

# Diurnal Variation in the Core Interthreshold Zone in Women and its Sex Difference

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## Abstract

**Background:** The core interthreshold zone (CIZ) is defined as the range between core temperature ( $T_c$ ) at the onset of shivering and the  $T_c$  at the onset of sweating under consistent mean skin temperatures of 28°C to 30°C. A previous study demonstrated a diurnal change in the CIZ for male subjects and its relationship to the cutaneous sensation threshold zone (CSZ). In the present study, diurnal changes in the CIZ and the CSZ for young Japanese female subjects were investigated using the same experimental protocol from the study of male subjects and the sex differences in these responses were then examined.

**Methods:** The CIZ and the CSZ were measured in 10 female subjects who participated in three experiments in a single day during the morning, afternoon, and evening in the summer of 2014 (single-day experiment), and six female subjects who participated in the same experiments on the morning of day 1, the afternoon of day 2, and the evening of day 3 during the summer of 2016 (multiple-day experiment).

Air temperature was controlled at 25°C. Each subject wore a suit perfused with 25°C water at a rate of 600 cc/min, and exercised at 50% of their maximum work rate on an ergometer for 10–15 min until their sweating rate increased. They then remained seated, without exercising, until their oxygen uptake increased. Rectal temperature, skin temperature at seven sites, the forehead-sweating rate, and oxygen uptake were continuously monitored throughout the experiment. Cutaneous warm and cold sensation thresholds were measured at three sites using 1-cm<sup>2</sup> and 2-cm<sup>2</sup> probes.

**Results:** The results from the single-day experiment demonstrated that the CIZ was proportional to core temperature prior to exercise ( $T_{c-init}$ ) whereas the results from the multiple-day experiment demonstrated that the CIZ increased continuously from morning to evening despite almost a constant  $T_{c-init}$ . The CIZ appeared to be proportional to the CSZ measured with the 2-cm<sup>2</sup> probe. When compared with the results from the previous study of men, no significant sex difference was observed between the CIZ of 0.25±0.07°C for female subjects and 0.21±0.05°C for male subjects.

**Conclusion:** No significant sex difference or diurnal variation in the CIZ was confirmed. Continuous increase in the CIZ from morning until evening is expected in both men and women under a normal  $T_c$  circadian rhythm.

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## Introduction

The core interthreshold zone (CIZ) is defined as the range between the core temperature ( $T_c$ ) at the onset of shivering and  $T_c$  at the onset of sweating, and is recognized as an important factor for thermoregulatory defense. Since both the  $T_c$  and mean skin temperature  $\overline{T_{sk}}$  contribute to the control of sweating and shivering, constant  $\overline{T_{sk}}$  is required to be independent of thermal responses due to changes in  $\overline{T_{sk}}$ . Although three different experimental methods have been proposed to keep  $\overline{T_{sk}}$  constant<sup>1, 2, 3</sup>, Kakitsuba et al.<sup>4</sup> devised an alternative method using water-perfused suits, following the method proposed by Mekjavic et al.<sup>3</sup>, and demonstrated a seasonal change in the CIZ, and light dependence of the CIZ, which indicated the possible incorporation of a non-visual pathway into the human thermoregulation<sup>5</sup>.

Another previous study found that the peripheral interthreshold zone (PIZ) was proportionally correlated with the CIZ<sup>6</sup>. This finding suggested that diurnal variation in the CIZ could be correlated with the cutaneous sensation threshold zone (CSZ), a determinant of the PIZ. In a series of CIZ studies carried out from 2014 to 2015, diurnal changes in the CIZ for Japanese male subjects were investigated by measurement of the CSZ using a thermal simulator<sup>7</sup>. The results demonstrated that the CIZ is not dependent on the time of a day but is strongly dependent on  $T_c$ , which implies that the CIZ may be widest in the early morning but becomes narrower towards evening following a normal  $T_c$  circadian rhythm. This diurnal variation corresponded well with that reported by Tayefeh et al.<sup>8</sup>, who demonstrated that the interthreshold range at 03h: 00 was twice that observed

at the other study times of 08h: 00, 15h: 00, and 20h: 00, although a different method was used. Sex differences in the sweating-to-vasoconstriction interthreshold range were studied by Anderson et al.<sup>9</sup> and Lopez et al.<sup>10</sup>, who reported that no significant sex differences were evident in the range, whereas both thresholds from female subjects were 0.2 to 0.3°C higher than those from male subjects.

In the present study, considering the possibility of both seasonal and light exposure effects on the CIZ, the diurnal variations in the CIZ and the CSZ for Japanese young female subjects were investigated, and the sex differences in the responses were then compared with the results for the male subjects reported by Kakitsuba and Mekjavic<sup>7</sup>.

