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Diurnal and menstrual cycles in body temperature are regulated differently: A 28-day ambulatory study in healthy women with thermal discomfort of cold extremities and controls

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Diurnal cycle variations in body-heat loss and heat production, and their resulting core body temperature (CBT), are relatively well investigated; however, little is known about their variations across the menstrual cycle under ambulatory conditions. The main purpose of this study was to determine whether menstrual cycle variations in distal and proximal skin temperatures exhibit similar patterns to those of diurnal variations, with lower internal heat conductance when CBT is high, i.e. during the luteal phase. Furthermore, we tested these relationships in two groups of women, with and without thermal discomfort of cold extremities (TDCE). In total, 19 healthy eumenorrheic women with regular menstrual cycles (28–32 days), 9 with habitual TDCE (ages 29 ± 1.5 year; BMI 20.1 ± 0.4) and 10 controls without these symptoms (CON: aged 27 ± 0.8 year; BMI 22.7 ± 0.6; $p < 0.004$ different to TDCE) took part in the study. Twenty-eight days continuous ambulatory skin temperature measurements of distal (mean of hands and feet) and proximal (mean of sternum and infraclavicular regions) skin regions, thighs, and calves were carried out under real-life, ambulatory conditions (i-Buttons® skin probes, sampling rate: 2.5 min). The distal minus proximal skin temperature gradient (DPG) provided a valuable measure for heat redistribution from the core to the shell, and, hence, for internal heat conduction. Additionally, basal body temperature was measured sublingually directly after waking up in bed. Mean diurnal amplitudes in skin temperatures increased from proximal to distal skin regions and the 24-h mean values were inversely related. TDCE compared to CON showed significantly lower hand skin temperatures and DPG during daytime. However, menstrual cycle phase did not modify these diurnal patterns, indicating that menstrual and diurnal cycle variations in skin temperatures reveal additive effects. Most striking was the finding that all measured skin temperatures, together with basal body temperature, revealed a similar menstrual cycle variation (independent of BMI), with highest and lowest values during the luteal and follicular phases, respectively. These findings lead to the conclusion that in contrast to diurnal cycle, variations in CBT variation across the menstrual cycle cannot be explained by changes in internal heat conduction under ambulatory conditions. Although no measurements of metabolic heat production were carried out increased metabolic heat generation during the luteal phase seems to be the most plausible explanation for similar body temperature increases.

Keywords: Ambulatory measurement, basal body temperature, diurnal cycle, internal heat conductance, menstrual cycle, skin temperatures

INTRODUCTION

Diurnal time courses of skin temperature and core body temperature (CBT) are among the most often-studied physiological functions in humans. Diverse investigations using different kinds of protocols provide plausible explanations of how the endogenous circadian time course of CBT is generated. The crucial mechanism seems to be the phase relationship between the circadian rhythms of body-heat production and heat loss, whereby the amplitudes of both patterns are similar, with a trough during the subjective night and a peak during day. CBT, which represents about 70% of body-heat content (Burton, 1935), increases when heat production surpasses heat loss (e.g. in the morning) and declines when the inverse pattern occurs (e.g. in the evening) (Aschoff et al., 1974). These underlying circadian patterns are primarily governed by the suparachiasmatic nuclei (SCN) in the preoptic anterior hypothalamus (Moore & Danchenko, 2002).

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Body heat under resting conditions is mainly produced by inner organs (e.g. liver, kidney). The skeletal muscles seem to play only a minor role, a relationship that can be drastically changed under real-life conditions, for example, by exercise-induced thermogenesis, a so-called ''masking effect'' (Aschoff, 1983; Minors & Waterhouse, 1989; Waterhouse et al., 2005). This chronobiological term subsumes all changes occurring on endogenous circadian patterns without affecting SCN, however, with possible consequences to modulating circadian phase and the amplitude of heat production and/or heat loss, and, hence, subsequently the pattern of CBT. Food intake via diet-induced thermogenesis (e.g. by non-shivering thermogenesis) represents a further prominent masking effect on CBT (Kräuchi et al., 2012; Lowell & Spiegelman, 2000; van Marken Lichtenbelt, 2012).

Sensible body-heat loss changes usually occur via changing skin blood-flow and skin temperatures, and, hence, changing heat redistribution from the core to the shell (Sessler, 2008), i.e. internal heat conductance (Aschoff & Heise, 1972) and body-heat loss. The distal skin regions (e.g. hands, feet) represent the main thermo-effector sites for sensible heat loss (Aschoff et al., 1974). Especially when the arteriovenous anastomoses (AVAs; shunts between arterioles and venules) are opened, body heat loss by withdrawal of the skin sympathetic nerve activity is very efficiently activated (Hales & Molyneux, 1988), for example, during the nocturnal trough of CBT, when sleep usually occurs. The distal-proximal skin temperature gradient (DPG) provides a selective measure for thermoregulatory skin blood-flow through AVAs and consequent heat redistribution (internal heat conductance) and heat loss via the extremities (Aschoff, 1992; Rubinstein & Sessler, 1990). It has even been stated that changes in internal heat conductance reflect almost exclusively variations in skin blood-flow (Aschoff, 1992).

In addition to the distinct circadian rhythmicity of CBT occurring in both men and women, the menstrual cycle in fertile women generates a further regular modulation of CBT, with a larger period of about 28 days but a similar amplitude of about 0.2 °C (Kelly, 2006). In contrast to the relatively well-understood circadian regulation of CBT, the menstrual cycle variation is not fully understood, especially not under real-life conditions. More or less consistent findings are available showing higher metabolic heat production in the luteal than in the follicular phase (Buffenstein et al., 1995; Schmidt, 1972; Webb, 1986). However, it is still a matter of debate whether reduced internal heat-conductance represents an additional mechanism to increase CBT in the luteal phase (Shechter et al., 2011). Furthermore, differences in diurnal rhythmicity of thermoregulatory processes between the menstrual phases are crucial. Ambulatory and controlled lab studies have shown that circadian amplitude in CBT during the luteal phase is lower than during the follicular phase, mainly due to elevated nocturnal values (Cagnacci et al., 2002; Lee, 1988; Nakayama et al., 1992; Shechter et al., 2011). However, skin temperatures have been investigated mainly under lab conditions and showed no differences between follicular and luteal phases (Frascarolo et al., 1990; Shechter et al., 2011) or higher skin temperatures in the luteal phase (for review, see Marsh & Jenkins, 2002). The sole study conducted under ambulatory conditions reported higher skin temperatures on the abdominal region during the luteal phase; however, measurements were registered exclusively during sleep episodes (Chen et al., 2009). To our knowledge, no diurnal ambulatory study exists for skin temperatures throughout an entire menstrual cycle.

