Is core temperature the trigger of a menopausal hot flush?

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SHORT TITLE: core temperature does not induce a hot flush

CONFLICT OF INTEREST: None

DISCLAIMERS: None

FIGURES: 3 **TABLES: 1**

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Abstract

OBJECTIVE: Menopausal hot flushes negatively impact quality of life and may be a biomarker of cardiovascular and metabolic disease risk; therefore understanding the physiology of hot flushes is important. Current thinking is that a small elevation (~0.03-0.05^{o}C) in core temperature surpasses a sweating threshold (that is reduced in the menopause), sweating is activated, and a hot flush ensues. Nevertheless, more recent studies examining thermoregulatory control question whether core temperature *per se* can explain the trigger for a hot flush. The primary aim of this study was to assess the contribution of increases in core temperature on the occurrence of menopausal hot flushes.

METHODS: For this purpose, 108 hot flushes were objectively assessed in a laboratory setting in 72 symptomatic postmenopausal women (aged 45.8±5.1 yrs; BMI 25.9±4.5 kg/m^{2}) from 5 previously reported studies. Women rested, wearing a tube lined suit (or trousers) which was perfused with 34^{o}C water. A subset then underwent mild heat stress (48°C water). Sweat rate, skin blood flow, blood pressure, heart rate, skin and core temperature were measured continuously throughout. A hot flush was objectively identified during rest (spontaneous hot flush) or mild heating as an abrupt increase in sternal sweat rate. Further, a subset of symptomatic post- (n=22) underwent whole-body passive heating for 60 mins to identify core temperature thresholds and sensitivities for sweat rate and cutaneous vasodilation, which were compared to a subset of pre-menopausal women (n=18). Data were analysed using t-tests and/or general linear modelling, and are presented as mean (95% CI).

RESULTS: In the 20 mins prior to a spontaneous hot flush, core temperature increased by 0.03±0.12^{o}C ($P<0.05$), but only 51% of hot flushes were preceded by an increase in core temperature. During mild heating, 76% of hot flushes were preceded by an increase in core temperature. The temperature thresholds for sweating were similar but the vasodilatory threshold was higher in post-menopausal compared to pre-menopausal women (37.1±0.2 vs. 36.8 ±0.3°C, $P = 0.06$).

CONCLUSION: We provide new evidence that menopausal hot flushes are unlikely triggered by an increase in core temperature. These findings provide important information about the physiology of hot flushes that have implications for treatment and management options for menopausal hot flushes.

Key words: menopause, hot flush, thermoregulation, core temperature

Introduction

The vast majority of women experience hot flushes during the menopause [1], which cause significant reductions in quality of life [2, 3] and increase the risk of metabolic and cardiovascular disease [4, 5]. Therefore, understanding the physiology of hot flushes in symptomatic women is important. Hot flushes are characterized by subjective feelings of intense heat as well as peripheral vasodilation [6] and are physiologically defined as increases in chest sweating (>0.002 $mg \cdot cm^{-2} \cdot min^{-1}$ per second) or sternal skin conductance (>2 μmho/30 seconds). Nevertheless, the trigger for the onset of a hot flush is not fully established. Alterations in the thermoregulatory [7] and sympathetic nervous systems [8] have been implicated as triggers for a hot flush, as have changes in neurotransmitters in the brain [9, 10].

Freedman (1995) proposed that hot flushes are triggered by small increases in core temperature, ranging from 0.03-0.05°C. This conclusion was based on both laboratory and ambulatory studies [11, 12] of continuously measured core temperature and sternal skin conductance in post-menopausal females. For example, in one study 65% of hot flushes in 8 women during sleep were preceded by an increase in core temperature of ~0.035°C within a 30 min window preceding the hot flush event [13]. In a subsequent study they reported that symptomatic post-menopausal women (i.e., those that experience frequent hot flushes) display a reduced core temperature range between the onset of shivering and sweating, when compared to asymptomatic women (i.e., no flushes) [14]. This narrower core temperature range was primarily characterised by a lower core temperature threshold for the onset of sweating, but it is currently unknown if such temperature thresholds change during the menopause, e.g., relative to pre-menopausal women. Taken together, these findings suggested that when an increase in core temperature surpasses the lowered sweating threshold, sweating is activated and a hot flush will ensue.

