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Effect of the menstrual cycle phase on foot skin temperature during menthol application in young women

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ABSTRACT

According to the literature, the arteriovenous anastomoses in the peripheral parts (ex. hands and feet) respond thermal stimulation susceptibly. Thus, the feet are sensitive to cold stimulation. The aim of the present study was to investigate the effect of menstrual cycle on skin temperature (T_{sk}) of the foot during menthol application in young women. T_{sk} and partial cutaneous blood flow in the foot, tympanic temperature, blood pressure, heart rate, thermal sensation and pleasantness during the preovulatory (P), luteal (L), and menstrual (M) phases during menthol application in young women using thermography, laser Doppler flowmetry, a digital blood pressure monitor, and VAS scale were examined at 25 °C. After application of the 0.5% menthol solution to the right foot, the measurements were continued for 20 min. The T_{sk} of the second and third right toes in the P phase were lower than that in the L phase. The T_{sk} of the little right toe in the P phase was lower than that in the L and M phases. No significant differences were observed in the T_{sk} of the dorsum of right foot, cutaneous Laser-Doppler flow in the right great toe, tympanic temperature, blood pressure, heart rate, thermal sensation and pleasantness among the phases. The menstrual cycle phase did not affect T_{sk} in the dorsum of the foot, but it affected T_{sk} in some toes during menthol application.

1. Introduction

In a questionnaire-based survey, women who experienced subjective coldness sensations in daily life experienced a sensation of coldness in their feet (Takatori, 1992). Even in the healthy young women, it is common to feel coldness in the feet in the cold. The concentrations of plasma female hormones fluctuate during the menstrual cycle, with the plasma estradiol (E_2) concentration being greater in the preovulatory phase (P phase) and lower in the luteal phase (L phase). The plasma E_2 and progesterone concentrations are lower in the menstrual phase (M phase). In the healthy young women, the cutaneous blood flow in the great toe determined by Laser-Doppler flowmetry was greater in the P phase than in the L phase during mild local cooling (24.7 °C) of the foot (Uchida et al., 2018b). In general, the augmentation of cutaneous blood flow results in an increase of skin temperature (T_{sk}). Thus, the menstrual cycle might influence the control of T_{sk} of feet in young women in the cold. The increase of heat dissipation from the skin induces thermal unpleasantness in the cold. These results indicated that the menstrual cycle might affect the coldness sensation in young women in the cold.

The cooling activates the peripheral cold receptors expressed in the sensory nerves of the skin such as transient receptor potential melastatin-8 (TRPM8) and TRPA1 (Peier et al., 2002; Story et al., 2003). Menthol, which is one of the ingredients used as mint in herbal products, is used in products for providing a cold sensation and as an agonist of TRPM8. Young women felt colder with menthol application than with vehicle application to the foot under the same experimentally-controlled local temperature conditions (temperature decrease, 35 °C–25 °C) (Yamazaki and Sone, 2017). The results indicated that menthol application affected the cold sensation experienced in the foot in young women; however, they did not consider the menstrual cycle in the subjects and added thermal stimulus to the foot during menthol application. Thus, it is not clear whether the effect of the menstrual cycle on the thermoregulatory responses was induced by menthol application and whether menthol application itself had an effect on the T_{sk} of the foot. In animal study, systemic E_2 administration suppressed core temperature during the application of menthol, but not cinnamaldehyde that was an agonist of TRPA1 to body trunk in ovariectomized rat (Uchida et al., 2018a; Uchida and Atsumi, 2019). The results indicated that E_2 which fluctuated in menstrual cycle might affect the

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thermoregulatory responses via TRPM8, not TRPA1 in female rats. The change of body temperature affects $T_{sk,}$ thermal sensation, and pleasantness in the cold. Thus, the menstrual cycle might affect $T_{sk,}$ thermal sensation, and pleasantness during menthol application in young women.

The aim of the present study was to validate the hypothesis that the T_{sk} of the toes in the P phase increased that in other phases, and, the increase of heat dissipation induced greater cold sensation and thermal unpleasantness during menthol application in the P phase. The T_{sk} of the dorsum and the toes of the foot, skin blood flow in that part of the foot, tympanic temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and thermal sensation and thermal pleasantness were assessed and compared among the P, L, and M phases.

2. Methods

2.1. Subjects

Ten young Japanese women (age: 23 ± 1 years; body weight: 53.7 ± 1.8 kg; body height: 159.0 ± 1.2 cm; body mass index: 21.2 ± 0.5) that had regular menstrual cycle at least three months, were not amenorrhea and anovulation, and did not take any hormonal contraceptives participated in the present study. They provided informed consent for the experimental protocol, which was approved by the Human Investigation Committee of Nara Women's University.

2.2. Experimental protocols

Experiments were conducted in the P phase, on the day that the first positive result on an ovulation prediction kit (New dotest® LH; ROHTO Pharmaceutical Co., Ltd., Osaka, Japan), in the L phase, three days before the estimated date of the next menses, and in the M phase, on the day during the menstrual phase based on our previous study (Uchida et al., 2018b). According to the instruction manual, the ovulation prediction kit detected the increased urinary lutenizing hormone before ovulation day. Our previous study showed that the E_2 concentration is higher level, and the progesterone concentration is lower level at the first positive day. This is the P phase. On the other hand, the late luteal phase is defined as 1–5 days before the start of menstruation. E_2 concentration in the late luteal phase is lower than in the P phase. Progesterone concentration in the late luteal phase is greater than that in the P phase (unpublished data), and the current study adhered fundamentally to the previous study for the definition of the phases. Subjects sent photograph of reaction of ovulation prediction kit to experimenter every day, then experimenter judged the first positive result. Experiments were performed between 8:00 a.m. and 12:00 in the summer in Japan (from July to September 2018) to avoid seasonal acclimation to a cold environment.

