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EFFECT OF ENDOGENOUS 17ß ESTRADIOL ON CORE TEMPERATURE AND SKIN BLOOD FLOW IN HEALTHY, EUMENORRHEIC WOMEN: A REPORT OF THREE STUDIES

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These studies were done to describe the pre-ovulatory phase core temperature decrease in healthy, eumenorrheic women as a change in the regulated body temperature set point. In Study 1, subjects walked at a moderate exercise intensity wearing personal protective equipment. In Study 2, the environment mimicked that under the PPE in the first study during cycle exercise when dressed in t-shirts and shorts. In Study 3, the environment from the first study was used while the subjects exercised on a cycle ergometer. PPE was not worn in this last study. Subjects in all studies showed a decrease in resting core temperature and elevated serum estradiol for the pre-ovulatory phase experiments. In all studies, subjects (n=4; n=3; n=5; respectively) were studied in the early follicular phase (EF, days 2-6) and in the pre-ovulatory phase (PO, days 8-12) of the menstrual cycle. Lower resting core temperature (esophageal) and elevated serum estradiol for the pre-ovulatory phase experiments were observed in all subjects. Taken together, the observations from the three studies support the theory that there is a decreased regulated body temperature during exercise in the pre-ovulatory phase of the menstrual cycle. This finding holds despite varying clothing, mode of exercise and environmental conditions.

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EXECUTIVE SUMMARY

These studies were done to describe the pre-ovulatory phase core temperature decrease in healthy, eumenorrheic women and associate this change in core temperature with alterations in temperature regulation that indicate the regulated body temperature was reset to a lower temperature. Specifically, sweating and/or cutaneous vasodilation were characterized during exercise-heat stress, although environmental conditions, exercise mode or clothing worn were different in each study. In the first study women walked at a moderate exercise intensity in conditions of uncompensable heat stress created by wearing personal protective equipment. In the second study the environmental conditions mimicked those at the skin (under the PPE) from the first study with the women doing cycle ergometer exercise dressed in t-shirts and shorts. In the third study the environmental conditions of the first study were used while the subjects exercised on a cycle ergometer. PPE was not worn in this last study. Subjects in all studies showed a decrease in resting core temperature and elevated serum estradiol for the pre-ovulatory phase experiments. In all studies, subjects (n=4; n=3; n=5; respectively) were studied in the early follicular phase (EF, days 2-6) and in the pre-ovulatory phase (PO, days 8-12) of the menstrual cycle. Lower resting core temperature (esophageal) and elevated serum estradiol for the pre-ovulatory phase experiments were observed in all subjects.

In study 1 the ambient temperature was set to 30°C and 30% rh. Estradiol concentration increased from 42±24 pg/ml (EF) to 123±31 pg/ml (PO); esophageal temperature was 37.02±0.20°C in EF and 36.76±0.28°C in PO; end exercise esophageal temperature was 38.37±0.26°C in EF compared to 38.04±0.52°C in PO ($p<0.05$). Exercise tolerance (40% peak aerobic power) was not different between early follicular experiments and pre-ovulatory experiments, both averaging 60 min. The esophageal temperature for sweating

onset was lower in PO experiments (EF: 36.88±0.27°C and PO: 36.64±0.35°C, $p<0.05$).

The environmental conditions in Study 2 were intentionally oppressive (38°C, 60% rh) to approximate the conditions at the skin under PPE observed in Study 1. Unfortunately, the combination of exercise intensity (40% peak aerobic power) and environmental conditions prevented detailed analysis of sweating and skin blood flow responses. However, core temperatures and serum estradiol concentrations were as expected and core temperature showed a similar pattern during the early follicular and pre-ovulatory phases as seen in Study 1. Exercise tolerance ranged from 20 to 60 minutes. The average resting esophageal temperature was 37.10±0.31°C in EF and 36.95±0.28°C during PO experiments ($p<0.05$). Serum estradiol was 44±20 ng/ml and 255±35 ng/ml in EF and PO experiments, respectively ($p<0.05$). End exercise esophageal temperature was 38.28±0.26°C in EF and 38.19±0.19°C during PO ($p<0.05$).

In Study 3, the ambient dry bulb temperature was 30°C and 30% rh. Resting esophageal temperature was 36.82±0.10°C during PO and 36.91±0.07°C in EF experiments ($p<0.05$). Serum estradiol was 30±5 ng/ml and 155±60 ng/ml in EF and PO experiments, respectively ($p<0.05$). During exercise (50% peak aerobic power), the T_{es} threshold for onset of forearm blood flow was at a lower esophageal temperature in the pre-ovulatory experiments (PO: 36.95 ± 0.16°C) than in the early follicular phase (EF: 37.06 ± 0.15°C, $p<0.01$). However, forearm blood flow was not different during exercise at any time between experiments. The T_{es} threshold for onset of forearm sweating was at a lower esophageal temperature in the pre-ovulatory experiments (PO: 36.95 ± 0.14°C) than in the early follicular phase (EF: 37.14 ± 0.08°C, $p<0.05$).