To measure differences in DPG as a measure of changed internal heat conductance between diurnal and menstrual time courses, we planned to study these rhythms continuously and under ambulatory, real-life conditions over 28 days in subjects with regular reported menstrual cycles. The main aim of the study was to determine whether menstrual cycle variations in distal and proximal skin temperatures exhibit similar patterns to those of diurnal variations, with lower internal heat conductance when CBT is high, i.e. during the luteal phase. Therefore, we compared two groups of healthy women with respect to their diurnal and menstrual time courses of distal and proximal skin temperatures. One group consisted of women with thermal discomfort of cold extremities (TDCE), a symptom belonging to the vascular dysregulation syndrome (Flammer & Mozaffarieh, 2007). The other group consisted of women without these complaints (CON). We previously had shown that TDCE in comparison to CON exhibit exaggerated circadian amplitudes, particularly in distal skin temperatures, under both controlled lab and real-life conditions (Gompper et al., 2010; Vollenweider et al., 2008). It is, therefore, possible to challenge the question of whether differences in diurnal amplitudes in skin temperatures disclose differences in their menstrual cycle amplitudes. CBT was measured daily sublingually directly after waking up in bed, the so-called basal body temperature.

METHODS

Subjects

Eumenorrheic, healthy women between the ages of 20 and 40 years were recruited by means of a notification at the University of Basel informing potential volunteers about the opportunity to participate in a scientific research project. The study was approved by the local ethics committee (Ethikkommission beider Basel) for research on human subjects and met the ethical standards of Chronobiology International (Portaluppi et al., 2010). The nature, purpose, and risks of the study were explained, and written informed consent was received from all subjects before admission to the study.

Subjects were explicitly informed that they could stop the experiment at any time. The study was designed and conducted in accordance with the tenets of the Declaration of Helsinki.

Nine women with thermal discomfort of cold extremities (TDCE) and 10 women without TDCE (CON) were selected by means of screening questionnaires, as previously described, excluding the criteria of difficulty initiating sleep (Gompper et al., 2010). Two questions referring to TDCE were used for its definition: (1) During the past month, how intensively did you suffer from cold hands? (2) During the past month, how intensively did you suffer from cold feet? The answers were assessed on a Likert scale: ''not at all'' = 1; ''a little'' = 2; ''quite'' = 3; ''extraordinarily'' = 4. The criteria for TDCE were fulfilled if the subject answered both questions with either ''quite'' or ''extraordinarily'' (a 3 or a 4). CON had to answer both questions with ''not at all'' or ''a little'' (a 1 or a 2). These criteria were then independently validated by finger skin-temperature measurements (Kräuchi et al., 2008), whereby TDCE exhibited significant lower skin temperatures than CON in a sample of total 251 subjects. In the previous 6 months, all subjects had been non-smokers, had not been taking oral contraceptives, had had a regular menstrual cycle of 28 days ± 1 day (self-reports), none was recently pregnant and no gave recently birth (one women had a 2-year-old child); and, within 2 months before the study, had maintained a regular sleep-wake cycle with no change of time zone. Subjects with any known disease, for example, migraine, premenstrual syndrome, epilepsy, or allergies, were excluded. No subjects were on medications and had not donated blood within 3 months before the study. Subjects with drug or excessive alcohol or caffeine use (>4 cups/day) were excluded, too. The study was carried out within 1 year.

Skin temperature recordings

Eleven skin temperatures were recorded from each subject under normal living conditions during a 4-week ambulatory protocol. Wireless temperature sensors (DS 1922L Thermochron iButton; diameter × height: 17 × 6 mm, resolution: 0.0625 °C, accuracy: 0.5 °C; Maxim, Dallas, TX) were used to record skin temperatures continuously at 2.5-min intervals (weekly readout). The iButtons were fixed to the skin with thin, air-permeable adhesive surgical tape (Fixomull®, Beiersdorf, Hamburg, Germany) on the left and right side of the body on wrists (palm side of the wrist on the os lunatum), feet (on the inner calcaneus bone), calves, thighs and infraclavicular regions, and one on the sternum (Gompper et al., 2010; Kräuchi et al., 2012). The temperature sensors were worn in real-life conditions, including when taking a shower and participating in sports. We excluded data during and half an hour after such an episode as well as after exchanging a surgical tape. The missing data were replaced by the average of data 30 min before and after that episode (only <0.5% of the data were lost). None of the subjects lost a probe. Temperature data, including time stamps, were then transferred to the statistics program (see below). Proximal skin temperature was defined as the mean skin temperature of the left and right infraclavicular regions and sternum. Distal skin temperature was defined as the mean skin temperature of the wrists and feet. All other skin measurements were calculated as the mean of the left and right side of the body. The mean skin temperature was calculated according to the modified formulae of Hardy-Dubois (1938), cited in Choi et al. (1997) as $T_{sk} = 0.09T_{hands} + 0.11T_{feet} + 0.15T_{calves} + 0.15T_{thigh} + 0.30T_{infraclv.} + 0.12T_{sternum}$.

Measurement of basal body temperature

Daily measurements of morning sublingual temperature (T_{su}) were used as basal body temperature. A single measurement of oral temperature (3 min sublingually) was taken directly after waking up in bed, using a digital thermometer (Geratherm® digital, Geratherm Medical AG, Geschwenda, Germany).

Statistical analysis

First, all skin-temperature data was adjusted to the beginning of menses (=day 1). The beginning of menses was based on self-reports. Not all women exhibited an exact 28-day menstrual cycle (range: 27–29 days; see comment under Study Limitation below). The subjects started the study randomly with respect to their individual first day of menses. For each skin region, the individual data rows started at midnight (=0°°) on day −14 and ended at 24°° on day 14. The time series of the entire data set were binned into 2-h means (12 values per diurnal cycle) and then into 14 two-day means (total: 6 skin regions × 14 values per menstrual cycle × 12 values per diurnal cycle = 1008 values per subject). In general, time courses were statistically tested by analyses of variance for repeated measures (rANOVA). Huynh-Feldt's correction was used to adjust the covariance matrix for violations of sphericity. Following rANOVA, all *p* values were based on Huynh-Feldt's-corrected degrees of freedom; however, original degrees of freedom are reported. Post-hoc analyses, including alpha-error correction for multiple comparisons, were carried out according to the procedure of Curran-Everett (2000).