The notion that a hot flush is triggered by an increase in core temperature exceeding the sweating threshold persists despite later findings from the same group that reported; (i) natural fluctuations in core temperature across a 24 hr period that are similar in symptomatic and non-symptomatic women [15]; (ii) symptomatic women can and frequently do have increases in core temperature of similar magnitude (i.e., 0.035 ^{o}C) that do not trigger a thermoregulatory response and/or a hot flush [15]; and (iii) no change in hypothalamic activity (as a marker of change in core temperature), via functional magnetic resonance imaging, prior to and during a hot flush [16]. When taken together, it is possible that increases in core temperature *per se* do not accurately explain the trigger for a hot flush. This information is important given that the current understanding regarding increases in core temperature triggering hot flushes has contributed to recommendations for post-menopausal women to avoid situations of environmental heat stress, including to dress appropriately, and to avoid exercise, as advocated in recent guidelines (North American Menopause Society) [17]. Therefore, the primary aim of this study was to assess the contribution of increases in core temperature to the occurrence of menopausal hot flushes. A secondary aim was to compare the sweating and vasodilatory temperature thresholds between symptomatic post-menopausal and pre-menopausal women.

Methods

Participants

In 72 postmenopausal women (aged 45.8±5.1 yrs; BMI 25.9±4.5 kg/m^2), we performed a secondary analysis of 108 hot flushes from 5 experimental studies designed for other purposes [8, 18-21]. Studies were performed in laboratories in Texas, USA or Liverpool, UK either in the morning after an overnight fast or early afternoon at least 2 hours postprandial. Participants refrained from alcohol and exercise for 24 h, and caffeine for 12 h prior to data collection. Participants were amenorrheic for at least 12 months and were experiencing at least 4 hot flushes a day, as verified by a 7 day hot flush frequency questionnaire [22].

Participants were free from cardiovascular and metabolic diseases and were not taking hormone therapy or any other treatments to alleviate hot flush symptoms. To compare sweating and vasodilatory threshold responses in menopausal women with that observed in non-menopausal individuals, additional data were obtained from 18 pre-menopausal women [23]. Measurements in all studies were collected using the same experimental procedures. Participants were provided with both written and verbal explanations of all study procedures and gave written consent before enrolling in the study. All procedures and written consents were approved by the Research Ethics Committee/Institutional Review Board at each Institution.

Experimental Protocol

Measurements were conducted in a temperature-controlled laboratory (24-26°C). Participants were placed in a tube-lined jacket and trousers (Med-Eng., Ottawa, Canada), which covered the entire body except for the head, feet and the forearm (n=52) [8, 18, 20], or just wore the trousers with a loose fitting t-shirt (n=20) [19, 21]. Participants rested in a semi-recumbent position for 30 minutes while water (34°C) was perfused through the garments to control skin temperature. A subset of participants (n=23) were then exposed to mild warming by perfusing water at 40-44^{o}C through trousers to increase skin temperature in an attempt to provoke hot flashes [19, 21]. Similarly, a subset of post-menopausal (n=22) and pre-menopausal (n=18) women were exposed to whole-body passive heating by perfusing 48^{o}C water through both the top and bottom garments for ≥60 min Participants were monitored throughout passive heating for 60 minutes or until a 1°C increase in core body temperature occurred.

Measurements

Heart rate (HR) was obtained from an electrocardiogram (PowerLab, AD Instruments, Oxford, UK or Space-Labs, Redmond, WA), alongside with continuous beat-by-beat finger arterial

blood pressure (BP) (Finapress, Amsterdam, Netherlands). To verify continuous BP measured at the finger, an automated blood pressure (Dinamap, Gersweiler, Germany or SunTech Medical Instruments, Raleigh, NC) was obtained at regular intervals. Mean skin temperature was measured via the average of thermocouples (within-subject variation 0.18^{o}C, [24]) at the chest, upper back, lower back, abdomen, thigh and calf [8, 19, 20] or chest, tricep, calf, and thigh [18], attached to the skin. Core temperature was measured from an ingestible pill telemetry system taken at least 2 h before the commencement of data collection (CoreTemp, HQ_{Inc}, Palmetto, FL within-subject variation 0.03^{o}C [25]). Local sweat rate was recorded continuously from the dorsal forearm and the mid-sternum (not covered by the water-perfused suit) using capacitance hygrometry. Dry 100% nitrogen gas was supplied through acrylic capsules (surface area = 2.32 or 2.83 cm^2) attached to the skin's surface at a flow rate of 150 ml min^{-1}, with the humidity of the gas flowing out of the capsules measured by a capacitance hygrometer (Viasala, Helsinki, Finland; within-subject variation 0.44 RH%, [26]). Local cutaneous blood flow was also measured at the forearm and chest using laser-doppler flowmetry probes (Periflux System 5001, Perimed AB, Jarfalla, Sweden or Moor Instruments, Wilmington, DE). Laser Doppler flow probes were affixed with an adhesive heating ring in close proximity to each ventilated sweat rate capsule or the sweat rate capsule was attached to the Laser Doppler probe. Data were sampled at 50 Hz (PowerLab, AD Instruments, Oxford, UK or Biopac Systems, Santa Barbara, CA; within-subject variation 2 AU [27]). Cutaneous blood flow was divided by mean arterial pressure to provide cutaneous vascular conductance (CVC).