Taken together, the observations from the three studies support the theory that there is a decreased regulated body temperature during exercise in the pre-ovulatory phase of the menstrual cycle. This finding holds despite varying

clothing, mode of exercise and environmental conditions. Both initiation of sweating and cutaneous vasodilation occur at a decreased T_{es} threshold during exercise showing that active temperature regulation occurs during exercise to maintain the lower core temperature during the pre-ovulatory phase of the menstrual cycle.

Female soldiers have been and will continue to be deployed to geographical areas that cause substantial heat strain. Knowledge of the varied responses of women to the heat stress incurred by these locations will aid in the prevention of possible heat injury. Thermoregulatory control of sensible (dry) and evaporative heat loss is altered during the menstrual cycle. Continued research is necessary to determine if the changes observed alter (improve or impair) the risk for heat injury in female soldiers.

INTRODUCTION

Scientific Background

The reproductive endocrines influence thermoregulation in women, as core temperature is regulated at a higher temperature during the mid-luteal phase compared to the early-follicular phase of the menstrual cycle, and core temperature appears to be regulated at a lower core temperature in the late-follicular or pre-ovulatory phase compared to the early-follicular phase of the menstrual cycle. Co-incident with changes in the regulated resting core temperature was altered sweating onset (22).

A transient decrease in core temperature before ovulation occurs when circulating estradiol is starting to increase (1;3;5;11). The two events are probably related as intradermal estradiol injection decreased core temperature (5). That said, there are conflicting results regarding estrogen replacement therapy and the regulation of core temperature (2;17;23). However, recent data from our laboratory (22) and a study of postmenopausal women (23) suggest the elevation of circulating estradiol in eumenorrheic women and supplemental estrogen in postmenopausal women resets the brain's set-point to lower core temperature. These experiments suggest that core temperature is regulated at a lower temperature during the pre-ovulatory phase of the human menstrual cycle. Further support for this hypothesis awaited determination that all thermoregulatory effectors exhibit a similar reduction in the core temperature thresholds for initiation of effector response during the 17ß-estradiol surge. Additional studies were needed to show that thermoregulatory effector functions other than sweating are similarly affected by increased endogenous 17ß-estradiol in order to fully substantiate the hypothesis.

Purpose

The purpose of the three studies was to verify that the decreased core temperature observed during the pre-ovulatory phase in eumenorrheic women is a

transient event associated with increased circulating estradiol. Further, the thermoregulatory studies conducted provided evidence that this decreased core temperature was defended or regulated. Finally, alterations in the thermoregulatory effectors that control heat loss were examined during the phase when circulating estradiol was elevated to fully ascertain its association on temperature regulation.

Military Relevance

Increasing numbers of active duty and reserve populations are female. Women comprise approximately 15% of the U.S. Army and constitute a substantial part of units deployed for peace keeping and humanitarian aid missions. During Operation Desert Shield/Storm there were over forty thousand female service members deployed. These recent military actions have highlighted unique medical and health issues for female service members.

These studies were done under USAMCMR STO 3.T (Environmental Injury - Demonstrate The Efficacy Of Strategies To Prevent And Treat Environmental Illnesses, Injuries And Performance), specifically Task A "Study mechanisms controlling active cutaneous vasodilation for thermoregulation in humans: Impact of neural, hormonal and endothelial factors in regional cutaneous vasodilation". An objective of STO 3.T is to reduce the incidence of environmental injury to soldiers during mission performance.

This series of experiments provided scientific information regarding women exposed to exercise and/or stressful environmental conditions. Female soldiers are deployed to geographical areas causing substantial physiological heat strain. The thermal responses in women were characterized during the combined severe stressors of exercise, environment and/or a restrictive clothing system in two menstrual cycle phases. These experiments required specific control for menstrual cycle phase to understand and account for the interaction of multiple regulatory systems (reproductive cycle, fluid volume regulation, and thermoregulation) during severe heat stress in the

human female. Understanding the varied responses of women to heat stress aids in the prevention of possible heat injury.

