Modulation of muscle metaboreceptor activation upon sweating and cutaneous vascular responses to rising core temperature in humans

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ABSTRACT

The present study investigated the role of muscle metaboreceptor activation on human thermoregulation by measuring core temperature thresholds and slopes for sweating and cutaneous vascular responses during passive heating associated with central and peripheral mechanisms. Six male and eight female subjects inserted their lower legs into hot water (43°C) while wearing a water perfusion suit on the upper body (34°C). One minute after immersion, an isometric handgrip exercise 40% of maximum voluntary contraction was conducted for 1.5 min in both control and experimental conditions, while post exercise occlusion was performed in the experimental condition only for 9 min. The post exercise forearm occlusion during passive heating consistently stimulated muscle metaboreceptors, as implicated by significantly elevated mean arterial blood pressure throughout the experimental period ($P < 0.05$).

Stimulation of the forearm muscle metaboreceptors increased sweating and cutaneous vascular responses during passive heating, and was associated with significant reductions in esophageal temperature threshold of sweating and cutaneous vasodilation ($\Delta$threshold, sweating: $0.33 \pm 0.05$ and $0.16 \pm 0.04^\circ C$, cutaneous vascular conductance: $0.38 \pm 0.08$ and $0.16 \pm 0.05^\circ C$ for control and experimental, respectively, $P < 0.05$). The slopes of these responses were not different between the conditions. These results suggest that muscle metaboreceptor activation in the forearm accelerates sweating and cutaneous vasodilation during passive heating associated with a reduction in core temperature thresholds, and may be related to central mechanisms controlling heat loss responses.

KEYWORDS: Group III and IV muscle afferents, eccrine sweat gland, cutaneous active vasodilation
INTRODUCTION

Animal studies have determined that sympathetically mediated thermal sweating and cutaneous vasodilator responses originate from the activation of thermosensitive neurons in the anterior hypothalamus/preoptic area associated with core (hypothalamic) temperature elevation (4, 12-15, 35, 45). In addition, descending signals from the hypothalamus area are discharged through a central neural pathway that includes the brainstem (4, 10). Sweating and cutaneous vascular responses are associated with central neural activation following core temperature elevation in humans, and have been evaluated by a function of the elevation in core temperature. For example, the core temperature at which sweating and cutaneous vasodilation initiate is believed to reflect the initiation of central drive for heat loss responses, while the slopes for these responses to rising core temperature are assumed to reflect peripheral organ (sweat glands and cutaneous vessels) thermosensitivity (34). Although the core temperature threshold and slope for heat loss responses are likely affected by other factors (e.g. skin temperature and analysis method) (7, 33), an analysis would be beneficial for understanding thermoregulatory mechanisms (central or peripheral) in humans. In addition, non-thermal factors, such as neural reflexes from working muscles, contribute to sweating and cutaneous vascular adjustments (20, 22, 44, 48). Since the somatosensory afferent signals from working muscles connect to the medulla oblongata and hypothalamus (38, 49), it has been proposed that these afferent inputs may modify temperature-dependent thermoregulatory mechanisms. However, the influence of neural reflexes from working muscles on the thermoregulatory system represented by core temperature threshold and slope of heat loss responses has not been investigated.

The muscle metaboreflex is a well-studied afferent reflex that involves the activation of group III and IV sensory muscle afferent nerves that respond to muscle metabolic products of contraction known as muscle metaboreceptors. Under mild hyperthermic conditions (∼0.3°C
elevation of esophageal temperature, \( T_e \), isolated activation of muscle metaboreceptors caused by post-isometric handgrip exercise forearm occlusion induces sweating without the influence of cutaneous vascular conductance (CVC) on non-glabrous skin, which is dominated by adrenergic cutaneous vasoconstrictor activity \( (2, 5, 23, 25) \). This muscle metaboreflex effect on the sweating response was also confirmed under hyperthermic conditions \( (\sim -1.4^\circ C \text{ elevation of } T_e) \) while the CVC, which is modified by active cutaneous vasodilator activity, was attenuated \( (5, 8) \). Thus, isolated activation of muscle metaboreceptors independently induces a sweating response during slight to severe hyperthermic conditions, and suppresses CVC when the cutaneous blood vessels are dominated by active cutaneous vasodilator activity. Despite clear influences of isolated muscle metaboreflex activation on sweating and cutaneous vascular responses during constant thermal conditions, it is unknown as to whether activation of the muscle metaboreceptors modifies central or peripheral mechanisms of heat loss responses, represented by core temperature thresholds and slopes for these responses.