Hot flush identification

The onset of a hot flush was objectively identified as a transient and pronounced spontaneous increase in sternal sweat rate (>0.002 mg·cm^{-2}·min^{-1} per second), during both normothermia (n=52) and passive heating (n=56). Participants also informed the researcher of a self-reported feeling of a hot flush and again once the feeling had dissipated. The end of each hot flush was objectively identified as the return of sweat rate to pre hot flush baseline values,

inclusive of any hot flushes during passive heating. Because of the variance in the length of hot flushes, each hot flush episode was divided into eight equal segments, with each segment representing 12.5% of hot flush duration. Sweat rate data were evaluated at the following time points: pre-flush baseline (2 min), the final five second period at the end of each of the aforementioned segments, and for 2 min following the end of the hot flush. Following the identification of a hot flush, data were extracted from the 20 min period before the flush, as well as after the flush, in 1 min averages.

Identification of core temperature change prior to a hot flush

To identify the core temperature responses before each hot flush we firstly identified the 20 min period prior to the onset of the hot flush. The frequency of at least a 0.01^{o}C increase, decrease or no change in core temperature are presented as a count (and as a percentage) in Table 1, along with the overall mean change in core temperature that occurred in the 20 min prior to the objective onset of all hot flushes. In an attempt to accommodate for a potential time lag in gut temperature compared to the gold standard pulmonary artery temperature [28], we also arbitrarily shifted the gut temperature values back by 5 mins in normothermia and 10 mins [28] during passive heating (Table 1).

Identification of temperature thresholds and sensitivities for sweating and cutaneous vasodilation in response to passive heating

The goal of whole body heat stress is an increase in core temperature to enable examination of temperature thresholds (temperature at which cutaneous vasodilation and /or sweating begins) and sensitivities (the rise in skin blood flow or sweat produced after the temperature threshold) for sweating and cutaneous vasodilation. For this purpose, the temperature thresholds for the onset of sweating (mean body temperature) and cutaneous vasodilation (core body temperature) were calculated in a blinded fashion by the same analyst for each study [29] and are reported as the change from normothermic baseline. The sensitivity of the sweating responses were estimated from the slope of the relationships between sweat rate

and mean body temperature beyond the mean body temperature threshold for the onset of sweating and any sweat rate plateau. Skin blood flow sensitivity was estimated in the same way but using the rate of CVC per unit change in core temperature. This was calculated for n= 22 post-menopausal and n=18 pre-menopausal women who underwent whole-body passive heating for 60 mins [23, 30].

Statistical analysis

To examine whether core temperature (and other thermoregulatory variables) increased prior to a hot flush, one way repeated measures general linear models were employed with a factor of time (19 levels). Significant main effects of time were followed up with least significant difference (LSD) corrected planned comparisons comparing each time point prior to the onset of the hot flush relative to time point 19 (i.e. 19 min prior to onset of hot flush). Independent sample t-tests were employed for the comparison of temperature thresholds for sweating and cutaneous vasodilation between premenopausal and postmenopausal women. Data are presented in as mean and 95% confidence intervals unless otherwise stated.