Three USARIEM Protocols were done: "Thermoregulation in women during exercise wearing chemical protective clothing", *Approved December 1992*; "Skin blood flow and thermoregulatory sweating in women during exercise in a simulated micro-environment of chemical protective clothing", *Approved February 1994;* "Maximal skin blood flow in women: Effect of endogenous reproductive steroids on percentage of maximal skin blood flow during exercise" *Approved September 1996.*

METHODS

General Procedures

After being apprised of the potential risks, 12 women volunteered to participate in the experiments (Study 1, Study 2 or Study 3; Table 1). Each subject (in each specific study) was tested during a period of low serum 17ß estradiol (early follicular phase, EF) and during a period of high serum 17ß estradiol (late follicular phase, pre-ovulatory phase, PO). This required a normal menstrual cycle defined by regular periodicity and no oral contraceptive use. Daily basal body temperature (BBT) was measured and used to predict test days in a subsequent menstrual cycle. Testing in the follicular phase was done on days 2-6 (day 1 = first day of menstrual flow) and in the late follicular phase (days 8-12). Subjects fasted overnight, and refrained from drinking alcohol 24 h prior to an experiment. Water ingestion was permitted until the experiment started. The time of experiments was approximately the same time of day for each subject for all experiments (starting between 0700-0730 h) to control for circadian differences in skin blood flow and thermoregulation. Upon arriving at the laboratory each morning, a 10 ml blood sample was taken for the measurement of estradiol (RIA,

Diagnostics Products Corporation) to accurately (post hoc) define the early follicular and pre-ovulatory menstrual cycle phases.

Table 1. Summary of the three studies.

Study Conditions	Measurements Made
Study 1	
Ambient Conditions: 30°C, 30% rh	Core and surface temperatures
Treadmill Exercise:	Heart rate
40% peak aerobic power	Whole body sweating rate
PPE worn	Local sweating responses
	Tolerance time
Study 2	Core and surface temperatures
Ambient Conditions: 38°C, 60% rh	Heart rate
Cycle Exercise:	Local sweating responses
40% peak aerobic power	Cutaneous blood flow responses
Singlet and shorts worn	Tolerance time
Study 3	
Ambient Conditions: 30°C, 30% rh	Core and surface temperatures
Cycle Exercise:	Heart rate
50% peak aerobic power	Local sweating responses
Singlet and shorts worn	Cutaneous blood flow responses

Study 1

This protocol was conducted to characterize the interaction between menstrual cycle phase, exercise and clothing (with high thermal resistance) during treadmill exercise. Four women participated in these experiments after giving their informed consent. Their average (±SD) age was 25.3±9.6 yr., height 1.68±0.05 m., mass 63.0±11.0 kg, BMI (body mass index, kg/m^2) 22±3, and maximal aerobic power 2.66±0.30 $L \cdot min^{-1}$. Subjects swallowed a thermistor probe for esophageal temperature measurement (T_{es}) and surface thermocouples were placed at eight sites (area

weighted) to estimate mean skin temperature (T_{sk}, (15)). Each subject dressed in standard military clothing covered by a chemical protective clothing ensemble (PPE; jacket, trousers, hood, mask, over-boots and gloves) with high resistance to heat transfer. Whole body sweating was determined as the change in body weight from pre- to post-exercise. Oxygen utilization was measured during treadmill exercise by an automated method (SensorMedics™). Heart rate was measured from the ECG. Local sweating rate on the arm was measured with a ventilated dew-point sensor (7). After equilibration with the environment (15-30 min), exercise (for up to 75 minutes) at 40% of maximal aerobic power began. T_{es} , T_{sk} and local sweating rate were measured every 30 seconds. Heart rate was measured every 5 minutes. Ambient temperature was set to 30°C, at an ambient water vapor pressure of 10 Torr (30% rh).

Study 2

In this study, we tried to characterize differences in the control of skin blood flow and local sweating rate in the same environmental conditions as the micro-environment under the chemical protective clothing in Study 1, as it was impossible to measure skin blood flow under chemical protective clothing during exercise in Study 1. Three women participated after giving their informed consent. Their average age was 37±6 years, mass 67.2±4.5 kg, height 1.65±0.08 m, and BMI 24±2 (body mass index, kg/m^2). Prior to actual testing, each individual's peak aerobic power was assessed while cycling (modified seated ergometer) in a temperate environment. Peak aerobic power averaged 2.35±0.20 $L \cdot min^{-1}$. From this test the relative exercise intensity for each woman was calculated and used on both test days. An esophageal thermistor probe was used for core temperature measurement (see Study 1 for details). Surface thermocouples were placed at eight sites to estimate mean skin temperature (15). Perfusion of the skin of the forearm and the chest, used as an index of skin blood flow (SkBF), was estimated by laser doppler velocimetry (Transonic Instruments). Laser probe placement was similar for both experiments for each subject. Whole body

sweating was determined as the change in body weight from pre- to post-exercise. Local sweating rate on the arm was measured with a ventilated dew-point sensor described above. Heart rate was measured from the ECG. Subjects wore running shorts, shoes, socks, singlet and underwear. Ambient temperature was set to 38°C with dewpoint temperature set to 30°C (60% rh). A 15-minute rest period was followed by moderate cycle exercise (40% peak aerobic power) for up to 60 minutes.