The temporal association (phase relationship) between menstrual cycles of the T_{sk} nighttime-segment and the T_{su} was performed by a cross-correlation analysis using multiple regression analyses for each time lag with subjects as random variables for intercepts.

To compare a rough measure of menstrual cycle variations (doubled menstrual cycle amplitude) in T_{su} and T_{sk}, the difference between ''luteal'' (mean values of menses day −14 to −1) and ''follicular'' (mean values of menses day 1 to 14) phases was calculated. Because basal body temperature (T_{su}) was measured once per day, in the morning, directly after sleep, in bed,

the mean night value of T_{sk} from 01 to 06°° was taken for comparison. Least square regression analyses were performed to compare linear relationships between the 2 variables.

Statistical differences between 2 groups (CON vs. TDCE) were calculated either by ANOVA or by Mann–Whitney *U* test.

The critical alpha-level of statistical significance was set at $p = 0.05$. Group data were expressed as mean ± SEM. ANOVA were performed using Statistica™ 9 software (StatSoft, Tulsa, OK).

RESULTS

Biological and sleep parameters

Biological and sleep parameters taken from screening questionnaires are listed in Table 1. TDCE were significantly slimmer than CON (lower BMI) and reported a 6.6 min longer sleep-onset latency (SOL) ($p = 0.027$) and more intense complaints of cold extremities, particularly hands ($p < 0.05$). Sleep timing did not differ between CON and TDCE.

Daily estimation of sleep timing (times of lights off and lights on, as well as sleep duration) using daily sleep logs did not differ between CON and TDCE, and no menstrual cycle modulation occurred. Three-way-rANOVA with factors GROUP (CON vs. TDCE), SLEEPTIME (light off vs. lights on) and MENSDAY (28 days) did not reveal significant main effects (exception: SLEEPTIME) and interaction terms (all $p > 0.6$). To visualize sleep timing in relation to diurnal time courses of DPG, and distal and proximal skin temperatures, the median ±40% percentiles of time of lights off and lights on are shown in Figure 2 above the time axis. Analysis of SOL by the same procedure as described previously revealed significant higher values in TDCE than CON (11.8 ± 1.2 min vs. 7.7 ± 1.1 min; calculated with log-transformed values; $p = 0.044$, one-tailed test); no effects of MENSDAY and no significant interaction with MENSDAY * GROUP were found.

TABLE 1. Biological and sleep parameters screening questionnaire (mean ± SEM).

Group:	TDCE	CON	*p*
N	9	10	
Age	29 ± 1.5 year	27 ± 0.8 year	n.s.
BMI	20.1 ± 0.4	22.7 ± 0.6	**0.004**
SOL	14.6 min ± 1.0	8.0 min ± 1.3	**0.027**[a]
Loff	23.3 h ± 0.3	23.0 h ± 0.2	n.s.
Lon	7.4 h ± 0.5	7.1 h ± 0.2	n.s.
MSFsc	4.77 ± 0.21	4.50 ± 0.30	n.s.
Cold feet	3.00 ± 0.00	1.40 ± 0.16	<**0.0001**[b]
Cold hands	3.22 ± 0.15	1.00 ± 0.00	<**0.0001**[b]
Cold feet–hands	−0.22 ± 0.15	0.40 ± 0.16	**0.04**[b]
Mens cycle duration	28d ± 1(range)	28d ± 1(range)	n.s.

BMI, body mass index (body weight/body hight^2, kg/m^2); SOL, sleep onset latency; Loff, lights off; Lon, lights on; MSFsc, mid-sleep time on free days corrected for sleep deficit (Roenneberg et al., 2004). Arithmetic means ± SEM are listed.

[a]ANOVA with log-transformed values was calculated; retransformed SOL values are presented.

[b]Chi-square statistics. Questions: During the past 4 weeks I suffered from cold hands (or feet, respectively): The answers were assessed on a Likert scale: ''not at all'' = 1, ''a little'' = 2, ''quite'' = 3, ''extraordinarily'' = 4.

Significant *p*-values are given in bold ($p < 0.05$), a trend to statistical significance is given in bold-italicized values ($p < 0.1$).

Analyses concerning diurnal and menstrual cycles

The data set was statistically tested by four-way-rANOVA using the following factors and levels: GROUP (CON vs. TDCE), REGION (thighs, calves, feet, hands, sternum, and infraclavicular regions), MENSDAY (14 two-day means), and DIURNAL (12 two-hour means). Table 2 summarizes the results, revealing significant variation within menstrual cycle (MENSDAY: $p < 0.0001$). All other factors (GROUP, DIURNAL, REGION) tested in two-, three-, and four-way interactions did not significantly ($p > 0.2$) influence the main effect MENSDAY.

First, skin temperatures revealed a significant pattern with respect to diurnal cycle (DIURNAL: $p < 0.0001$). Significant interactions with factors GROUP and REGION occurred (DIURNAL * REGION * GROUP, $p = 0.0502$ and DIURNAL * REGION, $p < 0.0001$). In the top panel of Figure 1, diurnal time courses of CON and TDCE are depicted for each skin region (mean ± SEM of pooled data over all menstrual cycle days per subject). Significant differences between the groups were found, with reduced hand skin temperatures in TDCE between 10 and 22°°. The other distal skin sites (feet and calves) tended to reduced levels only during daytime in TDCE.

TABLE 2. Four-way analysis of variance for repeated measures of skin temperature data (four-way rANOVA).

	DF	F value	*p* Value
GROUP	1,17	1.480	0.2383
MENSDAY	13,221	4.720	<**0.0001**
REGION	5,85	109.5	<**0.0001**
DIURNAL	11,187	78.92	<**0.0001**
MENSDAY * GROUP	13,221	0.766	0.6614
REGION * GROUP	5,85	3.501	**0.0078**
DIURNAL * GROUP	11,187	0.980	0.4187
MENSDAY * REGION	65,1105	1.037	0.4184
DIURNAL * REGION	55,935	38.54	<**0.0001**
DIURNAL * MENSDAY	143,2431	1.004	0.4703
MENSDAY * REGION * GROUP	65,1105	0.928	0.5466
MENSDAY * DIURNAL * GROUP	143,2431	1.047	0.3793
DIURNAL * REGION * GROUP	55,935	2.013	***0.0502***
DIURNAL * REGION * MENSDAY	715,12155	0.974	0.5340
MENSDAY * REGION * DIURNAL * GROUP	715,12155	0.905	0.6844

A row of 1008 data points per subject was analyzed by a four-way rANOVA [GROUP ($N = 9$ TDCE vs. $N = 10$ CON); REGION (six skin regions); MENSDAY (14 two-day means); DIURNAL (12 two-hour means)].

