Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 4, pp. 899–908, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0047-L

# Cardiovascular, Behavioral, and Subjective Effects of Caffeine Under Field Conditions

ILSE HÖFER[1] AND KARL BÄTTIG

*Behavioral Biology, Swiss Federal Institute of Technology Zürich, Schorenstrasse 6, CH-8603 Schwerzenbach, Switzerland*

Received 5 April 1993

HÖFER, I. AND K. BÄTTIG. *Cardiovascular, behavioral, and subjective effects of caffeine under field conditions.* PHARMACOL BIOCHEM BEHAV 48(4) 899–908, 1994.—The effects of continuous and intermittent caffeine abstinence and their time course were investigated under field conditions. After 3 days with habitual coffee, subjects were switched for 9 days to regular instant coffee ($n$ = 40), decaffeinated coffee ($n$ = 40), or an intermittent regime (2 days decaff, 1 day caff, repeated, $n$ = 40). Subjects were blind to the caffeine treatment. Motor activity was assessed continuously; subjective variables, blood pressure (BP), and heart rate (HR) were assessed by the subjects six times per day (electronic diary). Compliance was confirmed by the different caffeine concentrations in daily saliva samples. Continued caffeine consumption showed no effects. Caffeine abstinence resulted in increased HR, decreased motor activity, subjective wakefulness, and well-being, and in increased headaches and use of analgetics. The subjective effects and headaches were transient, i.e., they disappeared after a few days of abstinence and weakened over successive, separated abstinence periods. BP was not affected by the caffeine treatment. The intermittent onset of caffeine consumption resulted in increased wakefulness, whereas the other variables normalized to baseline level.

Coffee Caffeine Placebo controlled Human Field experiment Electronic diary Blood pressure Heart rate Motor activity Wakefulness Well-being Headache

THE acute effects of caffeine have been widely studied in the laboratory with intermediate to high single doses (150–400 mg) in caffeine-naive or abstaining subjects. Thus, caffeine may result in increased subjective wakefulness, nervousness, mood disturbances (8), increased sleep latency and decreased sleep duration and quality (16,34,35), increased blood pressure (BP) and decreased heart rate [HR; (19,20)]. The cardiovascular effects are suspected to be mediated by peripheral vasoconstriction (5) and by baroreceptor activity (18). The chronic effects of caffeine have been investigated less extensively. According to early studies with similar caffeine doses, increased BP readings [(13,24), cf. also (20)], and increased subjective stimulation (8) are observed for the first few days, i.e., the data suggest a rapid development of tolerance. This is underlined by the results from cross-sectional studies where coffee consumption showed little or even a negative relationship with blood pressure (3,12,19,27,29).

In everyday life, caffeine is consumed in much smaller single doses, e.g., in coffee (60–120 mg/cup), spread over the whole day, and often in a habitual way. Recently, the effects of everyday caffeine consumption on cardiovascular parameters have been investigated in semichronical field studies comparing habitual consumption of regular coffee with placebo or coffee-free diet. Caffeine abstinence was associated with decreased SBP (1,6,32), decreased DBP (32), or no DBP changes (1,6), or no BP changes at all (26). Heart rate, too, was found to increase (32), to decrease (1), or to be not affected (6). One reason for these contradictious results may be seen in the type of BP and HR measurements. All studies considered casual measures in the laboratory once per month or week, only Van Dusseldorp and co-workers (32) further used subject-measured readings at home, which showed changes in all three parameters. The time course of abstinence effects was not considered in these field studies, although this seems to be an important issue taking into account the rapid tolerance to caffeine for cardiovascular effects and to caffeine abstinence for fatigue, headache, nervousness, and mood disturbances (10,11).

Simultaneous assessments of subjective effects were included in only one of the mentioned field studies. Van Dusseldorp and Katan [(30), referring to the same study as (32)] reported a higher prevalence of headache in the first week

[1] To whom requests for reprints should be addressed.

with decaffeinated coffee (42%) as compared to the rest of the study (caffeine consumption and rest of decaff period: 7%). Furthermore, the subjects fell asleep more easily in the decaff than in the caffeine period (88 vs. 85; scale 0–100).

The effect of caffeine on spontaneous motor activity has been rarely investigated in humans [(4,23); cf. also (22)] and in none of the field studies, although its increasing effect is well established by animal experiments (11).

The present study was undertaken to clarify the effects of caffeine abstinence and their time course under field conditions. Cardiovascular parameters, motor activity, and subjective ratings were assessed in parallel during 3 days with consumption of habitual coffee (baseline) and 9 days with experimental instant coffee. One group continued caffeine consumption (control group), one group was switched to decaffeinated coffee, and a third group received decaffeinated coffee and caffeine containing coffee in an intermittent schedule. The continuous decaff group served to determine the time course of abstinence effects, i.e., decrease, increase or constancy. The intermittent group was used to study also the effects of starting caffeine consumption and to determine the time course of repeated abstinence periods.

## SUBJECTS

Subjects were healthy, nonsmoking volunteers who were paid for participation (200 + ca. 80 SFr ≈ 180 US$). They were recruited by newspaper ads asking for nonsmoking coffee consumers between 20 and 45 years of age. At the first phone contact, further criteria for participation were checked: amount of habitual coffee consumption (4–10 cups/day), no regular use of decaffeinated coffee, no use of black tea and cola (or moderate use and renunciation during the study), no smoking, no regular use of medicaments, no pregnancy, general good health, normal blood pressure (self-reported), no shift work (especially no work during the night), and no work driving a car, truck, etc. The characteristics of the 60 male and 60 female subjects are summarized in Table 1; the blood pressure and heart rate measures in this table, with the expected sex differences, refer to the assessment in the laboratory at the end of the field study (cf. procedure).

An additional 29 subjects started the program, but they either did not complete the whole period ($n$ = 14) or obviously did not follow the required measurement schedule ($n$ = 15, two of whom restarted a second time successfully). Recruitment of male subjects proved to be especially difficult, due both to a lower response rate to ads and to more problems with noncompliance.

## DESIGN

The subjects were randomly assigned to three groups with different treatment in the experimental phase: one group (T+) continuously received caffeine-containing instant coffee (caffeinated coffee), one group (T−) continuously received decaffeinated instant coffee, and the third group (T±) received decaffeinated coffee for 2 days and caffeine-containing coffee for the third day, this schedule was repeated three times (intermittent group; decaffeinated coffee on the final day). Subjects were blind with respect to the caffeine treatment.

