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Farzin Tayefeh · Olga Plattner · Daniel I. Sessler
Takehiko Ikeda · Danielle Marder

Circadian changes in the sweating-to-vasoconstriction interthreshold range

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Abstract Thermoregulatory defenses are characterized by thresholds, the core temperatures triggering each response. Core body temperature is normally maintained within the interthreshold range, temperatures between the sweating and vasoconstriction thresholds that do not trigger autonomic defenses. This range usually spans only some 0.2°C, but it remains unknown whether similar precision is maintained during the circadian core temperature cycle of about 0.8°C. Accordingly, we evaluated the interthreshold range at four times of the day. We studied ten male volunteers, each at 3 a.m., 8 a.m., 3 p.m., and 8 p.m. At least 12 h elapsed between tests, and the order was randomly assigned. At each study time, volunteers were warmed peripherally until sweating was observed. Skin temperature was subsequently kept constant while core temperature was decreased by central-venous infusion of ice-cold fluid until peripheral vasoconstriction was detected. The volunteers were not permitted to sleep during threshold determinations, although sleep was not otherwise controlled. The core temperature triggering an evaporative water loss of 40 $g \cdot m^{-2} \cdot h^{-1}$ identified the sweating threshold. Similarly, the vasoconstriction threshold was defined by the core temperature triggering the initial decreases in plethysmographic finger tip blood flow. The interthreshold range at 3 a.m. was twice that observed at the other study times ($P < 0.05$). Our data suggest that autonomic control of body temperature is reduced at 3 a.m., even when sleep is denied. This result contradicts the general perception that circadian variation alters the thermoregulatory target temperature, but not precision of body temperature control.

F. Tayefeh · O. Plattner · D.I. Sessler (✉) · T. Ikeda · D. Marder
Department of Anesthesia and Perioperative Care,
University of California, San Francisco,
San Francisco, California 94143-0648, USA

D.I. Sessler
Ludwig Boltzmann Institute for Clinical Anesthesia and
Intensive Care, Vienna, Austria

D.I. Sessler
Outcomes Research Laboratory, Department of Anesthesia and
General Intensive Care, University of Vienna, Vienna, Austria

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Introduction

Thermoregulatory defenses are characterized by thresholds, the core temperatures triggering each response at a given mean skin temperature. Core body temperature is normally maintained within the interthreshold range, temperatures between the sweating and vasoconstriction thresholds that do not triggering autonomic thermoregulatory defenses [31)]. The interthreshold range usually spans only approximately 0.2°C [(18]. Such precision is maintained during the first phase of pyrogenic fever [24)] and during both the luteal and follicular phases in women [12]. However, the interthreshold range is markedly augmented during the second phase of pyrogenic fever [24] and after administration of sedatives [15] or anesthetics [1]. It is believed generally that circadian variation alters the thermoregulatory target temperature, but not the precision of body temperature control. However, the extent to which the circadian cycle alters the sweating and vasoconstriction thresholds – and therefore the interthreshold range – has yet to be formally evaluated. Accordingly, we determined the interthreshold range at four times of the day.

Materials and methods

With approval of the Committee on Human Research at the University of California, San Francisco, and informed consent, we evaluated ten volunteers. They were generally healthy, but not conditioned, athletes. Morphometric characteristics included: age 28 ± 4 years, weight 77 ± 11 kg, height 181 ± 8 cm, and body fat 19 ± 2% [5]. Food intake was not controlled. They were minimally clothed during the protocol, and rested supine on a standard operating room table in a room maintained at about 21–22°C.

Protocol

The volunteers were each evaluated on four occasions, at approximately 3:00 a.m., 8:00 a.m., 3:00 p.m., and 8:00 p.m.. At least

12 h elapsed between tests, and the order was randomly assigned. The volunteers were not permitted to sleep during threshold determinations, although sleep was not otherwise controlled. Before the first study, a 16-*g* catheter was inserted into the vena cava via the internal jugular vein using standard techniques. This catheter was sutured in position, covered with a sterile bandage, and remained in place throughout the about 3-day-long study.

