Effect of short-term exercise-heat acclimation on ventilatory and cerebral blood flow responses to passive heating at rest in humans

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Fujii N, Tsuji B, Honda Y, Kondo N, Nishiyasu T. Effect of short-term exercise-heat acclimation on ventilatory and cerebral blood flow responses to passive heating at rest in humans. J Appl Physiol 119: 435–444, 2015. First published July 9, 2015; doi:10.1152/japplphysiol.01049.2014.—Heat acclimation increases hyperventilation and cerebral hypoperfusion in resting humans. We tested the hypothesis that short-term exercise-heat acclimation would alleviate these effects. Twenty healthy male subjects were divided into two groups that performed exercise training in the heat (TR-HEAT, n = 10) or cold (TR-COLD, n = 10). Before and after the training, the subjects in both groups participated in passive heat tests at rest. Training was performed at 37°C (TR-HEAT) or 10°C (TR-COLD) and entailed four 20-min bouts of cycling at 50% peak oxygen uptake separated by 10-min recoveries daily for 6 consecutive days. After TR-HEAT, esophageal temperature was lowered when measured before and during passive heating, as was the esophageal temperature threshold for cutaneous active vasodilation, whereas plasma volume was increased (all P < 0.05). These traditional indices of successful heat acclimation were not all induced by TR-COLD (all P > 0.05). TR-HEAT had no significant effect on passive heating-induced increases in minute ventilation, even when evaluated as the esophageal temperature threshold for increases in minute ventilation and the slope relating minute ventilation to esophageal temperature (all P > 0.05). By contrast, TR-HEAT attenuated the passive heating-induced reduction in the cerebral vascular conductance index (middle cerebral artery mean blood velocity/mean arterial pressure) (all P < 0.05). TR-COLD did not attenuate the increase in minute ventilation or the decrease in the cerebral vascular conductance index observed during passive heating (all P > 0.05). These data suggest that in resting heated humans, short-term heat acclimation achieved through moderate-intensity exercise training (i.e., 50% peak oxygen uptake) in the heat does not influence hyperthermia-induced hyperventilation, but it does potentially attenuate cerebral hypoperfusion.

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heat acclimation is the result of the repeated hyperthermia or of the exercise training itself, we also evaluated the effects of exercise training in the cold.

MATERIALS AND METHODS

Ethical approval. This study was approved by the Human Subjects Committee of the University of Tsukuba and conformed to the provisions in the Declaration of Helsinki. All participants provided written informed consent before participating.

Subjects. Twenty healthy men participated in this study. None of the subjects were smokers and none were taking prescription medication. Subjects were randomly divided into two groups: one that performed exercise training in the heat (TR-HEAT, n = 10) and served as the experimental group, and one that exercised in the cold (TR-COLD, n = 10) and served as the control group. As designed, we selected subjects so as to match characteristics between the groups (Table 1). In consideration of the potential effect of natural acclimatization, all experiments were conducted between November and March.

Experimental procedures. The experimental procedures for TR-HEAT and TR-COLD were as follows. Initially, a peak oxygen uptake test (details of the procedure are available elsewhere (15, 47)) was carried out, and 2–4 days later, a passive-heat test (see below for details) was performed. Within 7 days after finishing the first passive-heat test, subjects began a 6-day period of exercise training in a hot (TR-HEAT) or cold (TR-COLD) environment (see below for details). Eighteen to 48 h after completion of training, a second passive-heat test was conducted, which was followed 24–48 h later by a second peak oxygen uptake test. Several blood variables (see below for details) were also recorded before heating in the first and second passive-heat tests. Subjects were asked to abstain from strenuous exercise, alcohol, and caffeine for 24 h before each passive-heat test and peak oxygen uptake test. To standardize each subject’s hydration status, they were all asked to consume the same meal and to drink 500 ml of water on the night before the passive-heat tests. In addition, they consumed a light breakfast and 300 ml of water 2 h before the passive-heat test and peak oxygen uptake test. To standardize each subject’s hydration status, they were all asked to consume the same meal and to drink 500 ml of water on the night before the passive-heat tests. In addition, they consumed a light breakfast and 300 ml of water 2 h before the passive-heat tests. By doing this, plasma osmolality, a known index of body fluid status, was established at around 290 mosmol/l (Table 1), which was considered euhydration (38).

