Esophageal temperature threshold for sweating decreases before ovulation in premenopausal women

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Core temperature (Tc) in some women decreases transiently before ovulation (2, 3, 11, 20, 28, 29) when basal body temperature is monitored during a complete menstrual cycle. Around the same time, designated here as the preovulatory phase of the menstrual cycle, 17β-estradiol (E2) is starting to surge. Approximately 24 h after the peak in E2, the luteinizing hormone (LH) surge occurs (19), triggering ovulation about a day later. It is not known whether E2 plays a direct role in the preovulatory decrease in Tc, but injection of intramuscular estrogen is followed by a decrease in Tc the next day (3). Recently Cagnacci et al. (8) reported that E2 increased markedly in women in the preovulatory phase (677 pg/ml) during multiple follicle development induced by follicle-stimulating hormone (FSH) injections. At this time, vaginal temperature was measured over the course of a 24-h period. In these women, the 24-h mean vaginal temperature was significantly decreased in the preovulatory phase (36.95°C) compared with the early follicular phase (37.14°C).

In postmenopausal women, there are conflicting reports about the effect of estrogen-replacement therapy (ERT) on Tc. Transdermal estrogen administration did not decrease resting Tc in postmenopausal women (6, 7). Yet, ERT (per os) in postmenopausal women was associated with decreased resting Tc (34). Both sweating and cutaneous vasodilatory Tc thresholds were decreased during exercise in postmenopausal women treated with ERT, compared with postmenopausal women who were not treated with exogenous estrogen. These data indicate that ERT (per os) resets the brain set-point temperature (Tset) to a lower temperature.

E2 implants in ovariectomized rats were reported to increase evaporative water loss during heat stress compared with rats not given the steroid (1). Whether this response was related to an estrogenic effect on the hypothalamic Tset is unknown.

Taken together, the majority of the literature cited above supports the idea that increased circulating estrogen plays a part, perhaps by initiating a cascade of cellular events, in decreasing the regulated body temperature via decreased Tset. However, there are no group data describing thermoregulatory effector function in premenopausal women when circulating E2 peaks before ovulation (Fig. 1), although there are many reports describing thermoregulatory effector function for women in the early follicular (low E2 and progesterone) and luteal (high E2 and progesterone) phases of the menstrual cycle (4, 15–18, 22, 27, 32). To confirm that estrogen plays some role in resetting Tset to a lower temperature, initiation of thermoregulatory effectors must occur at a lower Tc in response to exercise, heat stress, or a cold stress after exposure to estrogen.

The purpose of this study was to test the hypothesis that the decreased Tc observed in the preovulatory phase of eumenorrheic women is the result of a transiently decreased regulated body temperature. We tested the hypothesis by measuring the esophageal temperature (Tes) and sweating rate of women exercising under conditions of uncompensable heat stress in the follicular and the predicted preovulatory phases of the menstrual cycle and used endocrine measures to provide an indication of menstrual cycle phase. The Tes threshold for onset of sweating in exercising women was determined to be greater in the early follicular phase (F; days 2–6) than in the preovulatory phase (Preov-2; days 9–12) of the menstrual cycle, providing evidence that the regulated body temperature was decreased in the preovulatory phase.
METHODS

Six healthy women (4 soldiers, 2 civilians) volunteered to participate in this study after being apprised of the risks and purpose of the study. An informed consent statement was signed by each subject. The mean age was 26.7 ± 10.1 (SD) yr, height was 1.70 ± 0.05 m, mass was 62.6 ± 12.3 kg, and body surface area was 1.72 ± 0.17 m². Maximal aerobic power was 42.7 ± 5.2 ml·kg⁻¹·min⁻¹. Experiments were conducted at an ambient temperature of 30.1 ± 0.3°C, black globe temperature of 30.3 ± 0.3°C, and ambient dew-point temperature of 11.1 ± 1.1°C. Wind speed in the environmental chamber averaged 0.7 m/s at the back and 0.2 m/s at the chest. There were at least three sessions during which subjects were familiarized to the investigators and the measurement techniques used in the experimental protocol before the two experiments were done.