The purpose of the present study was to investigate the influence of muscle metaboreceptor activation on core temperature thresholds and slopes for sweating and cutaneous vasodilation in humans. We conducted post exercise forearm occlusion to stimulate muscle metaboreceptors during a progressive increase in core temperature by passive heating. This post exercise occlusion is generally conducted for 2–3 min, which is not a sufficient period of ischemia to detect core temperature threshold and slope for sweating and cutaneous vasodilation when performed concurrently with passive heating. Therefore, we extended the post exercise ischemic period to 9 min to detect the core temperature threshold of heat loss responses combined with passive heating. We hypothesised that the activation of muscle metaboreceptors during passive heating would reduce the core temperature threshold for inducing sweating response, which would increase the threshold for cutaneous vasodilation without affecting the thermosensitivity of these responses.
MATERIALS AND METHODS

Ethical approval

Each subject was informed of the study’s purpose and the procedures involved prior to providing written informed consent. This study was approved by the Human Subjects Committee of the Graduate School of Human Development and Environment, Kobe University (Kobe, Japan), and conformed to the standards set forth in the latest revision of the Declaration of Helsinki.

Participants

The study participants included six male and eight female subjects (age: 21.9 ± 0.7 years, height: 164.7 ± 2.0 cm, and weight: 56.8 ± 2.2 kg). The volunteers included from unfit individuals to participants who engaged in regular exercise. No subject was receiving medication, and all were non-smokers. The sample size of 14 was larger than the minimal sample size of 10, which was calculated by power analysis based on an effect size of 1.00 for the estimated reduction of core temperature threshold for sweating by muscle metaboreflex with 80% power and a significance level of 0.05. All female subjects were normally menstruating and were tested during a self-reported follicular phase.

Experimental protocol

Isometric handgrip exercise with or without post exercise forearm occlusion (experimental or control, respectively) was performed during passive heating (lower-leg hot water bath) in an environmental chamber (SR-3000; Nagano Science, Osaka, Japan) maintained at an ambient temperature of 27°C and relative humidity of 50% with minimal air movement. Subjects wore
a water perfusion suit (Allen-Vanguard, Ottawa, Canada) on the upper body with a shirt and shorts to maintain a constant skin temperature by 34°C water. After entering the chamber, maximum voluntary contraction (MVC) was assessed in the semi-supine position. Two MVCs of the dominant forearm flexors were performed using a handgrip dynamometer (TKK5710b; Takei Kiki Kogyo, Niigata, Japan), and the highest result was used to calculate 40% of the MVC. The subjects were seated for at least 40 min and baseline data were recorded for 5 min. Following the baseline recording, both lower legs were inserted into hot water (43°C) for 15.5 min while the water temperature of the water perfusion suit was maintained throughout the lower-leg heating. The isometric handgrip exercise was performed for 1.5 min during 1–2.5 min of passive heating using a visual feedback system to maintain the target force in both control and experimental conditions. Ten seconds before the end of the exercise, blood flow to the exercising arm was occluded by inflation of a pneumatic cuff on the upper arm to a pressure of 250 mmHg in the experimental trial. The occlusion traps muscle metabolites in the forearm before the cessation of exercise to stimulate muscle metaboreceptors during this ischemic period. To determine the core temperature threshold for the onset of heat loss responses during the ischemic period, the occlusion period should be prolonged compared with the prevailing occlusion period (2-3 min) in the present study. To validate prolonged post exercise forearm occlusion, pilot studies were conducted using an occlusion period of 9 min in three subjects, which confirmed that the cardiovascular responses were similar to those of a shorter occlusion period (2-3 min) from a number of previous studies (1, 3, 5, 11, 23, 29). Therefore, the post exercise forearm occlusion was sustained for 9 min during 2.5–11.5 min of passive heating in the present study. In the control trial, the cuff was also applied to the upper arm without inflation to equalise the condition. Since the sudomotor neurons are modulated by respiration (27), we used an auditory signal to maintain the respiratory frequency at 15 cycles/min during the experiment.
Measurements

In all experiments, we recorded the esophageal temperature ($T_{es}$), local skin temperature at
seven sites (forehead, abdomen, forearm, hand, thigh, tibia, and foot), sweat rate (SR) and skin
blood flow (SkBF) on the forearm, heart rate (HR), and arterial blood pressure.