Passive-heat test. The purpose of the passive-heat test was to induce clear hyperthermia-induced hyperventilation. To do that, we increased subjects’ esophageal temperature to 39.0°C or until they could no longer endure the heat. On the days of the passive-heat tests, each subject came to the laboratory at 8:30 A.M. and rested for 30 min by sitting in a chair in a room where an ambient temperature of 25°C, relative humidity of 50%, and wind speed of <0.2 m/s were maintained. A blood sample was collected from a warmed fingertip while the subject sat steadily in a chair, after which the subject voided urine, and body mass was recorded. Subjects then donned a water-perfused suit that covered the upper body with the exception of the head, hands, and left arm. The water-perfused suit was covered with an impermeable garment, and the subject’s right hand was covered with a cotton glove to minimize sweat evaporation, and thus heat loss from the upper body. This was necessary because evaporative heat loss can greatly attenuate the rate of increase in body core temperature, thereby prolonging heating time. Subjects then moved into a water-filled bathtub where they sat in a chair for 30 min. The temperature of water in the tub was set to ~35°C with aid of a heater, and subjects were immersed to the level of the iliac crest. We determined in pilot experiments that it is difficult to increase esophageal temperature by more than 2.0°C using only a water-perfused suit. For that reason, we also entirely immersed both legs in heated water. The water in the bathtub was circulating through the water-perfused suit. After all measurements were started, subjects rested for 5 min. The water in the bathtub was then replaced with the aid of a pump to set the water temperature to ~41°C, which caused the subject’s body temperature to rise.

Exercise training. Subjects in both groups performed exercise training for 6 consecutive days. The protocol consisted of four 20-min bouts of cycling at 50% peak oxygen uptake, each separated by a 10-min recovery period (15, 56). For the TR-HEAT group, the training was carried out in a hot environment (37°C, 50% relative humidity); for the TR-COLD group, it was in a cold environment (10°C, 50% relative humidity). Heart rate and esophageal temperature were monitored during the training. Wind speed was controlled to increase esophageal temperature to the desired level (see RESULTS for details). Due to technical difficulties, esophageal temperature was not recorded for one subject in the TR-HEAT group. During each training session, ad libitum intake of a commercially available sports drink (6.7% carbohydrate, 21 meq/l Na+, 16.5 meq/l Cl−, 5 meq/l K+, osmolality 323 mosmol/kg H2O (Pocari Sweat; Otsuka, Tokyo, Japan) was allowed during the recovery between exercises. The temperature of the sports drink was set to ~38°C to minimize fluctuations in esophageal temperature.

Measurements. Esophageal and skin temperature data were collected via copper constantan thermocouples, sampled, recorded on a computer (ThinkPad A21p; IBM) every 1 s using a data logger system (WE7000; Yokogawa, Japan), and averaged over 30-s periods. Temperature data were recorded continuously from the start of the normothermic baseline measurements to the end of heating. To obtain esophageal temperatures, we had each participant insert a thermocouple into the esophagus via the nasal passage to a distance equivalent to one-fourth of the subject’s height. The location of the probe within the esophagus was estimated to be posterior to the lower border of the left atrium (50). Prior to its being positioned in the esophagus, the thermocouple was calibrated by immersing it and a standard mercury thermometer in a water bath, the temperature of which was then increased from 35° to 40°C in 0.5°C steps. After calibration, we calculated a correction formula so that the esophageal thermocouple-read temperatures matched those of the mercury thermometer. Skin temperature was measured at six sites (chest, back, lower leg, abdomen, thigh, and calf), and mean skin temperature was calculated using method described by Taylor et al. (44), which weighted the six sites as follows: 22% chest, 21% upper back, 19% lower back, 14% abdomen, 14% thigh, and 11% calf.

Heart rate was recorded every 5 s using a heart rate monitor (Vantage NV; Polar, Kempele, Finland) and averaged over 30-s periods. The right arm was placed on a table at heart level, and arterial pressure was measured every 1 min using an automated sphygmo-
nometer (STBP-780; Nippon Colin, Aichi, Japan). Mean arterial pressure was calculated as the diastolic arterial pressure plus one-third of the pulse pressure.