Figure 1, constructed from data presented by Steiner and Cameron (31), shows how circulating E₂ and progesterone vary during the follicular, preovulatory, and luteal phases of an idealized menstrual cycle. The endocrine profiles depicted in Fig. 1 were the basis for conducting the present study during the follicular and preovulatory phases. One experiment was done in early follicular phase (days 2–6), and the other experiment was done 1 or 2 days (days 9–12) before estimated ovulation. Both experiments were conducted at the same time of day, between 0700 and 0930, to control for the circadian rhythm in Tₑ (33). Four subjects were studied first in the F phase, whereas two subjects were studied first in the Preov-2 phase due to time constraints for some of the subjects.

The preparations for testing were the same for each experiment. The volunteer rested for 20 min in the environmental chamber before a venous blood sample was drawn for later analysis of plasma E₂, progesterone, and LH. She exited the environmental chamber to eat a light breakfast. Approximately 30 min after breakfast, the volunteer reentered the environmental chamber dressed in shorts, tee-shirt, underwear, and socks. About 30 min later, she inserted a thermocouple probe intranasally, then swallowed it into the esophagus for Tₑ measurement. The position of the esophageal thermocouple was adjusted to the position in the esophagus where the temperature was greatest. This method presumably locates the thermocouple in close proximity to the aortic depression of the esophagus. The probe was secured to the nose by adhesive tape. In several subjects, a temperature telemetry pill (Human Technologies, St. Petersburg, FL) was taken with breakfast. One woman had a gag response to the esophageal probe, which did not remit with familiarization. For this subject (S4) the telemetry pill data were used exclusively as the measurement of Tₑ because she could not tolerate the esophageal thermocouple. Telemetry pill data were shown earlier to correlate well with the Tₑ response to exercise (21).

Surface temperature was measured by using thermocouples placed at eight sites, and local temperatures were weighted for local area of skin at each site to estimate mean skin temperature (Tₑ) (23). Whole body sweating was determined as the change in body weight from preexercise to postexercise values, corrected for water trapped in the clothing. Heart rate was measured by electrocardiography. Local sweating rate (mₛ) was measured from the ventilated dew-point temperature of the upper arm, as described previously (23). After instrumentation, each subject was assisted in dressing in a chemical protective clothing system (clo = 2.1; moisture permeability coefficient = 0.32; thermal resistance = 0.4 m²·K·W⁻¹). Wearing this clothing system ensured that the women exercised under conditions of uncompensable heat stress (24).

Once the volunteer was dressed, she sat on a chair that was placed on the treadmill for collection of resting data. The Tₑ was monitored during collection and it had to be stable ±0.1°C before exercise. Resting data were collected for 14 min. The volunteer stood at the end of the resting period, and the chair was removed from the treadmill. The treadmill was started (belt speed 1.34 m/s, grade 2%), and exercise began at minute 15. The subject worked until volitional exhaustion or until the investigators stopped the experiment because the subject had reached the safety limits of the tests. When the investigators stopped the test, it was either because heart rate exceeded 90% of maximal heart rate for 5 consecutive min or because heart rate exceeded 95% of maximal heart rate at any time. Work was done at ~225 W·m⁻². Tₑ, ventilated dew-point temperature of the upper arm, and local skin temperatures were measured twice each minute. Heart rate was measured every 5 min.

The Tₑ threshold for onset of sweating was determined by calculating the linear regression equation of Tₑ and mₛ as Tₑ began to increase at the beginning of exercise. Because the subjects sweated during rest, the Tₑ threshold for sweating was calculated for each individual by using the mₛ measured at rest.

Mean body temperature (T_b) was calculated as

\[ T_b = (0.9 \times Tₑ) + (0.1 \times Tₘₚ) \]

Serum E₂, progesterone, and LH concentrations were determined for each blood sample by commercially available radioimmunoassay kits (Coat-a-Count, Diagnostic Products, Los Angeles, CA). Samples were immediately processed, then quickly frozen, so that samples from each subject were run in the same assay (in duplicate) to avoid interassay variability.

Hormonal differences between the follicular and preovulatory experiments were determined by using paired Student’s t-tests. Differences between Tₑ, Tₘₚ and Tₘₚ, and local mₛ during exercise were determined by two-way analyses of variance (experimental time × menstrual cycle phase) with repeated measures. Differences in the resting Tₑ, Tₘₚ and Tₘₚ; the Tₑ threshold for sweating; local and whole-body sweating rates; and the slope of the mₛ/Tₑ relationship between menstrual cycle phases were also determined by using paired Student’s t-tests. The probability for each reported difference is indicated in RESULTS.