Study 3

Differences in the control of skin blood flow and local sweating rate were examined during cycle ergometer exercise in this study in the same ambient conditions of Study 1. The third study was done because the ambient conditions in Study 2 were oppressive enough to limit exercise time in one subject. Five healthy, eumenorrheic women participated in the study following informed consent. Their average age was 35±9 years, height 1.68±0.04 m, mass 66.9±5.8 kg, and BMI 24±2 (body mass index, kg/m^2). Prior to actual testing, each individual's peak aerobic power was assessed while cycling (modified seated ergometer) in a temperate environment. Peak aerobic power averaged 2.30±0.25 $L \cdot min^{-1}$. Relative exercise intensity was calculated from peak aerobic power for each woman and used on both test days, thus ensuring similar conditions for each subject (i.e. a similar increase in T_{es}).

Subjects entered the environmental test chamber dressed in shorts, singlet, shoes, socks and underwear. The ambient dry bulb temperature was 30°C and the ambient dew-point temperature was 12°C (30% rh). Electrocardiographic leads were attached to the torso. A thermocouple encapsulated in waterproof insulation was swallowed for the measurement of esophageal temperature (T_{es}). Subjects were weighed and then sat on the chair of the modified cycle ergometer. Thermocouples (copper-constantan) were attached to the skin at eight sites. A mercury-in-silastic strain gauge was placed on the forearm for the measurement of forearm blood flow (FBF) by venous occlusion

plethysmography (6;24). The strain gauge was placed around a section of forearm distal to the main mass of the muscles to decrease the proportion of muscle in the whole arm cylinder measured. The forearm was suspended at the wrist with a sling apparatus anchored at two points to minimize movement artifact. The strain gauge was positioned on the arm near the height of the heart. Perfusion of the skin of the forearm, also used as an index of skin blood flow (SkBF), was estimated by laser-Doppler flowmetry (Vasamedics Laserflo BPM^2; 2.0 mW at 760-800 nm). Briefly, the Vasamedics Laserflo BPM^2 presents "flow" (calculated by a patented algorithm) proportional to the mean frequency of the red blood cells multiplied by the mean number of Doppler shifts per photon. An automatic blood pressure monitor (Datascope, Inc., Paramus NJ) was used to determine systolic and diastolic blood pressure.

After all instruments were attached to the subject, a 15-minute control period was started. Esophageal and skin temperatures, forearm blood flow, skin blood flow, and local sweating rate were measured every 0.5 min, and arterial blood pressure and heart rate were measured every 5 min. Subjects exercised for 30 min at 50% peak aerobic power during which time the temperature, blood flow and heart rate measurements were made at the same time intervals as during rest. Blood pressure was measured every 2.5 min. Exercise ended after 30 min and subjects recovered for five minutes. After the experiment, the subject was weighed.

Data Analyses.

Physiologic responses for each study were analyzed by two-way analysis of variance between menstrual cycle phases. T tests were done to compare data between groups when time was not an included factor. Specifically, paired T tests were done to compare change in esophageal temperature and estradiol concentration at rest. Significant differences were accepted as $\alpha = 0.05$. Data were not compared between Study 1, Study 2 and Study 3.

RESULTS AND DISCUSSION

These studies were done to describe the pre-ovulatory phase core temperature decrease in healthy, eumenorrheic women and associate this change in core temperature with alterations in temperature regulation that indicate the regulated body temperature was reset to a lower temperature. Specifically, sweating and/or cutaneous vasodilation were characterized during exercise-heat stress, although environmental conditions, exercise mode or clothing worn were different in each study. In the first study women walked at a moderate exercise intensity in conditions of uncompensable heat stress created by wearing personal protective equipment. In the second study the environmental conditions mimicked those at the skin (under the PPE) from the first study with the women doing cycle ergometer exercise dressed in t-shirts and shorts. In the third study the environmental conditions of the first study were used while the subjects exercised on a cycle ergometer. PPE was not worn in this last study. Subjects in all studies showed a decrease in resting core temperature and elevated serum estradiol for the pre-ovulatory phase experiments.