Forearm cutaneous blood flow (left arm) was estimated using venous occlusion plethysmography with the aid of a mercury-silastic strain gauge (53). This estimation is based on the fact that forearm muscle blood flow changes little during passive-heat stress at rest (11); consequently, any increase in forearm blood flow under those conditions likely reflects increased cutaneous blood flow. Other details for this method, including rationales and limitations, were provided in our previous report (15). The left forearm was loosely supported by slings at the wrist, with the forearm extended in front of the subject. To facilitate venous return, the left arm was elevated 0.1 m above the level of the heart. To account for changes in perfusion pressure, which were mainly determined from arterial blood pressure, forearm vascular conductance was calculated as forearm blood flow divided by mean arterial pressure and expressed as ml·100 ml tissue⁻¹·min⁻¹·100 mmHg⁻¹. From forearm vascular conductance, we estimated cutaneous active vasodilation, which was achieved through cholinergic sympathetic nerve-dependent vasodilatation (22).

Mean blood velocity in the middle cerebral artery (MCA), an index of cerebral blood flow, was measured using transcranial Doppler ultrasound (WAKI 1-TC; Atys Medical, Soucieu-en-Jarrest, France) with the subject in a seated position in a water-filled bathtub and averaged over 30-s periods. A 2-MHz Doppler probe was placed over the right side of the temporal window and fixed with an adjustable headband. The cerebral vascular conductance index was estimated as the MCA mean blood velocity divided by the mean arterial pressure (cm⁻¹·s⁻¹·mmHg⁻¹), and was also expressed as the value normalized to the normothermic baseline (i.e., %baseline). The sample size for the cerebral vascular conductance index in the TR-HEAT group was 9, because we could not detect the mean blood velocity signal from the MCA in one subject. In a preliminary experiment carried out under normothermic resting conditions, the subjects in a seated position (n = 9), we found the interday reproducibility of the MCA mean blood velocity and the cerebral vascular conductance index to be high and statistically significant. This is based on the observations that data in the preliminary experiment meet the criteria described by Bland and Altman (3) and an intraclass correlation coefficient. The sample size for the cerebral vascular conductance index in the TR-HEAT group was 9, because we could not detect the mean blood velocity signal from the MCA in one subject. In a preliminary experiment carried out under normothermic resting conditions, the subjects in a seated position (n = 9), we found the interday reproducibility of the MCA mean blood velocity and the cerebral vascular conductance index to be high and statistically significant. This is based on the observations that data in the preliminary experiment meet the criteria described by Bland and Altman (3) and an intraclass correlation coefficient. As with minute ventilation, slopes relating tidal volume, respiratory frequency, and end-tidal CO₂ pressure to esophageal temperature were evaluated within a range above the body core temperature threshold for hyperthermia-induced hyperventilation. The body core temperature threshold and sensitivity of cutaneous active vasodilation were also evaluated on the basis of esophageal temperature threshold for increases in forearm vascular conductance and the slope relating forearm vascular conductance to esophageal temperature, respectively (15). Peak cutaneous active vasodilation was evaluated by averaging forearm vascular conductance values over the final 5 min of heating. As an indirect index of cerebrovascular CO₂ reactivity, we evaluated the slope relating the cerebral vascular conductance index (both in cm⁻¹·s⁻¹·mmHg⁻¹ and %baseline) to the end-tidal CO₂ pressure within a temperature range above the body core temperature threshold for hyperthermia-induced hyperventilation. To clarify whether the magnitude of adaptation differs depending on whether the subjects trained in the cold or heat, the changes in the main variables before and after training (i.e., data shown in Figs. 1–5 and Table 1) were calculated and compared between groups. In addition, the changes in esophageal temperature from normothermic baseline (time 0) observed during passive-heat stress were evaluated and compared before and after TR-HEAT.

**Fig. 1.** Time course of changes in esophageal temperature during passive-heat tests before (filled circles) and after (open circles) exercise training in the cold (A, n = 10) or in the heat (B, n = 10). Time 0 indicates normothermic baseline before heating. *P < 0.05 vs. time 0. †P < 0.05 before vs. after each training period. ††P < 0.05 between groups for training-induced changes in esophageal temperature evaluated at each time point. Values are means ± SD.
Time-course data collected at the normothermic baseline (time 0) and during passive heating were analyzed using two-way repeated-measures ANOVA. We set one factor as training (before, after) and the other as time (time 0 and every 5 min of heating). The time-course data were analyzed within a time period during which all the subjects remained (25 min in TR-COLD and 30 min in TR-HEAT). After determining an interaction (training × time) or each main effect, post hoc multiple comparisons were carried out using Tukey’s honestly significant difference test. In addition, two-tailed paired t-tests were used to evaluate training-induced changes where appropriate. Two-tailed unpaired t-tests were used to compare esophageal temperature and heart rate values during exercise training between the TR-COLD and TR-HEAT groups. Two-tailed unpaired t-tests were also employed to compare changes in the main variables before and after training between groups. All values are reported as means ± SD. P < 0.05 was considered significant.