The $T_{es}$ and local skin temperature were measured using a copper-constantan thermocouple.

For $T_{es}$, the tip of the thermocouple was covered with silicone, and $T_{es}$ was measured at a
distance of one-fourth of the standing height from the external nares. Mean skin temperature
($\bar{T}_{sk}$) was calculated using the following formula (32):

$$\bar{T}_{sk} = T_{forehead} \times 0.07 + T_{abdomen} \times 0.35 + T_{forearm} \times 0.14 + T_{hand} \times 0.05 + T_{thigh} \times 0.19 + T_{tibia} \times 0.13 + T_{foot} \times 0.07.$$

The SR on center of the non-dominant ventral forearm (contralateral arm of handgrip
exercise) was measured continuously using the ventilated-capsule method. Dry nitrogen gas
was flushed for at least 1 h before each experiment to obtain stable values. The humidity of the
nitrogen flowing out of the capsules was measured with a capacitance hygrometer (HMP50;
Vaisala, Helsinki, Finland). SkBF on the forearm was measured continuously using
laser-Doppler velocimetry (ALF21; Advance, Tokyo, Japan) located adjacent to the ventilated
capsule. CVC was calculated from the ratio of SkBF to mean arterial blood pressure (MAP)
and is expressed as a percentage of the baseline (100%). $T_{es}$, local skin temperatures, SR, and
SkBF were recorded at 1-s intervals using a data logger (MX100; Yokogawa, Tokyo, Japan).
HR and arterial blood pressure were continuously measured from the non-dominant middle
finger using the Finometer system (Finometer; Finapres Medical Systems, Amsterdam, The
Netherlands); MAP was subsequently derived.
Follow-up analysis

Two follow-up studies (studies I and II) were performed to assess whether pain or discomfort following a longer period of cuff compression affected heat loss responses. Three subjects were recruited for follow-up study I (two male, one female). The same passive heating protocol as described above was performed with or without upper arm cuff compression (220 mm Hg), while the isometric exercise was not performed in either condition. This protocol was conducted to determine whether mental or psychological stresses following cuff compression on the upper arm *per se* without the accumulation of muscle metabolites affected heat loss responses.

Three subjects were recruited in follow-up study II (two male, one female). The same isometric handgrip exercise protocol was conducted with post exercise occlusion for 9 min under normothermic conditions (ambient temperature, 27°C; relative humidity, 50%). This protocol was performed to determine whether mental or psychological stresses following post exercise occlusion affected heat loss responses independent of core temperature elevation. In both studies (I and II), the same physiological parameters as described above were measured, along with the palm SR, which is highly sensitive to mental and psychological stresses.

Data and statistical analyses

All variables were averaged every 30 s during passive heating. The SR was expressed by changes from the baseline ($\Delta$SR). The mean body temperature ($T_b$) was calculated as $0.8 \times T_{es} + 0.2 \times T_{sk}$ (46). The $\Delta$SR and CVC were plotted against the changes in $T_{es}$ ($\Delta T_{es}$) and $T_b$ ($\Delta T_b$) during passive heating. $T_{es}$ and $T_b$ thresholds for the onset of sweating and cutaneous vasodilation and the slopes for these responses were defined by using KaleidaGraph (version 4.5) with user defined original equation based on the segmented linear regression analysis.
method reported by Cheuvront et al. (7). This analysis was conducted based on the data from start of passive heating to the end of forearm occlusion (∼11.5 min) in the experimental condition. Since the onset of sweating and cutaneous vasodilation was delayed in the control compared with the experimental condition, segmented linear regression analysis was conducted based on the data until the end of the heating (∼15.5 min) in the control. When CVC was increased during isometric handgrip exercise, the data during exercise was excluded from regression analysis to assess the threshold and slope for cutaneous vasodilation. Two subjects were excluded from the analysis because one male subject did not show cutaneous vasodilation and one female subject did not start sweating during the post exercise occlusion period.