The field study lasted 2 weeks: day 0 served to train and habituate to the measurement routine (three measures; data not used); days 1 to 3 served as baseline measures during which subjects consumed their habitual coffee; days 4 to 12 served as experimental period with instant coffee. The data of day 13 (variable end depending on report to the lab) were not used for statistical analyses.

## TREATMENT

The caffeine-containing coffee was Nescafe Gold de luxe (56 mg caffeine in 2 g coffee), the decaffeinated coffee was Nescafe Serenade (2 mg caffeine in 2 g coffee). The instant coffee was offered in coded neutral packets for a single cup (caffeine: 1, 3; decaffeinated: 2, 4). The hand-filled transparent plastic packets used in the beginning of the study (26 subjects) contained on the average 2.1 g instant coffee (SD 0.22); the automatically filled opaque packets used thereafter contained 2.0 g (SD 0.05). To make the experimental conditions as comparable as possible, all subjects received packets with codes changing according to the schedule of the intermittent group.

For each day of the experimental period, the subjects received a plastic bag with a fixed number of coffee packets, corresponding to the number of habitually consumed cups of coffee, increased by two.

In addition, subjects received some packets with decaffeinated coffee (Nescafe Serenade, packets on market) to use in cases when the coffee packets for a special day were not sufficient.

TABLE 1

SAMPLE CHARACTERISTICS (MEAN ± SD, PERCENT)

| Variable | Males | Females | Significance of Sex Effect |
|---|---|---|---|
| $n$ | 60 | 60 | |
| Age (years) | 31.0 ± 7 | 32.4 ± 7 | NS |
| Height (cm) | 177.6 ± 5 | 166.4 ± 6 | * |
| Weight (kg) | 75.2 ± 9 | 60.9 ± 8 | * |
| SBP (mm Hg) | 121.1 ± 11 | 107.6 ± 9 | * |
| DBP (mm Hg) | 74.9 ± 10 | 67.9 ± 9 | * |
| Heart rate (bpm) | 70.1 ± 10 | 74.5 ± 8 | † |
| Oral contraceptives (%) | 0 | 17 | |
| Coffee consumption (cups/day) | 5.6 ± 2 | 5.8 ± 2 | NS |
| Cup size (0.11) | 1.7 ± 0.5 | 1.8 ± 0.5 | NS |

Significance level: *$p < 0.001$, †$p < 0.05$; NS, not significant.

## PARAMETERS

### *Electronic Diary*

Subjects were required to fill out an electronic diary (Organizer II, PSION PLC, England) six times per day. The measurement periods (MP) were:

MP 1—wake up
MP 2—after breakfast / before start of work
MP 3—before lunch break / end of morning work
MP 4—after lunch break / start of afternoon work
MP 5—end of work / before dinner
MP 6—going to bed.

The electronic diary regularly asked for scalometric ratings (range 1-20) of subjective mood (translated from German: awake, nervous, sleepy, stressed, dull, nausea, headache, muscle/joint ache). Further questions varied from one MP to the other—MP 1: sleep quality, time of falling asleep, time of awakening; MP 2: coffee consumption, eaten s.th. for breakfast, mood; MP 3: coffee consumption, morning demanding, annoying; MP 4: coffee consumption, eaten s.th. for lunch, general well-being; MP 5: coffee consumption, afternoon demanding, annoying, coffee strength, taste, stimulating effect, caffeine content; MP 6: coffee consumption, evening demanding, annoying. Further questions were designated as additional questions, and a bonus of 1 Swiss Frank was paid for each MP with additional questions answered to increase subjects' motivation. These were for MP 1: problems with falling asleep, sleeping through, awakening; MP 2: coffee strength, taste, stimulating effect; MP 3: stomach/bellyache, tooth ache, general indisposition; MP 4: lunch taste, content, hurried; MP 5: day exciting, tiring, gratifying, in general; MP 6: evening entertaining, quiet, boring, active, enjoyable. Furthermore, the cardiovascular measures were to be typed into the electronic diary.

### *Cardiovascular Parameters*

Blood pressure and heart rate were measured with an automatic device (HEM-815F, Omron Corp., Japan) by the subjects themselves, three times at each MP. Subjects were instructed to insert the left forefinger completely into the cuff and to sit quietly with arms crossed in front of the chest to prevent changes of BP values due to hydrostatic influences.

## MOTOR ACTIVITY

Motor activity was assessed continuously with an activity monitor (Gaehwiler Electronics, Switzerland). The monitor was to be worn at the wrist of the nondominant arm, and to be taken off for wet activities (shower, swimming, etc.) and certain sport activities (judo, basketball, etc.). The monitors were programmed to start measurements for 1-min intervals at 0000 h of day 1.

## CAFFEINE CONCENTRATION

Once per day (late afternoon, before dinner) the subjects collected saliva samples with cotton rolls (Salivette, Sarstedt, Germany). Subjects were instructed to collect the samples at least 15 min after drinking or eating, and to keep them in the freezer for the rest of the field period. Caffeine concentrations in saliva ($\mu$mol/l; except for day 1) were determined automatically on a Cobas-Bio (Roche, Switzerland) with an enzymatic immunoassay method (Emit, Syva) at the Institut für Klinische Chemie, Universitätsspital Zürich. Caffeine in saliva is correlated with concentrations in plasma (21,36) and with coffee consumption (12).

## DIARY

Diary booklets served to register special events, including taking off the activity monitor, use of medicaments, time of saliva sample, and alcohol consumption.

## QUESTIONNAIRE

A self-constructed questionnaire asked for general information (age, sex, etc., working schedule, use of medicaments), and detailed information on caffeine consumption habits. Subjects had to indicate how many cups of regular coffee, decaffeinated coffee, black tea, herbal tea, and cola beverages (in dl) they habitually consume at various times of the day (wakeup, breakfast, morning break, . . . after dinner).

## PROCEDURE

At the first telephone contact, subjects got general information about the aims and procedure of the study, and participation criteria were checked. In case of acceptance, subjects were mailed the questionnaire, three packets of instant coffee (with caffeine) to test the appropriate amount of water, together with an invitation for the introductory session in the lab.

Introductory sessions were held on Wednesdays for groups of one to eight subjects (mixed with respect to experimental groups) and lasted about 1 h. The aim of the study was explained to be the investigation of daily changes of blood pressure, heart rate, motor activity, and mood, and of the influence of coffee with varying caffeine content on these daily changes. It was explained that the instant coffee contained various amounts of caffeine, never more than regular coffee, and that the caffeine content might change from one day to the other. Subsequently, the subjects were instructed how to use the equipment (electronic diary, blood pressure device, activity monitor, saliva samples) they were given in a handbag together with written instructions. One measurement on the electronic diary including cardiovascular measures was completed during the session and controlled by the experimenter. Furthermore, subjects were informed about the measurement periods, with special emphasis on regularity, and separation of the measures. Subjects were instructed how to manage the instant coffee program, to use only those packets prepared for the particular day and to abstain from all other caffeine sources (tea, cola, medicaments; chocolate in small amounts only; to order decaffeinated coffee in a restaurant). Finally, subjects were encouraged to call the hotline in case of problems or questions. At the end of the introductory session, the subjects gave their written consent.