RESULTS

Post hoc verification for the timing of the E₂. The objective in studying the women in the preovulatory phase was reached for most of the subjects (4 of 6). For
for sweating was decreased (P ≤ 0.05) from 36.88 ± 0.27°C during F to 36.64 ± 0.35°C during Preov-2 (Table 2). Tesk during rest was decreased (P ≤ 0.05) during Preov-2 (34.91 ± 0.28°C) compared with F (35.32 ± 0.26°C, Table 2). Tc was significantly decreased during rest in the Preov-2 group (P ≤ 0.05). Figure 2 shows Tc during both rest and exercise for each subject for the two experiments. Tc for S4–S7 was obviously decreased during rest compared with the early follicular phase. During exercise, the difference in Tc between the two menstrual cycle phases was maintained in S5–S7. The Tc of S4 was decreased at the beginning of exercise, but there was a rapid increase in Tc due to an accelerated rate of increase in Tc. By 17 min of exercise, Tc during the preovulatory phase was equal to Tc during the early follicular phase in S4 (Fig. 2). Tc was measured by telemetry pill in this subject. The method of determining Tc may have been a factor in this rapid increase observed in the preovulatory phase, as we have previously observed a rapid change (decrease) in Tc measured by telemetry pill during rest when Tc was stable (21).

The m (mg·cm⁻²·min⁻¹), whole body sweating rate (g/min), and the slopes of the individual m/Tes linear regression equations were not significantly different between phases (Table 3). Heart rate was not different between experiments. For graphic demonstration, the mean linear regression lines (m/Tes) were plotted by using the mean sweating thresholds for each menstrual cycle phase as the origin of the regression lines (Fig. 3). The graph demonstrates that the Tes threshold for initiation of local sweating was significantly decreased in the preovulatory phase compared with the early follicular phase.

Progesterone and LH data are presented in Table 1. These data indicate that the LH surge had not occurred, and progesterone was not elevated in any of the subjects when the experiments were conducted.

**DISCUSSION**

The present study provides evidence that women have a decreased regulated body temperature during the preovulatory phase. The data to support this statement are 1) the decreased resting Tesk, 2) the decreased resting Tsk, 3) the decreased Tc during rest, and 4) the decreased Tes threshold for onset of sweating during exercise.

It is important to examine the individual data to assess whether E2 consistently played a causal role in the thermoregulatory responses. The transient characteristic of the preovulatory E2 surge must be kept in mind. During the preovulatory phase, the timing of when the E2 surge might occur for each subject was estimated. Ovulation was estimated as 14 days before the onset of menses (35) determined from the known normal length of the menstrual cycle for each woman. Based on this estimate, the preovulatory-phase experiment was scheduled 1 or 2 days before ovulation. Obviously, this method is not precise enough to predict the peak E2 perfectly, but it was effective in pinpointing preovulatory thermoregulatory responses for four of six subjects in this study. The corridor of the E2 surge
within the menstrual cycle is fairly narrow, and a 1-day difference could mean studying the woman when the surge was just beginning, ongoing, nearing completion, or just ending. This continuum might have been mapped for each woman if serial samples had been drawn every 20 min during the estimated time of the E2 surge. Given that the thermoregulatory experiments in the present study were constrained to a specific time of day

Table 3. Sweating responses for the individual subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Local Sweating Rate, mg·cm⁻²·min⁻¹</th>
<th>Slope (Local Sweating/Tₑₑ), mg·cm⁻²·min⁻¹°C⁻¹</th>
<th>Sweating Rate, g/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>1.08</td>
<td>1.68</td>
<td>20.0</td>
</tr>
<tr>
<td>S3</td>
<td>0.97</td>
<td>0.31</td>
<td>8.6</td>
</tr>
<tr>
<td>S4</td>
<td>0.38</td>
<td>3.03</td>
<td>11.5</td>
</tr>
<tr>
<td>S5</td>
<td>1.03</td>
<td>0.92</td>
<td>12.5</td>
</tr>
<tr>
<td>S6</td>
<td>0.69</td>
<td>1.67</td>
<td>14.3</td>
</tr>
<tr>
<td>S7</td>
<td>1.23</td>
<td>1.86</td>
<td>19.4</td>
</tr>
<tr>
<td>Mean (n = 4)</td>
<td>0.83</td>
<td>1.87</td>
<td>14.4</td>
</tr>
<tr>
<td>SD</td>
<td>0.38</td>
<td>0.87</td>
<td>3.5</td>
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</tbody>
</table>