Physiological data during passive heating were compared using two way-repeated measured ANOVA (condition × passive heating time) with comparisons of BL, pre-handgrip exercise (0.5-1.0 min of passive heating), end-handgrip exercise (2.0-2.5 min), post exercise occlusions (3.5-4.0, 5.5-6.0, 7.5-8.0, and 9.5-10.0 min), end-occlusion (11.0-11.5 min), and post-cuff deflations (13.0-13.5 and 15.0-15.5 min). Post hoc analysis was conducted using Bonferroni’s test. A paired Student’s \(t\)-test was performed to compare the differences of \(T_{es}\) and \(T_b\) thresholds and slopes for SR and CVC between conditions. All data satisfied homogeneity of variance. When the normality test (Shapiro-Wilk test) failed, data was natural logarithm transformed for ANOVA or Wilcoxon signed-rank test (between conditions). Statistical significance was set at \(P < 0.05\). All statistical analyses were performed using SigmaPlot (version 12.5, Systat Software, California, USA).

RESULTS

As shown in Figure 1, the changes in \(T_{es}\), \(T_{sk}\), and \(T_b\) during passive heating until the end of occlusion were similar between conditions, while the \(T_{es}\) and \(T_b\) were decreased in the
experimental condition after cuff deflation compared with that of control, although these changes were not significant. Therefore, in the present study, thermal status was well controlled during the period of post exercise occlusion. The changes in HR and MAP during isometric handgrip exercise were similar between the conditions. The HR during post exercise occlusion, which is a period of metaboreceptor stimulation in the forearm, was higher than that of control, although these differences were not significant ($P > 0.05$). In contrast, the changes in MAP during post exercise occlusion were significantly higher in the experimental conditions compared with that of control throughout the period ($P < 0.05$, Fig. 1).

Forearm muscle metaboreceptor stimulation significantly increased $\Delta SR$ during passive heating compared with that of control from 8 min of heating to the end of post exercise occlusion (Fig. 1). The $\Delta SR$ in the experimental condition returned to control levels when muscle metaboreceptor stimulation was stopped by the cuff deflation (Fig. 1). The higher $\Delta SR$ caused by muscle metaboreceptor stimulation during passive heating was due to significantly lowered $T_{es}$ and $T_b$ thresholds for the onset of sweating ($P < 0.05$ and $P < 0.01$, respectively, Table 1, Fig. 2). In contrast, the slopes of sweating during passive heating was not influenced by muscle metaboreceptor activation ($P > 0.05$, Table 1, Fig. 2).

The CVC during passive heating with the activation of muscle metaboreceptors was significantly higher than that of control condition during the period of post exercise occlusion (Fig. 1). The higher cutaneous vasodilation caused by metaboreceptor stimulation returned to control levels after the cessation of the stimulus (Fig. 1). As with sweating, the higher CVC of muscle metaboreceptor stimulation during passive heating was associated with a reduced $T_{es}$ and $T_b$ thresholds for cutaneous vasodilation, while there was a trend toward a difference in absolute $T_{es}$ and $T_b$ thresholds ($P < 0.1$), and that of $\Delta$ values were significant ($P < 0.05$, Table 1). The slopes of the cutaneous vasodilation was not different between the conditions ($P > 0.05$, Table 1).
Follow-up analysis

Changes in average SR and CVC on the forearm in three subjects as a function of \( \Delta T_b \) during passive heating with and without arm cuff compression in the absence of the isometric handgrip exercise are shown in Figure 3 (upper panel). Arm cuff compression \textit{per se} did not affect SR or CVC on the forearm during passive heating (Fig. 3). The existence of cuff compression for 9 min did not increase the SR on the palm, which is highly sensitive to mental and psychological stresses (data not shown).

Changes in SR on the forearm and palm, as well as CVC on the forearm, during post isometric handgrip exercise occlusion for 9 min under normothermic conditions are shown in Figure 3 (lower panel). The SR on the palm increased during the post isometric exercise occlusion period in two subjects. However, the occlusion did not increase SR on the forearm in any of the subjects (Fig. 3). CVC on the forearm remained at baseline levels throughout the post isometric handgrip exercise period (Fig. 3), consistent with previous observations (2, 5, 23, 25).