During the 2-week period of the study, subjects were generally contacted twice (day 5, day 9) by phone and asked for any questions. At the second phone call, an individual date was arranged to bring the equipment back to the lab.

In this final session, data from the electronic diary and the activity monitor were transferred to a PC. After a rough check of data quality (completeness, regularity), blood pressure was measured at the arm with a semiautomatic device (HEM-403C, Omron Corp., Japan; subjects sitting, two to three measurements). Finally, subjects were paid for participation in case of sufficient data quality. Afterwards, subjects got mailed graphic outputs of their motor activity and of 5 days of the electronic diary.

*Data Handling and Statistics*

The activity data were set to missing for the time periods when the monitor was not worn (diary booklets). The valid measures were averaged for the periods from MP to MP (times from electronic diary).

Blood pressure and heart rate measures were averaged for each MP after checking for data quality. To rule out input errors, systolic and diastolic BP had to have a minimal difference of 10 mmHg. For all triplets of SBP, DBP, and HR exceeding a range of 10 points (mmHg, beats per minute = bpm) an outlier control was executed. If the ratio between the larger and the smaller difference (between the lower two and the higher two values) exceeded three, the distant value was cancelled, and only the remaining two values that were closer together were averaged.

Due to high intercorrelations (intra- and interindividual) some ratings from the electronic diary were averaged: Wakefulness refers to the mean of the individual items awake, sleepy, and dull (the latter two transposed in direction); stress refers to the mean of the items nervous and stressed (How do you feel at the moment, MP 1 to 6). Day positive refers to the mean of the ratings gratifying and in general; similarly day exhaustive, evening positive, and evening quiet are averaged variables.

Caffeine consumption was summed up over a complete day (electronic diary; questionnaire).

The resulting 39 variables were analyzed with full factorial analyses of variance (ANOVA; program BMDP 2V on VAX 9000/VMS). The between-subjects factors considered were sex (S) and treatment group (T); the within-subject factors were day (D), and, in case of several measures per day, measures (M). Individual missing values were set to the subject's mean of the corresponding variable. This method can be considered as conservative, as it tends to reduce differences between repeated measures (day, measure). The number of subjects and, thus, the degrees of freedom of the ANOVA error terms slightly differ between the dependent variables, as some data sets were missing due to technical problems (additional questions from ED, motor activity, caffeine in saliva).

As the effects of the caffeine manipulation emerge as complex subeffects of the ANOVA effects day and day × treatment (or higher interactions with sex or measure), special contrast analyses were used (25). Contrast analysis tests the difference of (two) groups of cell means from the ANOVA (weighted in a special manner) against the corresponding error term from the ANOVA. In case of significant day and day × treatment effects, the planned contrasts within treatment groups (T+, T−, T±) compared baseline days with experimental days (differentiating caffeine and decaff days; B/+, B/−). Additionally, the initial effect in the decaff group compared baseline days with the first 3 days with decaffeinated coffee (T−: B/4–6).

In case of parallel changes for the caffeine and decaff periods (from baseline), further comparisons were undertaken to see if this change was more pronounced in the decaff than in the caffeine group (interaction T+/T− × B/instant). For the intermittent group, the difference between the two instant coffee types was tested (±).

## RESULTS

The results section concentrates on the effects of caffeine abstinence (contrast analysis) and ignores effects of the other factors (sex, treatment as main effects, measurement period). For the caffeine group, no differences were obtained between habitual and experimental days with respect to the cardiovascular, activity and subjective variables (except coffee ratings).

*Control of Experimental Variations*

The caffeine concentration in saliva reflected the treatment (Fig. 1a): in the caffeine group, saliva caffeine decreased from habitual to instant coffee [B/+: $F(1, 1130) = 7.83$, $p < 0.01$], which might be due to the well-documented lower caffeine content in instant as compared to noninstant coffee. In the decaff group, too, saliva caffeine decreased from habitual to instant coffee [B/−: $F(1, 1130) = 462.89$, $p < 0.001$), and this decrease was significantly more pronounced than in the caffeine group [T+/T− × B/instant: $F(1, 1130) = 175.16$, $p < 0.001$]. In the intermittent group, saliva caffeine was decreased on decaff days [B/−: $F(1, 1130) = 371.95$, $p < 0.001$] but not on the intermittent caffeine days [B/+: $F(1, 1130) = 0.53$, NS]. The total daily coffee consumption (Mean 5.3 ± 1.8, Figure 1a), as registered on the electronic diary, slightly decreased from habitual to instant coffee [all groups, B/instant: $F(1, 1254) = 4.66$, $p < 0.05$], but the treatment groups did not differ with respect to this decrease [DT: $F(11, 1254) = 0.78$, NS]. As was to be expected with ad lib consumption, the individual daily figures varied from day to day (maximal difference, habitual: 1.9 ± 1.5; instant: 3.9 ± 1.6), but were considerably correlated (mean $r = 0.50$). Coffee consumption was spread over the whole day, and highest with breakfast (means ranging from 0.8–1.6 for the intervals between MPs).

*Subjective Ratings of Coffee*

The instant coffee was generally rated lower than the habitual coffee with respect to taste, strength, stimulating effect, and caffeine content [all groups, B/instant: $F(1, 1133) = 119.79, 114.93, 97.94, 276.61$, all $p < 0.001$; Fig. 1a,b]. The day × treatment interactions failed to reach significance except for rated caffeine content [$F(11, 1133) = 0.69, 1.26, 1.32$, NS, $2.12$, $p < 0.01$; same order as before], but complex interactions with sex and measurement period emerged [taste, DTS: $F(11, 1133) = 1.83$, $p < 0.05$; strength, DMTS: $F(11, 1133) = 1.67$, $p < 0.05$; caffeine content, DTS: $F(11, 1133) = 2.02$, $p < 0.05$]. The contrast analyses revealed that the instant coffees were rated similarly in the continuous groups [T+/T− × B/instant: $F(1, 1133) = 0.40, 2.03, 3.55, 3.77$; all NS; for taste, strength, stimulating, caffeine content, respectively], whereas in the intermittent group the decaffeinated coffee was rated lower than the regular instant coffee [+/−: $F(1, 1133) = 0.65$, NS; $20.17$, $p < 0.001$; $10.01$, $p < 0.01$; $25.40$, $p < 0.001$]. These differences were mainly caused by the female subsample and by the ratings in the afternoon (MP 5).