Experiments were performed in the morning to avoid the effects of activity performed before the experiment. The experimental room was maintained at 25.3 ± 0.0 °C with a relative humidity of 56.3 ± 1.5%. Subjects were not disturbed drinking water before the experiment to avoid the dehydration; however, they were limited to drink water and eat foods during measurements to avoid a diet induced thermogenesis. The subjects wore the short-sleeved shirts and skirts or pants. The details of subjects' clothing were not controlled, because their clothing were almost same in the experiment. Their socks were removed before the experiment. Subject's thermal pleasantness were not controlled before the experiment.

Women experience a coldness sensation even in a warm room (23–26 °C) where most people feel thermally comfortable (American Society of Heating, Refrigerating, and Air-Conditioning Engineers, 1972) called "hie-sho" in Japan. Before the experiment, the subjects answered a 10-question hie-sho interview (Nagashima et al., 2002) in the experimental room to assess the magnitude of coldness. The interview includes the questions about coldness of body, and the subjects checked who scored more than seven were defined as experiencing hie-sho (Nagashima et al., 2002). According to the standard score, all subjects were not hie-sho. No significant differences were observed in the hie-sho score among the phases.

The subjects rested in a seated position, and T_{sk}, cutaneous blood flow, tympanic temperature, blood pressure (SBP, DBP), HR, and thermal sensation and thermal pleasantness were measured using infrared thermography (Thermo Shot F30; Nihon Avionics, Tokyo, Japan), laser Doppler flowmetry (Omegaflo FLO-C1 HP; OMEGAWAVE, INC., Tokyo, Japan), a tympanic thermometer (Kenonkun C-510; OMRON HEALTHCARE Co., Ltd., Kyoto, Japan), a digital blood pressure monitor (UB-351, A&D Company, Ltd., Tokyo, Japan), and the VAS scale, respectively. After the rest period, the 0.5% menthol (L-menthol, Nacalai Tesque, Kyoto, Japan) solution in 25% ethanol (500 μl; temperature: 25.3 °C) was applied using a piece of tissue paper (Kimwipe) to the right dorsum of the foot and toes except nail quickly, we continued the measurements for 20 min. The menthol solution followed the previous study (Yamazaki and Sone, 2017). In the end of the experiment, the saliva was corrected with a kit (Salivette® Cotton, Sarstedt, Nümbrecht, Germany) for measurements of E_2 and progesterone concentrations. The kit was centrifuged, and the saliva was stored at −80 °C.

We tried to perform all experiments in one menstrual cycle; however, it took three months to finish menthol application trials in the summer (from July to September 2018), because the subjects sometimes could not come to the experiment on the phase due to the illness and personal necessity. We needs another three months to finish control application (25% ethanol solution) in the menstrual cycle; however, if we perform the experiments, it becomes the winter (from October to December), and we could not avoid the seasonal adaptation. Thus, we could not perform the control application trials.

2.3. Measurements

The T_{sk} of the right toes (specifically, the great, second, third, fourth, and little toes) and of the dorsum of the foot (including the head of the metatarsal bone area, the tarsometatarsal joint area, and the transverse tarsal joint area) was measured using infrared thermography at 5-min intervals (Fig. 1). Laser-Doppler flow (LDF) of lateral surface of the right great toe and lateral surface of the transverse tarsal joint area was measured using laser Doppler flowmetry as an index of cutaneous blood flow at 15-s intervals, and was averaged every 5 min (Fig. 1). The areas of T_{sk} and two measurement points of LDF were selected based on the previous study (Uchida et al., 2018b).

Tympanic temperature was measured at 5-min intervals. A cuff of digital blood pressure monitor was wrapped around left arm of subject, and was measured at 5-min intervals, and the mean arterial pressure (MAP) was calculated as (SBP − DBP)/3 + DBP. The skin vascular conductance was calculated as the change in LDF(%)/MAP. Tympanic temperature, blood pressure, and HR were measured to check that menthol application to the right foot did not affect systemic responses.

The baselines of tympanic temperature were not different among the phases (P phase, 36.6 ± 0.1 °C; L phase, 36.7 ± 0.1 °C; M phase, 36.4 ± 0.1 °C). The baselines of the SBP (P phase, 114 ± 3 mmHg; L phase, 115 ± 4 mmHg; M phase, 114 ± 2 mmHg), DBP (P phase, 72 ± 3 mmHg; L phase, 73 ± 3 mmHg; M phase, 72 ± 3 mmHg), HR (P phase, 86 ± 3 bpm; L phase, 87 ± 3 bpm; M phase, 86 ± 3 bpm), and MAP were not different among the phases. The baselines of the skin vascular conductance (great toe, P phase, 118 ± 5%; L phase, 117 ± 5%; M phase, 117 ± 4%; lateral surface of the transverse tarsal joint area, P phase, 118 ± 5%; L phase, 117 ± 5%; M phase, 117 ± 4%) was not different among the phases. No significant differences were observed in the change in tympanic temperature, SBP, DBP, HR, MAP, and skin vascular conductance from the baseline among the phases. No significant interactions between time and the phases were