RESULTS

Esophageal temperature and heart rate during exercise training. During training, esophageal temperature at the end of exercise remained nearly unchanged from day 1 to day 6 in the TR-COLD (37.8–38.0°C) and TR-HEAT (38.5–38.7°C) groups. Heart rate at the end of exercise gradually decreased from 141 ± 10 beats/min on day 1 to 132 ± 7 beats/min on day 6 in the TR-COLD group, and from 168 ± 19 beats/min on day 1 to 158 ± 17 beats/min on day 6 in the TR-HEAT group. On each day, esophageal temperature and heart rate were higher in the TR-HEAT than TR-COLD group (all P < 0.05), suggesting temperature and cardiac strain during training were greater in the TR-HEAT group.

Heat acclimation achieved through exercise training in a hot environment. Compared with the values recorded before training, TR-HEAT increased plasma volume (Table 1) and reduced esophageal temperature at normothermic baseline (time 0) by 0.26°C and the temperature during heating by 0.19 to 0.37°C (Fig. 1B). The lower esophageal temperature during heating disappeared when evaluated as the change in esophageal temperature from normothermic baseline (all P > 0.06), indicating that TR-HEAT-induced reductions in esophageal temperature during heating were mainly a result of a lower baseline esophageal temperature. TR-HEAT also reduced the body core temperature threshold for cutaneous active vasodilation by 0.25°C (36.47 ± 0.30 vs. 36.22 ± 0.28°C, P = 0.020). The changes elicited by TR-HEAT indicate that heat acclimation was successfully achieved through TR-HEAT. On the other hand, there were no differences in the values obtained before and after TR-COLD for plasma volume (Table 1), normothermic baseline esophageal temperature [36.34 ± 0.23 vs. 36.26 ± 0.25°C; post hoc comparisons were not made due to the absence of a main effect or interaction, Fig. 1A], or body core temperature threshold for cutaneous active vasodilation (36.54 ± 0.39 vs. 36.49 ± 0.36°C, P = 0.625). It thus appears that 6 days of exercise training employed in the present study did not, by itself, cause changes to indicate heat acclimation.

Minute ventilation. TR-COLD increased minute ventilation by 9.0 l/min at minute 25 of heating, whereas TR-HEAT did not affect minute ventilation at normothermic baseline or at any time during heating (Fig. 2, A and B). This may indicate that the effect of training on ventilatory responses during heating differs depending on whether one is training in the cold or heat.

Minute ventilation response to increasing esophageal temperature. The body core temperature thresholds for hyperthermia-induced hyperventilation determined before and after TR-COLD (38.31 ± 0.60 vs. 38.09 ± 0.61°C, P = 0.137) and TR-HEAT (37.57 ± 0.67 vs. 37.32 ± 0.64°C, P = 0.149) were similar (Fig. 3, A and B). The training-induced change in the

Fig. 2. Time course of changes in minute ventilation and end-tidal CO2 pressure during passive-heat tests before (filled circles) and after (open circles) exercise training in the cold (A and C, n = 10) or in the heat (B and D, n = 10). Time 0 indicates normothermic baseline before heating. *P < 0.05 vs. time 0. †P < 0.05 before vs. after each training period. Values are means ± SD. Training-induced changes in minute ventilation and end-tidal CO2 pressure evaluated at each time point did not differ between groups (all P > 0.099).
body core temperature threshold was similar between the TR-COLD and TR-HEAT groups ($-0.22 \pm 0.42$ vs. $-0.25 \pm 0.50°C$, $P = 0.873$). Sensitivities of hyperthermia-induced hyperventilation determined before and after TR-COLD ($27.7 \pm 22.0$ vs. $32.9 \pm 24.5\text{ l·min}^{-1} \cdot ^{\circ }\text{C}^{-1}$, $P = 0.209$) and TR-HEAT ($23.0 \pm 24.3$ vs. $27.8 \pm 31.8 \text{ l·min}^{-1} \cdot ^{\circ }\text{C}^{-1}$, $P = 0.698$) also did not differ (Fig. 3, A and B). Likewise, there was no difference in the training-induced change in sensitivity between TR-COLD and TR-HEAT groups ($2.5 \pm 12.1$ vs. $4.8 \pm 37.5 \text{ l·min}^{-1} \cdot ^{\circ }\text{C}^{-1}$, $P = 0.972$). As with minute ventilation, the slopes relating tidal volume, respiratory frequency, and end-tidal CO$_2$ pressure to esophageal temperature were unaffected by TR-COLD or TR-HEAT (all $P > 0.05$, data not shown). From these findings we can infer that short-term exercise-heat acclimation does not affect hyperthermia-induced hyperventilation at rest.