*Cardiovascular Parameters and Motor Activity*

SBP and DBP showed no differences between days with habitual coffee, caffeinated and decaffeinated instant coffee [DT: $F(11, 1254) = 1.06, 1.01$, NS; Fig. 2a). This was confirmed by additional analyses adjusting for activity, and for the daily minimum and maximum. Heart rate, however, was higher on days with decaffeinated coffee in the decaff group [B/−: $F(1, 1254) = 30.28$, $p < 0.001$; Fig. 2a]. The same was obtained in the intermittent group [B/−: $F(1, 1254) = 13.30$, $p < 0.001$], and this increased level was maintained on

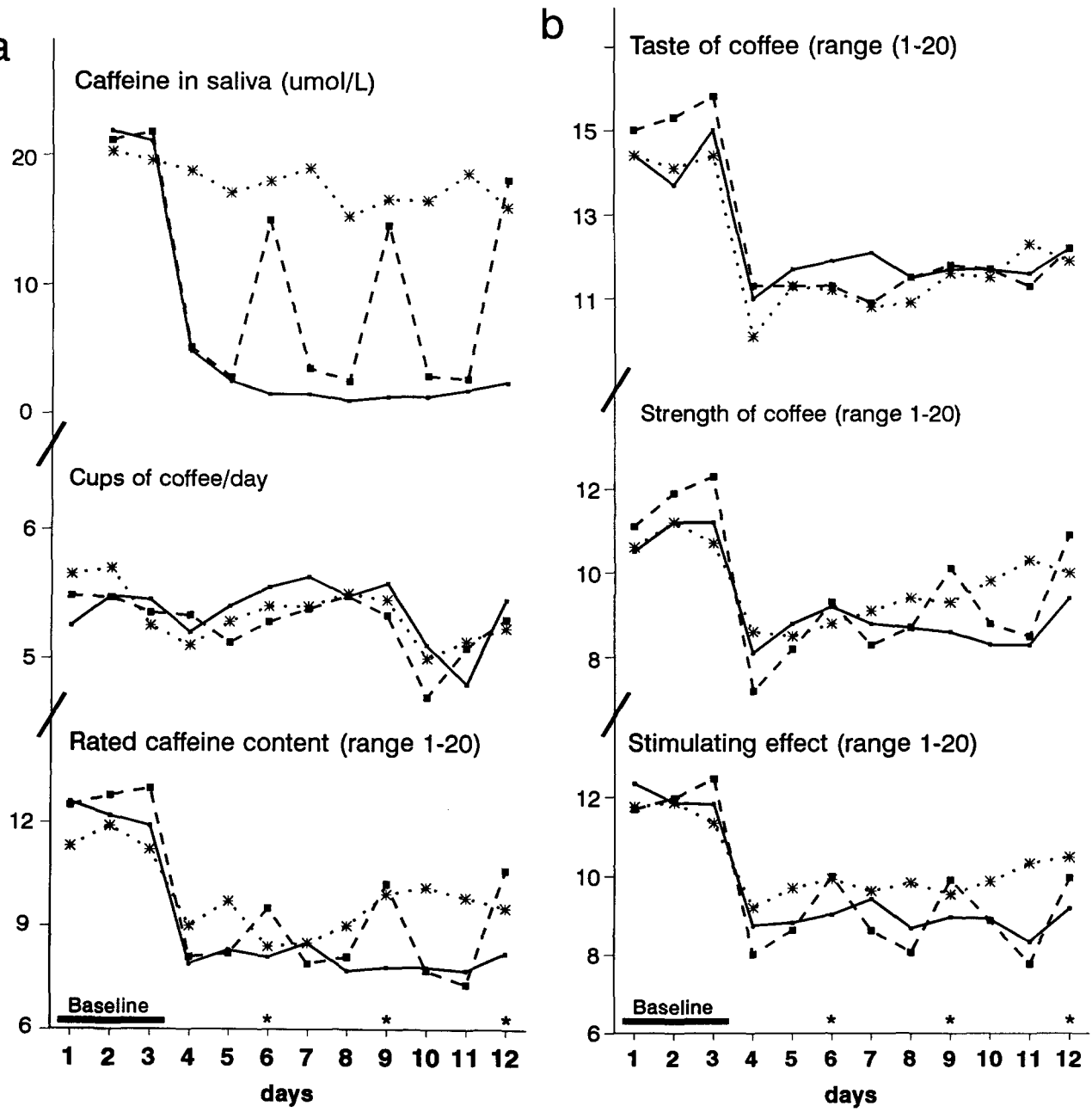


FIG. 1. (a,b) Daily means (in part averaged over MPs) for variables associated with compliance and blindness in the three treatment groups: (*···*) T+ caffeine, (—) T− decaff, (■--■) T± intermittent. The stars on the x-axis indicate the days when the intermittent group received instant coffee with caffeine.

the intermittent days with caffeinated instant coffee [B/+: $F(1, 1254) = 7.30, p < 0.01$; +/−: $F(1, 1254) = 0.28$, NS]. On the other hand, motor activity (Fig. 2a) was lower on days with decaffeinated coffee in the decaff group [B/−: $F(1, 1243) = 8.70, p < 0.01$]. In the intermittent group, too, motor activity was decreased on the days with decaffeinated coffee [B/−: $F(1, 1243) = 27.90, p < 0.001$], but normalized to baseline level on the intermittent days with caffeinated coffee [B/+: $F(1, 1243) = 1.34$, NS].