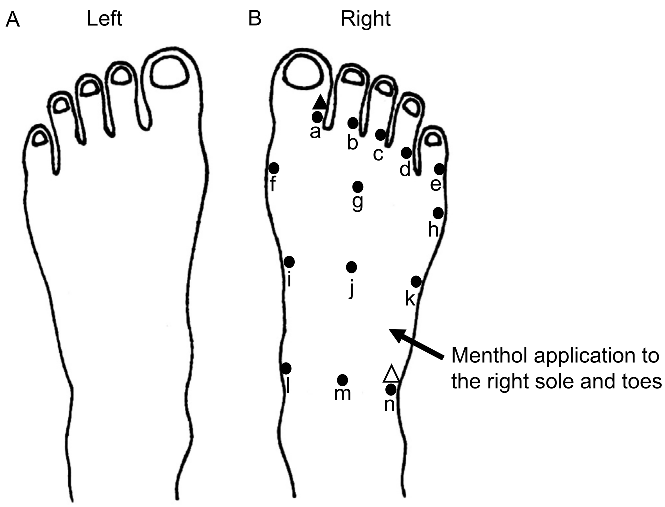

Fig. 1. Schematic of the left (A) and right (B) feet. The black circles denote the regions in which the skin temperature (T_{sk}) was analyzed, specifically at the right great, second, third, fourth, and little toes (B-a, b, c, d, and e, respectively), medial, central, and lateral surfaces of the left head of the metatarsal bone areas (B-f, g, and h, respectively), medial, central, and lateral surfaces of the right tarsometatarsal joint areas (B-i, j, and k, respectively), and medial, central, and lateral surfaces of the transverse tarsal joint areas (B-l, m, and n, respectively) in the dorsum of the foot. The black and white triangles denote the regions in which the laser Doppler flowmetry probes were placed. The menthol solution was applied to the right dorsum of the foot and toes, except the nails.

observed in the change in tympanic temperature, SBP, DBP, HR, MAP, and skin vascular conductance from the baseline.

Thermal sensation and pleasantness of the application area and whole body were assessed every 5 min. We instructed subjects to separate thermal sensation from thermal pleasantness. Subjects were asked to show their sensation by marking on a 15-cm line rating scale which was labeled "neutral" 2.5 cm from the right end and "cold" or "unpleasant" 2.5 cm from the left end. Before each experiment, they were instructed in the procedure, and that the meanings of the points "cold" and "unpleasant" were "maximum cold" and "maximum unpleasant", respectively. We expressed thermal perception by measuring the length from the neutral point to the marked point. The scale followed the previous study (Matsuda-Nakamura et al., 2015).

The saliva was determined by E_2 and progesterone kit in duplicate (Elecsys® Estradiol E2IV, Progesterone III; Roche Diagnostics, Rotkreuz, Switzerland) at SRL, Inc (Tokyo, Japan); however, the samples were not measured correctly because the amount of the samples were not enough.

2.4. Statistics

Data were presented as the means ± standard errors. The T_{sk} from the surface of the head of the metatarsal bone areas, tarsometatarsal joint areas, and transverse tarsal joints in the dorsum of the foot were averaged from the T_{sk} obtained from three points in each area (Fig. 1B–f, g, and h; Fig. 1B–i, j, and k; and Fig. 1B-l, m, and n, respectively). The baseline value (the mean for the 10 min before menthol application), changes in T_{sk} (ΔT_{sk}), LDF, tympanic temperature, and SBP, DBP, HR, MAP, and skin vascular conductance from the baseline levels were calculated. Differences between the P, L, and M phases in $\Delta T_{sk,}$ LDF, change in tympanic temperature, SBP, DBP, HR, MAP, skin vascular conductance, and thermal sensation and pleasantness were assessed by a repeated-measures two-way analysis of ANOVA using SPSS Statistics 21 (IBM Corp., Armonk, NY, USA). Post-hoc tests were performed to identify significant differences at specific time points among the phases using Tukey-Kramer's test. The null hypothesis was rejected at a level of $p < 0.05$.

3. Results

3.1. Change in skin temperature (ΔT_{sk})

Fig. 2 showed the typical thermograms of feet in the rest period (A) and menthol application and the period after the application (B). Fig. 3 showed ΔT_{sk} in the lateral surface of the right great, second, third, fourth, little toes (A, B, C, D, and E), and the lateral surface of transverse tarsal joint in the dorsum of the foot (F). The baselines of T_{sk} in the great toe (P phase, 36.5 ± 0.5 °C; L phase, 36.4 ± 0.5 °C; M phase, 35.9 ± 0.5 °C), second toe (P phase, 36.2 ± 0.6 °C; L phase, 35.9 ± 0.5 °C; M phase, 35.4 ± 0.6 °C), third toe (P phase, 36.1 ± 0.6 °C; L phase, 35.8 ± 0.5 °C; M phase, 35.4 ± 0.5 °C), fourth toe (P phase, 36.1 ± 0.6 °C; L phase, 35.9 ± 0.6 °C; M phase, 35.5 ± 0.5 °C), little toe (P phase, 34.1 ± 0.4 °C; L phase, 33.4 ± 0.4 °C; M phase, 33.3 ± 0.5 °C), and lateral surface of