End-tidal CO$_2$ pressure and cerebral vascular conductance index. TR-COLD led to a reduction in end-tidal CO$_2$ pressure of 6.1 mmHg at minute 25 of heating (Fig. 2C) that should be the result of higher minute ventilation (Fig. 2A). Apparently, TR-HEAT did not affect end-tidal CO$_2$ pressure at normothermic baseline or at any time during heating (Fig. 2D).

Mean blood velocity in the MCA at normothermic baseline recorded before and after TR-COLD ($57 \pm 15$ vs. $55 \pm 11 \text{ cm/s}$, $P = 0.378$) and TR-HEAT ($53 \pm 14$ vs. $58 \pm 17 \text{ cm/s}$, $P = 0.314$) did not differ. TR-COLD had no significant effect on the cerebral vascular conductance index measured at normothermic baseline and throughout the heating period (difference during heating was $0.3$–$4.4%$ baseline) (Fig. 4C). On the other hand, TR-HEAT increased the cerebral vascular conductance index by $3.2$–$5.7%$ baseline during heating (Fig. 4D). Moreover, the training-induced change in the cerebral vascular conductance index, expressed as an absolute ($\text{cm·s}^{-1} \cdot \text{mmHg}^{-1}$) or relative (% baseline) value, was greater in TR-HEAT than TR-COLD at minute 10 of heating (Fig. 4, B and D). On the basis of these results, we suggest short-term exercise-heat acclimation partially alleviates the cerebral hypoperfusion that occurred during passive heating at rest.

Cerebral vascular conductance index response to decreasing end-tidal CO$_2$ pressure. When presented in terms of cm·s$^{-1} \cdot$mmHg$^{-1}$, training did not alter the cerebrovascular CO$_2$ reactivity index in the TR-COLD group (0.007 ± 0.005 vs. 0.006 ± 0.003 cm$^{-1} \cdot$mmHg$^{-1} \cdot$mmHg$^{-1}$, $P = 0.331$) or TR-HEAT group (0.008 ± 0.003 vs. 0.006 ± 0.005 cm$^{-1} \cdot$mmHg$^{-1} \cdot$mmHg$^{-1}$, $P = 0.201$) (Fig. 5, A and B). However, when employing %baseline, TR-COLD tended to reduce the cerebrovascular CO$_2$ reactivity index (1.5 ± 0.5 vs. 1.0 ± 0.4% baseline mmHg$^{-1}$, $P = 0.098$), whereas TR-HEAT significantly reduced the index (1.3 ± 0.3 vs. 0.9 ± 0.4% baseline mmHg$^{-1}$, $P = 0.036$) (Fig. 5, C and D). This shows that short-term heat acclimation may reduce cerebrovascular CO$_2$ reactivity.

Metabolic and respiratory pattern variables. TR-COLD increased CO$_2$ output by 51 ml/min and 83 ml/min at minutes 20 and 25 of heating, respectively, and the respiratory exchange ratio by 0.11 (from 1.02 ± 0.15 to 1.13 ± 0.19) and 0.22 (from 1.07 ± 0.21 to 1.29 ± 0.26) (all $P < 0.05$). These increases should be due to the higher minute ventilation (Fig. 2A). CO$_2$ output and respiratory exchange ratio were not affected by TR-HEAT at normothermic baseline or during heating (all $P > 0.05$). Tidal volume, respiratory frequency, and oxygen uptake at normothermic baseline and at each measured time point during heating were not influenced by TR-COLD or TR-HEAT (all $P > 0.05$). Heating increased CO$_2$ output, the respiratory exchange ratio, tidal volume, respiratory frequency, and oxygen uptake from the normothermic baseline, irrespective of group or training (all $P < 0.05$).