Factors GROUP and DIURNAL did not significantly influence factor MENSDAY in either interaction term, indicating independent time courses of DIURNAL and MENSDAY.

Significant *p*-values are given in bold ($p < 0.05$), a trend to statistical significance is given in bold-italicized values ($p < 0.1$).

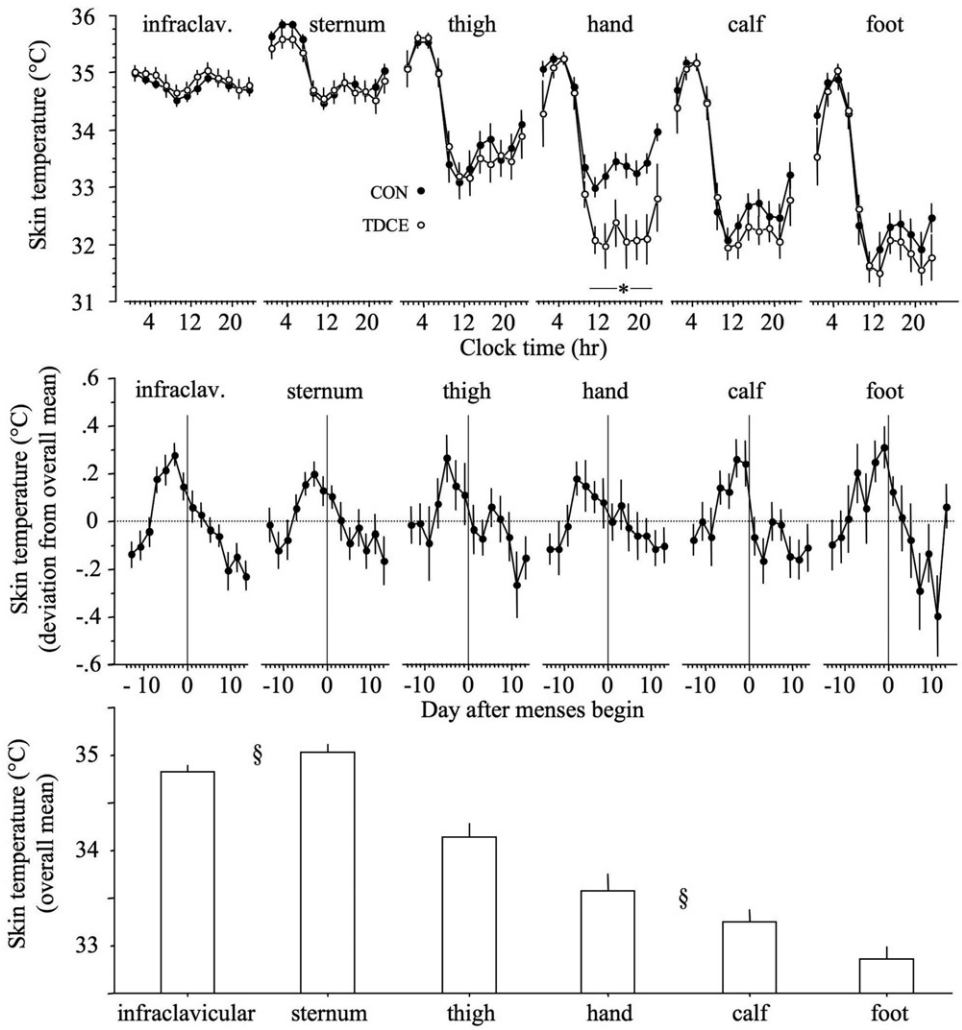

FIGURE 1. The top panel compares diurnal time courses (hourly means) in skin temperatures of CON ($N=10$, black dots) and TDCE ($N=9$, open dots) for all skin regions (mean ± SEM of pooled data over all menstrual cycle days). Asterisks indicate significant differences between TDCE and CON ($p<0.05$). In the middle panel, menstrual cycle variations in daily means of 24-h mean skin temperatures are presented as deviation from individual overall mean for all skin regions (mean ± SEM; $N=19$ women, 10 CON, and 9 TDCE). In the bottom panel, the mean overall temperatures + SEM (pooled data over all menstrual cycle days and diurnal pattern per subject; $N=19$ women, 10 CON, and 9 TDCE) are depicted for all measured skin regions. § indicates non-significant differences between infraclavicular regions and sternum, and hand and calf. All other skin regions are significantly different from each other. *Note*: Proximal skin regions exhibit highest and distal skin regions lowest overall mean skin temperatures, whereas diurnal amplitudes show the inverse order. In contrast, menstrual cycle variations are similar in all six skin regions. In comparison to CON, distal skin temperatures during daytime (most pronounced in hands) are lower in TDCE (see also Figure 4). For statistics, see text.

In general, similar patterns in skin temperatures were found; especially, the afternoon peak seemed to be similar in all skin regions and in both groups. The diurnal amplitudes increased from proximal to distal skin regions (infraclavicular region < sternum < thigh < hand < calf < foot).

Second, Figure 1 (middle panel) shows the similarity in menstrual cycle patterns of all skin temperatures (MENSDAY: $p<0.0001$), with maximum and minimum values at the end of luteal and follicular phases. For an easier comparison of the patterns, data (24-h mean per subject) was plotted after subtraction of the individual overall mean values per skin region (data of TDCE and CON are pooled). BMI did not significantly influence this finding [no significant effect of factor BMI (median-split of BMI data) on MENSDAY (5-way rANOVA), data not shown].

Third, the 24-h overall mean values (Figure 1, bottom panel; pooled data over all menstrual cycle days and diurnal pattern per subject) exhibits highest values in proximal and lowest in distal skin sites (REGION: $p<0.0001$). This rank order is more or less opposite to the rank order of diurnal amplitudes (see Figure 1 top panel).