*Wakefulness and Sleep Variables*

Subjective wakefulness was rated lower on days with decaffeinated coffee (Fig. 2b). In the decaff group, this effect was nonsignificant for the whole decaff period [B/−: $F(1, 1254) = 3.50, p < 0.10$], but highly significant for the first 3 days with decaffeinated coffee [B/4–6: $F(1, 1254) = 16.16, p < 0.001$]. In the intermittent group, wakefulness was decreased on the days with decaffeinated coffee [B/−: $F(1, 1254) =$

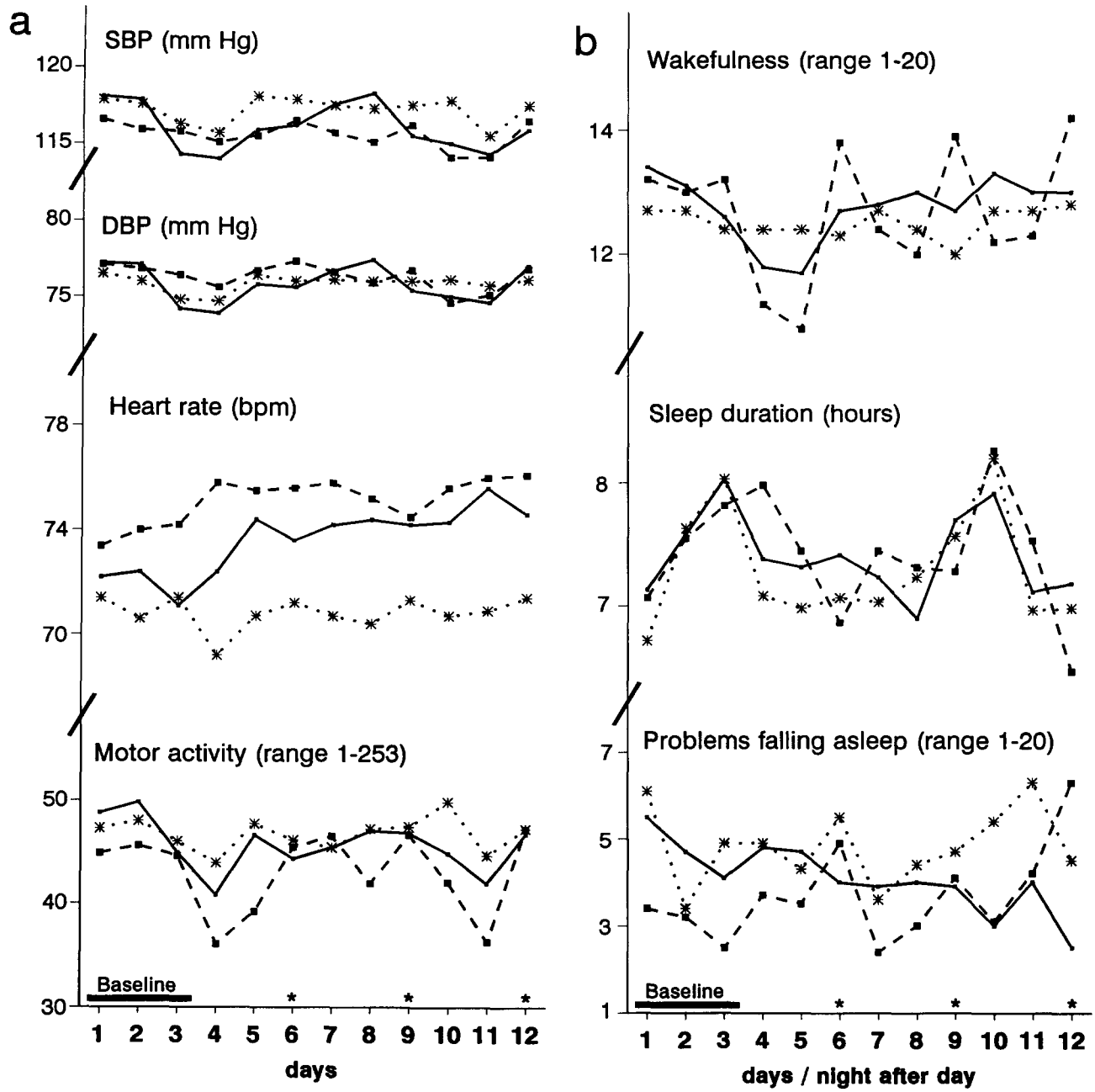


FIG. 2. (a–d) Daily means (in part averaged over MPs) for BP and the variables affected by caffeine in the three treatment groups: (*···*) T+ caffeine, (—) T− decaff, (■--■) T ± intermittent. The stars on the x-axis indicate the days when the intermittent group received instant coffee with caffeine.

38.60, $p < 0.001$], and was increased over baseline level on the intermittent days with caffeinated coffee [B/+: $F(1, 1254) = 11.40, p < 0.001$].

Problems falling asleep were somewhat decreased on days with decaffeinated coffee and increased on the intermittent caffeine days [Fig. 2b; T−, B/−: $F(1, 1133) = 3.95$, $p < 0.05$; T±, B/−: $F(1, 1133) = 0.43$, NS; T±, +/−: $F(1, 1133) = 12.53$, $p < 0.001$]. Sleep duration, as calculated from the subject-recorded times of falling asleep and of wakeup, was shortened after the intermittent caffeine days [B/+: $F(1, 1254) = 16.67$, $p < 0.001$; Fig. 2b). Problems with sleeping through or awakening and overall sleep quality were not affected by the caffeine treatment.

*Headache*

Headache was increased on the days with decaffeinated coffee (Fig. 2c). This effect was obtained in the decaff group