Mean arterial pressure, heart rate, and forearm vascular conductance. Neither TR-COLD nor TR-HEAT affected mean arterial pressure, heart rate, or forearm vascular conductance at normothermic baseline or at any time during heating (all $P > 0.05$). Mean arterial pressure increased from normothermic baseline at minute 25 of heating before (92 ± 6 to 100 ± 10 mmHg) and after (92 ± 6 to 96 ± 8 mmHg) TR-HEAT (both $P < 0.05$). In the TR-HEAT group, mean arterial pressure did not change from normothermic baseline to minute 30 of heating before (90 ± 8 to 94 ± 8 mmHg) or after (89 ± 7 to 93 ± 6 mmHg) TR-HEAT (both $P > 0.05$). Heating increased both heart rate (by 49–59 beats/min) and forearm vascular conductance, irrespective of group or training (all $P < 0.05$).

Mean skin temperature. Heating caused mean skin temperature to increase by 3.7–4.6°C in both groups (all $P < 0.05$).
Sensitivity and peak of cutaneous active vasodilation. Compared with values before training, TR-COLD did not affect the sensitivity (11.9 ± 6.0 vs. 14.6 ± 7.8 ml·100 ml tissue⁻¹·min⁻¹·100 mmHg⁻¹·°C⁻¹, \( P = 0.268 \)) or peak (19.4 ± 6.1 vs. 20.3 ± 7.1 ml·100 ml tissue⁻¹·min⁻¹·100 mmHg⁻¹·°C⁻¹, \( P = 0.807 \)) of cutaneous active vasodilation. Likewise, TR-HEAT did not affect the sensitivity (14.1 ± 5.4 vs. 16.0 ± 6.1 ml·100 ml tissue⁻¹·min⁻¹·100 mmHg⁻¹·°C⁻¹, \( P = 0.345 \)) or peak (20.0 ± 6.6 vs. 20.0 ± 6.0 ml·100 ml tissue⁻¹·min⁻¹·100 mmHg⁻¹·°C⁻¹, \( P = 0.922 \)) of cutaneous active vasodilation.

DISCUSSION

Hyperthermia causes hyperventilation and cerebral hypoperfusion in resting humans. We are the first to report an effect of short-term exercise-heat acclimation on ventilation and cerebral circulation during passive heating at rest. We found that...
during passive heating, the values obtained for increases in ventilation, body core temperature threshold for increased ventilation, and slope relating ventilation to body core temperature before training did not differ from those obtained after 6 days of exercise training in a hot environment (37°C). However, the cerebral vascular conductance index during passive heating was higher after training than before. The same training in a cold environment (10°C) did not attenuate the increase in minute ventilation or decrease in cerebral vascular conductance index during passive heating. This suggests that in resting heated humans, short-term heat acclimation induced by moderate-intensity exercise training (i.e., 50% peak oxygen uptake) in the heat does not affect hyperthermia-induced hyperventilation, but it likely alleviates cerebral hypoperfusion.

Heat acclimation achieved by exercise training in a hot environment. Earlier studies showed that short-term heat acclimation achieved through exercise training in a hot environment induces increases in plasma volume (15, 16, 24, 30, 42), reductions in body core temperature under both normothermic and hyperthermic conditions (6, 15, 16, 24, 32, 56), and reductions in the body core temperature threshold for cutaneous active vasodilation (56). Similar adaptations were induced by TR-HEAT in the present study (see Table 1 for plasma volume, Fig. 1B for body core temperature, and the Results section for cutaneous active vasodilation).

Effect of heat acclimation on ventilation during heating. TR-HEAT had no effect on minute ventilation during passive heating (Fig. 2B). In addition, TR-HEAT was found not to affect the body core temperature threshold or the sensitivity of hyperthermia-induced hyperventilation (Fig. 3B). These findings show that short-term exercise-heat acclimation does not affect hyperthermia-induced hyperventilation occurring at rest. The unchanged sensitivity observed in the present study is consistent with earlier results obtained during exercise (2, 15). However, the lack of change in body core temperature threshold in the present study differs from the findings reported by Beaudin et al. (2), demonstrating that short-term heat acclimation, during which body core temperature increased to levels comparable to those achieved during TR-HEAT in the present study (38.5–39.0°C vs. 38.5–38.7°C), lowered the body core temperature threshold for hyperthermia-induced hyperventilation during incremental exercise. Thus the effect of short-term heat acclimation on the body core temperature threshold for hyperthermia-induced hyperventilation appears to differ depending on whether one is resting or exercising.