## Experimental procedure

### Subjects

The experiments were performed in a climatic chamber at Meijo University, Nagoya, Japan. Ten Japanese females, aged 20 to 24 years, participated in the experiments carried out in the summer of 2014 (single-day experiment), and six Japanese females, aged 20 to 22 years, participated in the experiments conducted over three days in the summer of 2016 (multiple-day experiment). No subjects took part in both experiments. All subjects were required to sleep before midnight and wake at 07h: 00 for three days at home prior to the experimental day to reproduce the daily circadian rhythm they would experience during the experiment. Subject activities were monitored using an Acti-heart device (CamNtech Co. Ltd., Cambridge, UK) because they were instructed not to engage in vigorous exercise for a prolonged period of time.

The maximum work capacity of the subjects

was estimated prior to the experiment during an incremental load exercise on a cycle ergometer. The subjects pedaled at a rate of 60 rpm, and the work rate was increased incrementally by 10 W/min until the subjects were exhausted or could no longer maintain the required cadence. In addition, based on the procedure outlined by Drinkwater<sup>11</sup>, anthropometric measurements of skinfold thickness at multiple sites, including the girth, length, and bone breadth of specific body compartments, were taken for each subject. The obtained values were then used to estimate the regional weights of skin, adipose tissue, skeletal muscle, bone, and residual tissues. The adiposity was estimated from the formula proposed by Kakitsuba and Mekjavic<sup>12</sup>. Body surface area (BSA) was calculated using Kurazumi's formula<sup>13</sup>, as it was developed for Japanese morphology. The mean ( $\pm$ standard deviation [SD]) height, weight, BSA, and adiposity for the subjects in the single-day experiment were  $159.2 \pm 5.98$  cm,  $51.7 \pm 4.88$  kg,  $1.50 \pm 0.06$  m<sup>2</sup>, and  $0.39 \pm 0.06$ , respectively, whereas they were  $154.6 \pm 3.45$  cm,  $50.4 \pm 4.78$  kg, and  $1.48 \pm 0.07$  m<sup>2</sup> and  $0.37 \pm 0.05$ , respectively, for the subjects in the multiple-day experiment. There were no significant differences in body size or body composition between the groups of subjects.

In the single-day experiment, the subjects participated in three consecutive experiments in a single day: morning (08h: 30–11h: 00), afternoon (13h: 00–15h: 30), and evening (17h: 00–19h: 30). Following the morning and afternoon tests, each subject was passively rewarmed with a heater for 1 h to restore their core temperature. In the multiple-day experiment, the subjects participated in experiments on the morning of day 1, the afternoon of day 2, and the evening of day 3 without any rewarming procedure. All trials were performed during the luteal phase of each subject's menstrual cycle. All subjects gave their informed consent to participate in the study and were fully aware that they could withdraw from the study at any time without prejudice. The study protocol was approved by the ethics review committee at Meijo University. (Table 1)

### Experimental protocol

Because the effect of lighting and season on the CIZ was confirmed in a previous study<sup>5</sup>, luminance was carefully controlled at 1,000 lx, and all experiments were

conducted from August to September, as described in the experimental protocol of our previous study<sup>7</sup>.

The  $\overline{T}_{sk}$  as calculated using the equation proposed by Hardy and DuBois<sup>14</sup>, was maintained at 28° C using a water-perfused suit (Cool Tubesuit; Med-Eng Systems, Inc., Ottawa, Ontario, Canada; Photograph 1). Subjects wore the water-perfused suit and remained seated on a cycle ergometer for 5 to 10 min without exercise until  $\overline{T}_{sk}$  decreased to 28–29°C. The subjects then continued exercising at 50% of their maximum work rate on the cycle ergometer. The exercise was terminated at the onset of sweating, which occurred after 10–15 min. The subjects then remained seated on the cycle ergometer for an additional 100 min. The onset of shivering was observed when the oxygen uptake started to increase during the last part of the test, while the  $\overline{T}_{sk}$  remained at 28°C. The CIZ was defined as the rectal temperature ( $T_{re}$ ) at which the sweating rate ( $S_{wr}$ ) and oxygen uptake were elevated above median resting levels. Examples of the change in  $T_{re}$  and  $\overline{T}_{sk}$  are shown in Fig. 1.

### Measurements

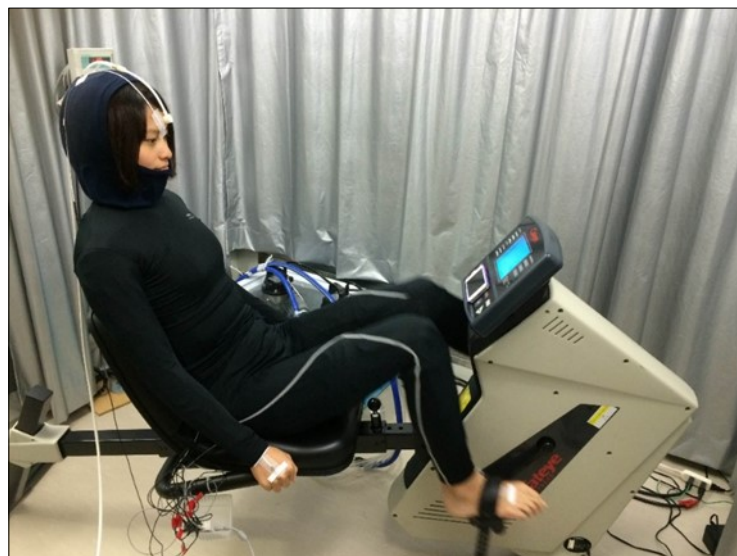
The  $T_{re}$  and skin temperatures were monitored at seven sites (forehead, forearm, back of hand, abdomen, chest, anterior thigh, and calf) using thermistors, and the values were stored every 10 s using a data logger system (Cadac2 Model 9200A; Cadac, Tokyo, Japan). For rectal temperatures, a thermistor was inserted 15 cm past the anal verge. The  $S_{wr}$  was measured at the forehead with a sweat rate monitor (Model SKD-4000; Skinos Co., Ltd., Nagoya, Japan). Oxygen uptake was monitored with a gas analyzer (Respiromonitor RM-300i; Minato Medical Science Co. Ltd., Tokyo, Japan).

