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Rate and Gender Dependence of the Sweating, Vasoconstriction, and Shivering Thresholds in Humans

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Background: **The range of core temperatures *not* triggering thermoregulatory responses ("interthreshold range") remains to be determined in humans. Although the rates at which perioperative core temperatures vary typically range from 0.5 to 2°C/h, the thermoregulatory contribution of different core cooling rates also remains unknown. In addition, sweating in women is triggered at a slightly greater core temperature than in men. However, it is unknown whether the vasoconstriction and shivering thresholds are comparably greater in women, or if women tolerate a larger range of core temperatures without triggering thermoregulatory responses. Accordingly, the authors sought to (1) define the interthreshold range; (2) test the hypothesis that, at a constant skin temperature, the vasoconstriction and shivering thresholds are greater during rapid core cooling than during slowly induced hypothermia; and (3) compare the sweating, vasoconstriction, and shivering thresholds in men and women.**

Methods: **Eight men and eight women participated. The men participated on 2 separate days; no anesthesia or sedatives were administered. On each day, they were cutaneously warmed until sweating was induced and then were cooled by a central venous infusion of cold fluid. The cooling rates were 0.7 ± 0.1°C/h on 1 day and 1.7 ± 0.4°C/h on the other, randomly ordered. Skin temperature was maintained near 36.7°C throughout each trial. The women were studied only once, in the follicular phase of their menstrual cycles, at the greater cooling rate.**

Results: **The interthreshold range was ≈ 0.2°C in both men and women, but all thermoregulatory response thresholds were ≈ 0.3°C higher in women. All thresholds were virtually identical during slow and fast core cooling.**

Conclusions: **Our findings confirm the existence of an interthreshold range and document that its magnitude is small. They also demonstrate that the interthreshold range does not differ in men and women, but that women thermoregulate at a significantly higher temperature than do men. Typical clinical rates of core cooling do not alter thermoregulatory responses. (Key words: Measurement techniques, blood flow: volume plethysmography. Temperature, regulation: setpoint; shivering; sweating; threshold; vasodilation. Thermoregulation: hyperthermia; hypothermia.)**

HUMANS maintain exquisite control of core body temperature, such that measurements obtained at the same time on different days rarely deviate more than several tenths of a degree.[1] Precise control results from aggressive thermoregulatory responses that are triggered by small deviations from a physiologically determined target temperature. The core temperature triggering a thermoregulatory response, at a fixed skin temperature, defines the "threshold" for that response. Important autonomic responses include sweating during hyperthermia and vasoconstriction followed by shivering during hypothermia. Core temperatures between the sweating and vasoconstriction thresholds do not trigger autonomic responses, and these temperatures define the "interthreshold range."[2]

All general anesthetics so far tested substantially reduce the vasoconstriction threshold[3–7] and increase the sweating threshold.[8,9] The result is an interthreshold range spanning ≈ 4°C at typical doses of most general anesthetics,[2] a range far exceeding normal values. Although epidural and spinal anesthesia presumably do not directly alter central thermoregulatory processing, regional anesthesia nonetheless decreases the vasoconstriction and shivering thresholds ≈ 0.5°C and appears also to increase somewhat the sweating threshold.[10] These data suggest that major conduction anesthesia also slightly increases the interthreshold range. However, we cannot make a definitive statement concerning changes in the interthreshold range induced by general or regional anesthesia because the interthreshold range in *nonanesthetized* humans has yet to be determined. Furthermore, thermoregulatory responses in the post-

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operative period (when residual anesthetic concentrations are small) probably resemble those in nonanesthetized individuals. A fuller understanding of these responses, and of the effects of residual anesthesia, thus requires better identification of normal thermoregulatory thresholds.

Evaluation of the interthreshold range in humans has proven difficult because skin temperature contributes a small, but significant, fraction of the input to the thermoregulatory system.[11-14] Therefore, studies evaluating the interthreshold range ideally would maintain constant skin temperature while manipulating core temperature sufficiently to trigger sweating and vasoconstriction. Such manipulations are difficult because the skin is the body's major heat exchanger. Using a water immersion protocol, Mekjavic *et al.* demonstrated that the core temperature range between the sweating and shivering thresholds was approximately 0.6°C; however, this study apparently did not evaluate vasoconstriction.[15] Consequently, the magnitude of the interthreshold range remains unknown. It even is unknown if an interthreshold range exists in nonanesthetized humans; plausible alternatives include warm- and cold-response thresholds that are identical or perhaps overlap.[16]

A factor potentially confounding some thermoregulatory studies is that response thresholds depend not only on static temperatures but also on the rate at which temperatures change. For example, rapid changes in skin temperature markedly augment cutaneous contribution to the sweating threshold.[12,17] The rates at which core temperatures decrease during surgery and increase during postanesthetic recovery vary considerably. Rates of perioperative core temperature change depend on the type of surgery, ambient conditions, and applied warming; clinically observed rates typically range from 0.5 to 2°C/h.[18,19] However, the extent to which the rate of change of core body temperature influences thermoregulatory responses remains unknown.