Several possible mechanisms could explain the hyperthermia-induced hyperventilation observed in humans. Increases in hypothalamic temperature reportedly cause a robust increase in respiratory drive in rats (4). It has been shown that the effect of skin temperature on hyperthermia-induced hyperventilation is minimal in humans (18, 47), and that muscle (in goats) (20) and intra-abdominal (in rabbits) (34) temperatures contribute little to the increase in ventilation. We therefore suggest that an increase in brain temperature, likely at the hypothalamus, is a major factor responsible for hyperthermia-induced hyperventilation in humans. In addition, we previously found that carotid chemoreceptors contribute to hyperthermia-induced hyperventilation in resting heated humans (13). On the basis of our present finding that TR-HEAT has no effect on hyperthermia-induced hyperventilation, we suggest that short-term exercise-heat acclimation may not modulate the hypothalamic temperature-dependent and/or carotid chemoreceptor-dependent mechanisms that mediate hyperthermia-induced hyperventilation in resting humans. On the other hand, an in vitro study demonstrated that heat exposure can induce some temperature-insensitive hypothalamic neurons to change into warm-sensitive neurons (31), which may account for the increase in the thermosensitivity of the hypothalamus. This adaptation within the hypothalamus may also be induced by short-term exercise-heat acclimation, which in turn, may enhance hyperthermia-induced hyperventilation. By contrast, noradrenaline sensitizes carotid chemoreceptors (21), so that reductions in the noradrenaline concentration achieved through short-term exercise-heat acclimation (19) may deactivate carotid chemoreceptors, resulting in less hyperthermia-induced hyperventilation. Short-term exercise-heat acclimation may simultaneously induce both of the opposing effects outlined above, resulting in no change in hyperthermia-induced hyperventilation.

Effect of heat acclimation on cerebral blood flow during heating. The cerebral vascular conductance index during passive heating was partially increased by TR-HEAT (Fig. 4D). This suggests that short-term exercise-heat acclimation diminishes cerebral hypoperfusion to some extent during hyperthermia at rest. One possible explanation is a reduction in cerebrovascular CO2 reactivity. If the cerebrovascular CO2 reactivity was blunted after TR-HEAT, a given reduction in arterial CO2 pressure induced by hyperthermia-induced hyperventilation would have less impact on cerebral circulation than before. Although we did not directly evaluate cerebrovascular CO2 reactivity in the present study, this possibility is indirectly supported by our finding that the slope relating cerebral vascular conductance index to end-tidal CO2 pressure is reduced after TR-HEAT (Fig. 5D).

However, blunted cerebrovascular CO2 reactivity cannot explain the higher cerebral vascular conductance index observed after 5 and 10 min of passive heating (Fig. 4D), times at which significant hypocapnia had not occurred (Fig. 2D). Thus one or more other adaptations also appear to be involved in the higher cerebral vascular conductance index. The role of cerebral sympathetic nerve activity in the modulation of cerebral circulation was demonstrated in a human study showing that unilateral trigeminal ganglion stimulation reduced MCA mean blood velocity at rest (49). Because hyperthermia is a potent activator of sympathetic nerve activity (36), cerebral hypoperfusion during hyperthermia may be due in part to cerebral vasocostriction induced by sympathetic stimulation. Indeed, during the early phase of passive heating (minutes 5–15), a period when hyperthermia-induced hyperventilation was not clearly detected, the cerebral vascular conductance index was reduced by up to ~20% (Fig. 4D), with little change in end-tidal CO2 pressure (Fig. 2D). The decrease in the cerebral vascular conductance index without a change in end-tidal CO2 pressure is also clearly depicted in Figure 5. This non-CO2-dependent cerebral hypoperfusion during heating is consistent with the findings of earlier studies (5, 13, 35), though this has not been always observed (1, 26). Given that sympathetic nerve activity, evaluated on the basis of noradrenaline concentration during heating was reduced following short-term exercise-heat acclimation (19), the cerebral sympathetic vasocostriction during hyperthermia may have been blunted following TR-HEAT, contributing to the higher cere-
bral vascular conductance index observed during passive heating at rest. Further studies will be needed to determine whether hyperthermia does indeed cause sympathetic cerebral vasoconstriction independently of CO₂ and, if so, whether this effect is blunted by heat acclimation.