DISCUSSION

The present study investigated the modification of muscle metaboreceptor activation on thermoregulatory mechanisms in humans. Our results support our hypothesis that muscle metaboreceptors activation in the forearm during passive heating would significantly reduce the \( T_{es} \) and \( T_b \) thresholds of sweating, suggesting that the muscle metaboreflex accelerates sweating through central thermoregulatory mechanism for inducing the response. Contrary to our hypothesis, the \( T_{es} \) and \( T_b \) thresholds for cutaneous vasodilation were reduced by activation of muscle metaboreceptors, suggesting that muscle metaboreceptors activation has similar
influence on the core temperature thresholds for sweating and cutaneous vasodilation.

Furthermore, the results demonstrated that the slopes of sweating and cutaneous vasodilation that may reflect the peripheral thermosensitivity of sweat gland and cutaneous blood vessels were not influenced by muscle metaboreceptor activation during passive heating.

Skin temperature modifies the core temperature threshold for inducing heat-loss responses (33, 45). Our results in Figure 1 show that the changes in $\overline{T}_{sk}$, $T_{es}$, and $T_b$ during the period of passive heating with post exercise occlusion were essentially similar, suggesting that thermal influences on heat-loss responses were not affected by the occlusion. In addition, the elevation of MAP throughout the 9 min post exercise occlusion period was consistent with previous cardiovascular studies of the muscle metaboreflex (1, 6, 29), suggesting that muscle metaboreceptors were consistently activated throughout the occlusion period. Because many previous studies in thermoregulatory and cardiovascular fields used the method of post exercise muscle occlusion, we believe that the intramuscular metaboreceptors were primarily responsible for the differences in sweating and cutaneous vascular responses between control and experimental conditions in the present study.

In humans, thermal stimulation activates the brainstem, including the midbrain, pons, and medulla, as well as anterior hypothalamus/preoptic area (9, 10, 37), implying that the brainstem is an efferent thermoregulatory central pathway for inducing a sweating response (10).

However, magnetic resonance imaging in humans confirmed that muscle metaboreceptors activation in the forearm caused by post exercise occlusion excites the lateral and dorsomedial medulla, which might correspond to the regions of rostral ventrolateral medulla and nucleus tractus solitarii (cardiovascular center) (40). In addition, somatosensory afferent signals connect with the paraventricular nucleus of the hypothalamus through the spinohypothalamic tract or through brainstem activation (38). Therefore, it was assumed that the afferent signals
from muscle metaboreceptors might be integrated in the hypothalamus and/or the brainstem to accelerate the descending sympathetic discharge inducing a sweating response.

The muscle metaboreceptors stimulation did not induce sweating on forearm in normothermia (Fig. 3) while it did increase during the passive heating (Fig. 1). This would suggest a possible contributions of core, skin, or muscle temperatures for inducing sweating response by muscle metaboreflex. Our present and previous studies have implied that non-thermal stimulations such as isometric handgrip exercise (21, 24), short-term intense dynamic exercise (48, 52), as well as muscle metabo- (2, 23) and mechano-receptors (3) stimulations induce sweating only if the sweating was initiated prior to these interventions in hot conditions. Therefore, we speculate that the afferent signals from muscle metaboreceptors would augment the activity of thermoregulatory center when this center is already activated by increasing core or skin temperatures. In addition, it has been suggested that an elevation of muscle temperature would augment the responsiveness of muscle afferents (26, 39), implying that the elevated muscle temperature associated with passive heating would influence sweating response caused by muscle metaboreceptors in the present study.

Previous studies have reported that the muscle metaboreflex suppresses cutaneous vasodilation during steady state hyperthermic conditions (5, 8). However, we observed enhanced cutaneous vasodilation upon muscle metaboreceptor stimulation during a dynamic increase in core temperature. A reduction in cutaneous blood flow caused by muscle metaboreflex during hyperthermia would occur only if the initial levels of cutaneous blood flow prior to activation of the muscle metaboreflex were high (e.g., more than 50% of maximum cutaneous vasodilation) (31, 43). Therefore, it was assumed that the magnitude of cutaneous blood flow prior to muscle metaboreceptor stimulation would be too small to reduce blood flow in the present study. On the other hand, two possible mechanisms may explain the reduction in $T_{es}$ and $T_b$ thresholds of cutaneous vasodilation in the present study. Firstly,
cholinergic sudomotor nerve activity may influence cutaneous active vasodilation (16, 17, 19).