Some previous studies have concluded that sweating in women is triggered at a slightly greater core temperature than in men and that women may secrete less sweat per unit area than do men.[8,20,21] Others have reported no difference.[22,23] In any case, it remains unknown whether the vasoconstriction and shivering thresholds are comparably greater in women or whether women tolerate a larger range of core temperatures without triggering thermoregulatory responses.

Accordingly, we sought to confirm the presence of and to quantify the interthreshold range. We also tested the hypothesis that, at a constant skin temperature, the vasoconstriction and shivering thresholds are greater (and the interthreshold range smaller) during rapid core cooling than during slowly induced hypothermia. Finally, we compared the sweating, vasoconstriction, and shivering thresholds in men and women.

Materials and Methods

With approval from the Committee on Human Research at the University of California, San Francisco and informed consent from the volunteers, we studied eight men and eight women. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. None of the volunteers was a conditioned athlete. Women not using oral contraceptives were studied during the first 10 days (follicular phase) of their menstrual cycles. Those using oral contraceptives were studied during the first 3 weeks of their cycles. All women reported regular menstrual cycles.

Core hyperthermia sufficient to trigger sweating was induced by forced-air warming. Subsequently, hypothermia was induced by central venous infusion of cold lactated Ringer's solution. During each study, skin temperature was maintained at that recorded at the sweating threshold by manipulating the output from forced-air warming devices. Male volunteers were studied on 2 consecutive days: during rapid core cooling on 1 day and during slowly induced hypothermia on the other, randomly assigned. Because gender dependence of thermoregulatory response thresholds was more likely than rate dependence, the interthreshold range in women was evaluated only once, during rapid core cooling.

Treatment Protocol

Studies started at approximately 10:30 AM but, to avoid circadian temperature fluctuations, were timed so that thermoregulatory responses were triggered at the same time of day. All volunteers were minimally clothed during the trials and reclined on their backs on a standard operating room table.

After skin-surface thermocouples were applied (see Measurements, below), cutaneous evaporative heat loss was prevented by wrapping each volunteer's body with thin plastic sheeting below the neck. Two disposable forced-air warming covers (model 300, Augustine Medical, Eden Prairie, MN) were positioned to cover

the skin below the neck, one each to cover the upper and lower body. The covers were connected to Bair Hugger forced-air warmers (model 200, Augustine Medical) that were set on "low" ($\approx$ 37°C) while other study monitors were being attached.[24] A 16-G catheter was inserted into the superior vena cava *via* the internal jugular vein using standard technique.

Core hyperthermia was induced by increasing the settings on both Bair Hugger forced-air warmers to "medium" ($\approx$ 40°C). At this setting, skin temperature was $\approx$ 36.8°C, which roughly equalled core temperature. Because metabolic heat could not be dissipated under this circumstance, core body temperature increased gradually. We were thus able to induce sweating without inducing excessively high skin-surface temperatures that would be difficult to maintain during subsequent cooling. Active warming was continued until a sustained increase in cutaneous evaporative water loss was detected (*e.g.*, > 50 $g \cdot m^{-2} \cdot h^{-1}$).

Volunteers then were linearly cooled by central venous infusion of lactated Ringer's solution at $\approx$ 3°C.[25] The solution was cooled by passing it through an aluminum cardiopulmonary bypass heat exchanger immersed in an ice-and-water slurry. To induce rapid core cooling, the initial infusion rate was 0.1 $ml \cdot kg^{-1} \cdot min^{-1}$, then increased $\approx$ 5 ml/min, at 5-min intervals, to achieve the desired rate of core temperature cooling ($\approx$ 1.5–2.0°C/h). To achieve slow induction of hypothermia, the initial infusion rate of 0.1 $ml \cdot kg^{-1} \cdot min^{-1}$ was increased $\approx$ 3 ml/min at 5-min intervals until a core temperature cooling rate of $\approx$ 0.3–0.5°C/h was obtained. Cooling continued until sustained shivering was detected using indirect calorimetry. Female volunteers were cooled using the rapid infusion protocol.