Maintenance of mean skin temperature, while simultaneously extracting 120 W/m<sup>2</sup> of heat, was achieved by having the subjects wear the water-perfused suit. The water perfusing the suit was pumped at a rate of 600 cc/min (Water Pump Model Super Tepcon; Terada, Tokyo, Japan) from a water bath maintained at 25°C with a heat exchanger (Cool Mate Model TE-105M; Toyo Seisakusho Co., Tokyo, Japan). A diagram of the cooling system is shown in Fig. 2.

Before each test, cutaneous warm and cool sensation thresholds were measured at the anterior

Table 1. Rectal temperature prior to exercise, sweating and shivering thresholds and core interthreshold zone in the female subjects

Year	Periods	Rectal temperature prior to exercise (°C)	Sweating threshold (°C)	Shivering threshold (°C)	Core interthreshold zone (°C)
Single-day experiment (n=10)	morning	36.90	37.15	36.81	0.34
	afternoon	36.94	37.07	36.77	0.30
	evening	36.72	36.94	36.67	0.27
Multiple-day experiment (n=6)	morning	37.20	37.15	37.00	0.15
	afternoon	37.14	37.15	36.94	0.21
	evening	37.15	37.11	36.87	0.25
means±SD		37.01± 0.19	37.09± 0.08	36.84± 0.12	0.25± 0.07



Photograph 1. A female subject wearing a water-perfused suit.

This photograph is of a female subject wearing a water-perfused suit and exercising at 50% of her maximum work rate on a cycle ergometer.

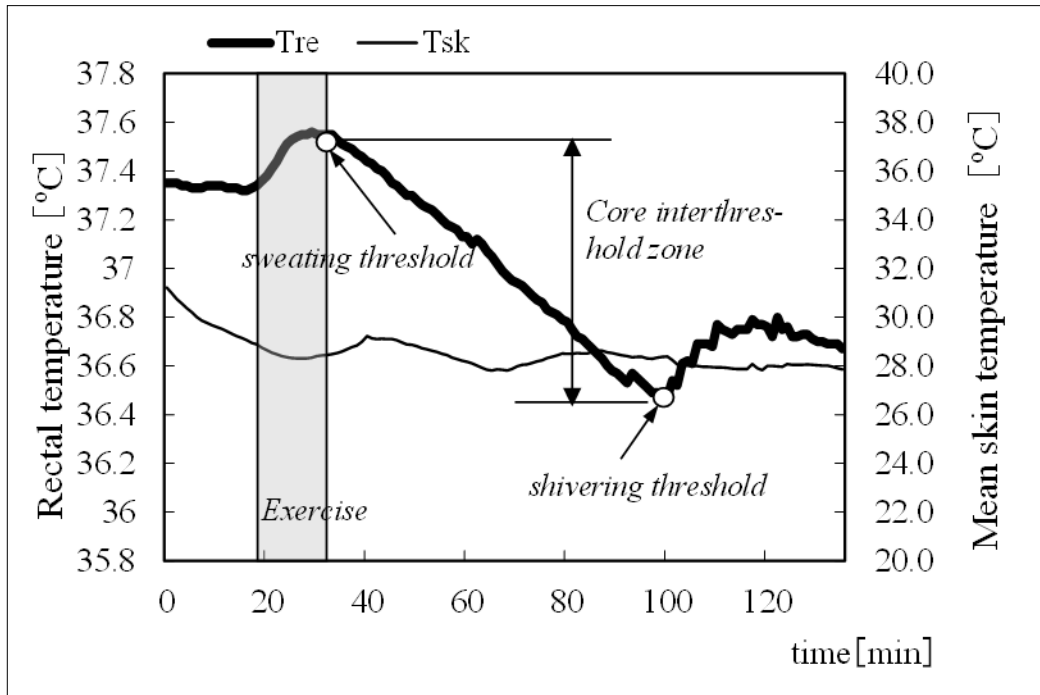


Figure 1. An example of changes in rectal temperature and mean skin temperature during the experiment.

The  $T_{re}$  and  $\bar{T}_{sk}$  indicate rectal temperature and mean skin temperature, respectively when one of the female subjects underwent in the single-day experiment. The onset of sweating was observed during exercise. Following exercise, the subjects rested until shivering was observed at 70 to 90 min after the beginning of exercise.