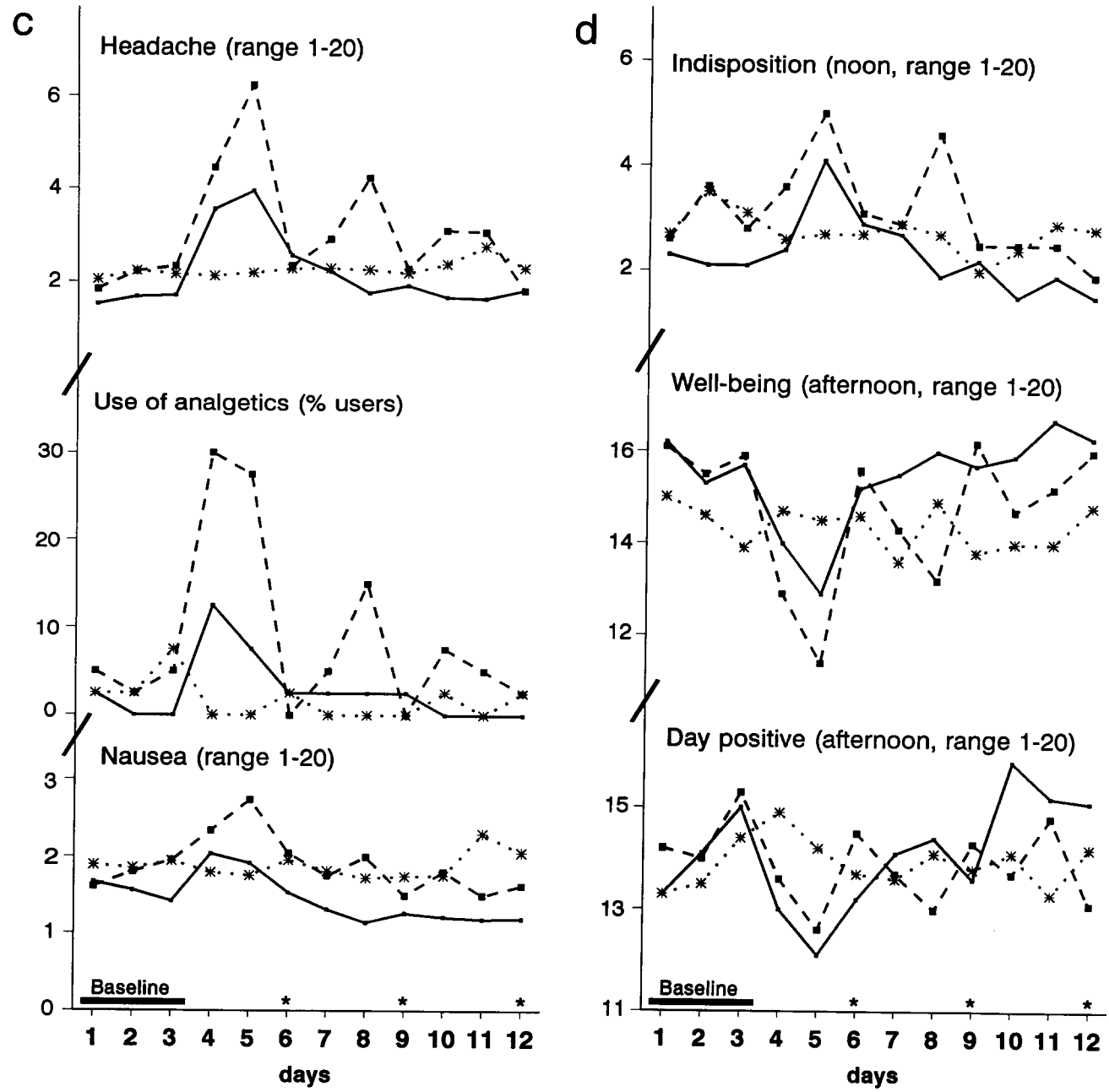


FIG. 2. Continued.

[B/−: $F(1, 1254) = 13.53$, $p < 0.001$], and in the intermittent group [B/−: $F(1, 1254) = 82.19$, $p < 0.001$]. Headache dropped to baseline level on the intermittent caffeine days [B/+: $F(1, 1254) = 0.01$, NS). Similarly, analgetics were used more on decaff days (Fig. 2c). This effect was significant in the decaff group only for the first days of caffeine abstinence [B/4-6: $F(1, 1254) = 7.63$, $p < 0.01$], and also for the intermittent group [B/−: $F(1, 1254) = 26.85$, $p < 0.001$]; on the intermittent caffeine days, the use of analgetics dropped to baseline level [B/+: $F(1, 1254) = 1.91$, NS]. Furthermore, nausea tended to increase during the first days of caffeine abstinence [T−, B/4-6: $F(1, 1254) = 3.54$, $p < 0.10$; T±, +/−: $F(1, 1254) = 5.59$, $p < 0.05$; Fig. 2c).

*Subjective Well-Being*

Mood ratings in the afternoon (but not in the morning) were more negative in the first days with decaffeinated coffee in the decaff group [Fig. 2d; B/4-6: general well-being: $F(1, 1133) = 17.81$, $p < 0.001$; day positive: $F(1, 1133) = 10.95$, $p < 0.01$; general indisposition: $F(1, 1133) = 6.98$, $p < 0.01$] and also in the intermittent group [B/−: $F(1, 1133)$

$= 40.13$, $p < 0.001$; B/− $F(1, 1133) = 5.80$, $p < 0.05$; +/−; $F(1, 1133) = 9.61$, $p < 0.01$; same order as before].

Subjective stress, various ratings of aches (muscle/joint, tooth, stomach), mood after breakfast, and ratings of parts of the day (morning, afternoon, evening as demanding or tiring, day exhausting, evening positive, or quiet) were not influenced by the caffeine treatment.

## DISCUSSION

The reported field study concentrated on the effects of continuous or intermittent caffeine abstinence on physiological, behavioral, and subjective parameters and the time course of these effects.

Compliance with the study regime was high, as can be demonstrated by the considerably different caffeine concentrations in saliva on caffeine and decaff days. The blindness of the subjects with respect to the caffeine content of the instant coffee might be questioned due to the coffee ratings. The differences seem to increase over time (within day and between day, cf. Fig. 1, intermittent group), and females seem to be more sensitive to caffeine content. On the other hand, many subjects complained that they were unable to rate the caffeine content, subjects in the continuous groups guessed that they had had different coffee types, and none of the subjects in the intermittent group consciously detected the schedule of caffeine change. Thus, it can be concluded that most subjects were blind with respect to the coffee's caffeine content.

The study revealed that caffeine abstinence is associated with increased heart rate, decreased motor activity, wakefulness and increased problems falling asleep, headache and nausea, and decreased well-being at noon or during the afternoon. Longer-lasting abstinence seems to result in increased positive evaluations of the day (day positive) and decreased problems falling asleep. Blood pressure, however, and several subjective ratings were not affected by caffeine abstinence. The onset of caffeine consumption after 2 days of abstinence increased wakefulness and problems falling asleep and decreased sleep duration.

The lack of caffeine effects on BP might astonish, taking into consideration the well-documented increases after acute doses in the laboratory (19) and the sophisticated design of the reported study with many regular BP assessments. One reason for this lack might be seen in the possible lack of validity of the unusual method used for BP measurement. However, the method shows the usual sex differences (SBP: 121 vs. 112; DBP: 77 vs. 75), systematic changes across the day and the week (data not shown), a good retest-reliability between the mean of days 1 to 6 vs. 7 to 12 ($r = 0.91, 0.87$ for SBP, DBP), and an acceptable correlation between the overall mean of the finger measures and the measures assessed in the laboratory with the traditional arm method ($r = 0.56, 0.43$ for SBP, DBP). On the other hand, the long-term caffeine vs. placebo (or noncoffee) effects on BP from other field studies are far from impressive. From the seven recent studies, two reported no BP effects of caffeine abstinence (2,26), four reported small BP decreases between 1 and 6 mmHg (1,6,32, 33), and one even BP increases (17). The BP decreases further depended on assessment or statistical methods: results differed between laboratory and subject measures (32,33) or different body positions (6), changes were significant only when integrating several weeks (1), in comparison to boiled coffee (33). Furthermore, the usual placebo, decaffeinated coffee, may be associated with conditioned or noncaffeine BP increases, as is also suggested by the varying BP effects of different coffee preparations independent of caffeine content (31). Summarizing the results, switching to decaffeinated coffee has at best a minimal effect on blood pressure.