Study 1

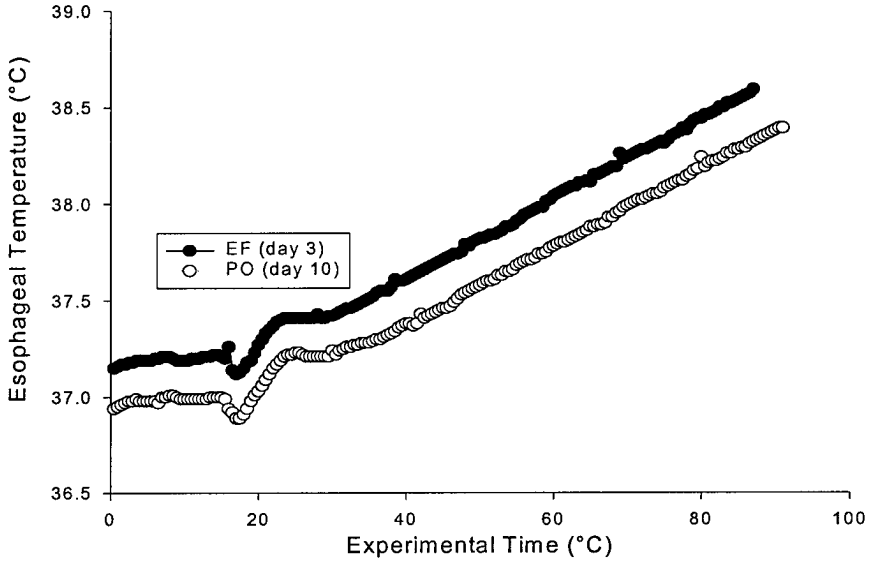
Core and skin temperatures, heart rate, metabolic rate and sweating rate during the first half of the human menstrual cycle were measured. Experiments were run (during two distinct hormonal profiles) under extremely severe conditions created by a combination of exercise intensity, clothing with a high thermal resistance and low evaporative capacity, and warm environmental conditions. This combination caused core temperature to increase ~1.4°C during exercise as skin temperature remained above 36.0°C and heart rate approached 170 beats per minute. Although significant differences in core temperature were observed at rest and during exercise in each menstrual cycle phase studied, the change in esophageal temperature during exercise and exercise time were not affected by menstrual cycle phase. End exercise

esophageal temperature was 38.37+0.26°C in EF compared to 38.04+0.52°C in PO ($p<0.05$). Exercise tolerance was not different between early follicular experiments and late follicular experiments, averaging 60 min.

Estradiol concentration increased from 42±24 pg/ml (EF) to 123±31 pg/ml (PO) and resting esophageal temperature was 37.02+0.20°C in EF and 36.76±0.28°C in PO ($p<0.05$). The esophageal temperature for sweating onset was lower in PO experiments compared to EF experiments (36.64+0.35°C and 36.88+0.27°C, $p<0.05$). A representative esophageal pattern during exercise for early follicular and pre-ovulatory experiments is shown in Figure 1.

The environmental conditions imposed limited dry heat flux between the skin and the clothing, and limited dry heat flux through the clothing. The relatively non-porous clothing worn resisted transmission of water vapor and prevented significant evaporative heat loss. Whole body sweating averaged 14.4±4.5 g/min (~0.9 L/h) in EF and 11.7±4.8 g/min (~0.7 L/h) in PO, but only part of this water evaporated.

Figure 1

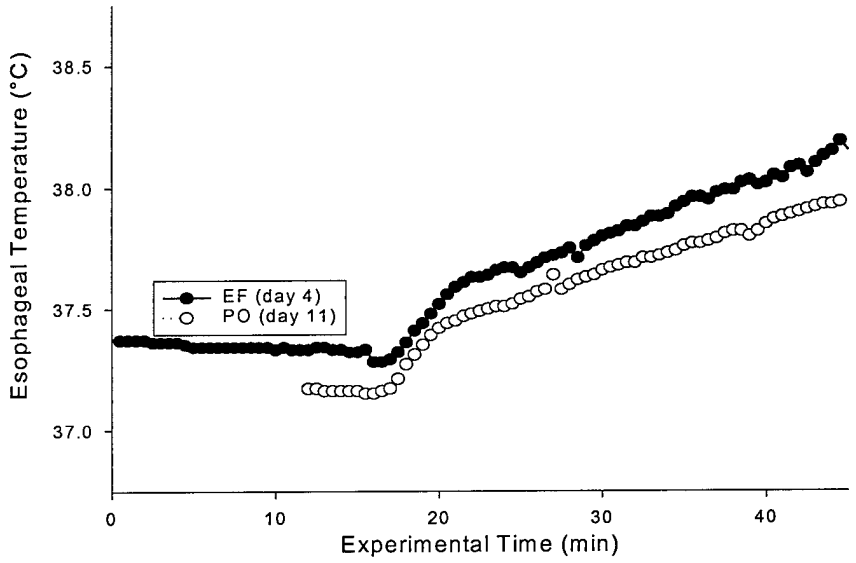


The changing hormonal environment in the PO phase was associated with changes in regulated body temperature. These experiments were ended when a subject reached physiologic limits (high heart rate and/or high internal temperature) set *a priori* and the investigative staff stopped the experiments. Whether heat tolerance may have been different between the menstrual cycle phases if exercise continued beyond this point cannot be answered because data collection was limited by the experimental design.