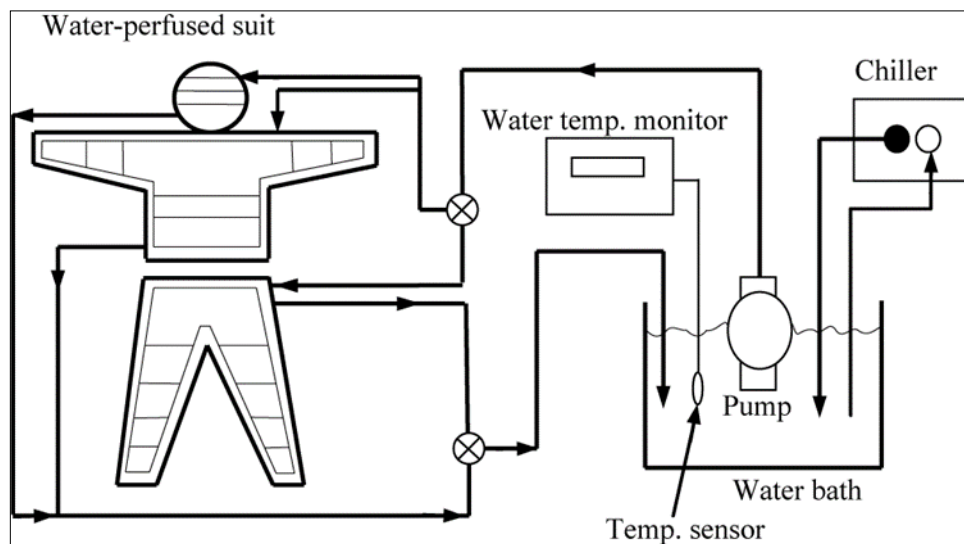


Figure 2. Diagram of the cooling system for the water-perfused suit.

A chiller cooled the water in the bath and a pump supplied cool water to the vinyl tubes incorporated in the suit. After water was perfused through the tubes, it was returned to the water bath and cooled again.

forearm, posterior forearm, and anterior thigh using a thermal stimulator controlled by a Peltier element (Intercross-230, Intercross, Co., Tokyo, Japan). To register any diurnal variations in peripheral thermosensitivity, regardless of the size of the thermode, two probes were used so the contact area when applied to the skin was either 10 × 10 mm or 20 × 20 mm. Once the probe surface temperature became equal to the skin temperature, i.e., adaption temperature, it was changed at a rate of 0.1°C/s and continuously changed until the subject felt a warm or cool sensation. The CSZ was then determined as the temperature range between the warm and cool sensation thresholds.

### Statistical analysis

All physiological variables measured are presented as means ± SD. A comparison of the variables between the three daytime periods was analyzed using repeated measures analysis of variance. The Bonferroni test was used for post-hoc analysis of significant differences set at  $p < 0.05$ .

### Results

#### *Diurnal Variation in the CSZ*

The CSZ and average skin temperature at three sites before measurement ( $T_{sk-av}$ ) in the single-day experiment and the multiple-day experiment are shown in Fig. 3. Results from the single-day experiment showed a continuous diurnal decrease in the CSZ measured with both the 1-cm<sup>2</sup> probe and the 2-cm<sup>2</sup> probe, whereas results from the multiple-day experiment showed that the CIZ increased significantly ( $p < 0.05$ ) from morning to afternoon and decreased significantly ( $p < 0.01$ ) from afternoon to evening in the case of measurement with the 1-cm<sup>2</sup> probe. Almost no change in the CSZ was found when measured with the 2-cm<sup>2</sup> probe. As indicated in Fig. 4, however, the CSZ was inversely ( $r = -0.81$ ) correlated with the  $T_{sk-av}$  when measured with the 2-cm<sup>2</sup> probe.

#### *Diurnal Variation in the CIZ*

The diurnal variations in the CIZ, together with rectal temperature before exercise ( $T_{c-init}$ ), shivering and sweating thresholds in the single-day and the multiple-day experiments, are shown in Fig. 5. The  $T_{c-init}$ , the shivering and sweating thresholds decreased

continuously from morning to evening in the single-day experiment. Since the sweating threshold decreased more than the shivering threshold, the CIZ decreased from morning to evening. It is interesting to note that the difference between  $T_{c-init}$  and the sweating threshold increased as  $T_{c-init}$  decreased towards evening. In the multiple-day experiment, the  $T_{c-init}$  and the sweating threshold remained unchanged whereas the shivering threshold continuously decreased from morning to evening. As a result, the CIZ increased continuously from morning to evening. The relationship between the CIZ and the CSZ is shown in Fig. 6. The CIZ was proportionally correlated ( $R^2 = 0.71$ ) with the CSZ measured with the 2-cm<sup>2</sup> probe.