Secondly, blood pressure elevation following muscle metaboreceptor stimulation would likely stimulate arterial baroreceptors to increase CVC (18) and, in turn, induce cutaneous blood vessel distention (47). Although the precise mechanisms for accelerating cutaneous vasodilation were not identified in the present study, the differences in absolute $T_{es}$ and $T_b$ thresholds for cutaneous vasodilation were not significant between conditions ($P < 0.1$), implying a competition for delaying and accelerating cutaneous vasodilation by muscle metaboreflex and other factors, respectively.

Follow-up studies were performed to assess the precise influence of muscle metaboreceptor stimulation on heat loss responses using the post isometric exercise occlusion method. Follow-up study I indicates that forearm muscle ischemia per se without handgrip exercise does not affect the onset of sweating and cutaneous vasodilation or the sensitivities of these responses during passive heating. In the present study, the absence of SR on the palm, which is highly sensitive to mental stresses, indicates a weak influence of mental stresses on physiological responses during arm cuff compression for 9 min. In addition, the results from follow-up study I suggest that potential stimulation of muscle mechanoreceptors by cuff compression (30, 50) does not affect sweating and/or cutaneous vascular responses. Results from follow-up study II imply that the post isometric handgrip exercise conducted for 9 min may induce mental stresses, as evidenced by the increased SR on the palm (Fig. 3). However, and most importantly, such psychological sweating on the palm was not observed on the forearm under normothermic conditions in any of the three subjects. Based on these follow-up studies, we believe that post exercise forearm occlusion for 9 min may induce psychological stresses independent of arm cuff compression, but does not significantly affect sweating and cutaneous vascular responses on the forearm during passive heating.
In addition, it was reported that muscle metaboreceptor stimulation (e.g., ~14 min)
increased circulatory hormones such as adrenaline, noradrenaline, and arginine vasopressin
(36), which could influence sweating and cutaneous vascular responses (17, 41). Since none of
these humoral parameters were measured in the present study, we cannot exclude the
possibility that the humoral factors associated with muscle metaboreceptor activation would
affect sweating and cutaneous vascular responses.

Limitations

Cortical activation, such as that from the somatosensory cortex and insula, has been associated
with the unpleasantness of post exercise forearm occlusion in humans (40). Such mental
stresses can induce psychological sweating even in non-glabrous skin (28). Although we
believe that the influence of mental stresses on non-glabrous sweat response following post
handgrip exercise forearm occlusion would be minimal based on our follow-up studies, it was
impossible to exclude the influence of mental stresses following post exercise occlusion. In
addition, similar to CVC, sustained blood pressure elevation during the post exercise occlusion
period indicated a possible influence of arterial baroreceptors activation on sweat responses.
However, it is likely that the increase and/or decrease of arterial baroreceptors activation does
not influence sweating response during activation of muscle metaboreceptors by
administration of sodium nitroprusside (42) and passive heat stress by phenylephrine infusion
(51), but may influence CVC (18). Although these studies suggest that the influence of arterial
baroreceptor loading on sweating response was minimal, it is still unclear whether baroreceptor
loading does not modulate the core temperature threshold for sweating response.

Perspectives and Significance

Although it is known that temperature-dependent hypothalamic activation induces sweating
and cutaneous vasodilation through a central neural pathway (e.g. brainstem), there have been no studies of the role of muscle metaboreceptors on thermoregulatory mechanisms, including the slopes of these responses. We demonstrated that the activation of muscle metaboreceptors reduced the temperature threshold for sweating and cutaneous vasodilation during passive heating without affecting these slopes. These results suggest that the muscle metaboreflex accelerates sweating and cutaneous vasodilation by central thermoregulatory mechanisms (e.g., hypothalamic activation) rather than peripheral thermosensitivities in humans. This provides important insight into the mechanisms of thermoregulation in humans.