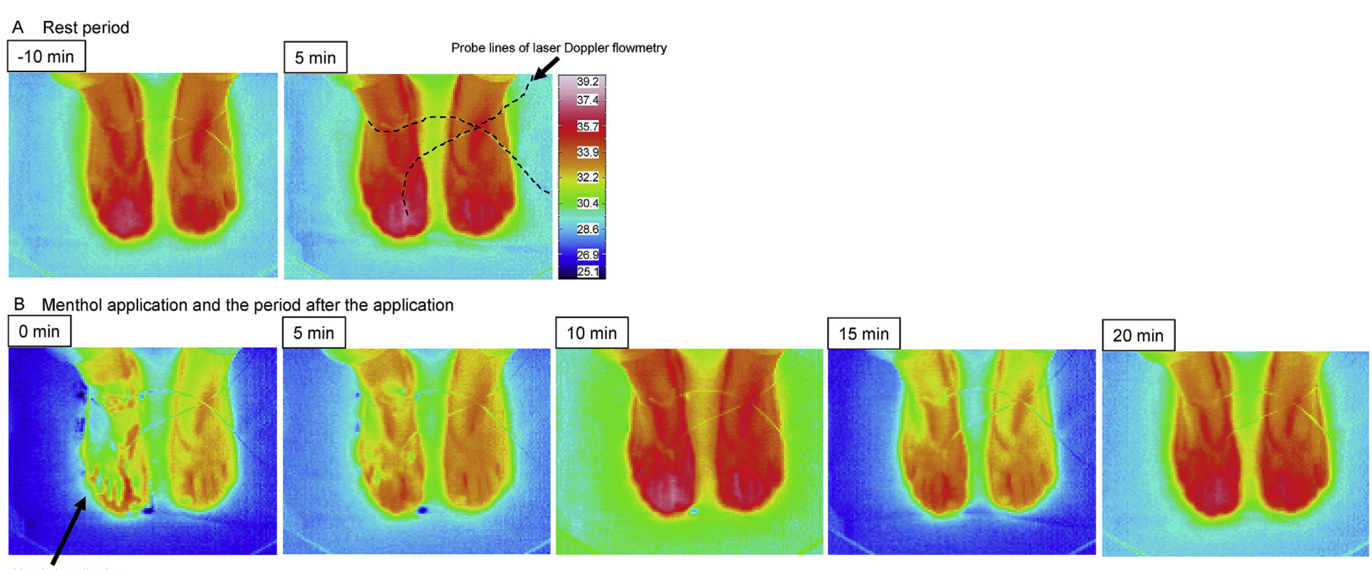

Fig. 2. Typical thermograms of the feet. The thermograms were obtained from one subject in the P phase during the rest period (A) and during menthol application and the period after the application (B). The hashed lines indicate the probe lines for laser Doppler flowmetry.