A further separate analysis of the data provides information with respect to thermoregulatory processes in the body (see introduction) by comparing two subgroups of pooled skin temperatures, i.e. of distal and proximal skin regions. The time courses of distal (mean hands and feet) and proximal (mean of

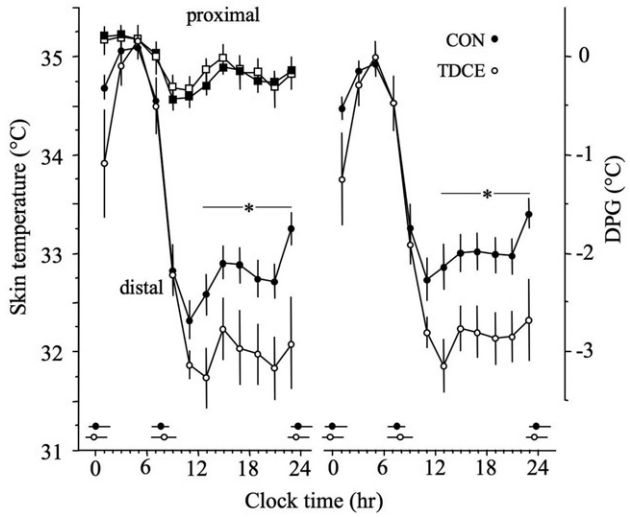

FIGURE 2. Left panel compares diurnal time courses (2-h means) of distal (dots) and proximal (squares) skin temperatures in CON ($N = 10$, black dots and squares) and TDCE ($N = 9$, open dots and squares). Before statistical analyses, the individual means over all menstrual cycle days were calculated. Right panel shows the diurnal time course (2-h means) of distal minus proximal skin temperature gradient (DPG; corresponds to the rANOVA interaction term REGION*DIURNAL) of CON (black dots) and TDCE (open dots). In comparison to CON, distal skin temperatures and DPG are significantly reduced in TDCE during daytime (10–22°°). Horizontal dots and lines above time axes indicate bedtime and rising time [10, 50 (=dots) and 90% percentiles]. No differences in sleep times occurred between TDCE and CON. All values are means ± SEM of individually pooled data over all menstrual cycle days. Asterisks and curved lines indicate significant differences between TDCE and CON ($p < 0.05$).

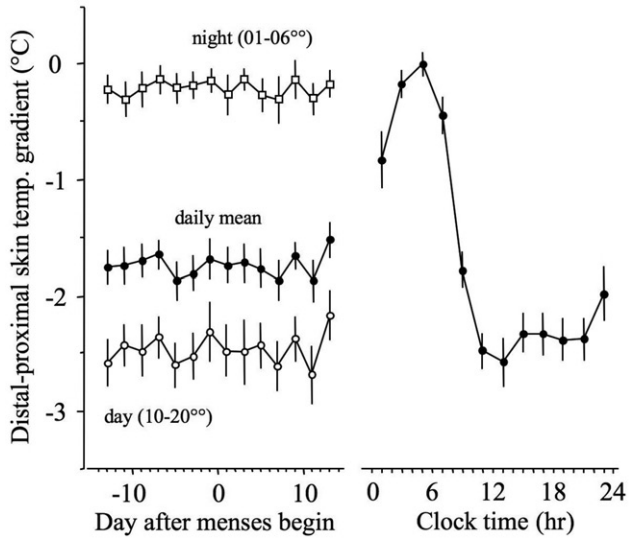

FIGURE 3. Comparison of diurnal time course of distal minus proximal skin temperature gradient (DPG; black dots, right panel) with daytime (mean 10–20°°, open dots), nighttime (mean 01–06°°, open squares) and daily mean (0–24°°, black dots) DPG values across the menstrual cycle (left panel). Values are mean ± SEM of $N = 19$ women (10 CON and 9 TDCE). *Note*: DPG as a measure for body heat redistribution and distal heat loss exhibits large diurnal variations; however, no modulation occurred by menstrual cycle, either for daytime, nighttime, or daily mean DPG values.

infraclavicular regions and sternum) skin temperatures were calculated and tested in a similar four-way-rANOVA as described above with factors GROUP (CON vs. TDCE), DISPRO (distal vs. proximal), MENSDAY (14 two-day means) and DIURNAL (12 two-hour means). Nearly identical results were found. MENSDAY again revealed only a significant main effect [MENSDAY: $F(13,221) = 5.35 < 0.0001$], and no significant interaction terms including MENSDAY occurred (all $p > 0.4$). Therefore, the diurnal profile can be shown with pooled data over all menstrual cycle days [GROUP * DISPRO * DIURNAL: $F(13,187) = 2.480$, $p = 0.0407$]. Figure 2 (left panel) exhibits lower distal skin temperatures in TDCE than in CON; however, only between 12 and 24°°; no differences were found in proximal skin temperatures. Furthermore, the interaction term ''DISPRO * DIURNAL'' represents the diurnal difference between distal and proximal skin regions and, therefore, the diurnal variations of the distal-proximal skin temperature gradient (DPG, see introduction). The diurnal pattern of DPG (Figure 2, right panel; pooled data over all individual menstrual cycle days) summarizes the selective differences during daytime between CON and TDCE, with significantly lower DPG values between 12 and 24°° in TDCE than in CON.

The differences between diurnal and menstrual cycle variations in DPG are highlighted in Figure 3. A highly significant diurnal pattern in DPG [DIURNAL*DISPRO: $F(11,187) = 61.11$, $p < 0.0001$; right panel] contrasts with relatively stable 24-h mean DPG values with respect to the menstrual cycle days [MENSDAY*DISPRO: $F(13,221) = 0.919$, $p = 0.5339$, left panel], but also in daytime (mean between 10 and 20°°) and nighttime (mean between 01 and 06°°) -segments ($p > 0.5$, left panel).

Next, an overall analysis using weighted mean temperatures (T_{sk}) of all measured skin regions with daytime (T_{sk} day, mean between 10 and 20°°) and nighttime (T_{sk} night, mean between 01 and 06°°) -segments were calculated to compare menstrual cycle variations of T_{sk} with basal body temperature (T_{su}; measured early in the morning directly after sleep in bed; 10 of the total of 560 T_{su} data points were missing). Visual inspection of the graphs in Figure 4 reveals similar time courses with maximal and minimal values at the end of the luteal and follicular phases. A three-way-rANOVA confirmed a significant main effect MENSDAY [$F(13,221) = 7.00$, $p < 0.0001$]; no interaction terms of MENSDAY with factors GROUP (CON vs. TDCE) and REGION (T_{sk} vs. T_{sk} day vs. T_{sk} night) reached the level of significance (all $p > 0.23$). This analysis indicates no differences in menstrual cycle variations between T_{su}, T_{sk} night and T_{sk} day, and between TDCE and CON.