Follicular

<table>
<thead>
<tr>
<th>Subject</th>
<th>Local Sweating Rate, mg·cm⁻²·min⁻¹</th>
<th>Slope (Local Sweating/Tₑₑ), mg·cm⁻²·min⁻¹°C⁻¹</th>
<th>Sweating Rate, g/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>0.03</td>
<td>1.43</td>
<td>13.7</td>
</tr>
<tr>
<td>S3</td>
<td>0.97</td>
<td>0.71</td>
<td>8.0</td>
</tr>
<tr>
<td>S4</td>
<td>0.46</td>
<td>1.53</td>
<td>9.0</td>
</tr>
<tr>
<td>S5</td>
<td>0.81</td>
<td>0.62</td>
<td>6.3</td>
</tr>
<tr>
<td>S6</td>
<td>0.79</td>
<td>1.22</td>
<td>13.7</td>
</tr>
<tr>
<td>S7</td>
<td>1.21</td>
<td>2.07</td>
<td>19.3</td>
</tr>
<tr>
<td>Mean (n = 4)</td>
<td>0.82</td>
<td>1.36</td>
<td>12.1</td>
</tr>
<tr>
<td>SD</td>
<td>0.31</td>
<td>0.61</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Preovulatory

Fig. 2. Mean body temperatures during follicular and preovulatory experiments for each subject (S1-S7; S2 not shown). Subjects rested for 14 min beginning at time 0. Exercise was initiated at minute 15.

Fig. 3. Mean esophageal temperature (Tₑₑ) thresholds for sweating during follicular and preovulatory experiments (S4-S7). Lines represent mean regression equation calculated from individual Tₑₑ and upper arm sweating rate data collected during transient period of exercise for each subject for each experiment.

Means ± SD are for S4–S7.
to avoid confounding the data by the circadian cycle (33) and the estimated time of 1–2 days preceding ovulation, it was recognized that the few hours of time for the experiment would not necessarily be coincident with the E2 peak or time of optimal effect on the target tissues. It might be expected that there is a fixed amount of time required between activation of estrogen receptors and completion of the cellular events leading to thermoregulatory adaptations. In addition, the cellular effects of increased E2 may be longer lasting than the E2 surge. Consequently, the individual thermoregulatory data were examined in light of the E2 data for each individual.

It was presumed that E2 had been increased for a long enough duration in the preovulatory phase to achieve thermoregulatory adaptations in four women (S4, S5, S6, S7; Fig. 1) because all were observed to have a decreased Tes and Tb at rest in addition to a decreased Tc threshold for sweating (Fig. 2 and Tables 1 and 2). These observations are consistent with the hypothesis that increased circulating endogenous E2 was associated with a decreased regulated Tb during the preovulatory phase of the menstrual cycle. Although two subjects (S1 and S3) responses were not characteristic of the group, their data do not refute the hypothesis and may provide clues about the timing of the thermoregulatory adaptation in relation to the E2 surge. In one case (S1), it might be presumed that the preovulatory experiment was done after the E2 surge had peaked and was on the lower portion of the descending limb of the surge. If the experiment were conducted ~1 day after E2 exposure, then the adaptations responsible for the decreased Tc threshold for onset of sweating and modest decrease in resting Tes may have persisted beyond the preovulatory E2 surge.

If the preovulatory experiment was conducted on S3 shortly after the initiation of the E2 surge, E2 activation of cellular adaptations within the target tissues may have just started. That would explain why there were no apparent changes in thermoregulation in this woman between the two cycle phases. The new observations reported here suggest that resting Tes and Tsk might be monitored under controlled ambient conditions to determine whether previous E2 conditioning had occurred.