During induced hypothermia, average skin temperature was maintained near values measured at the onset of sweating ($\approx$ 36.7°C) by adjusting the settings on the Bair Hugger forced-air warmers. To prevent large skin temperature perturbations when the Bair Hugger settings were changed, two cotton blankets were placed between the forced-air warming covers and the plastic sheeting covering the skin surface. In addition, the upper body warmer was modified by the manufacturer to allow continuous adjustment of the air temperature. Average skin temperature in the male volunteers was maintained at the same value on each study day.

Measurements

The percentage of body fat in the volunteers was determined using infrared interactance (Futrex 1000, Futrex, Hagerstown, MD).[26]

Core temperature was measured at the right tympanic membrane using Mon-a-Therm thermocouples (Mallinckrodt Anesthesia Products, St. Louis, MO). 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. Core temperature was also measured in the distal esophagus using disposable thermocouple probes (Mallinckrodt Anesthesia Products) in seven of the volunteers. The esophageal probes were positioned using the formula of Mekjavic and Rempel.[27] Control core temperature was 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%.[28] Temperatures were recorded from thermocouples connected to two calibrated Iso-Thermex 16-channel electronic thermometers having an accuracy of 0.1°C and a precision of 0.01°C (Columbus Instruments, Columbus, OH).

The rate of sweating was determined using a ventilated capsule situated on the chest as previously described.[8] Water loss was measured on the chest because this site usually is among the first to sweat.[29] All analog and serial thermoregulatory data were recorded at 5-min intervals, using a modification of a previously described data-acquisition system.[25]

Absolute right fingertip blood flow was measured at 5-min intervals by venous occlusion volume plethysmography, as previously described.[30] We recorded fingertip blood flow because arteriovenous shunt constriction is the first autonomic response to hypothermia in humans. Active capillary vasodilation has a higher threshold than sweating and was not evaluated in this study.[31]

Table 1. Morphometric and Environmental Data

	Age (yr)	Weight (kg)	Height (cm)	Fat (%)	T_{Rm} (° C)	H_{Rm} (%)
Men	26 ± 4	72 ± 8	180 ± 4	16 ± 5	23 ± 2	30 ± 9
Women	27 ± 5	60 ± 10	168 ± 6*	24 ± 6*	21 ± 1	29 ± 11

Values are mean ± SD for the age, weight, height, percentage of body fat, prevailing room temperature (T_{Rm}), and prevailing room humidity (H_{Rm}) for male and female volunteers.

* Significant differences between men and women.

Oxygen consumption was measured using a Deltatrac metabolic monitor (SensorMedics, Yorba Linda, CA). The monitor measures the oxygen concentration in exhaust gas drawn at a constant flow of 40 l/min through a clear plastic canopy placed over the volunteer's head; it is accurate to 4 ± 2%. Oxygen consumption is determined from the difference in oxygen content between the mixed exhaust gas and the inspired room air. Measurements were averaged over 1-min intervals and recorded every 5 min.

Heart rate was monitored continuously using three-lead electrocardiography. Oxyhemoglobin saturation 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, Madison, WI). Hemodynamic data and saturations were recorded at 20-s intervals using IdaCare version 1.3 (Hermes System, Belgium), a Macintosh (Apple, Cupertino, CA)-based patient information management software. The thermoregulatory and IdaCare data-acquisition systems operated asynchronously on a Macintosh FX computer.

Data Analysis

The average skin temperature, absolute fingertip blood flow, and oxygen consumption measured at the onset of sweating were considered baseline values. The tympanic membrane temperatures at which sweating was detected and at which fingertip blood flow decreased substantially from baseline values were considered the sweating threshold and vasoconstriction threshold, respectively. The tympanic membrane temperature triggering a sudden increase of 30% or more in oxygen consumption, sustained for at least 5 min, defined the shivering threshold. We used oxygen consumption as our index of shivering because nonshivering thermogenesis contributes little,[32,33] if anything,[34] to cold defense in adult humans. The vasoconstriction and shivering thresholds were determined after completion of each study by an investigator blinded to the rate of core cooling and the core temperature.

The difference between the sweating and vasoconstriction thresholds identified the interthreshold range. The difference between the vasoconstriction and shivering thresholds identified the vasoconstriction to shivering range; similarly, the difference between the sweating and shivering thresholds defined the sweating to shivering range. The activation thresholds and ranges for the male volunteers (fast *vs.* slow cooling) were compared using two-tailed, paired *t* tests. The thresholds and ranges for the female volunteers were compared with those for the males during rapid cooling using two-tailed, unpaired *t* tests. The correlation between esophageal and tympanic temperature was evaluated using linear regression. All values are expressed as means ± standard deviation; differences were considered significant when $P < 0.05$.