The temporal association (phase relationship) between menstrual cycles of the T_{sk} night and the T_{su},

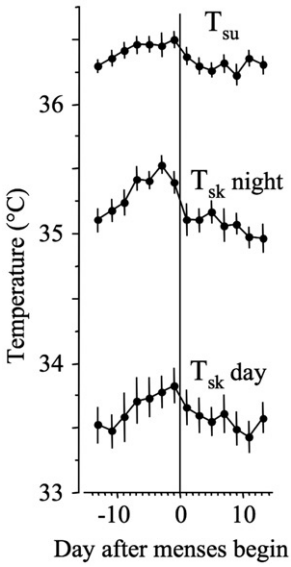

FIGURE 4. Menstrual cycle (mean ± SEM; $N = 19$, 10 CON, and 9 TDCE) of mean-weighted skin temperatures (T_{sk} night: mean 01–06°°, middle panel; T_{sk} day: mean 10–20°°, bottom panel) and basal body temperature (T_{su}; sublingual temperature measured directly after sleep in bed, top panel). No significant interaction term REGION * MENSDAY occurred. *Note*: Similar time courses occurred in T_{sk} (day and night) and T_{su}, with maxima and minima during the luteal and the follicular phases, respectively, indicating no differences in internal heat conductance across the menstrual cycle.

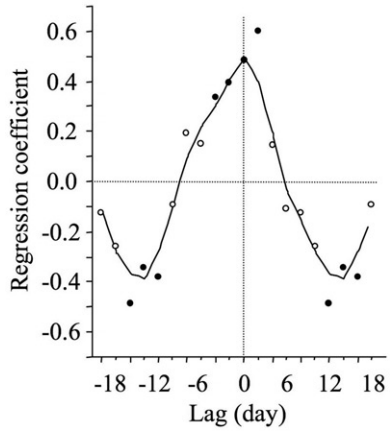

FIGURE 5. Cross-correlation curve between menstrual cycles of T_{sk} night (mean values 01–06°°) and basal body temperature (T_{su}). Lag 0 = T_{sk} night is in phase with T_{su}. Two-h mean data of Figure 4 was used for the analysis. Positive lags indicate a phase advance of T_{sk} night in respect to the phase of T_{su}. Based on the finding that no differences between the groups were found the cross-correlogram is presented for the total number of subjects (Mean of $N = 19$ women, 10 CON, and 9 TDCE). The black line represents a lowness-fit (locally weighted scatterplot smoother, tension: 20%; Cleveland, 1979) to the data. Black and white dots indicate significant and non-significant correlations ($p < 0.05$). *Note*: The menstrual cycle of T_{sk} night and T_{su} are in phase.

was tested by a cross-correlation analysis using multiple regression analyses for each time lag with subjects as random variables for intercepts (Figure 5). The analysis was carried out for TDCE and CON separately, however, no differences between them were found (Mann–Whitney *U*-test for all time lags). Therefore, the cross-correlogram is shown for the total number of subjects ($n = 19$). To capture the general pattern of the cross-correlogram, a lowness-fit [locally weighted scatterplot smoother, tension: 20%; Cleveland, 1979] was applied to the data. Maximum regression-coefficients were found at lag 0, indicating the menstrual-cycle patterns of the two variables are in phase.

To compare menstrual cycle variations (amplitudes) of the T_{sk} nighttime (T_{sk} night; mean between 01 and 06°°), segment with those of the T_{su}, a linear regression analysis was performed (Figure 6). The menstrual cycle variations (ΔT_{sk} night or ΔT_{su}) were defined as the difference between the luteal and follicular phases, a rough measure for menstrual cycle amplitude (doubled amplitude; luteal phase = mean value of 14 days before menses begin; follicular phase = mean value of day 1–14 after menses begin). A significant linear correlation was found with the following equation: ΔT_{sk} night = 0.161 ± 0.058 + 0.962 ± 0.319 * ΔT_{su}; means ± sem; $r = 0.590$, $p = 0.0078$. These findings indicate that not only are the individual phases of the menstrual cycles of T_{sk} night and T_{su} associated, but also their amplitudes. The slope of 0.962 indicates an equal change of ΔT_{su} and ΔT_{sk}.

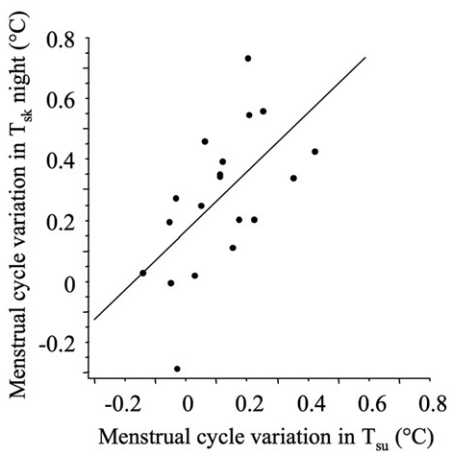

FIGURE 6. Linear correlation between individual menstrual cycle variations in basal temperature (ΔT_{su}, sublingually measured temperature) and mean skin temperature during the night (ΔT_{sk} night; weighted mean of six skin regions; night value: means 01–06°°). Each data point represents differences between the luteal and follicular phases (mean value of days 14–28 after menses begin = luteal phase values minus mean value of day 0–13 after menses begin = follicular phase values). ΔT_{sk} night = 0.161 + 0.962* ΔT_{su}; $r = 0.590$, $p = 0.0076$. *Note*: ΔT_{sk} night varied to a similar extent with ΔT_{su} (slope = ca.1.0).

Furthermore, the menstrual cycle variation in daytime T_{sk} (ΔT_{sk}; 0.101 ± 0.067 °C), nighttime T_{sk} (ΔT_{sk} night; 0.270 ± 0.054 °C), and T_{su} (ΔT_{su}; 0.113 ± 0.033 °C), and the diurnal variations in T_{sk} [difference between night (mean 01–06°°) and day (mean 10–20°°) values: 1.572 ± 0.077 °C] were statistically compared by one-way-rANOVA [$F(3,54) = 137.36$, $p < 0.0001$]. Post-hoc

analyses revealed a manifold larger diurnal than menstrual cycle variation in T_{sk} (daytime and nighttime segments) and in T_{su}. The latter exhibited the lowest menstrual cycle variation (statistical trend, $p<0.1$). Additionally, a significant ($p=0.013$) intercept of the linear equation was found, indicating significantly higher values, at least of ΔT_{sk} nighttime compared to ΔT_{su}.

DISCUSSION

This ambulatory study reveals clear differences between diurnal and menstrual cycles in skin temperatures, allowing conclusions about the distinct regulation of diurnal and menstrual cycles in CBT. The main finding is that characteristics of menstrual cycles in distal and proximal skin temperatures did not significantly differ. All skin temperature rhythms exhibited similar menstrual cycle amplitudes and phases with maxima and minima at the end of the luteal and follicular phases, respectively (Figures 1 and 4). In contrast, diurnal cycles in distal skin temperatures exhibited larger amplitudes and lower daily means compared to proximal skin temperatures (Figures 1 and 2), confirming our previous findings (Gompper et al., 2010; Kräuchi, 2007; Kräuchi et al., 2012).