Results

Identification of core temperature change preceding a spontaneous hot flush: We observed 52 hot flushes (i.e., spontaneous hot flushes) in 34 women. The mean change in core temperature across the 20 min period prior to a hot flush was 0.03±0.12 ^{o}C (Table 1). The main effect of time was statistically significant over the 20 min period ($P<0.01$) but there was no significant increase at any time point prior to the hot flush relative to time point 19. When counted, only 51% of hot flushes were actually preceded by a core temperature increase of at least 0.01 °C across the prior 20 min time period; thus 49% of the hot flushes were not preceded by an increase in core temperature. When the correction for a potential time lag in gut temperature (i.e., 5 min delay) was applied, mean core temperature did not show an increase (-0.04± 0.12 ^{o}C) and only 36% of the hot flushes were preceded by a core temperature increase (Table 1). Nevertheless, there was still a statistically significant change

in core temperature over the 20 mins preceding the hot flush, but this was a core temperature decrease rather than an increase ($P<0.05$).

Identification of core temperature change preceding a hot flush during mild heating: We observed a total of 56 hot flushes from 39 women during mild heating. The mean change in core temperature across the 20 min period prior to a hot flush was 0.13±0.20 ^{o}C (Table 1). The main effect of time was statistically significant over the 20 min period ($P<0.01$). As illustrated in Figure 1, relative to time point 19, core temperature was statistically higher 12 min prior the hot flush and remained higher thereafter until the flush onset. Only 76% of hot flushes were preceded by a core temperature increase. When the correction for the time lag in gut temperature during heating (i.e.,10 min delay) was applied, core temperature increased by 0.15± 0.17^{o}C ($P<0.05$) and 72% of the hot flushes were preceded by a core temperature increase (Table 1).

Physiological responses that precede a spontaneous normothermic hot flush: In the 20 min period preceding a hot flush event there were increases in mean skin temperature, HR, as well as chest and forearm skin blood flow (main effects of time, $P<0.05$). As illustrated in Figure 2, the following are the times prior to the hot flush when the indicated variables were significantly elevated relative to time point 19: Heart rate 3 mins prior, chest and forearm skin blood flow 1 mins prior whilst mean skin temperature was elevated at all time points relative to time point 19. Sweating and arterial blood pressure did not change during the 20 min period prior to a hot flush (main effect of time, $P>0.05$; Figure 2).

Temperature thresholds and sensitivities for sweating and cutaneous vasodilation in response to 60 min of whole-body passive heating: The change in mean body temperature from normothermic baseline to the onset of chest and forearm sweating was similar between post and pre-menopausal women ($P>0.14$; Figure 3). After the onset of sweating during the whole-body heat stress, the rate of chest and forearm sweating was 0.25 (0.10, 0.40) mg·cm^{2}·min^{-}

^{1}·°C and 0.31 (0.18, 0.43) mg·cm^{2}·min^{-1}·°C lower respectively in post compared to pre-menopausal women (P<0.001, Figure 3).

The change in core temperature from normothermic baseline to onset of chest and forearm cutaneous vasodilation was similar in post compared to pre-menopausal women (P>0.37; Figure 3). The rate of cutaneous vasodilation at the chest was similar in post compared to pre-menopausal women (P=0.21), while this value was lower in post compared to pre-menopausal women P=0.04; Figure 3).

Discussion

The aim of this study was to assess the contribution of increases in core temperature on the occurrence of menopausal hot flushes. We provide new evidence that small/subtle changes in core temperature in symptomatic post-menopausal women are unlikely to be the trigger for a hot flush given that not all flushes were preceded by an increase in core temperature, even during mild heating, coupled with similar sweating thresholds between symptomatic post-menopausal and young pre-menopausal women. Collectively, these data provide important insight into the physiology of hot flushes and have implications for treatment and management for hot flushes.

We examined the core temperature responses before hot flushes that occurred in normothermic women (referred to as spontaneous hot flushes). We observed 52 hot flushes from 34 women with only 51% of hot flushes preceded by any increase in core temperature, which on average was an increase of ~0.03^{o}C. Put another way, 49% of the hot flushes were not preceded by any increase in core temperature. Whilst our data broadly support the previous findings in terms of magnitude of a core temperature change preceding a hot flush, the number of hot flushes preceded by an increase was less (51%) compared to previous research (65%)[13]. Given the current theory that an elevation in core temperature is the trigger for menopausal hot flushes, it may be fair to assume that the majority of women should experience a hot flush only when core temperature increases beyond a ‘set’ temperature