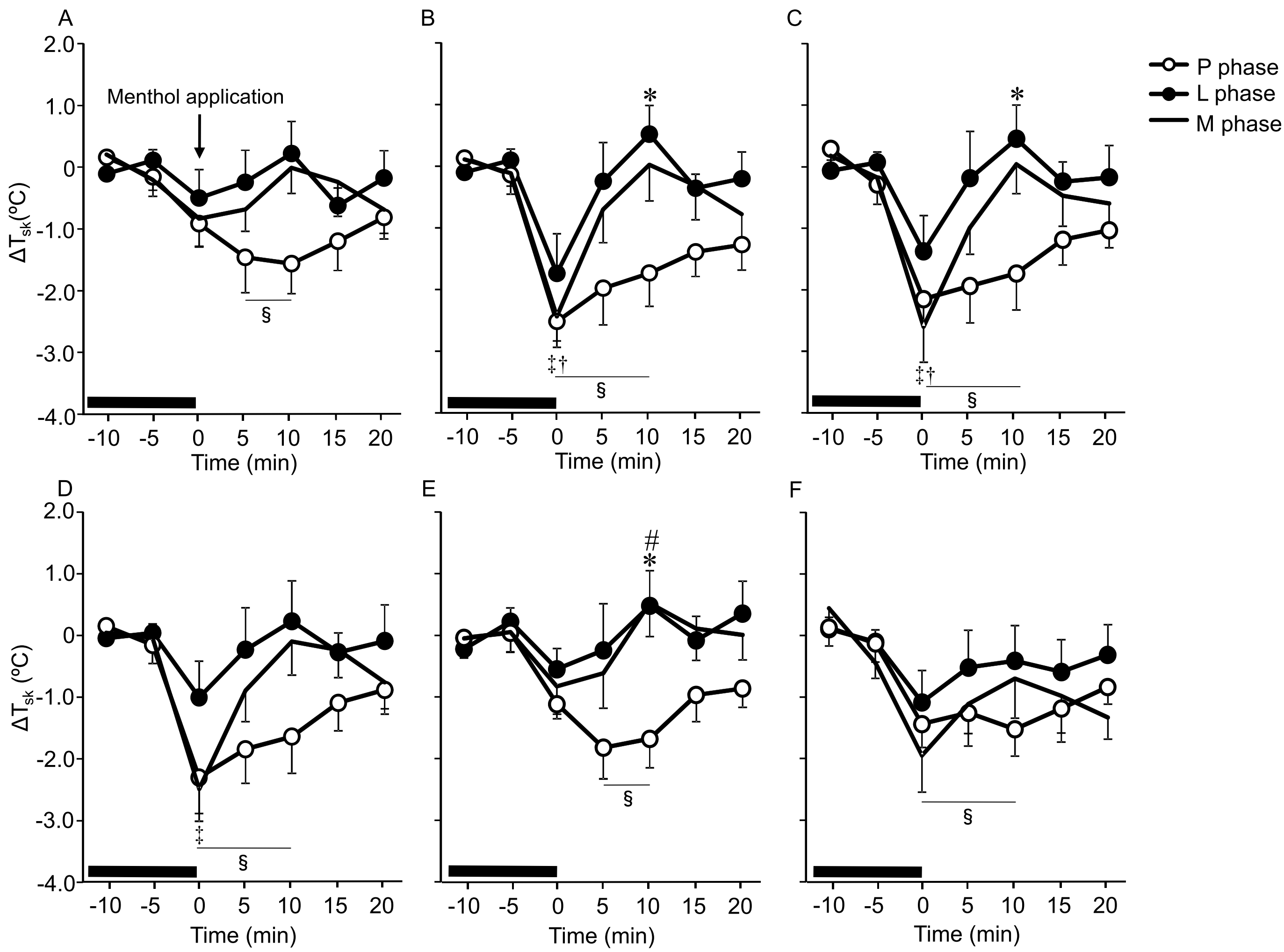

Fig. 3. ΔT_{sk} at the lateral surface of the right great, second, third, fourth, and little toes (A, B, C, D, and E, respectively), and the lateral surface of transverse tarsal joint in the dorsum of the foot (F). The values are presented as the mean ± standard error (P phase, n = 10; L phase, n = 10; M phase, n = 10). Significant differences between the P and L phases (*), and the P and M phases (#), and from the baseline in the F (§), L (†), and M (‡) phases ($p < 0.05$) are denoted. The rest period is shown at the bottom with the closed bar.

transverse tarsal joint in the dorsum of the foot (P phase, 33.6 ± 0.3 °C; L phase, 33.5 ± 0.4 °C; M phase, 33.5 ± 0.5 °C) were not different among the phases. No significant differences were observed in the ΔT_{sk} of the great and fourth toes and the lateral surface of transverse tarsal joint in the dorsum of the foot among the phases. No significant interactions between time and the phases were observed in the ΔT_{sk} of all areas. Two-way ANOVA indicated significant main effects of the phases [$F(1,12) = 4.40$, $p < 0.05$] and time [$F(2,23) = 11.10$, $p < 0.01$] on ΔT_{sk} of the second toe. The ΔT_{sk} in the P phase was lower [$p < 0.05$] than that in the L phase at 10 min (Fig. 3B). Two-way ANOVA indicated significant main effects of the phases [$F(1,17) = 3.70$, $p < 0.05$] and time [$F(3,27) = 8.76$, $p < 0.01$] on ΔT_{sk} of the third toe. The ΔT_{sk} in the P phase was lower [$p < 0.05$] than that in the L phase at 10 min (Fig. 3C). Two-way ANOVA indicated a significant main effect of the phases [$F(1,17) = 5.45$, $p < 0.05$] on ΔT_{sk} of the little toe. The ΔT_{sk} in the P phase was lower [$p < 0.05$] than that in the L and M phases at 10 min (Fig. 3E).

The T_{sk} of the great toe in the F phase was lower [$p < 0.05$] than the baseline at 5–10 min (Fig. 3A). The ΔT_{sk} of the second toe was lower than the baseline at 0 [F phase, $p < 0.01$; L phase, $p < 0.05$; M phase, $p < 0.01$], 5 [F phase, $p < 0.01$], and 10 [F phase, $p < 0.05$] min (Fig. 3B). The ΔT_{sk} of the third toe was lower than the baseline at 0 [F phase, $p < 0.05$; L phase, $p < 0.05$; M phase, $p < 0.01$], 5 [F phase, $p < 0.05$], and 10 [F phase, $p < 0.05$] min (Fig. 3C). The ΔT_{sk} of the little toe was lower [$p < 0.01$] than the baseline at 0–10 min (Fig. 3E). The ΔT_{sk} of the fourth toe was lower than the baseline at 0 [F phase, $p < 0.01$; M phase, $p < 0.05$], 5 [F phase, $p < 0.05$], and 10 [F phase, $p < 0.05$] min (Fig. 3D). The ΔT_{sk} of the lateral surface of transverse tarsal joint in the F phase was lower [$p < 0.05$] than the baseline at 0–10 min (Fig. 3F).

Fig. 4 showed ΔT_{sk} in the surface of the right head of the metatarsal bone, tarsometatarsal joint, and transverse tarsal joint in the dorsum of the foot (A, B, and C). The baselines of T_{sk} in the surface of the right head of the metatarsal bone (P phase, 34.7 ± 0.4 °C; L phase, 35.0 ± 0.5 °C; M phase, 34.4 ± 0.4 °C), tarsometatarsal joint (P phase, 34.8 ± 0.4 °C; L phase, 34.7 ± 0.3 °C; M phase, 34.4 ± 0.4 °C), and transverse tarsal joint (P phase, 34.4 ± 0.4 °C; L phase, 34.4 ± 0.4 °C; M phase, 34.2 ± 0.4 °C) in the dorsum of the foot were not different among the phases. No significant differences were observed in the ΔT_{sk} of the areas among the phases. No significant interactions between time and the phases were observed in the ΔT_{sk} of all areas.