#### *Sex Differences in the CSZ and the CIZ*

In a previous study [7], a series of experiments for male subjects was carried out in 2014 and 2015 using the same experimental protocol. Figure 7 shows the diurnal variation in the  $T_{c-init}$ , sweating and shivering thresholds, and CIZ in men. A CIZ of  $0.25 \pm 0.07^\circ\text{C}$  was observed for female subjects in the present study and a CIZ of  $0.21 \pm 0.05^\circ\text{C}$  was previously reported for the male subjects. Thus, no significant sex difference in the CIZ was confirmed. Moreover, the mean sweating  $T_c$  values for male and female subjects was  $37.09^\circ\text{C}$ , and the mean shivering  $T_c$  values for male and female subjects were  $36.89^\circ\text{C}$  and  $36.84^\circ\text{C}$ , respectively. Thus, no major sex difference in the threshold core temperature was also confirmed.

In Fig. 4, the CSZ measured with the 1-cm<sup>2</sup> probe for men is indicated together with the results from the female subjects. The CSZ measured with the 1-cm<sup>2</sup> probe for men was inversely correlated ( $r = 0.91$ ) with the average skin temperature before the experiment, and the CSZ of  $3.67 \pm 0.84^\circ\text{C}$  for female subjects was significantly narrower ( $p < 0.01$ ) than that of  $6.64 \pm 2.91^\circ\text{C}$  for male subjects, although both values cannot be directly compared because cutaneous temperature sensitivity depends on the contact area of the probe.

### Discussion

Diurnal variation of the CIZ was investigated in female subjects, while the  $T_c$  was maintained throughout the day as consistently as possible by conducting experiments sequentially on the same day in a

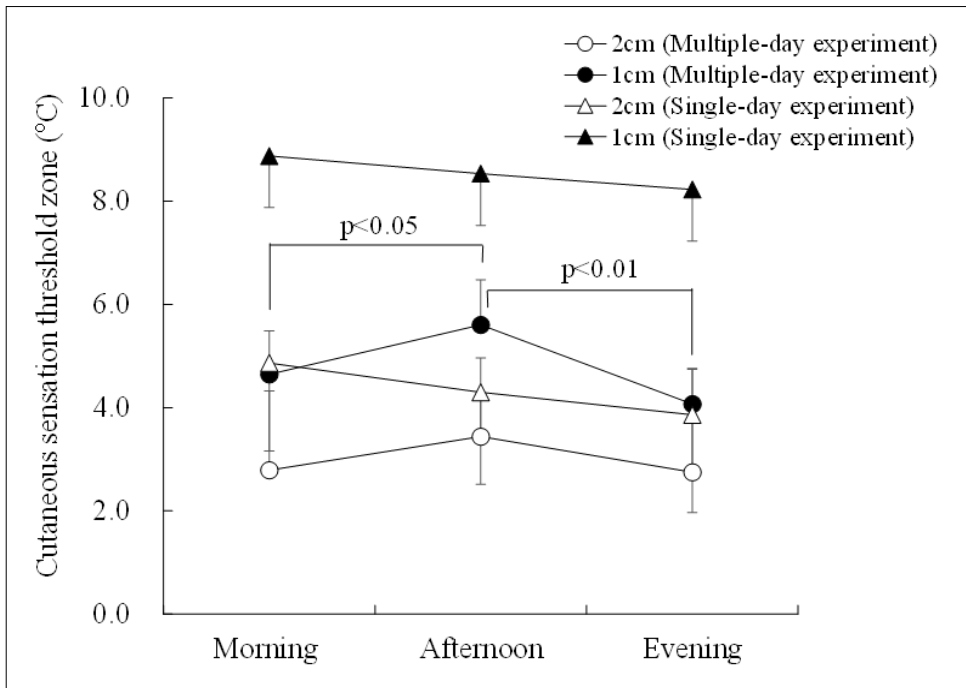


Figure 3. Diurnal variation in the cutaneous sensation threshold zone measured with 1-cm<sup>2</sup> and 2-cm<sup>2</sup> probes.

Results from the single-day experiment showed a continuous decrease in the cutaneous sensation threshold zone (CSZ), measured with both 1-cm<sup>2</sup> probe and 2-cm<sup>2</sup> probe; whereas results from the multiple-day experiment showed that the CSZ increased significantly ( $p < 0.05$ ) from morning to afternoon, and decreased significantly ( $p < 0.01$ ) from afternoon to evening, measured with 1-cm<sup>2</sup> probe.