Results

The ages, weights, heights, percentage of body fat, ambient humidity, and ambient temperatures for men and women are shown in table 1. The body habitus was nearly normal in all volunteers, but women were shorter and had a higher percentage of body fat. Control tympanic membrane temperatures in the men were 36.8 ± 0.2°C on the slow-cooling day, and 36.8 ± 0.1°C on the fast-cooling day.

One male volunteer was considerably smaller than the others, weighing even less than the average woman. Furthermore, he had less body fat than the other men. His response thresholds exceeded those in the other men by nearly three standard deviations. Therefore, his data were not included in the analysis.

The average skin temperatures during the cooling phase were similar on all study days (table 2). The rapid-cooling rate was approximately 2.5 times the

Table 2. Core Cooling Rates and Mean Skin Temperatures during the Cooling Period

	Cooling Rate (° C/h)	Skin Temperature (° C)
Men slow	0.7 ± 0.1*	36.7 ± 0.1
Men fast	1.7 ± 0.4	36.6 ± 0.1
Women fast	1.6 ± 0.3	36.8 ± 0.1

Data are presented as mean ± SD.

* Significant difference in the core cooling rate in men on the fast and slow cooling days. Women were studied only at the higher rate.

slow-cooling rate. The cooling rate in women did not differ significantly from that in men during rapid cooling.

In individual male volunteers, sweating occurred at virtually identical tympanic membrane temperatures on each study day. In all instances, the sudden increase in oxygen consumption (defining the shivering threshold) was accompanied by obvious involuntary muscular oscillations. Shivering also was triggered at the same temperature on both days. There was no statistically significant or clinically important difference between the vasoconstriction thresholds on the rapid and slow core-cooling days. The interthreshold range in men was $\approx$ 0.2°C on each study day.

The mean control tympanic membrane temperature for women was approximately 0.2°C higher than that for men (P = 0.06). Both the sweating and vasoconstriction thresholds were significantly greater in women than men (P = 0.01 and P = 0.02, respectively). Shivering was triggered at a higher temperature in women. However, neither the sweating-to-shivering temperature range (fig. 1) nor the interthreshold range in women differed significantly from that in men (table 3).

The average correlation coefficient between the tympanic and esophageal temperatures was 0.97 ± 0.01. The average difference between the two measurement sites (esophageal temperature minus tympanic membrane temperature) was 0.04 ± 0.1°C.

The male volunteers were given $\approx$ 4 l lactated Ringer's solution over an $\approx$ 1.5-h period during rapid core-cooling and $\approx$ 6 l over $\approx$ 3 h during slow core-cooling. The women received $\approx$ 3 l over a period of $\approx$ 1.5 h. There was no evidence of fluid overload, and fluid administration was well tolerated by all volunteers. There were no adverse hemodynamic changes, such as significant bradycardia (heart rate < 50 beats/min) or other cardiac arrhythmias, in any volunteer.

Discussion

Until recently, generally applicable methods did not exist in humans to vary core temperature, independently of skin temperature, sufficiently to evaluate both sweating and shivering thresholds. Because of such difficulties, even the existence of an interthreshold range has been disputed.[16] Using our isolated core-cooling technique,[25] we now confirm the existence of an interthreshold range in humans and identify its magnitude as being approximately 0.2°C.

The control core temperatures in the men were nearly identical on the 2 study days, which is consistent with an interthreshold range of only $\approx$ 0.2°C. We did not evaluate thermal perception (as an index of behavioral thermoregulation); however, studies in animals document that autonomic responses generally are mobilized before behavioral ones.[35] Our data thus suggest that the typical precise control of core temperature in humans most likely results from autonomic thermoregulatory control, not behavioral responses.

In a recent study by Mekjavic *et al.*,[15] male volunteers immersed in 28°C water exercised until they started sweating. They then stopped the exertion and passively cooled until they stopped sweating and subsequently started to shiver. They reported a 0.6 ± 0.2°C sweating-to-shivering range; in contrast, in our male volunteers, the range was 1.4 ± 0.6°C. Contrasting results are unlikely to result from a difference in core cooling rates

