostatic stress in normotensive men and women. As we evaluated the effects of long-term changes in coffee consumption on cardiovascular responses to stressors, our results add to the practical question of the value of abstaining from caffeine.

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