Study 2

Exercise time was variable between subjects and ranged from 20 to 60 minutes because the environmental conditions were oppressive and subject's thermal tolerance varied greatly. Estradiol concentration was 44±20 pg/ml (EF) and 255±35 pg/ml (PO; $p<0.05$). Resting esophageal temperature was 0.15°C lower during PO than EF experiments ($p<0.05$). End exercise esophageal temperature was 38.28 ± 0.26°C in EF and 38.19 ± 0.19°C in PO. The esophageal temperature for forearm blood flow onset was 0.12°C lower in the PO experiments. This supports the theory that the hypothalamic set point may be lower in the PO phase, indicated by the lowered esophageal threshold for sweating onset in Study 1, because another effector, skin vasodilation responded similarly. The combination of exercise intensity and environmental conditions prevented detailed analysis of sweating as subjects were sweating and the skin surface was fully wet with sweat at rest. Whole body sweating averaged 9.7 ± 4.7 g/min in EF and 12.3 ± 2.3 g/min in PO. Little of the secreted sweat evaporated due to the unfavorable water vapor pressure gradient between the skin and the ambient air. A typical core temperature pattern is shown in Figure 2. The large cutaneous blood volume at rest (high skin temperature and skin blood flow) further complicated complete analysis of skin blood flow characteristics between experiments. This high cutaneous blood volume likely contributed to the lack of the characteristic decrease in esophageal temperature at the beginning of exercise.

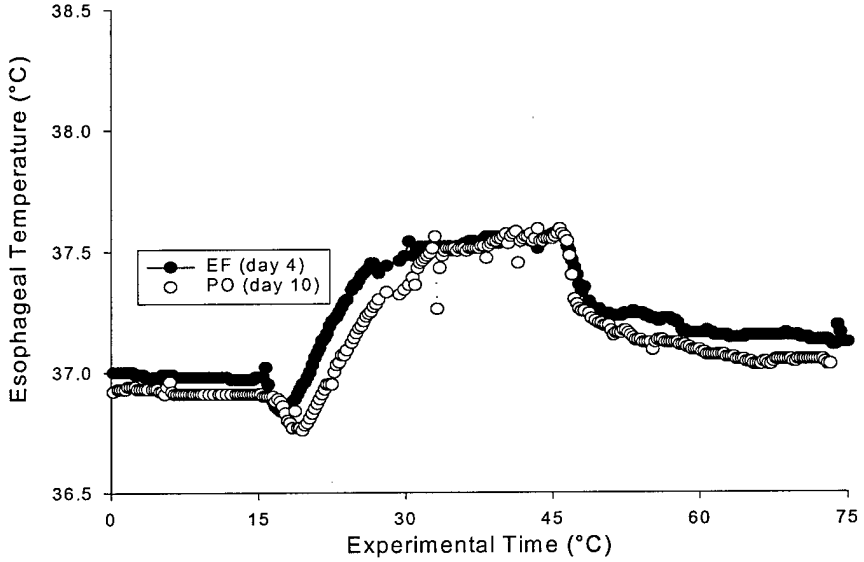
Figure 2



Study 3

Resting esophageal temperature was 0.10°C lower during PO than EF experiments ($p<0.05$). Serum estradiol was 30±5 pg/ml and 155±60 pg/ml in EF and PO experiments, respectively ($p<0.05$). During exercise, the onset for forearm blood flow was at a lower esophageal temperature in the pre-ovulatory experiments (36.95 ± 0.16 vs. 37.06 ± 0.15, $p<0.01$) confirming the observations from Study 2 under less stressful environmental conditions. Forearm blood flow was not different between experiments at any time during exercise. The onset of forearm sweating was at a lower esophageal temperature in PO experiments. These observations support the idea that regulated body temperature is lower during the pre-ovulatory estradiol surge. Figure 3 shows the response of an individual subject during exercise in the heat. This study provided the best set of environmental conditions and exercise intensity to thoroughly evaluate thermoregulatory changes associated with pre-ovulatory estradiol.

Figure 3



General Findings

The thermal responses in women were characterized during two menstrual cycle phases using several combinations of exercise, environment and/or restrictive clothing as stressors. The findings add additional support to our preliminary data from which it was concluded that increased production of 17ß-estradiol in the pre-ovulatory phase is tightly associated with thermoregulatory responses and are consistent with the hypothesis that 17ß estradiol is associated with a decreased hypothalamic set-point temperature or regulated body temperature in women (22). The observations that resting esophageal temperature and the esophageal temperature threshold for onset of sweating and/or cutaneous dilation during exercise were decreased in women at the same relative time as the 17ß-estradiol surge during the pre-ovulatory phase support the hypothesis.

Mean (±SD) subject data for the three studies are summarized in Tables 2 through 6 below.

Table 2. Study 1: Mean (+SD) resting core temperature (°C), resting mean skin temperature (°C), and core temperature at sweating onset (°C) during the early follicular phase (EF) and the pre-ovulatory (PO) phase of the menstrual cycle.