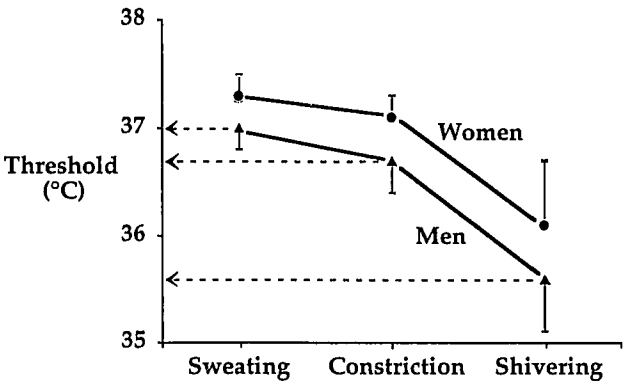

Fig. 1. The core temperature thresholds for sweating, vasoconstriction, and shivering in men and women. The skin temperature was kept constant at $\approx$ 36.7°C during each study. The sweating and vasoconstriction thresholds were significantly greater in women than in men. The interthreshold range (sweating-to-vasoconstriction) was $\approx$ 0.2°C in each gender. Temperatures between the top and middle arrows indicate the interthreshold range in men; similarly, temperatures between the middle and bottom arrows show the vasoconstriction-to-shivering range.

Table 3. Control Tympanic Membrane Temperatures, Sweating, Vasoconstriction and Shivering Thresholds, and Thermoregulatory Response Ranges in Men and Women

Temperature	Men Slow	Men Fast	Women Fast
Control core (° C)	36.8 ± 0.2	36.8 ± 0.1	37.0 ± 0.2
Sweating threshold (° C)	37.0 ± 0.2	37.0 ± 0.2	37.3 ± 0.2*
Constriction threshold (° C)	36.7 ± 0.3	36.7 ± 0.3	37.1 ± 0.2*
Shivering threshold (° C)	35.6 ± 0.5	35.6 ± 0.5	36.1 ± 0.6
Interthreshold range (° C)	0.23 ± 0.16	0.23 ± 0.18	0.18 ± 0.14
Constriction–shivering range (° C)	1.1 ± 0.6	1.2 ± 0.7	1.0 ± 0.5
Sweating–shivering range (° C)	1.4 ± 0.6	1.4 ± 0.6	1.2 ± 0.5

Data are presented as mean ± SD.

* Significant differences between the women and men during fast core cooling. There were no statistically significant differences between the men during slow and fast cooling.

because the rate in their study (0.8 ± 0.2°C/h) was similar to that on our slow-cooling day (0.7 ± 0.1°C). Furthermore, the thresholds we recorded were virtually identical when we augmented the cooling rate 250%. Other possible explanations for the divergent data include differences in hydrostatic pressure and subject position; however, neither factor likely is sufficient to account for the variation in results.[36]

An important difference between the studies is that skin temperature was ≈ 9°C less in the protocol of Mekjavic *et al.*[15] than in ours. The lower skin temperatures would be expected to increase all the thresholds roughly 1°C (assuming a linear 10% contribution of skin to thermoregulatory control[11-14]), and the observed difference in the shivering thresholds was ≈ 1.2°C. However, nonlinear aspects of thermal sensing and regulatory control are well established.[37] It therefore is likely that at least part of the observed large differences in the sweating-to-shivering range result from such nonlinearities in the response to differing static skin temperatures.

An additional difference between the protocols is that we studied generally sedentary individuals, rather than the "physically active" subjects evaluated by Mekjavic *et al.*[15] The sweating thresholds are a few tenths of a degree less in trained athletes than in sedentary individuals[38]; however, the effect of physical training on the shivering threshold remains unclear. An alternative explanation is that exercise *per se* might have reduced the sweating threshold in the protocol of Mekjavic *et al.* Consistent with this possibility, the observed difference in the sweating threshold with skin temperature clamped at 28°C (by water immersion) was only 0.4°C greater than in our protocol with skin temperature maintained at nearly 37°C. This difference is less than expected, and far less than the 1.2°C difference in shivering thresholds. These data suggest that at comparable skin temperature, the sweating threshold during exercise may be less than that during passive hyperthermia.

Mekjavic *et al.* defined the range of core temperature between sweating and shivering as the "null zone." Although this term implies that autonomic thermoregulatory responses are absent within this zone, it is well established that arteriovenous shunt vasoconstriction is initiated at higher temperatures than shivering.[39] To avoid confusion, we defined the interthreshold range as temperatures between the sweating and vasoconstriction threshold,[2] *i.e.,* temperatures *not* triggering autonomic thermoregulatory responses. Not surprisingly, vasoconstriction occurred after only a small amount of cooling (≈ 0.2°C), whereas shivering occurred after a much larger change in core temperature (≈ 1.4°C). The large vasoconstriction-to-shivering range and variance in shivering thresholds suggests that initiation of shivering is controlled less well than vasoconstriction. This is consistent with the notion that shivering may in large part be mediated by phylogenetically older centers,[40] specifically the spinal cord.[41,42]