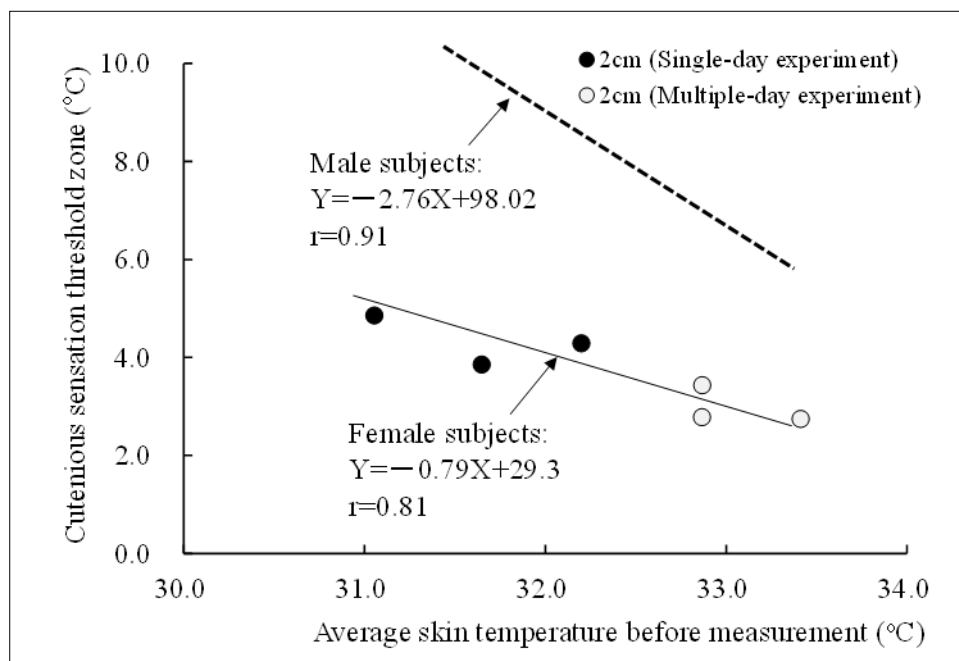


Figure 4. Relationship between the cutaneous sensation threshold zones measured with the 2-cm<sup>2</sup> probe and the average skin temperatures before measurement.

The result from the present study indicated that the cutaneous sensation threshold zone (CSZ) measured with a 2-cm<sup>2</sup> probe was inversely correlated with the average skin temperature before measurement. The hatched line indicates the CSZ for male subjects measured with a 1-cm<sup>2</sup> probe, as previously reported<sup>7</sup>.

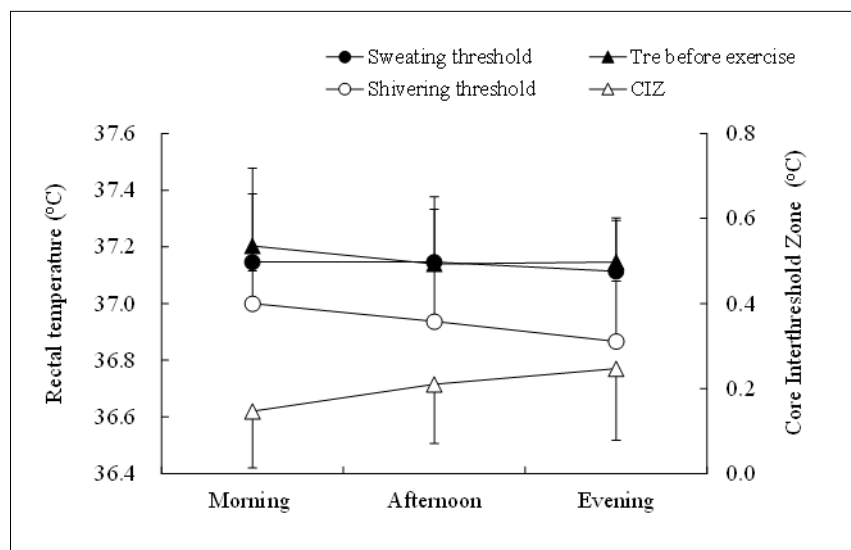
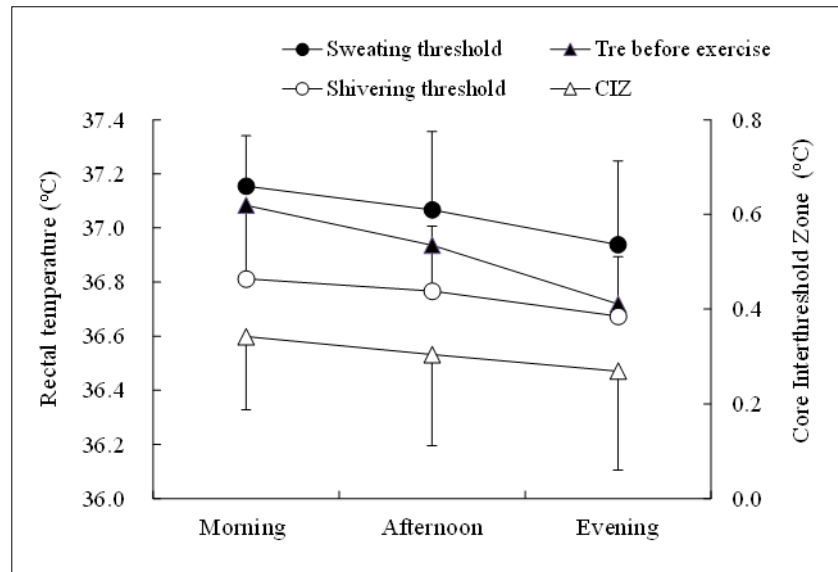


Figure 5. Diurnal variation in sweating and shivering thresholds, rectal temperature before exercise and core interthreshold zone.