Condition	T_C (°C)	T_{sk} (°C)	T_C (°C) onset
EF	37.02 (0.20)	35.32 (0.26)	36.88 (0.27)
PO	36.76 (0.28)	34.91 (0.28)	36.64 (0.35)

PO core temperature is significantly lower than EF ($p<0.05$). The esophageal temperature for the onset of regulatory sweating is significantly lower in EF ($p<0.05$).

Table 3. Study 1: Mean (+SD) end exercise core temperature (°C), mean skin temperature (°C), heart rate (bpm), and whole body sweating rate (g/min) during the early follicular phase (EF) and the pre-ovulatory (PO) phase of the menstrual cycle.

Condition	T_C (°C)	T_{sk} (°C)	Heart rate	Sweating
EF	38.37 (0.26)	36.58 (0.08)	170 (11)	13.2 (4.3)
PO	38.04 (0.52)	36.54 (0.52)	171 (14)	13.4 (4.3)

PO end exercise esophageal temperature is significantly lower than EF core temperature ($p<0.05$).

Table 4. Study 2: Mean (+SD) end exercise mean skin temperature (°C), core temperature (°C), whole body sweating rate (g/min) and heart rate (bpm) during the early follicular phase (EF) and the pre-ovulatory (PO) phase of the menstrual cycle.

Condition	T_{sk} (°C)	T_C (°C)	Sweating	HR
EF	36.63 (0.28)	38.28 (0.26)	9.7 (4.7)	158 (3)
PO	36.59 (0.05)	38.19 (0.19)	12.3 (2.3)	155 (11)

PO end exercise esophageal temperature is significantly lower than EF core temperature ($p<0.05$).

Table 5. Study 3: Mean (+SD) resting core temperature (°C), resting mean skin temperature (°C), and core temperature at vasodilation onset (°C) and core temperature at sweating onset during the early follicular phase (EF) and the pre-ovulatory (PO) phase of the menstrual cycle.

Condition	T_C (°C)	T_{sk} (°C)	T_C (°C) onset	m_s onset °C
EF	36.90 (0.08)	33.72 (0.29)	37.07 (0.13)	37.14 (0.08)
PO	36.81 (0.10)	33.76 (0.28)	36.95 (0.16)	36.95 (0.14)

PO resting esophageal temperature and onset esophageal temperature for cutaneous vasodilation and sweating are significantly lower than EF ($p<0.05$).

Table 6. Study 3: Mean (+SD) end exercise (30 minutes) core temperature (°C), mean skin temperature (°C), heart rate (bpm), and whole body sweating rate (g/min) during the early follicular phase (EF) and the pre-ovulatory (PO) phase of the menstrual cycle.

Condition	T_C (°C)	T_{sk} (°C)	Heart rate	Sweating
EF	37.41 (0.16)	33.27 (0.86)	125 (15)	10.7 (1.5)
PO	37.38 (0.12)	33.23 (0.91)	129 (11)	10.7 (1.5)

There were no differences between EF and PO end exercise data.

Some observations are consistent among the three studies: 1) Resting esophageal temperature is lower when circulating estradiol is elevated in the pre-ovulatory phase; 2) The lower esophageal temperature is regulated by appropriate heat loss mechanisms; and 3) Heat loss and/or heat storage were not affected by elevated circulating estradiol in the current studies. However, in each of the three separate studies, subjects discontinued exercise at a designated time or when physiological responses set *a priori* were exceeded. Studies 1 and 2 may have provided some evidence of altered thermal tolerance if subjects were allowed to proceed until volitional exhaustion. However, the rate of heat storage (increased esophageal temperature per minute; from Figures 1-3), or the absolute change in esophageal temperature in any pair of experiments (a single subject in EF and PO) in each of the studies was not different in EF or PO experiments. Esophageal temperature was generally lower at any time at rest or during exercise in PO experiments when circulating estradiol was higher. This finding may mean that higher tolerance to a given exercise-heat exposure might occur during PO, but this remained speculative due to the conditions and design of the current set of studies.

We studied the influence of endogenous estradiol (the 17ß estradiol surge before ovulation) during exercise and heat exposures in healthy, eumenorrheic women. The

environmental (micro- or macro-environment) stress delivered in Studies 1 and 2 was significant to increase esophageal temperature by 1.2 to 1.4°C in forty to sixty minutes. In Study 1, the clothing barrier prevented both evaporative and convective heat loss, and in Study 2 the ambient conditions were designed to minimize evaporative or convective heat loss. Differences in thermoregulatory control between the menstrual cycle phases studied were still observed in spite of these design constraints.