Substantial core temperature perturbations are most common in the perianesthetic period. We tested core cooling rates ranging from 0.7 to 1.7°C/h because these rates span the clinically observed speeds at which core temperatures change (excepting during cardiopulmonary bypass). Vasoconstriction and shivering were not triggered at a higher temperature during rapid core cooling, indicating that these responses to core hypothermia were not influenced by the tested rates of core temperature changes. These data suggest that pre-

viously determined thresholds are not confounded by protocols resulting in a variety of core cooling rates.[3,4,7]

The rate at which skin temperature changes distinctly alters thermoregulatory response thresholds.[12,43] However, rates of skin temperature change far exceeding 1.7°C/h were required to produce noticeable effects in these studies. In practice, body mass limits the speed at which core temperature can change. Consequently, rates of change much exceeding 1.7°C/h are rarely observed except during immersion hypothermia[44] and cardiopulmonary bypass.[45] Rates of core temperature change far exceeding those we tested have been evaluated in a water-immersion protocol in which release of limb tourniquets was used to augment the core cooling rate.[46] The shivering gain (slope of the oxygen consumption *vs.* core temperature curve) in that study was 60% greater when the core was cooled at 14°C/h than at 3°C/h. However, the authors concluded that the increase likely was artifactual, resulting from payback of the oxygen debt accumulated by the ischemic limbs. We did not compare rapid and slow core cooling in the female volunteers. But given the lack of rate dependence in men, it seems unlikely that the core cooling rate contributes significantly to thermoregulatory responses in women.

We[8] and others[20] have reported that the sweating threshold in women is greater than that in men. In contrast, others have not observed differences. Although the difference in our current volunteers (0.3°C) was somewhat less than in our previous ones (0.5°C), both studies confirm that there are significant differences in the responses of men and women to heat stress. Our data extend previous observations by documenting that the vasoconstriction and shivering thresholds also are increased in women. Because the increases in each response were comparable, the interthreshold range remained ≈ 0.2°C in each sex. The range of core temperatures tolerated without triggering autonomic responses thus is similar in men and women, but women thermoregulate at a slightly higher temperature than men.

The morphometric characteristics of our male and female volunteers were typical for each gender. We made no effort to match height, weight, and body fat in the men and women because morphometric differences between the sexes is typical. A natural consequence of this decision is that we are unable to distinguish the extent to which the threshold differences in the men and women resulted specifically from their gender, rather than from body habitus. Previous studies suggest that much of the difference—and perhaps all of it—can be attributed to the normal morphometric differences between the sexes.[20] Although none of our volunteers was a conditioned athlete, we did not specifically evaluate conditioning or exercise tolerance. It thus remains possible that conditioning may have contributed to the higher thresholds we observed in the women.

Women not taking oral contraceptives were evaluated during the first 10 days of their monthly cycles (follicular phase). Tympanic membrane temperatures 0.3–0.7°C higher are typical during the remaining portions of the month.[47,48] Consequently, had we studied thermoregulatory responses in women in the luteal phase of their cycles, differences between the men and women likely would have been even greater. Interestingly, differences in the thresholds in the follicular and luteal phases is greater early in the morning than in the afternoon.[23]

The male volunteers were given somewhat more fluid during slow core-cooling than during rapid induction of hypothermia. However, most of the administered lactated Ringer's solution would rapidly diffuse into the extracellular space (especially during the slow infusion), leaving relatively little remaining within the blood stream. It thus is unlikely that actual vascular volume expansion differed substantially in the two groups. Dehydration significantly increases the sweating threshold.[49] Similarly, excessive hydration may reduce it; however, the sweating threshold in this protocol was determined before fluid administration. Although dehydration synergistically augments vasoconstriction,[31] excess vascular fluid is unlikely to substantially alter vasomotor activity or shivering.

Distal esophageal temperature is considered among the most reliable core temperature monitoring sites. Tympanic membrane temperatures usually are ≈ 0.1°C less than esophageal temperature.[8] Nonetheless, extensive experience has shown that esophageal and tympanic membrane temperatures usually correlate extremely well during mild hyperthermia[8] and hypothermia.[50,51] In the present study, tympanic membrane temperatures rarely deviated more than 0.1°C from esophageal values, with an average correlation coefficient of 0.97. It therefore is unlikely that our conclusions would have altered substantially had we included esophageal temperature measurements in our data analysis.

In summary, the sweating-to-vasoconstriction interthreshold range was ≈ 0.2°C in men and women,

but all thermoregulatory response thresholds were ≈ 0.3°C greater in women. All study thresholds were virtually identical during slow and fast core-cooling. Our data confirm the existence of an interthreshold range and document that its magnitude is small. The rate of core cooling, in the range of 0.7–1.7°C, does not appear to alter thermoregulatory responses.