The ΔT_{sk} of the head of the metatarsal bone was lower [$p < 0.05$] than the baseline at 0–5 min (Fig. 4A). The ΔT_{sk} of the tarsometatarsal joint was lower than the baseline at 0 [F phase, $p < 0.01$; M phase, $p < 0.05$], 5 [F phase, $p < 0.01$], and 10 [F phase, $p < 0.01$] min (Fig. 4B). The ΔT_{sk} of the transverse tarsal joint was lower than the

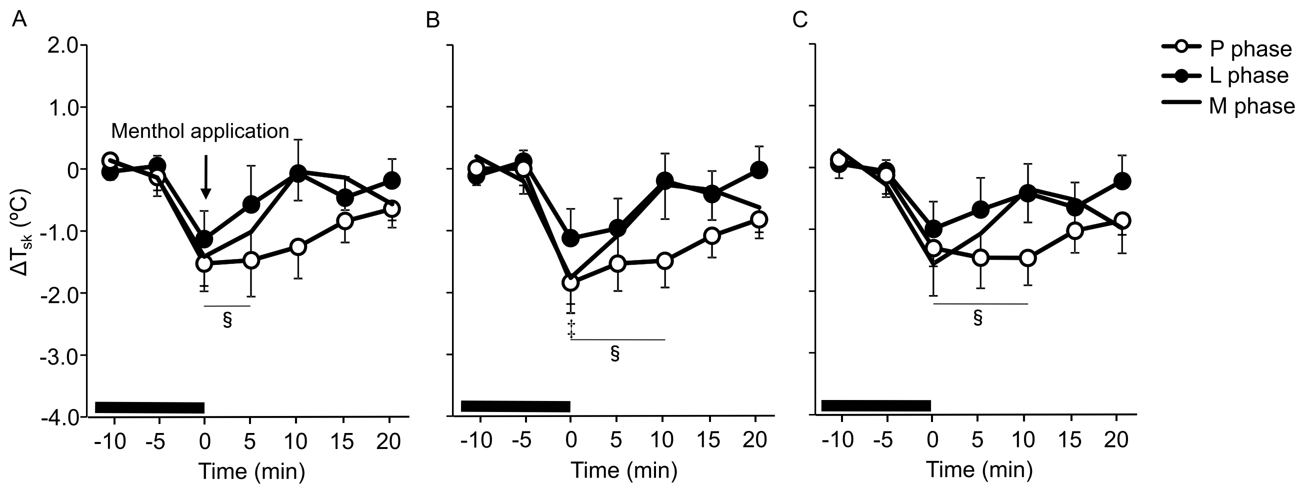

Fig. 4. ΔT_{sk} at the surface of the right head of the metatarsal bone, tarsometatarsal joint, and transverse tarsal joint in the dorsum of the foot (A, B, and C, respectively). Values are presented as mean ± standard error (P phase, n = 10; L phase, n = 10; and M phase, n = 10). Significant differences from the baseline in the F (§) and M (‡) phases ($p < 0.05$) are denoted. The rest period is shown at the bottom with the closed bar.

baseline at 0–10 [$p < 0.05$] min (Fig. 4C).

3.2. Laser Doppler flow (LDF)

Fig. 5 showed the LDF in the right lateral surface of the great toe and lateral surface of the transverse tarsal joint (A and B). No significant differences were observed in the LDF of them among the phases. No significant interactions between time and the phases were observed in the LDF of all areas. The LDF in the right lateral surface of the great toe was lower than the baseline at 20 min [$p < 0.01$] (Fig. 5A).

3.3. Thermal sensation and thermal pleasantness

Fig. 6 showed the thermal sensation and pleasantness for the application areas (A and B) and whole body (C and D). The baselines of the thermal sensation and pleasantness for the application area and whole body were not different among the phases. No significant differences were observed in the thermal sensation and pleasantness for the application area and whole body among the phases. No significant interactions between time and the phases were observed in the thermal sensation and pleasantness for the application area and whole body. The subjects in all phases felt colder than that in baseline at 0 min [$p < 0.01$] in the application area. The subjects in the P phase felt more unpleasant for the cold [$p < 0.01$] than that in the baseline at 0 min in the application area (Fig. 6B).

4. Discussion

The present study revealed that the ΔT_{sk} in the dorsum of the foot was not altered in the P phase, but a decrease in the ΔT_{sk} in some toes was observed in the P phase during menthol application in young women. The results were not consistent with our hypothesis. The hypothesis was formed based on the previous study that the T_{sk} in the great toe in the P phase increased by mechanical cool stimulus (Uchida and Atsumi, 2019). The explanation why the results were not consistent with the hypothesis was that our stimulation was only via TRPM8. The mechanical cool stimulus of 24.7 °C activates TRPM8 and other thermosensitive channel TREK2 (TWIK-related potassium 2). The TRP and TREK channels colocalizes in many sensory neurons (Lamas et al., 2019). The TREK2 itself and co-activation of TRPM8 and TREK2 might be involved in the increase of T_{sk} in the great toe in the P phase. These results indicated that the menstrual cycle phase influenced T_{sk} in some toes during menthol application.