During each study, volunteers were gradually warmed peripherally until sweating was observed (see Measurements below). The warming rate was usually only a few tenths of a degree centigrade per hour. Warming was induced with a circulating-water mattress (Cincinnati Sub-Zero Products, Cincinnati, Ohio, USA) and a forced-air cover (Augustine Medical). The warmers were individually controlled to maintain similar anterior and posterior skin temperatures, as well as comparable upper- and lower-body temperatures. Once sweating was detected, a constant, mean skin-surface temperature was maintained for the remainder of the test period.

Core temperature was decreased by central venous infusion of ice-cold Ringer's lactate solution (approximately 3°C) until peripheral vasoconstriction was detected. Cooling was restricted to 2°C/h or less, because this rate is unlikely to trigger dynamic thermoregulatory responses [17]. Typically, fluid was infused at 30–60 ml/min to obtain this rate of core cooling. The volunteers then resumed their normal activities until the subsequent test period.

Measurements

Core temperature was measured at the right tympanic membrane using thermocouples (Mon-a-Therm, Mallinckrodt Anesthesia Products, St. Louis, Mo., USA). Visual inspection with an otoscope confirmed that the ear canal was free of wax in each volunteer. The aural probe then was inserted by volunteers until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when volunteers easily detected a gentle rubbing of the attached wire. The probe was then securely taped in place, the aural canal occluded with cotton, and a gauze bandage positioned over the external ear. Initial core temperatures were recorded before cutaneous warming was started.

Area weighted, mean skin surface temperature was computed and displayed at 1-s intervals from measurements at 15 sites by assigning the following regional percentages to each area: head 6%, upper arms 9%, forearms 6%, hands 2.5%, fingers 2%, back 19%, chest 9.5%, abdomen 9.5%, medial thigh 6%, lateral thigh 6%, posterior thigh 7%, anterior calves 7.5%, posterior calves 4%, feet 4%, and toes 2% [7]. Temperatures were recorded from thermocouples connected to two calibrated 16-channel electronic thermometers having an accuracy of 0.1°C and a precision of 0.01°C (IsoThermex, Columbus Instruments, Columbus, Ohio, USA).

The rate of sweating was determined by a ventilated capsule situated on the chest as previously described [36]. Water loss was measured on the chest because this site is usually among the first to sweat [30]. All analog and serial thermoregulatory data were recorded at 1-min intervals, using a computerized data acquisition system. Absolute right finger tip blood flow was measured at 1-min intervals by venous occlusion volume plethysmography, as previously described [26]. We recorded finger tip blood flow because arterio venous shunt constriction is the first autonomic response to hypothermia in humans.

Heart rate was monitored continuously using three-lead electrocardiography. Oxyhemoglobin saturation (S_pO_2) was measured continuously using pulse oximetry and blood pressure was determined oscillometrically at 5-min intervals at the left upper arm using a Modulus CD Anesthesia System (Ohmeda).

Data analysis

The core temperature triggering an evaporative water loss of 40 $g \cdot m^{-2} \cdot h^{-1}$ identified significant sweating. The core temperature triggering significant sweating identified the threshold for this response. Similarly, the vasoconstriction threshold was defined by the core temperature triggering the initial decreases in plethysmographic finger tip blood flow. This threshold was determined post hoc by an investigator blind with respect to time of day and core temperature. The difference between the sweating and vasoconstriction thresholds defined the interthreshold range.

Mean skin temperature, mean arterial blood pressure, and heart rate during each study period were calculated as the average of values at the two thresholds. Results for the four study periods were compared using repeated-measures ANOVA and Dunnett's tests, with 3:00 a.m. considered the reference value.

Results

Mean skin temperature was well controlled during each study period, decreasing only 0.03 ± 0.07°C from the sweating threshold to the vasoconstriction threshold (Fig. 1). Ambient temperature and hemodynamic responses did not differ significantly at the four study times.