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References

1. Sessler DI, Lee KA, McGuire J: Isoflurane anesthesia and circadian temperature cycles. ANESTHESIOLOGY 75:985–989, 1991

2. Sessler DI: Perianesthetic thermoregulation and heat balance in humans. FASEB J 7:638–644, 1993

3. Sessler DI, Olofsson CI, Rubinstein EH, Beebe JJ: The thermoregulatory threshold in humans during halothane anesthesia. ANESTHESIOLOGY 68:836–842, 1988

4. Stϕen R, Sessler DI: The thermoregulatory threshold is inversely proportional to isoflurane concentration. ANESTHESIOLOGY 72:822–827, 1990

5. Sessler DI, Olofsson CI, Rubinstein EH: The thermoregulatory threshold in humans during nitrous oxide–fentanyl anesthesia. ANESTHESIOLOGY 69:357–364, 1988

6. Hynson JM, Sessler DI, Belani K, Washington D, McGuire J, Merrifield B, Schroeder M, Moayeri A, Crankshaw D, Hudson S: Thermoregulatory vasoconstriction during propofol/nitrous oxide anesthesia in humans: Threshold and Sp_{O_2}. Anesth Analg 75:947–952, 1992

7. Washington DE, Sessler DI, McGuire J, Hynson J, Schroeder M, Moayeri A: Painful stimulation minimally increases the thermoregulatory threshold for vasoconstriction during enflurane anesthesia in humans. ANESTHESIOLOGY 77:286–290, 1992

8. Washington D, Sessler DI, Moayeri A, Merrifield B, Prager M, McGuire J, Belani K, Hudson S, Schroeder M: Thermoregulatory responses to hyperthermia during isoflurane anesthesia in humans. J Appl Physiol 74:82–87, 1993

9. Lopez M, Ozaki M, Sessler DI, Valdes M: Physiologic responses to hyperthermia during epidural anesthesia and combined epidural/enflurane anesthesia in women. ANESTHESIOLOGY 78:1046–1054, 1993

10. Kurz A, Sessler DI, Schroeder M, Kurz M: Thermoregulatory response thresholds during spinal anesthesia. Anesth Analg 77:721–726, 1993

11. Benzinger TH, Pratt AW, Kitzinger C: The thermostatic control of human metabolic heat production. Proc Natl Acad Sci USA 47: 730–739, 1961

12. Wyss CR, Brengelmann GL, Johnson JM, Rowell LB, Silverstein D: Altered control of skin blood flow at high skin and core temperatures. J Appl Physiol 38:839–845, 1975

13. Nadel ER, Bullard RW, Stolwijk JA: Importance of skin temperature in the regulation of sweating. J Appl Physiol 31:80–87, 1971

14. Nadel ER, Cafarelli E, Roberts MF, Wenger CB: Circulatory regulation during exercise in different ambient temperatures. J Appl Physiol 46:430–437, 1979

15. Mekjavic IB, Sundberg CJ, Linnarsson D: Core temperature "null zone." J Appl Physiol 71:1289–1295, 1991

16. Cabanac M, Massonnet B: Thermoregulatory responses as a function of core temperature in humans. J Physiol (Lond) 265:587–596, 1977

17. Brengelmann GL, Wyss C, Rowell LB: Control of forearm skin blood flow during periods of steadily increasing skin temperature. J Appl Physiol 35:77–84, 1973

18. Frank SM, Beattie C, Christopherson R, Norris EJ, Rock P, Parker S, Kimball AW: Epidural *versus* general anesthesia, ambient operating room temperature, and patient age as predictors of inadvertent hypothemia. ANESTHESIOLOGY 77:252–257, 1992

19. Kurz A, Kurz M, Poeschl G, Faryniak B, Redl G, Hackl W: Forced-air warming maintains intraoperative normothermia better than circulating-water mattresses. Anesth Analg 77:89–95, 1993

20. Havenith G, van Midendorp H: The relative influence of physical fitness, acclimatization state, anthropometric measures and gender on individual reactions to heat stress. Eur J Appl Physiol 61:419–427, 1990

21. Avellini BA, Kamon E, Krajewski JT: Physiological responses of physically fit men and women to acclimation to humid heat. J Appl Physiol 49:254–261, 1980

22. Kolka MA, Stephenson LA, Rock PB, Gonzalez RR: Local sweating and cutaneous blood flow during exercise in hypobaric environments. J Appl Physiol 62:2224–2229, 1987