It is well documented that under controlled laboratory resting conditions (e.g. the constant routine protocol), skin-temperature rhythms of diverse skin regions can exhibit a wide spectrum of circadian phase positions (Aschoff et al., 1974; Kräuchi & Wirz-Justice, 1994; Kräuchi et al., 2006). For example, distal skin temperatures are nearly 180° out of phase compared to proximal skin temperatures and CBT, and, hence, DPG and internal heat conduction are low during daytime (Aschoff, 1983; Kräuchi et al., 2006; Kräuchi & Wirz-Justice, 1994). However, under real-life conditions, all skin temperatures are in phase and synchronized to the sleep-wake cycle, with maximal values during nighttime, confirming previous findings (Gompper et al., 2010). It can be assumed with certainty that CBT, which has not been measured continuously in this study (see below), is high during daytime and, therefore, about 180° out of phase compared to skin temperatures (Kolodyazhniy et al., 2012). The whole palette of regularly distributed behaviors across a day are potential zeitgebers with certain masking properties on the thermoregulatory system, for example, sleep, posture change, environmental light exposure, motor activity, and food intake. However, neither the synchronizing capacity [zeitgeber strength to circadian clock(s)] nor the extent of masking effects of each of these behaviors on the diurnal pattern of skin temperatures can be deduced from the current study's findings. Controlled prospective studies will show which of the everyday behaviors are important to synchronize skin temperatures to sleep-wake cycles. Additionally, in comparison to controlled, resting lab conditions, all body temperatures reveal higher diurnal amplitudes under ambulatory conditions, especially in the lower extremities. For example, the amplitude of foot skin temperatures is about tripled, from 0.7 to 2 °C (Aschoff, 1983; Gompper et al., 2010; Kräuchi & Wirz-Justice, 1994), and the amplitude of CBT is about doubled, from 0.25 to 0.5 °C (Aschoff, 1983). Taken together, a phase-angle difference between diurnal patterns of distal skin temperatures and CBT seems to be the crucial characteristic for CBT regulation across a masked diurnal or endogenous circadian time course (Aschoff, 1983; Kräuchi & Wirz-Justice, 1994). As a consequence, internal heat conductance changes according to time of day, with maximal values in the late evening, when heat loss is maximal and CBT is declining (Aschoff, 1983). The increased vasoconstrictory level during daytime (mainly in the lower distal skin regions, e.g. feet) can be declared in support of the increased heat production raising CBT at this time of day, leading to increased amplitude of the endogenous circadian rhythms of CBT produced by the internal clock system (SCN) and thereby helping to stabilize the overt phase of CBT (Minors & Waterhouse, 1992).

However, the phase relationships between skin temperatures and CBT across the menstrual cycle are fundamentally different to those across the diurnal cycle. The similar patterns of menstrual cycles in all skin temperatures and CBT with respect to phase (Figures 4 and 5) imply that DPG and internal heat conduction do not change across the menstrual cycle (Figure 3). In comparison to T_{sk} night, T_{su} exhibited reduced menstrual cycle amplitude (Figure 6). In our samples, the amplitude of T_{su}, measured only once per day, in the morning, is quite small, about half the previously reported reference values (Kelly, 2006), which could indicate an unreliable measure of CBT. This discrepancy can be explained either by differences in sample selection or by different methods of temperature recording (e.g. thermometer placement). Either way, the interpretation that reduced internal heat conductance in the luteal phase would contribute to increased CBT can be discarded, because a smaller menstrual cycle amplitude in T_{su} than in T_{sk} would instead lead to a higher internal heat conductance during the luteal phase.

A plausible explanation for the parallel increases in all skin temperatures and CBT during the luteal phase could be an increase in energy expenditure (EE) during the luteal phase. The observed parallel increases in all skin temperatures and CBT during the luteal phase, as indicated by a linear, inter-subject correlation between ΔT_{su} night and ΔT_{sk} night (slope not different than 1; Figure 6), can be interpreted as a consequence of increased EE and, hence, of increased CBT and T_{sk} and not of changed vasomotor activity (i.e. cutaneous vasoconstriction during that phase). In fact, there are many reports showing higher resting EE and food intake during the luteal phase in comparison to the follicular phase during wake time but also during the sleep phase (Allen et al., 2000; Bisdee et al., 1989; Howe et al., 1993;

McNeil & Doucet, 2012; Meijer et al., 1992; Schmidt, 1972). As CBT is increased during the luteal phase of the menstrual cycle, it would be reasonable to expect that skin temperatures would also be elevated; however, studies have published varying results, either increased luteal temperatures both at rest and during exercise, or no phase differences (for review, see Marsh & Jenkins, 2002). Frascarolo et al. (1990) found no differences in EE and skin temperatures but higher CBT in the luteal phase, leading, therefore, to increased internal heat conduction. However, findings of our ambulatory study clearly speak against a reduction of internal heat conductance during the luteal phase, even though heat production was not measured. It can be assumed that if the thermoregulatory system would favor body-heat retention (decreased internal heat conductance) during the luteal phase, reduced distal skin temperatures should be expected in comparison to proximal skin temperatures during that phase, and/or phase-angle differences between the menstrual cycles of skin temperatures to CBT should occur. Neither explanation could be confirmed by the current study.

It was recognized early on that an elevation in serum progesterone during the luteal phase of the menstrual cycle is associated with increased EE and higher CBT, but the mechanisms are still not fully understood. Progesterone rapidly increases the firing rate of cold-sensitive thermoregulatory neurons in the preoptic anterior hypothalamus and decreases the firing rate of warm-sensitive neurons (Nakayama et al., 1975), with consequent rise in CBT. In analogy to the well-described increased thermoregulatory thresholds during fever, a similar state has been suggested for the luteal phase (Charkoudian & Johnson, 2000; Moltz, 1993). However, in contrast to fever, many studies could discard this hypothesis that elevated prostaglandins during the luteal phase are responsible for increasing CBT (Baker et al., 2002; Cagnacci et al., 2002; Charkoudian & Johnson, 2000). It is well known that in parallel to the elevation of progesterone during the luteal phase, many other hormones and molecules that participate in the regulation of fuel use, metabolism, and/or food intake, e.g. catecholamines, thyroid hormones, free fatty acid (Buffenstein et al., 1995), are also increased. All these measures are known to have EE stimulating capacity, presumably by involving activation of non-shivering thermogenesis (Morrison et al., 2012; Tentolouris et al., 2006; Virtanen et al., 2013).