The results in the single-day experiment and the multiple day experiment are described in the upper part and the lower part of the figure, respectively. It was found that the core interthreshold zone (CIZ) decreased from morning to evening with decrease in rectal temperature before exercise ( $T_{c-int}$ ) in the single-day experiment, and the CIZ increased continuously from morning to evening although  $T_{c-int}$  remained almost unchanged in the multiple-day experiment.



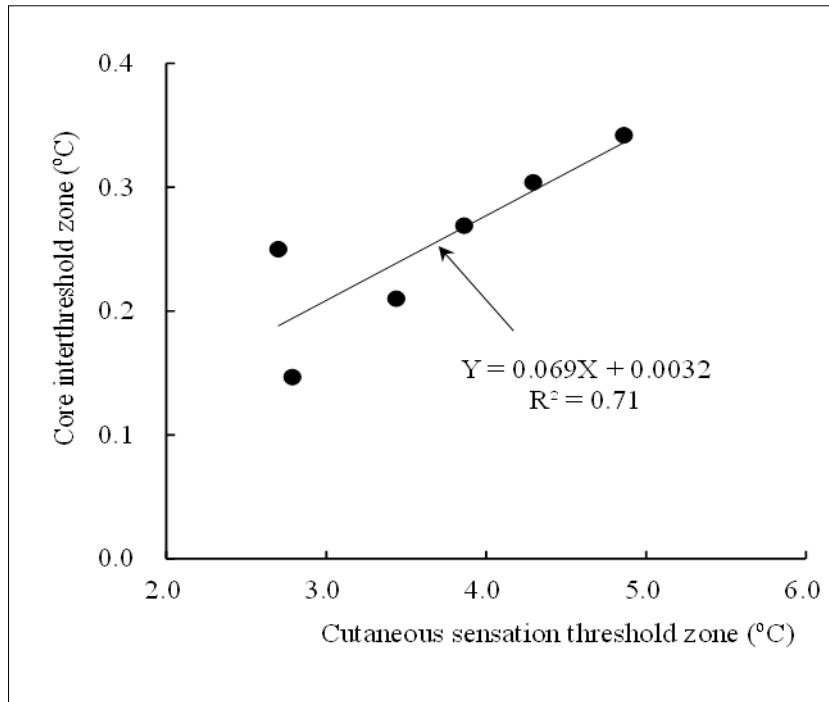


Figure 6. Relationship between core interthreshold zones and cutaneous sensation threshold zones measure with 2-cm<sup>2</sup> probe.

The core interthreshold zone was proportionally ( $R^2=0.71$ ) correlated with the cutaneous sensation zone measured with the 2-cm<sup>2</sup> probe.

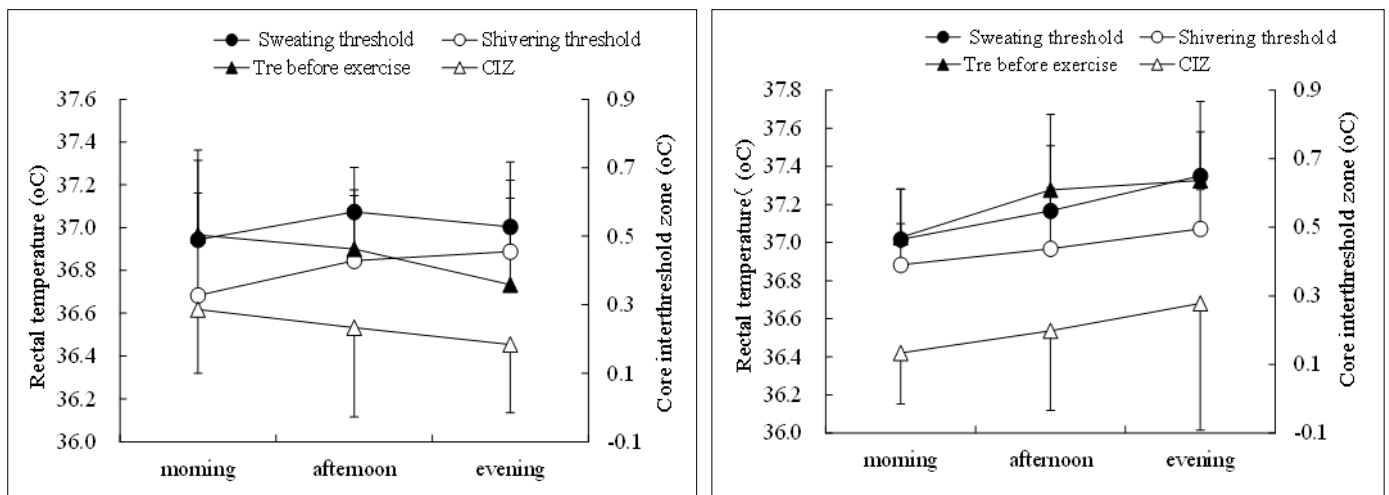


Figure 7. Diurnal variation in sweating and shivering thresholds, rectal temperature prior to exercise and core interthreshold zone in men.