Caffeine effects on heart rate have received less attention in the field studies, perhaps because most of them are dedicated to the clarification of caffeine's role in the development of hypertension. The HR increase under decaffeinated coffee, which even outlasts intermittent single days with caffeine consumption, as observed in the present study, might be expected as a reverse effect to the HR decrease after acute caffeine dosage [cf. (19)]. The increased heart rate together with nonaffected blood pressure might indicate a baroreceptor-mediated change in hemodynamics. Again, the results from other field studies are contradictious, showing increase (32), decrease (1) or no change (6,33). The increase under decaffeinated coffee observed in our study seems of special importance, as it is accompanied by parallel decreases of motor activity and wakefulness. The persistence of the HR increase on the intermittent caffeine days, however, might be caused by the normalized motor activity or the heightened subjective wakefulness on these days. Investigating caffeine abstinence effects on heart rate with continuous measurement devices would validate the reported results.

The transient decrease in wakefulness after sudden abstinence from caffeine is concordant with reports on withdrawal symptoms (7,9,10,14,15,28). The effects of caffeine on sleep parameters are less clearcut than the other reported effects. Continuous caffeine abstinence seems to reduce problems falling asleep on the long term. Van Dusseldorp and Katan (30), too, reported decreased problems falling asleep under decaffeinated coffee. On the other hand, caffeine consumption after abstinence seems to increase problems falling asleep and to decrease sleep duration. These latter results are concordant with results from studies on caffeine's effect on objective measures of sleepiness [delay until falling asleep, ability to resist falling asleep; (16,34,35); for review cf. (3)], whereas subjective measures were less influenced in these studies (16,34).

The prominent role of headache as a withdrawal symptom (8–10,14,28,30) is supported by our results. In the first 2 days of caffeine abstinence, 40 to 50% of the subjects indicated at least once a headache exceeding a rating score of 10, and 20 to 30% even exceeded a rating of 15. However, the headaches are limited to the first few days of caffeine abstinence and in most cases bearable, or reducible with analgetics, and relieved by caffeine. It remains unclear why the intermittent group developed more headache, used more often analgetics, and showed more pronounced changes in most subjective ratings in the first 2 days of abstinence than the continuous decaff group. Special analyses revealed no differences between these two groups nor between headachers and nonheadachers, e.g., with respect to coffee consumption, caffeine concentration, coffee ratings, subjective, or cardiovascular parameters for the same day or for baseline days.

The caffeine abstinence effects on ratings of well-being (nausea, indisposition; well-being, day positive in the afternoon) seem to be mediated by headaches. This is underlined not only by the parallelism of the changes (and correlations between the variables) but also by the fact that the ratings for well-being in the morning were not affected by caffeine abstinence—and headache, too, reached its maximum in the afternoon (MP 3–5).

Most caffeine abstinence effects seem to normalize to baseline level after 2–3 days: wakefulness, headache, use of analgetics, nausea, subjective well-being (cf. Fig. 2). This is under-

lined by the fact that the contrasts baseline vs. decaff days (B/−) often fail to reach significance, whereas the initial contrasts (B/4–6) reach significance (wakefulness, use of analgetics, indisposition, general well-being, day positive; tendency for nausea). Thus, the initial effect contrasts (B/4–6) explain more variance than the overall ones (B/−; ratios ranging from 2.85 to 148), and this is valid also for headache (ratio 3.87). The transient character of these withdrawal symptoms is further confirmed by the fact that they showed a decreasing trend over the three separate caffeine abstinence periods in the intermittent group. Correspondingly, contrasts including a linear trend from one abstinence period to the next (vs. baseline) explain more variance than the overall contrasts without linear trend (B/−; ratio ranging from 1.26 to 2.58). For motor activity the time course is less clearcut (cf. Fig. 2a; ratio 1.14).

With respect to the onset of caffeine consumption, no decrease of the effects over time (i.e., from day 6 to 9 to 12) can be observed for wakefulness, sleep duration, and problems falling asleep (cf. Fig. 2b; linear contrasts don't explain more variance than the B/+ contrasts).

Splitting the effects of caffeine abstinence into costs (negative effects: increased heart rate, headache, decreased motor activity, wakefulness, well-being) and benefits (positive effects: increased day positive, decreased problems falling asleep), the present study shows that the benefits seem to be less important than the costs, although the costs, too, may be considered as moderate. Furthermore, the present data give no hint of an increased coffee consumption to compensate for the decreased caffeine content and to avoid withdrawal effects. Thus, coffee consumption seems to be more than caffeine application.

In summary, the reported study revealed transient effects of caffeine abstinence on subjective wakefulness, well-being, and headaches, which also declined over successive abstinence periods. These results show that tolerance to caffeine abstinence develops rather quickly. On the other hand, the increase of heart rate and possibly the decrease of motor activity appear to be longer lasting and perhaps negative effects of caffeine abstinence.

ACKNOWLEDGEMENTS

We thank Peter Schmid for technical assistance, Jiri Kos and Stefan Berz for programming the software for the electronic diary and the analysis of the activity monitor data, and Bonnie Strehler for editorial assistance. Further, we thank Dr. K. Gautschi, Institut für Klinische Chemie Universitätsspital Zürich, for the determination of the caffeine concentrations in saliva. The study was supported by a grant from the Physiological Effects of Coffee (PEC) Committee, Paris.