In conclusion, we demonstrated that muscle metaboreceptor activation in the forearm lowers $T_{es}$ thresholds for sweating and cutaneous vasodilation during passive heating whilst this activation does not affect the slopes of these responses. This suggests that the muscle metaboreflex may accelerate the activity of temperature-dependent central thermoregulatory mechanisms for inducing sweating and cutaneous vasodilation in humans.
REFERENCES


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ACKNOWLEDGMENTS

We thank our volunteer subjects for participating in this study.

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Conception and design of research was undertaken by TA and NK, data collection and analyses was undertaken by TA, the manuscript was drafted by TA and NK, and all authors (TA, MI, YI, TN, SK, and NK) contributed to data interpretation, editing and revision of manuscript, and approved the final version.

GRANTS

This study was supported by a Grant-in-Aid for Scientific Research (B) (no. 23300231) from the Japan Society for the Promotion of Science from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.
Table 1. Esophageal temperature thresholds and slopes for sweating and cutaneous vasodilation during passive heating.

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<th>SR</th>
<th>CVC</th>
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<tr>
<td></td>
<td>Control condition</td>
<td>Experimental condition</td>
</tr>
<tr>
<td>$T_{es}$ Threshold ($^\circ$C)</td>
<td>37.11 (0.07)</td>
<td>37.00 (0.05)*</td>
</tr>
<tr>
<td>$\Delta$Threshold ($^\circ$C)</td>
<td>0.33 (0.05)</td>
<td>0.16 (0.04)**</td>
</tr>
<tr>
<td>Slope (SR: (mg/cm²/min)/$^\circ$C and CVC: %/$^\circ$C)</td>
<td>1.78 (0.85)</td>
<td>1.29 (0.28)</td>
</tr>
<tr>
<td>$T_b$ Threshold ($^\circ$C)</td>
<td>36.87 (0.07)</td>
<td>36.75 (0.06)*</td>
</tr>
<tr>
<td>$\Delta$Threshold ($^\circ$C)</td>
<td>0.76 (0.05)</td>
<td>0.59 (0.03)**</td>
</tr>
<tr>
<td>Slope (SR: (mg/cm²/min)/$^\circ$C and CVC: %/$^\circ$C)</td>
<td>1.68 (0.49)</td>
<td>1.50 (0.31)</td>
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The values given are the means ± SEM. $T_{es}$, Esophageal temperature; $T_b$, mean body temperature; SR, sweat rate on the forearm; CVC, cutaneous vascular conductance on the forearm. * Significantly different from control ($P < 0.05$). ** Significantly different from control ($P < 0.01$).
FIGURE LEGENDS

Figure 1. Changes in heart rate (HR), mean arterial blood pressure (MAP), esophageal temperature (Tₑₑ), mean skin temperature (Tₛₛ), mean body temperature (Tₑₑ), sweat rate (SR), and cutaneous vascular conductance (CVC) during passive heating with or without post-exercise muscle occlusion. # indicates a significant difference between conditions at a given time point (P < 0.05).

Figure 2. Relationships between Δ sweat rate (SR) or cutaneous vascular conductance (CVC) and Δ esophageal temperature (Tₑₑ) or Δ mean body temperature (Tₑₑ) during passive heating with or without post-exercise muscle occlusion. The data after the cessation of occlusion were eliminated in the experimental condition. The Tₑₑ and Tₑₑ thresholds for sweating and cutaneous vasodilation were significantly lowered by the post exercise forearm occlusion. On the other hand, the slopes of both sweating and cutaneous vascular responses were not significantly different between conditions in both Tₑₑ and Tₑₑ. Statistical data are shown in Table 1.

Figure 3. Changes in Δ sweat rate (SR) and cutaneous vascular conductance (CVC) as a function of Δ mean body temperature (Tₑₑ) during passive heating with or without arm cuff compression (n=3, follow-up study I). Cuff compression on the upper arm per se without an accumulation of muscle metabolites in the forearm did not affect SR or CVC responses during passive heating. The lower panel shows the changes in SR and CVC during post exercise occlusion for 9 min under normothermic conditions (n=3, follow-up study II). The increase in SR on the palm implies the presence of mental or psychological stresses, while the SR on the forearm was not influenced by occlusion.
Fig. 1
Fig. 2
Follow-up study I

Follow-up study II

Fig. 3