The menstrual cycle phase did not affect the tympanic temperature during menthol application and their baselines. The rectal temperature in young women in the L phase was greater than that in the follicular phase in a day. The difference in the rectal temperature between the L and follicular phases was 0.4 °C (Baker et al., 2001). The short measurement time and small time window might result in these differences. The menstrual cycle phase did not affect the SBP, DBP, HR, and MAP during menthol application. These results indicated that the menstrual

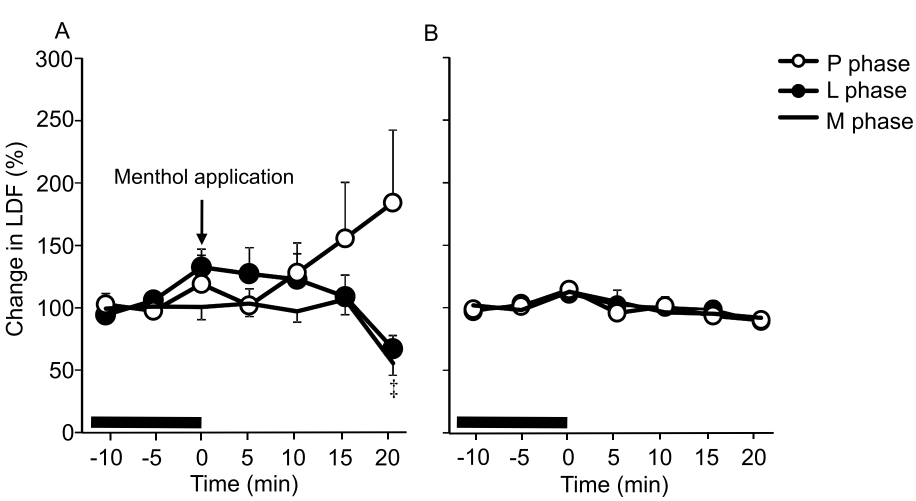

Fig. 5. Laser Doppler flow (LDF) in the right lateral surface of the great toe and lateral surface of the transverse tarsal joint (A and B). Values are presented as mean ± standard error (P phase, n = 10; L phase, n = 10; M phase, n = 10). Significant difference from the baseline in the M (‡) phase ($p < 0.05$) is denoted. The rest period is shown at the bottom with the closed bar.