change (i.e. 0.03-0.05ºC, [7, 11, 13]). However, our data do not support this hypothesis as only half of the hot flushes were preceded by an increase in core temperature. Previous research has likewise reported variability in core body temperature with hot flushes [31]. Therefore, in order to explore the theory in more detail we attempted to passively increase core temperature by at least 0.03ºC using mild heating, to 'provoke' a hot flush. We observed that not all women experienced a hot flush during mild heating, and that only 76% of the hot flushes that occurred were preceded by an increase in core temperature. On average, the increase in core temperature 20 min preceding a hot flush during mild heating was actually larger (~0.15ºC) relative to the increase in core temperature preceding a spontaneous hot flush (~0.03ºC), even when correcting for a time lag in gut temperature readings. Clearly, the larger increase in core temperature prior to the hot flushes during passive heating is due to the background thermoregulatory load. Of note, there were multiple segments of data where core temperature increased by at least ~0.15ºC that did not culminate in a hot flush, demonstrating that the increase in core temperature with passive heating itself was unlikely to be the primary trigger for the hot flush. Consistent with this thought, the larger increase in core temperature prior to a hot flush during mild heating supports the argument that a 0.03ºC increase, which is 'physiologically' very small and occurs frequently throughout everyday life in all post-menopausal women [15], is not an absolute trigger for a hot flush. Collectively, these findings suggest that core temperature does not consistently increase prior to hot flushes and the magnitude of the elevation in core temperature prior to a hot flush is unlikely to be the trigger of the thermoregulatory event.

In the current study we also revisited whether symptomatic post-menopausal women have a lower core temperature threshold for sweating [14]. This previous observation is intriguing given that (i) a lower threshold for sweating is usually associated with enhanced thermoregulatory function and higher levels of fitness [32, 33]; (ii) during the follicular phase of the menstrual cycle, which is characterised by high levels of oestrogen, the temperature threshold for sweating is lower [32] [34]; and (iii) aging (especially older age) is associated

with an increased core temperature threshold for sweating [35, 36]. We used an abrupt and exponential rise in sweating, relative to core temperature, as the gold standard marker for the sweating threshold [29]. We observed similar temperature thresholds for the onset of sweating in response to whole-body passive heating between symptomatic post-menopausal and young pre-menopausal women, but the amount of sweat produced after the threshold (slope) was significantly less in symptomatic post-menopausal women. This is the first time the sweating thresholds have been compared across these age ranges in females. Despite not evaluating a group of non-symptomatic post-menopausal women to compare temperature sweating thresholds with the symptomatic post-menopausal women, we would not expect non-symptomatic post-menopausal women to have a lower sweating threshold relative to the assessed pre-menopausal women. If anything that threshold would be higher given known effects of aging increasing the core temperature sweating threshold [35, 36].

A novel aspect of the current study was that we also compared cutaneous vasodilatory thresholds between symptomatic postmenopausal women and pre-menopausal. The core temperature threshold for cutaneous vasodilation were also similar but the increase in forearm skin blood flow after that threshold (slope) was significantly less in symptomatic post-menopausal women compared to pre-menopausal women. Taken together, the data suggest that postmenopausal women who experience hot flushes produce less sweat and vasodilate less as heat stress progresses, potentially suggesting that they are less efficient at heat dissipation. However, we recognize that those responses may be simply an effect of age, independent of hot flush symptomatic status.

It is conceivable that a hot flush as a thermoregulatory event can occur without the trigger being an increase in core temperature given the evidence of elevations in sweating and skin blood flow in the absence of alterations in core temperature via neural or non-neural/local mechanisms [37]. We show that the thermoregulatory series of events preceding a hot flush does not follow a typical temporal pattern that would be observed with increases in core temperature during passive heating [37]. Moreover, an elevation in efferent skin sympathetic

nerve activity prior to and during a hot flush (i.e., a neural response) which has been described previously [8], likely provokes or contributes to the magnitude of increases in sweating and skin blood flow in the absence of a core temperature increase. The finding of increased brainstem activity prior to hot flushes [16] may support the notion that hot flush responses are independent of the typical thermoregulatory control centres (e.g., pre-optic hypothalamic regions). Another alternative, albeit speculative, explanation is that the core temperature threshold for sweating during the menopausal transition is not fixed but transiently changes, such that a hot flush is triggered by the temporary shifting of the sweating threshold set-point below the individual's core temperature [38]. Under conditions of a fever initially the temperature threshold for the onset of sweating initially increases, thereby reducing the incidence of sweating, and later this threshold decreases provoking profound sweating [39]. Exogenous pyrogens from bacteria generally cause fever; yet, circulating endogenous pyrogens (cytokines) have been associated with menopausal hot flushes [40] and the interaction between such cytokines and temperature thresholds in symptomatic post-menopausal women warrants further investigation.