Initial core temperatures, mean skin temperatures, and the sweating and vasoconstriction thresholds were higher in the afternoon and evening than in the morning h. The sweating-to-shivering interthreshold range was 0.2–0.3°C at 8 a.m., 3 p.m., and 8 p.m.. In contrast, the sweating threshold was 36.6 ± 0.2°C at 3:00 a.m. and the vasocon-

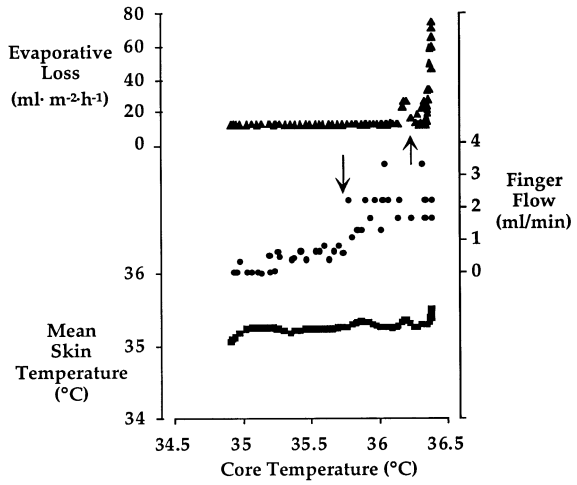

Fig. 1 A typical experiment, showing evaporative water loss, finger tip vasoconstriction, and mean skin temperature as a function of core temperature at 3 a.m.. The *arrows* indicate the sweating and vasoconstriction thresholds. The data were smoothed with a 5-min running-average filter, and are presented as means ± SD

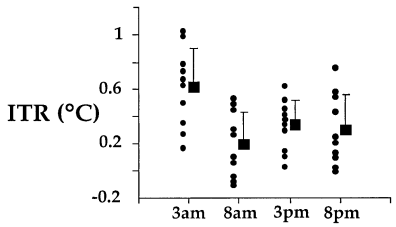

Fig. 2 The sweating-to-vasoconstriction interthreshold range (*ITR*) at each time of day. Data presented as means ± SD. Values at 3 a.m. differed significantly from those at other times

Table 1 Temperatures and hemodynamic observations. Data are presented as means±SD

Time	3 a.m.	8 a.m.	3 p.m.	8 p.m.
Ambient temperature (°C)	22±1	23±1	22±1	22±1
Mean arterial pressure (mmHg)	89±7	85±8	87±9	89±11
Heart rate (beats/minute)	66±9	67±12	68±12	70±10
Administered fluid volume (l)	3±2	2±1	2±1	3±2
Initial core temperature (°C)	36.4±0.4	36.3±0.2	36.7±0.2*	36.8±0.2*
Mean skin temperature (°C)	35.9±0.7	36.2±0.5	36.4±0.5*	36.5±0.4*
Sweating threshold (°C)	36.6±0.2	36.7±0.3	36.9±0.2*	37.1±0.2*
Vasoconstriction threshold (°C)	36.0±0.4	36.5±0.2*	36.6±0.3*	36.7±0.3*
Interthreshold range (°C)	0.61±0.3	0.2±0.2*	0.33±0.2*	0.33±0.3*

* $P<0.05$ vs. 3-a.m. value (ANOVA, Dunnett's test)

striction threshold was 36.0 ± 0.4°C (Table 1). Consequently, the interthreshold range was significantly greater at 3 a.m. (0.6 ± 0.3°C) than at the other times (Fig. 2).

Discussion

Initial core and mean-skin temperatures increased by approximately 0.4°C from 3 a.m. to 3 p.m.. This is considerably less than the 0.8 ± 0.2°C circadian amplitude observed in a previous investigation [32]. A major difference between these protocols is that sleep was denied in the current study whereas volunteers in our previous investigation slept normally. Consistent with the importance of this factor, others have observed that circadian amplitude is near 0.4°C when subjects are awake [33] but near 0.8°C when normal sleep is permitted [29].