23. Stephenson LA, Kolka MA: Menstrual cycle phase and time of day alter reference signal controlling arm blood flow and sweating. Am J Physiol 249:R186–191, 1985

24. Sessler DI, Moayeri A: Skin-surface warming: Heat flux and central temperature. ANESTHESIOLOGY 73:218–224, 1990

25. Sessler DI, Moayeri A, Stϕen R, Glosten B, Hynson J, McGuire J: Thermoregulatory vasoconstriction decreases cutaneous heat loss. ANESTHESIOLOGY 73:656–660, 1990

26. Conway JM, Norris KH, Bodwell CE: A new approach for the estimation of body composition: Infrared interactance. Am J Clin Nutr 40:1123–1130, 1984

27. Mekjavic IB, Rempel ME: Determination of esophageal probe insertion length based on standing and sitting height. J Appl Physiol 69:376–379, 1990

28. DuBois D, DuBois EF: A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17: 863–871, 1916

29. Seckendorf R, Randall WC: Thermal reflex sweating in normal and paraplegic man. J Appl Physiol 16:796–800, 1961

30. Rubinstein EH, Sessler DI: Skin-surface temperature gradients correlate with fingertip blood flow in humans. ANESTHESIOLOGY 73: 541–545, 1990

31. Rowell LB: Cardiovascular aspects of human thermoregulation. Circ Res 52:367–379, 1983

32. Jessen K: An assessment of human regulatory nonshivering thermogenesis. Acta Anaesthesiol Scand 24:138–143, 1980

33. Jessen K, Rabϕl A, Winkler K: Total body and splanchnic thermogenesis in curarized man during a short exposure to cold. Acta Anaesthesiol Scand 24:339–344, 1980

34. Hynson JM, Sessler DI, Moayeri A, McGuire J: Absence of nonshivering thermogenesis in anesthetized adult humans. ANESTHESIOLOGY 79:695–703, 1993

35. Satinoff E, Rutstein J: Behavioral thermoregulation in rats with anterior hypothalamic lesions. J Comp Physiol Psychol 71:77–82, 1970

36. Mekjavic IB, Bligh J: The increased oxygen uptake upon immersion: The raised external pressure could be a causative factor. Eur J Appl Physiol 58:556–562, 1989

37. Mekjavic IB, Morrison JB: A model of shivering thermogenesis based on the neurophysiology of thermoreception. IEEE Trans Biomed Eng 32:407–417, 1985

38. Baum E, Brück K, Schwennicke HP: Adaptive modifications in the thermoregulatory system of long-distance runners. J Appl Physiol 40:404–410, 1976

39. Sessler DI, Rubinstein EH, Moayeri A: Physiologic responses to mild perianesthetic hypothermia in humans. ANESTHESIOLOGY 75: 594–610, 1991

40. Satinoff E: Neural organization and evolution of thermal regulation in mammals: Several hierarchically arranged integrating systems may have evolved to achieve precise thermoregulation. Science 201:16–22, 1978

41. Herdman SJ: Recovery of shivering in spinal cats. Exp Neurol 59:177–189, 1978

42. Kosaka M, Simon E, Thauer R: Shivering in intact and spinal rabbits during spinal cord cooling. Experientia 23:385–387, 1967

43. Wurster RD, McCook RD: Influence of rate of change in skin temperature on sweating. J Appl Physiol 27:237–240, 1969

44. Giesbrecht GG, Bristow GK: A second postcooling afterdrop: more evidence for a convective mechanism. J Appl Physiol 73:1253–1258, 1992

45. Sladen RN, Berend JZ, Sessler DI: Rewarming and sweating during cardiopulmonary bypass. J Cardiothorac Vasc Anesth (in press)

46. Mittleman KD, Mekjavic IB: Effect of occluded venous return on core temperature during cold water immersion. J Appl Physiol 65:2709–2713, 1988

47. Hessemer V, Brück K: Influence of menstrual cycle on thermoregulatory, metabolic, and heart rate responses to exercise at night. J Appl Physiol 59:1911–1917, 1985

48. Hessemer V, Brück K: Influence of menstrual cycle on shivering, skin blood flow, and sweating responses measured at night. Am Physiol Soc 1902–1910, 1985

49. Nadel ER, Fortney SM, Wenger CB: Effect of hydration state on circulatory and thermal regulations. J Appl Physiol 49:715–721, 1980

50. Cork RC, Vaughan RW, Humphrey LS: Precision and accuracy of intraoperative temperature monitoring. Anesth Analg 62:211–214, 1983

51. Bissonnette B, Sessler DI, LaFlamme P: Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature. Anesth Analg 69: 192–196, 1989