Implications: Collectively, these data provide important insight for symptomatic women and health care professionals in understanding the triggers for hot flushes. A small increase in core temperature is unlikely to induce a hot flush, therefore recommendations for women to avoid conditions that may increase their core temperatures and to avoid/ not perform exercise should be reconsidered. We have shown previously that exercise training/increased fitness reduces the frequency and severity of hot flushes, along with a lowering of the temperature thresholds for sweating and cutaneous vasodilation in symptomatic post-menopausal women [18, 30]. Exercise training improves sympathetic activity, vascular function, sweat rate control in post-menopausal women all of which may be implicated in the trigger for a hot flush.

Conclusion: We provide new evidence that menopausal hot flushes are not triggered by an increase in core body temperature. It is possible that a hot flush ensues due to underlying control mechanisms that are non-thermoregulatory in nature, or are thermoregulatory in nature

and are triggered by a transient lowering of the core temperature threshold for the onset of sweating. These data provide important insight into the physiology of hot flushes and have important implications for lifestyle interventions as a potential treatment and management option for menopausal hot flushes.

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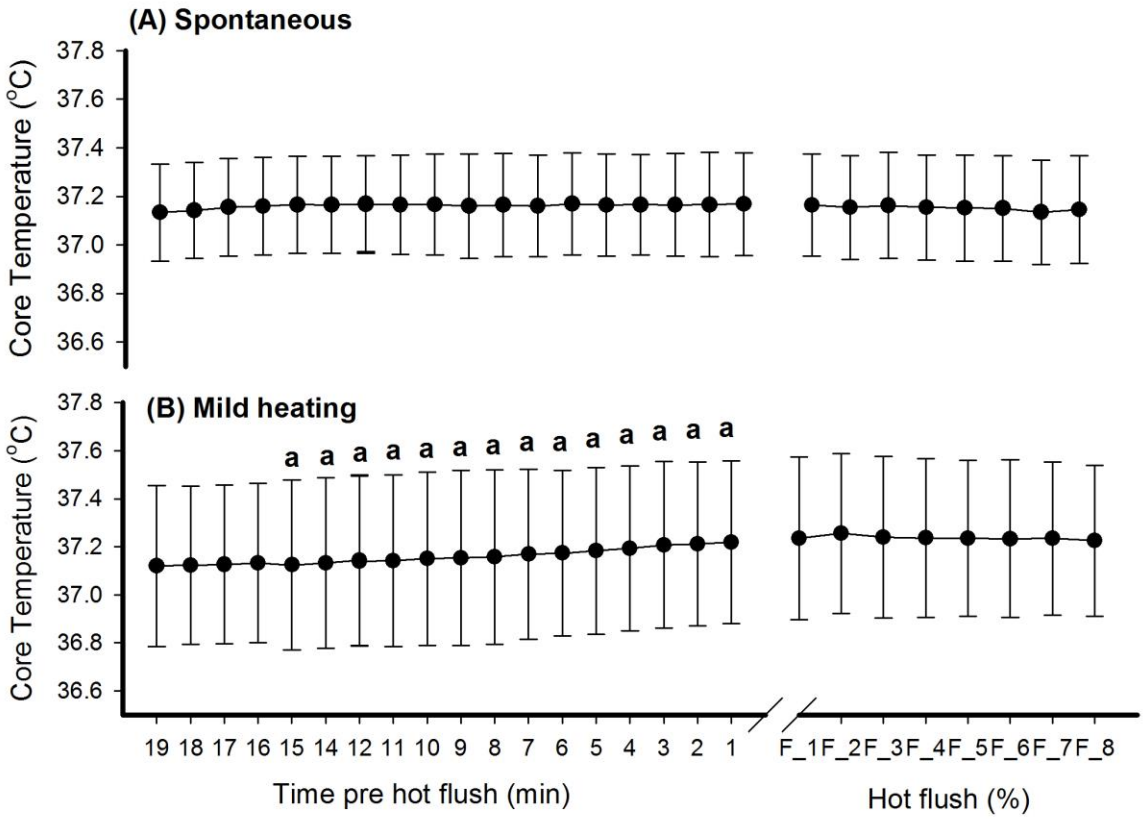
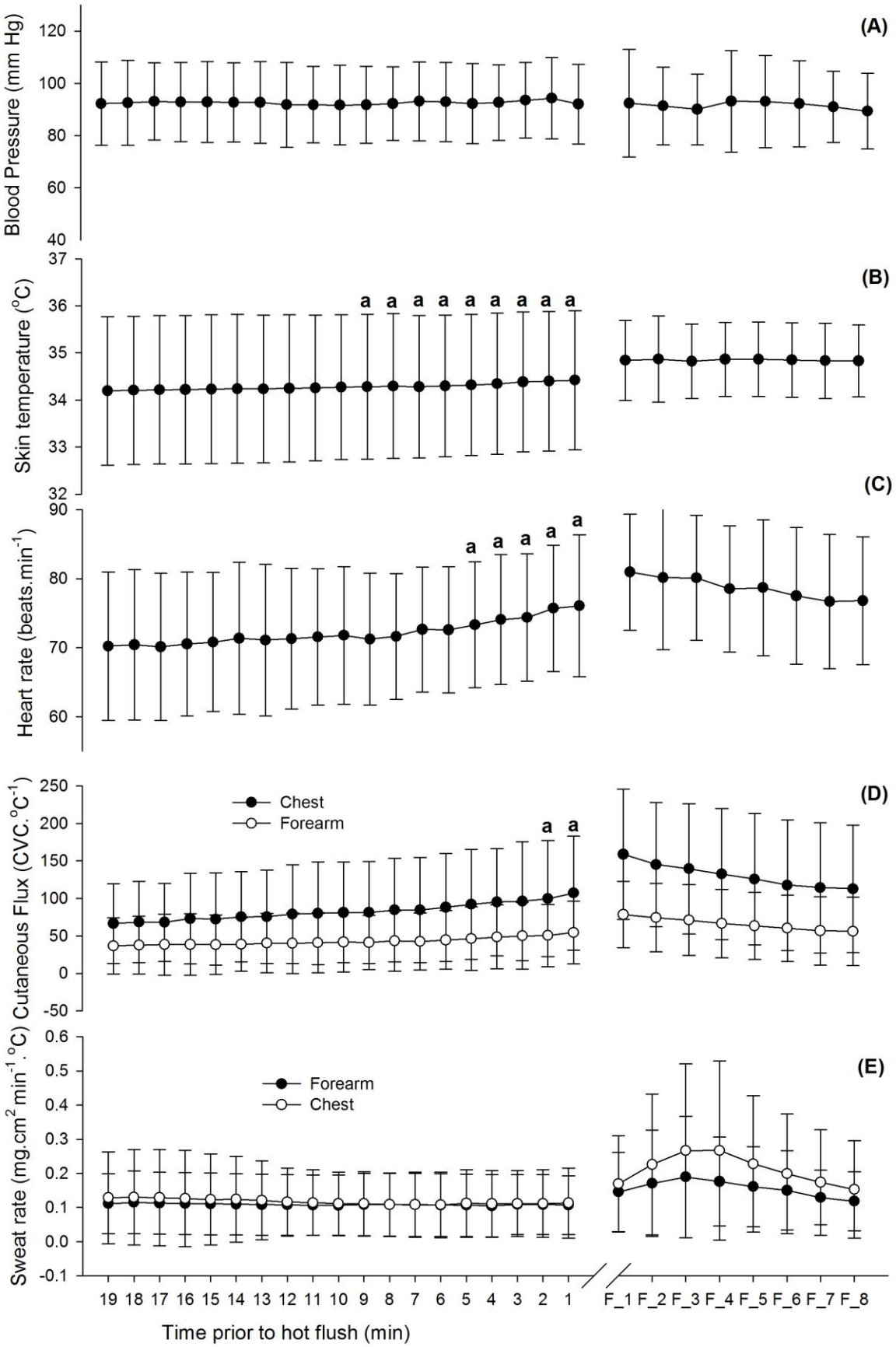
List of tables and figures


(A) Spontaneous
Core Temperature (°C)
37.8
37.6
37.4
37.2
37.0
36.8
36.6
(B) Mild heating
a a a a a a a a a a a a a
19 18 17 16 15 14 12 11 10 9 8 7 6 5 4 3 2 1
F_1F_2F_3F_4F_5F_6F_7F_8
Time pre hot flush (min)
Hot flush (%)