In this context, similarly to the increased EE during the sleep phase (e.g. Bisdee et al., 1989; Meijer et al., 1992) a significant menstrual cycle variation was also found for the nocturnal sleep phase in all skin temperatures, with maximal and minimal values occurring during the follicular and luteal phases. A similar finding has been published for skin temperature on the abdominal region measured under ambulatory conditions during the sleep phase (Chen et al., 2009). Under ambulatory conditions, the nocturnal sleep phase (mean: 01°° and 06°°) represents the behaviorally best ''controlled'' time-span across the diurnal cycle, because nearly all subjects were sleeping. It has been shown that during sleep, distal and proximal skin temperatures are increased to a similar level (DPG near 0), indicating a maximal vasodilatation in both regions. This is quite likely due to reduced skin sympathetic nerve activity, which plays a major role in vasoconstriction (Iwase et al., 2002; Kistler et al., 1998). It is interesting to note that even during this vasodilatated state, a clear menstrual cycle in all skin temperatures could be observed, but no changes in DPG (see Figure 3). This indicates, once more, that changes in internal heat conductance across the menstrual cycle do not occur.

Moreover, we have studied two groups of normal, regular-cycling women screened for suffering cold hands and feet. As expected, these two groups differed significantly in distal, but not proximal, skin temperatures selectively during daytime, but not during nighttime (Figures 1 and 2), confirming our previous findings (Gompper et al., 2010; Vollenweider et al., 2008). A further confirmation of our previous research (Gompper et al., 2010; Kräuchi, 2007; Kräuchi et al., 2008) found TDCE reported significantly lower sleep onset latency (SOL). Interestingly, in contrast to hands, no significant differences were found in foot skin temperatures between the groups during daytime (Figure 1). This can be explained by an accidental difference in screening values in subjective ratings of cold hands and feet (see Table 1). In fact, TDCE in comparison to CON rated cooler hands than feet. Nevertheless, TDCE exhibited significantly lower DPG values during daytime than CON (Figure 2), although no differences occurred between TDCE and CON with respect to menstrual cycle variations in body temperatures. Neither group differed significantly in amplitude and phase of diurnal patterns of both distal and proximal skin temperatures across the menstrual cycle, and SOL also did not change. This negative finding is in agreement with the observation that changes in DPG occur in parallel to changes in SOL. The menstrual cycle in CBT (basal body temperature; T_{su} measured in the morning) also did not differ between TDCE and CON. Because it was not possible to measure CBT over 28 days continuously in our sample, for example, by rectal thermometer, no direct comparisons between diurnal patterns of CBT and skin temperatures could be carried out. Both of the available ambulatory studies report elevated nocturnal CBT during the luteal phase (Coyne et al., 2000; Lee, 1988) similar to many controlled lab studies (e.g. Shechter et al., 2011), supporting at least the assumption of increased metabolic rate during nighttime. To summarize this finding, in spite of clear differences in the diurnal amplitude of DPG between TDCE and CON, no differences in menstrual cycles of skin temperatures could be observed between the groups. This finding indicates that women with different habitual internal

heat conductance (TDCE vs. CON) within a diurnal cycle exhibit parallel menstrual cycle variations in skin temperatures and CBT.

Finally yet importantly, it must be mentioned that a second maximum occurred in all skin temperatures in the afternoon (between 14 and 18°°) as previously reported (Gompper et al., 2010; Kräuchi et al., 2012; Martinez-Nicolas et al., 2011). Visual inspection of the data reveals similar amplitude and phases in all skin regions. This observation will be statistically analyzed together with environmental and seasonal influences and presented in a separate publication because it goes beyond the scope of the current publication.

Study limitation

No blood was collected for analyses of ovarian hormones and gonadotropins. The study was based on subjective reports of when menstruation began. Because each subject's entire data was adjusted accordingly, certain variation was possible in the menstrual phase estimation. However, the observed basal body temperature cycle gave the impression of correct alignment.

Not all women exhibited an exact 28-day menstrual cycle. However, for all subjects, data of 28 days were taken for analyses. As a consequence, there was a degree of imprecision in the time axis in six subjects (maximal range: 27–29 days).

It was not possible to measure CBT continuously over 28 days precluding a direct and precise analysis of, for example, internal heat conductance with respect to the diurnal cycle. Nevertheless, certain conclusions can be drawn because it is evident that CBT is higher during daytime and lower during nighttime (see Discussion section).

We collected no data about food intake, motor activity, and heat production, which would provide more accurate quantitative information about internal heat conductance and individual energy balance across the diurnal and menstrual cycle under ambulatory conditions.

CONCLUSION

In spite of the fact that CBT was measured only once, in the morning, and not continuously in this study, the analyses of distal and proximal skin temperatures revealed information about how differently the diurnal and menstrual cycles of CBT are generated under ambulatory conditions. The crucial mechanism for circadian-cycle regulation in CBT is a phase delay of heat loss with respect to heat production; as a consequence, CBT declines in the evening and increases in the morning (Aschoff, 1992; Aschoff et al., 1974; Aschoff & Heise, 1972; Kräuchi & Wirz-Justice, 1994). It is noteworthy that both heat production and CBT are reduced during nighttime (energy-saving mode) (Aschoff et al., 1974), and that we usually choose to sleep at this time (Kräuchi & Deboer, 2010). Under ambulatory, real-life conditions, all skin temperatures are in phase and stringently synchronized to the sleep-wake cycle, with minimal levels during daytime. Such a consistent vasoconstrictory level over all skin regions during daytime leads to reduced internal heat conduction. This increased ''body shell'' (Aschoff & Wever, 1958) is a relevant contribution to an additional elevation of CBT above the endogenous circadian peak occurring during this phase, and it leads to an increased diurnal amplitude of CBT under ambulatory conditions (masking effects).

In relation to the relatively fast 24-h diurnal cycle variations (Aschoff, 1983; Kräuchi & Wirz-Justice, 1994), the slow, 28-day waves of menstrual cycle in CBT seem to be regulated by a different mechanism. No change in internal heat conductance seems to be involved: all skin temperatures and CBT vary, with maxima and minima during the luteal and follicular phases, respectively. Taking together current findings and available literature, it can be hypothesized that increased EE is mainly responsible for the simultaneous increase in CBT and distal and proximal skin temperatures during the luteal phase, not changes in internal heat conductance. However, the cause of such an increase in EE during luteal phase remains to be found.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article. This study was supported by Schwickert-Stiftung and the Swiss National Science Foundation #32003B-116504/1.

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