Our data indicate that the precision of autonomic thermoregulatory control is halved in the early morning hours, even when subjects are deprived of sleep. Significantly greater core temperature deviations are thus required to trigger autonomic thermoregulatory defenses than at other times. Autonomic responses, however, are but one mechanism controlling body temperature. The other mechanism is behavioral compensation (i.e., putting on a sweater, opening a window). Humans usually constrict arterio-venous shunts before activating behavioral defenses, although behavior is usually used in preference to sweating or shivering. Animals are similar in preferentially activating at least some autonomic responses before behavioral ones. Nonetheless, it is well established that behavioral responses compensate when autonomic ones are insufficient [28]. The observed early morning autonomic imprecision will thus influence core temperature only to the extent that behavioral compensation also fails.

Mean skin temperature contributes some 10% to control of sweating [21] and about 20% to control of vasoconstriction and shivering [4]. It is thus necessary to maintain constant sentient skin temperature while determining core temperature response thresholds, or to compensate arithmetically for skin temperature perturbations [19]. Failure to consider the contribution of skin temperature leads to the conclusion that sweating and vasoconstriction occur simultaneously [3], although a distinctly non-zero interthreshold range is observed when skin temperature is controlled in non-exercise protocols [23].

There are three models that permit controlled core temperature changes in humans, while maintaining constant sentient skin temperature. The first uses regional anesthesia to block thermal sensation from the legs, with all thermal manipulations subsequently applied to the insensate lower body [16]. Aside from being invasive, applicability of this model is limited because both epidural [13] and spinal [14] anesthesia impair central thermoregulatory control. The second model was developed by Mekjavic; it uses water immersion to clamp skin temperature while the core gradually cools after exercise-induced hyperthermia [20]. A difficulty with this method, though, is that exercise per se significantly reduces the sweating threshold [18]. Since only small threshold modulations were anticipated, we avoided models requiring regional anesthesia or exercise, instead using one in which the core is cooled in isolation by central venous administration of cold fluid [4, 17]. The most notable limitation of this protocol is that it requires administration of some 2–3 l fluid. However, most of the administered lactate-Ringer's solution rapidly diffuses into the extracellular space, leaving relatively little remaining within the blood stream [34]. It thus is unlikely that actual vascular volume expansion approaches the administered volume. Dehydration significantly increases the sweating threshold [22]; conversely, excessive hydration may reduce it. However, the sweating threshold in this protocol was determined before fluid administration. Although dehydration synergistically augments vasoconstriction [25], excess vascular fluid is unlikely to alter vasomotor activity or shivering substantially.

Internal desynchronization of circadian pacemakers impairs thermoregulatory control [9, 10]. However, our volunteers were not denied circadian cues ("zeitgebers") [27] and were permitted normal daily activities except during the hours actually required for measurements. It is thus unlikely that they suffered internal dysynchonization or circadian phase-shift. Sleep influences circadian rhythms less than light [8], but it is nonetheless likely that results would differ had the volunteers been allowed to sleep. Furthermore, the results might well differ depending on specific sleep phases. We made no effort to test volunteers while asleep because our protocol

for testing thermoregulatory thresholds would surely have awakened the volunteers.

Our protocol was restricted to male volunteers because we [17, 36] and others [11] have shown that the sweating threshold is greater in women than men. However, the precision of thermoregulatory control is comparable in the two sexes [12, 17], at least during the luteal phase. It is therefore likely that the night-time thermoregulatory imprecision we observed applies also in women.

Distal esophageal temperature is, perhaps, the most reliable core temperature monitoring site. Tympanic membrane temperature usually is approximately 0.1°C less than esophageal temperature [35]. Nonetheless, extensive experience has shown that esophageal and tympanic membrane temperatures correlate extremely well during mild hyperthermia [36] and hypothermia [2, 6 17]. It therefore is unlikely that our conclusions would have altered substantially had we recorded esophageal rather than tympanic membrane temperatures.

In summary, our data suggest that autonomic control of body temperature is reduced at 3 a.m., even when sleep is denied. This result contradicts the general perception that circadian variation alters the thermoregulatory target temperature, but not precision of body temperature control. The extent to which impaired night-time autonomic control influences core temperature will depend on the ability of behavioral measures to compensate.

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