(A)
Blood Pressure (mm Hg)
120
100
80
60
40
(B)
Skin temperature (°C)
37
36
35
34
33
32
a a a a a a a a a
(C)
Heart rate (beats.min-1)
90
80
70
60
a a a a a
(D)
Cutaneous Flux (CVC.°C-1)
250
200
150
100
50
0
-50
Chest
Forearm
a a
(E)
Sweat rate (mg.cm2 min-1 .°C)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
Forearm
Chest
19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
F_1 F_2 F_3 F_4 F_5 F_6 F_7 F_8
Time prior to hot flush (min)
Hot flush (%)

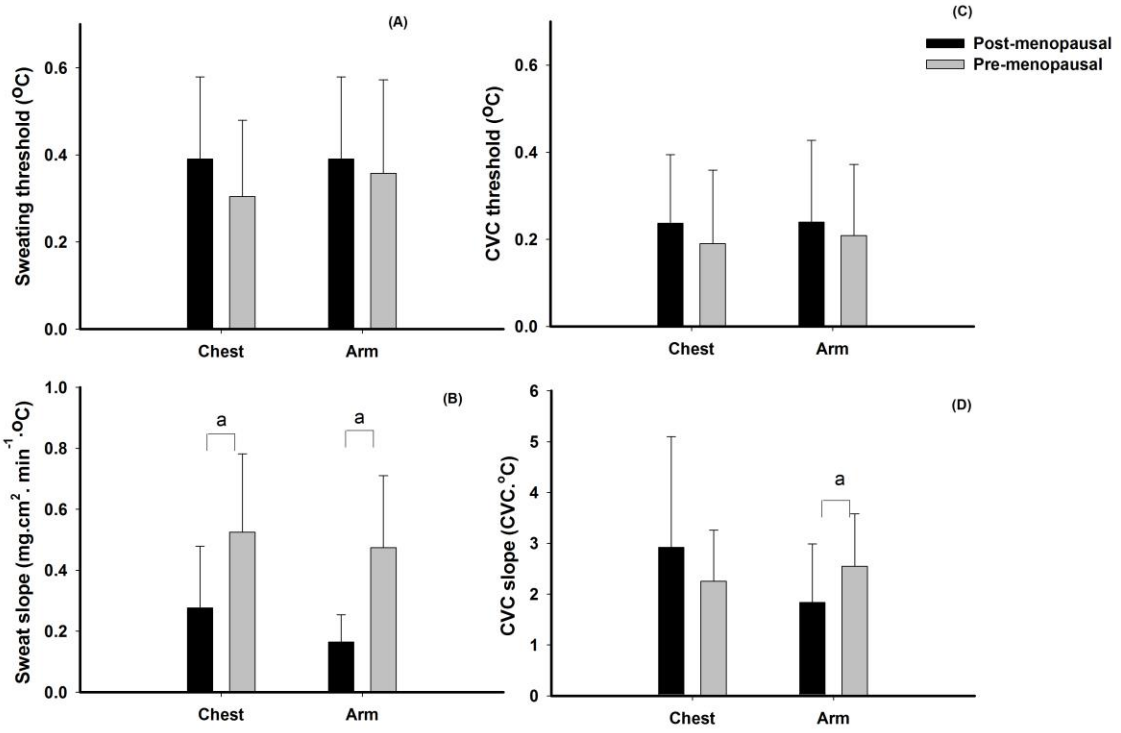

(A)
Sweating threshold (°C)
0.0
0.2
0.4
0.6
Chest
Arm
(C)
Post-menopausal
Pre-menopausal
CVC threshold (°C)
0.0
0.2
0.4
0.6
Chest
Arm
(B)
Sweat slope (mg.cm-2. min-1.°C)
0.0
0.2
0.4
0.6
0.8
1.0
a
a
Chest
Arm
(D)
CVC slope (CVC.°C)
0
1
2
3
4
5
6
a
Chest
Arm

Table 1

	Spontaneous hot flushes				Hot flushes during mild heating			
	Tc ^{o}C	↑	↔	↓	Tc ^{o}C	↑	↔	↓
Uncorrected	0.03 ± 0.12	24 (51%)	4 (4%)	21 (45%)	0.13 ± 0.17	41 (76%)	0 (0%)	13 (24%)
Corrected	-0.04 ±0.12	16 (36%)	1 (2%)	27 (61%)	0.15 ± 0.20	36 (72%)	0 (0%)	14 (28%)

N.B. Gut temperature delay correction 5 mins in normothermia (spontaneous) and 10 mins in hyperthermia (mild heating).

Tc, core temperature.