There are several mechanisms of action that could cause the decreased regulated body temperature as a consequence of the preovulatory E2 surge. Increased concentration of E2 acts directly on hypothalamic tissue. Silva and Boulant (30) reported that hypothalamic tissue slices from male rats were sensitive to E2 and temperature. Central hypothalamic thermosensitivity was determined in neurons within the preoptic area by rapidly changing the temperature by 3–5°C. The usual characteristic response of warm-sensitive neurons to rapidly increasing temperature is increased firing rate, and the usual response to rapidly decreasing temperature is decreased firing rate (5). A large portion of the warm-sensitive neurons studied in these experiments were excited by the addition of E2 such that firing rate increased when the medium temperature was held constant at ~36°C (30). There were also a few temperature-insensitive neurons that responded to E2. It was suggested that E2, by its excitatory action on the firing rate of warm-sensitive neurons, may act directly at the preoptic area/anterior hypothalamus to enhance heat loss (30). In one neuronal model of thermoregulation (5), increased firing rate of warm-sensitive neurons would be consistent with a decreased Tset. This may be a mechanism by which the regulated body temperature is decreased in women during the preovulatory phase.

E2 was shown to affect thermoregulation in the rat. Baker et al. (1) reported greater evaporative water loss during heat exposure when E2 was implanted after ovariectomy than when there was no hormonal supplementation. This observation is consistent with the in vitro thermosensitivity research mentioned above and with our results showing the decreased Tset threshold for sweating in women during the preovulatory phase of the menstrual cycle. Sweating rate did not increase in the preovulatory phase in the present study, likely because of the clothing worn and uncompensable heat stress.

Another plausible mechanism by which body temperature is regulated at a lower temperature during the preovulatory phase is by the direct action of E2 on the vascular endothelium to increase cutaneous vasodilation. This peripheral action might be multifaceted, induced by both vasodilatory mechanisms (9, 10, 25), such as stimulation of nitric oxide or prostacyclin synthesis (12, 36), and inhibition of vasoconstrictor activity (9, 14, 36). This postulated effect of endogenous E2 on the cutaneous vasculature awaits experimental verification in premenopausal women.

It has been suggested that the relative ratio of progesterone to estrogen (P/E2) is an important determinant of Tc during the menstrual cycle and pregnancy (26). Estrogen antagonizes the thermogenic effect of injected progesterone in males if the estrogen is injected 2–3 days preceding progesterone injection (13). Cagnacci et al. (8) have recently corroborated that theory by showing that mean 24-h vaginal temperature was directly correlated (r = 0.731, P < 0.0001) to P/E2. This relationship was determined from the 24-h vaginal temperature, serum estradiol, and serum progesterone during the early follicular and luteal phases from normally ovulating women and during the early follicular, preovulatory, and luteal phases of women who were injected with FSH to induce multiple follicle development. The mean 24-h vaginal temperature (36.95°C) during the preovulatory phase (P/E2 = 1.5) was significantly less in the women injected with FSH than during the early follicular phase (37.14°C) when P/E2 averaged 17.7. In the present study, the hormonal and the Tc data show a similar relationship. In the early follicular phase, the Tc averaged 37.02°C when the average P/E2 was 11.9. In the preovulatory phase, the mean Tc was 36.76°C when the average P/E2 was 4.1.

Thermoregulatory effector mechanisms were not measured in the study by Cagnacci et al. (8), but the Tc and estradiol data are consistent with a decreased regulated body temperature during the preovulatory phase compared with the early follicular phase.
In summary, the present study provides support for the hypothesis that increased production of E2 in the preovulatory phase is associated with thermoregulatory responses that are consistent with a decreased regulated body temperature in women. The observations that the resting Tes, Tsk, and Tb and the Tes threshold for onset of sweating during exercise were decreased in women at the same relative time as the E2 surge occurred during the preovulatory phase support the hypothesis. Further support for this hypothesis awaits the determination that all thermoregulatory effectors exhibit a similar reduction in the Tc thresholds for initiation of effector response during the preovulatory phase.

We appreciate the contributions of the women who participated in this study. The technical assistance of J. Staab, L. Levine, B. Cadarette, Sgt B. Mail, and Dr. C. L. V. Gabareé is gratefully acknowledged. Several physicians served as medical monitors on this study, including Cpt R. Lipton, Ltc P. Rock, Ltc K. Reynolds, Cpt P. Boosalis, Maj P. Amoroso, Maj S. Lijamo, and Maj M. Reardon. We appreciate their effort on our behalf. Drs. G. Lindsley, R. R. Gonzalez, and M. N. Sawka provided helpful criticisms of the manuscript.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation. Human subjects participated in these studies after giving their free and informed consent. Investigators adhered to Army Regulation 70–25 and US Army Medical Research and Materiel Command Regulation 70–25 on the Use of Volunteers in Research.

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Received 6 April 1998; accepted in final form 17 September 1998.

REFERENCES