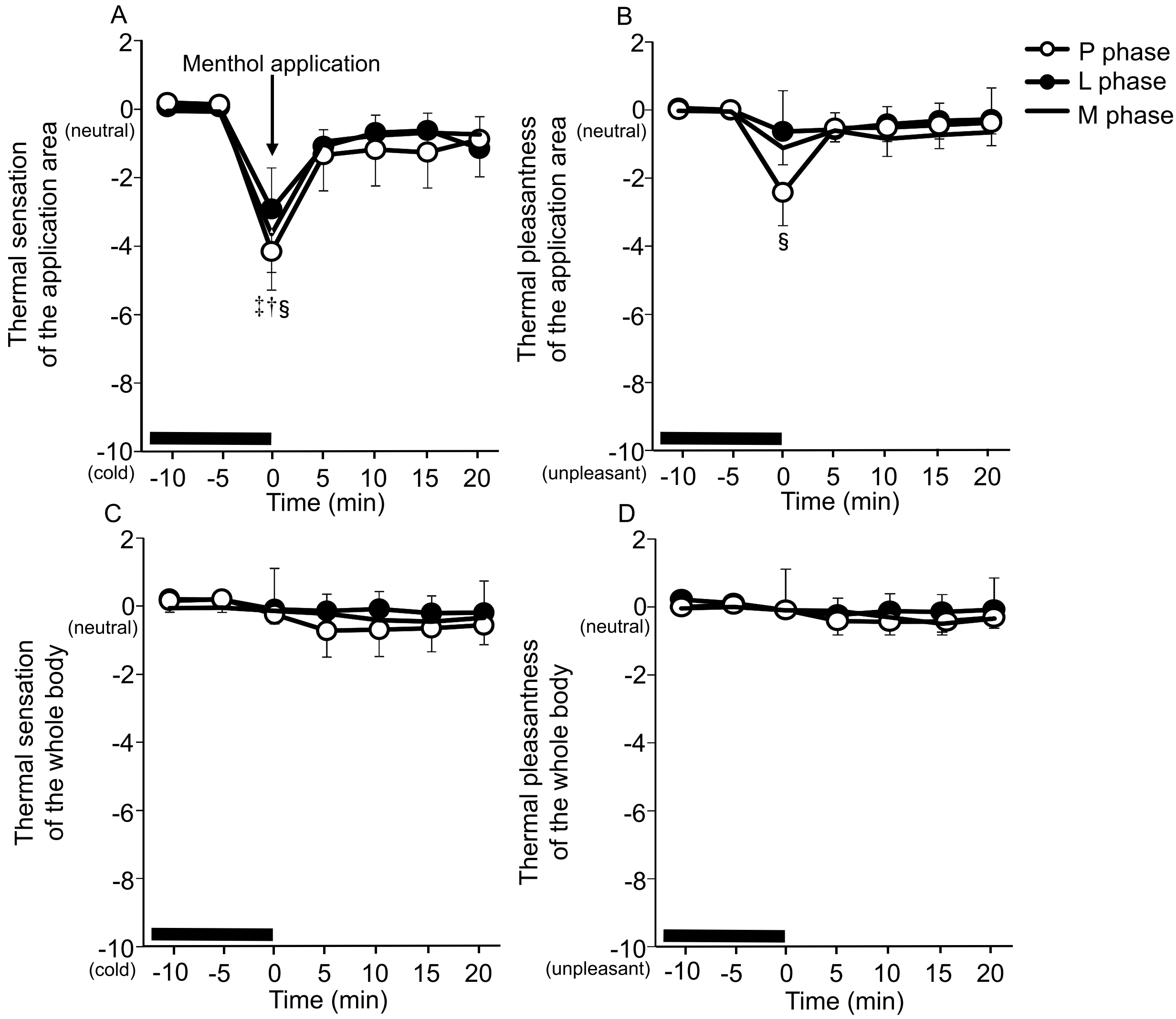

Fig. 6. Thermal sensation and pleasantness in the application area (A and B) and whole body (C and D). Values are presented as mean ± standard error (P phase, n = 10; L phase, n = 10; M phase, n = 10). Significant differences from the baseline in the F (§), L (†), and M (‡) phases ($p < 0.05$) are denoted. The resting period is shown at the bottom with the closed bar.

cycle phase did not affect the tympanic temperature and blood pressure during menthol application.

The menstrual cycle phase did not affect the LDF and the ΔT_{sk} in the great toe and on the lateral surface of the transverse tarsal joint; however, ΔT_{sk} in the other toes except the great and fourth toes during menthol application in the P phase was lower than that in other phases. There were no previous studies the effect of gonadotropin releasing hormone, luteinizing hormone, and follicle stimulating hormone on the T_{sk} in the cold. In animal study, E_2 administration to hypothalamus decreased T_{sk} of tail, a main heat dissipation organ in rats like hands and feet in human, in the cold (10 °C, 2 h) in ovariectomized rats (Uchida et al., 2010). These results indicated that E_2 had effect to decrease T_{sk} in the cold. In contrast, the result that oral administration of progesterone did not affect the T_{sk} in the finger in women during local water cooling (15 °C, 5 min) to the finger (Bartelink et al., 1994) indicated that progesterone did not affect T_{sk} in women during local cold stimulation. These results indicated that the T_{sk} in the P phase, which has higher E_2 and lower progesterone concentrations, might be lower than that in the M phase, which has lower E_2 and progesterone concentrations, in the cold, because E_2 concentration in the P phase is higher than that in the M phase. In addition, the T_{sk} in the P phase might be lower than that in the L phase, which has lower E_2 concentration than that in the P phase. The T_{sk} in the L phase might be lower than that in the M phase. Thus, it was reasonably that the ΔT_{sk} in these toes during menthol application in the P phase was lower than that in the M and L phases. In contrast, the result that similar ΔT_{sk} of these toes during menthol application between the L and M phases was seemed to be unreasonable. A possible explanation was that combination effect of E_2 and progesterone in the L phase cancelled the reductive action of E_2 on T_{sk} to suppress heat dissipation in the cold in the toes. These results indicated that the menstrual cycle phase affected the ΔT_{sk} in the toes during menthol application in young women.

The differences of the ΔT_{sk} in the toes except the great and fourth toes among the phases during menthol application were not seen in the dorsum of the foot. Arteriovenous anastomoses which have a deep orientation and large luminal diameters in the skin are important for heat dissipation, and affect $T_{sk.}$ Arteriovenous anastomoses in the tip of toe are more abundant than in the dorsum of the foot (Abramson, 1967). Thus, arteriovenous anastomoses might affect the T_{sk} of toes rather than dorsum of the foot. In contrast, the reason of the differences in the ΔT_{sk} between the great and forth toes and the other toes is unknown yet. There were no common differences in nerves and arteries between the great and forth toes and the other toes anatomically. It was speculated that E_2 in the P phase might induce cutaneous microvascular constriction of arteriovenous anastomoses in the tip of toe during menthol application. In addition, the regional difference of TRPM8 expression in sensory nerves between the toes and dorsum of the foot and the effect of E_2 on TRPM8 expression in the areas might affect it, though there were no previous studies. In consequence, there were regional differences of ΔT_{sk} in the phases during menthol application between the toes and dorsum of the foot.

The menstrual cycle phase did not affect the thermal sensation and thermal pleasantness of whole body; however, menthol application provided a sensation of coldness in the application area in all the phases. Our results about the effect of menthol, that is, the sensation of coldness, were consistent with the results that 2% menthol application to the forearm provided a strong sensation of coldness of the application area in men and women (Kotaka et al., 2014). In the P phase, the subjects experienced an unpleasant sensation of coldness of the application area, even though the level of sensations of coldness in the application area was the same as those in the other phases. The response might not represent the effect of the menstrual cycle; however, it was speculated that the coldness sensation greatly influenced unpleasant sensation of the application area in the P phase, though the reason was not known. In the fMRI human study, the local cold stimulation (18 °C) to the forearm activated the brain regions such as anterior cingulate cortex, insula, and interior parietal lobe in the thermoneutral. In addition, the medial frontal and anterior cingulate cortex were associated with thermal unpleasantness under the stimulation (Aizawa et al., 2019). In the animal study, the insula was associated with the facilitated thermoregulatory behavior by E_2 administration in the ovariectomized rats (Uchida et al., 2017). The TRPM8 expression in the sensory nerves of the skin of the dorsum of the foot and the activation of the brain regions during menthol application in the P phase might affect the responses.

The present study revealed that the menstrual cycle phase did not affect the ΔT_{sk} in the dorsum of the foot but affected the ΔT_{sk} in some toes during menthol application in young women. The limitations of the present study were that we could not measure female hormones from saliva and perform the control application to finish the experiments in the menstrual cycle in a same season.

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