These results were published in the previous study<sup>7</sup>. The results in the single-day experiment (upper part) and the multiple-day experiment (lower part) are described in the same manner to compare the results from the present study. The result from the single-day experiment indicated that the core interthreshold zone (CIZ) decreased from morning to evening with decrease in rectal temperature before exercise ( $T_{c-int}$ ) whereas the result from the multiple-day experiment indicated that the CIZ increased continuously from morning to evening with increase in  $T_{c-int}$ .

single-day experiment. Moreover, the typical diurnal rhythm of  $T_c$  was expected to be reproduced by conducting the experiments on sequential days in a multiple-day experiment. The experimental protocol was the same as the previously reported study of male subjects<sup>4, 5, 6, 7</sup>.

As shown in Fig. 4, the CSZ measured using the 2-cm<sup>2</sup> probe correlated well with the  $T_{sk-av}$  for the female subjects, whereas the CSZ measured with the 1-cm<sup>2</sup> probe correlated well with the  $T_{sk-av}$  for the male subjects. The CSZ of  $3.67 \pm 0.84^\circ\text{C}$  ( $n=16$ ) observed in the female subjects was significantly narrower ( $p < 0.01$ ) than the  $6.64 \pm 2.91^\circ\text{C}$  ( $n=16$ ) observed in the male subjects under an experimentally controlled  $T_c$  range. Thus, the CSZ values for male subjects were approximately 1.8 times wider than those for female subjects. However, both values cannot be directly compared because cutaneous temperature sensitivity depends on the contact area of the probe. Since probes with different contact areas have been used by many scientists<sup>15, 16, 17</sup>, cutaneous temperature sensitivity can be compared under various thermal conditions, as long as it was measured at a constant rate change of  $1^\circ\text{C/s}$ . Knowing that the CSZ for male and female subjects measured with a 1-cm<sup>2</sup> probe was 1.38 and 1.6 times wider, respectively, than the CSZ measured using a 2-cm<sup>2</sup> probe, it can be estimated that the CSZ for male subjects is wider than that for female subjects when measured with the same size probe. This sex difference in the CSZ agrees well with the results of a study by Golja et al.<sup>18</sup> who reported that females showed a significantly narrower CSZ than males.

No significant sex differences in the CIZ were confirmed. This result agrees with studies by Anderson et al.<sup>9</sup> and Lopez et al.<sup>10</sup> who reported no significant sex differences in the CIZ. They also demonstrated that both threshold temperatures of the female subjects were 0.2 to  $0.3^\circ\text{C}$  higher than those of male subjects. Unfortunately, no sex differences in threshold temperatures were confirmed in the present study. The reason may be due to a difference in mean skin temperature, because  $\overline{T_{sk}}$  was kept low at  $28\text{--}30^\circ\text{C}$  in the present study using a water-perfused suit, as opposed to the studies by Anderson et al.<sup>9</sup> and Lopez et al.<sup>10</sup> where the  $\overline{T_{sk}}$  was maintained higher at  $35\text{--}36^\circ\text{C}$ .

As shown in Fig. 5, the results from the single-day experiment indicated that the CIZ increased as the  $T_c$  increased. The results from the multiple-day experiment, in which we attempted to reproduce a typical  $T_c$  rhythm, were unexpected and demonstrated a continuous diurnal increase in the CIZ despite almost a consistent  $T_{c-init}$ . This suggests that the variations in the CIZ may depend on the diurnal rhythm of endogenous functions. For men (see Fig. 7), the CIZ increased  $0.26^\circ\text{C}$  and  $0.41^\circ\text{C}$  per unit increase in  $T_c$  in the single- and the multiple-day experiments, respectively. These increases were greater than the  $0.1^\circ\text{C}$  increase in the CIZ observed in women from the multiple-day experiment. This result suggests that the variations in the CIZ in men may also depend on the diurnal rhythm of endogenous functions.

Considering the standard  $T_c$  diurnal rhythm, which is a progressive increase in  $T_c$  in the morning, followed by a more gradual increase during the afternoon and then a relatively constant  $T_c$  during the evening, the CIZ in the morning is likely the narrowest CIZ of the day, which then widens during the afternoon and evening, as demonstrated in the previous study of men<sup>7</sup>.

## Conclusion

The results from the present study, together with those from the previous study of men, indicate no significant sex difference in the CIZ, and imply a diurnal increase in the CIZ in both men and women, due to an increase in  $T_c$  and the diurnal rhythm of endogenous functions if a normal  $T_c$  circadian rhythm is expected. Furthermore, the CSZ measured with a 2-cm<sup>2</sup> probe is inversely proportional to the average skin temperature before measurement.

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## Conflict of interest

The authors declare that they have no conflict of

interests.

### Abbreviations

CIZ = core interthreshold zone

CSZ = cutaneous sensation threshold zone

PIZ = peripheral interthreshold zone

$T_{c-init}$  = core temperature before exercise

$T_{sk-av}$  = average skin temperature at three sites before measurement

BSA = body surface area

$\overline{T}_{sk}$  = mean skin temperature

$T_{re}$  = rectal temperature

$T_c$  = core temperature

$E_{sk}$  = sweating rate.

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