The findings of the current studies are contradictory to conclusions made from one study when estradiol was given exogenously to women. Chang and colleagues administered high dose exogenous estradiol to healthy women in the mid- to late follicular phase of the menstrual cycle to facilitate heat loss and lower core temperature during exercise in a moderate environment (4). Those experiments were designed to mimic the high serum 17ß estradiol levels observed in the pre-ovulatory phase seen in eumenorrheic women. 17ß estradiol supplementation increased circulating 17ß estradiol concentration, but did not affect core temperature at rest or during exercise between two groups of healthy women. This finding may have been due to the fact that circulating 17ß estradiol levels far exceeded "normal" pre-ovulatory levels. Exogenous 17ß estradiol supplementation in eumenorrheic women may be problematic because the intact hypophyseal-hypothalamic-ovarian axis may be acting to counteract the exogenous medication. The use of exogenous 17ß estradiol supplementation over a short period without the synchronization of follicle stimulating hormone and luteinizing hormone timing (pulsatility and dose) may not have the same effect as occurs in eumenorrheic women. Alternately, a pharmacological dose of 17ß estradiol may not affect resting core temperature. The use of independent groups for comparisons may have further complicated the findings of that study. Perhaps a repeated measurement design may have teased out the 17ß estradiol influence on core temperature.

Exogenous hormonal treatment does provide useful information about how temperature regulation is affected. Historically (3;5), basal body temperature recordings

indicated that the pre-ovulatory decrease in resting core temperature was not observed in all women. Both the narrow corridor in which the 17ß-estradiol surge occurs, as well as some instances of anovulatory menstrual cycles, adequately explained why only about 50% of the basal body temperature profiles from one study (5) that showed the pre-ovulatory decrease in core temperature. Injection of estrogenic substances, in some cases, was associated with decreased core temperature a day or two after the injections began (1). Transdermal estrogen administration to postmenopausal women led to a greater decrease in resting core temperature after opiodergic blockade than in postmenopausal women who did not receive estrogen (2). Estrogen replacement therapy decreased resting core temperature and the threshold core temperatures for sweating and cutaneous vasodilation during exercise in postmenopausal women (23). The evidence and studies cited above support the hypothesis that regulated body temperature is altered by 17ß-estradiol or some factor(s) associated with it.

Summary

During the menstrual cycle, body temperature is regulated at several different set-point temperatures depending on menstrual cycle phase. In previous studies we have documented that regulated body temperature is increased by 0.3-0.5°C in the luteal phase compared to early follicular phase (8-10;12-14;20). Along with the increased regulated body temperature is a reduced plasma volume amounting to about 200 ml of plasma (21). Despite these luteal phase adaptations, it appears that for short duration exercise, women are no more susceptible to heat injury in the luteal phase compared to the early follicular phase. There is however one report that core temperature failed to equilibrate during the luteal phase during longer duration work (16). Yet, there are no published incidences of temperature regulation failure in women exercising during the luteal phase in laboratory experiments. It may be that fluid volume is controlled advantageously in women during the luteal phase by the reproductive

endocrines, estradiol and progesterone (18;19), thus preventing compromised thermoregulation.

Thermoregulation in women has not been thoroughly studied during menstrual cycle phases other than early follicular and mid-luteal phases. During the pre-ovulatory phase, we (22) initially reported that regulated body temperature might be decreased when circulating estradiol was near its peak in eumenorrheic women. Increased 17ß estradiol given exogenously may be linked to increase plasma volume in women. Therefore, we reasoned that the pre-ovulatory phase has potentially two protective mechanisms to prevent heat injury in that regulated body temperature is decreased by ~0.2°C and plasma volume is slightly increased (~200 ml). These two factors are scintillatingly similar to the temperature regulation adaptations that occur during acclimatization to heat. Heat acclimation affords improved temperature regulation in part due to a slightly increased plasma volume and better defense of the circulating fluid volume. The plasma volume expansion is fairly small, less that 500 ml. Yet, heat acclimation results in a lower core temperature for a given amount of work done.

The previous evidence to support the conclusion that body temperature is regulated at a lower temperature during the pre-ovulatory phase was for sweating only, and not for all thermoregulatory effector mechanisms. Before it could be concluded that women in the pre-ovulatory phase are better adapted to dissipate heat and thereby have reduced incidence of heat injury, the conclusion that the regulated body temperature is decreased had to be nailed down. The additional experiments described in this report were done to verify that both sweating and cutaneous vascular responses during exercise indicate that body temperature is regulated at a lower temperature in women during the pre-ovulatory phase.

CONCLUSIONS

Taken together, the observations from the three studies support the hypothesis that body temperature is regulated at a lower temperature during the pre-ovulatory phase of the menstrual cycle in healthy, eumenorrheic women. It has been suggested that estrogen supplementation might increase heat tolerance in women, and that women in the pre-ovulatory phase might be better adapted to dissipate heat and thereby have reduced incidence of heat injury. It is apparent from the current studies that the regulated body temperature is decreased during the pre-ovulatory estrogen elevation. However, the suggestion that heat tolerance might be enhanced in women during the pre-ovulatory phase or during exogenous estrogen supplementation requires further evaluation.

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