## REFERENCES

1. Bak, A. A. A.; Grobbee, D. E. A randomized study on coffee and blood pressure. J. Hum. Hypertens. 4:259–264; 1990.
2. Bak, A. A. A.; Grobbee, D. E. Caffeine, blood pressure, and serum lipids. Am. J. Clin. Nutr. 53:971–975; 1991.
3. Bättig, K. Coffee, cardiovascular and behavioral effects. Current research trends. Rev. Environm. Health 9:53–84; 1991.
4. Bättig, K.; Welzl, H. Psychopharmacological profile of caffeine. In: Garattini, S., ed. Caffeine, coffee, and health. New York: Raven Press; 1993:213–253.
5. Benowitz, N. L. Clinical pharmacology of caffeine. Annu. Rev. Med. 41:277–288; 1990.
6. Burr, M. L.; Gallacher, J. E. J.; Butland, B. K.; Bolton, C. H.; Downs, L. G. Coffee, blood pressure and plasma lipids: A randomized controlled trial. Eur. J. Clin. Nutr. 43:477–483; 1989.
7. Chait, L. D. Factors influencing the subjective response to caffeine. Behav. Pharmacol. 3:219–228; 1992.
8. Dreisbach, R. H.; Pfeiffer, C. Caffeine-withdrawal headache. J. Lab. Clin. Med. 28:1212–1219; 1943.
9. Griffiths, R. R.; Bigelow, G. E.; Liebson, I. A. Human coffee drinking: Reinforcing and physical dependence producing effects of caffeine. J. Pharmacol. Exp. Ther. 239:416–425; 1986.
10. Griffiths, R. R.; Evans, S. M.; Heishman, S. J.; Preston, K. L.; Sannerud, C. A.; Wolf, B.; Woodson, P. P. Low-dose caffeine physical dependence in humans. J. Pharmacol. Exp. Ther. 255: 1123–1132; 1990.
11. Griffiths, R. R.; Woodson, P. P. Caffeine physical dependence: A review of human and laboratory animal studies. Psychopharmacology (Berlin) 94:437–451;1988.
12. Höfer, I.; Bättig, K. Coffee consumption, blood pressure tonus and reactivity to physical challenge in 338 women. Pharmacol. Biochem. Behav. 44:573–576; 1993
13. Horst, K.; Buxton, R. E.; Robinson, W. D. The effect of the habitual use of coffee or decaffeinated coffee upon blood pressure and certain motor reactions of normal young men. J. Pharmacol. Exp. Ther. 52:322–337; 1934.
14. Hughes, J. R.; Higgins, S. T.; Bickel, W. K.; Hunt, W. K.; Fenwick, J. W.; Gulliver, S. B.; Mireault, G. C. Caffeine self-administration, withdrawal, and adverse effects among coffee drinkers. Arch. Gen. Psychiatry 48:611–617; 1991.
15. Hughes, J. R.; Oliveto, A. H.; Helzer, J. E.; Higgins, S. T.; Bickel, W. K. Should caffeine abuse, dependence, or withdrawal be added to DSM.IV and ICD-10? Am. J. Psychiatry 149:33–40; 1992.
16. Johnson, L. C.; Spinweber, C. L.; Gomez, S. A. Benzodiazepines and caffeine: Effect on daytime sleepiness, performance, and mood. Psychopharmacology (Berlin) 101:160–167; 1990.
17. MacDonald, T. M.; Sharpe, K.; Fowler, G.; Lyons, D.; Freestone, S.; Lovell, H. G.; Webster, J.; Petrie, J. C. Caffeine restriction: Effect on mild hypertension. Br. Med. J. 303:1235–1238; 1991.
18. Mosqueda-Garcia, R.; Tseng, C. J.; Biaggioni, I.; Robertson, R. M.; Robertson, D. Effects of caffeine on baroreflex activity in humans. Clin. Pharmacol. Ther. 48:568–574; 1990.
19. Myers, M. G. Effects of caffeine on blood pressure. Arch. Intern. Med. 148:1189–1193; 1988.
20. Myers, M. G.; Reeves, R. A. The effect of caffeine on daytime ambulatory blood pressure. Am. J. Hypertens. 4:427–431; 1991.
21. Nakazawa, K.; Tanaka, H. Pharmacokinetics of caffeine and dimethylxanthines in plasma and saliva. Yakugaku Zasshi 108: 653–658; 1988.
22. Nehlig, A.; Daval, J. L.; Debry, G. Caffeine and the central nervous system: Mechanisms of action, biochemical, metabolic and psychostimulant effects. Brain Res. Rev. 17:139–170; 1992.
23. Rapoport, J. L.; Jensvold, M.; Elkins, R.; Buchsbaum, M. S.; Weingartner, H.; Ludlow, C.; Zahn, T. P.; Berg, C. J.; Neims, A. H. Behavioral and cognitive effects of caffeine in boys and adult males. J. Nerv. Ment. Dis. 169:726–732; 1981.
24. Robertson, D.; Wade, D.; Workman, R.; Woosley, R. L.; Oates, J. A. Tolerance to the humoral and hemodynamic effects of caffeine in man. J. Clin. Invest. 67:1111–1117; 1981.
25. Rosenthal, R.; Rosnow, R. L. Contrast analysis. Focused comparisons in the analysis of variance. Cambridge: Cambridge University Press; 1985.
26. Rosmarin, P. C.; Applegate, W. G.; Somes, G. W. Coffee consumption and blood pressure. A randomized, crossover clinical trial. J. Gen. Intern. Med. 5:211–213; 1990.
27. Shirlow, M. J.; Berry, G.; Stokes, G. Caffeine consumption and blood pressure: An epidemiological study. Int. J. Epidemiol. 17: 90–97; 1988.
28. Silverman, K.; Evans, S. M.; Strain, E. C.; Griffiths, R. R. With-

drawal syndrome after the double-blind cessation of caffeine consumption. N. Engl. J. Med. 327:1109–1114; 1992.
29. Stensvold, I.; Tverdal, A.; Foss, O. P. The effect of coffee on blood lipids and blood pressure. Results from a Norwegian cross-sectional study, men and women, 40–42 years. J. Clin. Epidemiol. 42:877–884; 1989.
30. Van Dusseldorp, M.; Katan, M. B. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: A 12 week double blind trial. Br. Med. J. 300:1558–1559; 1990.
31. Van Dusseldorp, M.; Katan, M. B.; Van Vliet, T.; Demacker, P. N. M; Stalenhoef, A. F. H. Cholesterol-raising factor from boiled coffee does not pass a paper filter. Arteriosclerosis Thrombosis 11:586–593; 1991.
32. Van Dusseldorp, M.; Smits, P.; Thien, T.; Katan, M. B. Effect of decaffeinated vs. regular coffee on blood pressure. A 12-week, double-blind trial. Hypertension 14:563–569; 1989.
33. Van Dusseldorp, M.; Smits, P.; Lenders, J. W. M.; Thien, T.; Katan, M. B. Boiled coffee and blood pressure. A 14-week controlled trial. Hypertension 18:607–613; 1991.
34. Walsh, J. K.; Muehlbach, M. J.; Humm, T. M.; Dickins, Q. S.; Sugerman, J. L.; Schweitzer, P. K. Effect of caffeine on physiological sleep tendency and ability to sustain wakefulness at night. Psychopharmacology (Berlin) 101:271–273; 1990.
35. Zwyghuisen-Doorenbos, A.; Roehrs, T. A.; Lipschutz, L.; Timms, V.; Roth, T. Effects of caffeine on alertness. Psychopharmacology (Berlin) 100:36–39; 1990.
36. Zylber-Katz, E.; Granit, L.; Lecy, M. Relationship between caffeine concentrations in plasma and saliva. Clin. Pharmacol. Ther. 36:133–137; 1984.