It may be that the increase in plasma volume induced by TR-HEAT (Table 1) contributes in some way to the higher cerebral vascular conductance index, as plasma volume can influence the cerebral vascular response to physiological stimuli. For example, Carter et al. (8) demonstrated that the hypohydration (3% reduction in body mass) that accompanies a corresponding decrease in plasma volume exacerbates the cerebral hypoperfusion that occurs during standing. More recently, Schlader et al. (39) showed that in hyperthermic resting humans, an acute increase in plasma volume achieved by infusion of colloid solution, somewhat diminishes the cerebral hypoperfusion elicited by simulated hemorrhage (i.e., lower body negative pressure). Determination of whether the heat acclimation-induced increase in plasma volume observed in the present study is sufficient to alleviate the cerebral hypoperfusion during passive heating will require further investigation.

**Exercise training in a cold environment.** In contrast to TR-HEAT, minute ventilation was higher after TR-COLD, likely reflecting a tendency of increased sensitivity and decreased body core temperature threshold of hyperthermia-induced hyperventilation (Fig. 3A). Thus the effect of short-term exercise training on hyperthermia-induced hyperventilation may depend on the temperature during training. It was previously shown that short-term (10-day) cold acclimation can enhance the ventilatory response evaluated based on the hypoxic and hypocapnic ventilatory responses (23). Repeated cold exposure during TR-COLD may enhance hyperthermia-induced hyperventilation. It is also noteworthy that the slope relating the cerebral vascular conductance index to end-tidal CO₂ pressure during passive heating tended to be lower following TR-COLD (Fig. 5C). This should reflect the fact that the cerebral vascular conductance index after 25 min of heating was little affected by TR-COLD (Fig. 4C), despite the fact that TR-COLD reduced end-tidal CO₂ pressure (Fig. 2C). The absence of a change in slope is at variance with the study by Murrell et al. (25), who reported that 12 wk of exercise training did not influence cerebrovascular CO₂ reactivity evaluated during voluntary hyperventilation-induced hypocapnia under normothermic conditions. It may be that the effect of exercise training on cerebrovascular CO₂ reactivity differs between normothermia and hyperthermia. Importantly, given that the slope relating the cerebral vascular conductance index to the end-tidal CO₂ pressure was significantly reduced after TR-HEAT (Fig. 5D), it may be that heat acclimation is more effective than exercise training for modulating cerebrovascular CO₂ reactivity during passive heating at rest. Further studies will be needed to test the abovementioned possibilities.

**Considerations.** Five issues should be considered in the present study. First, although our subjects were successfully heat acclimated as evidenced by their increased plasma volume, lowered body core temperature, and lower body core temperature threshold for cutaneous vasodilation, subjects performed the second passive heat test 18–48 h after the end of TR-HEAT. Consequently, some time-dependent decay of the heat acclimation effect may have occurred. Second, relative physiological strain during passive heating may not be same before and after training. In particular, TR-HEAT led to increased plasma volume and reduced body core temperature, which may alleviate physiological strain during passive heating. We do not know whether a reduction in relative physiological strain occurred after TR-HEAT or, if so, the extent to which this affected our results. Third, we did not measure MCA diameter because transcranial Doppler ultrasound provides only blood velocity information. The influence of changes in arterial diameter on blood flow can be substantial, however. Based on Poiseuille’s law, a 5% reduction in MCA radius, which would be only about 0.0625 mm, assuming a radius of about 1.25 mm (40), can cause a 20% decrease in MCA blood flow. In that regard, one recent study demonstrated that hypocapnia induced by voluntary hyperventilation under normothermic conditions can lead to constriction of the MCA (10). This may have caused us to underestimate the magnitude of cerebral hypoperfusion during the latter part of the passive-heat test, where subjects developed hypocapnia due to hyperthermia-induced hyperventilation. Furthermore, it appears that cerebral blood flow and artery diameter are both increased during hyperthermia in dogs (9). If MCA diameter increased during hyperthermia in the present study, mean blood velocity could have been reduced in the artery without reducing the total blood flow. Hence we cannot exclude the possibility that some of the apparent reductions in cerebral vascular conductance index during the passive-heat stress test in the present study are attributable to MCA dilation. Fourth, although our main focus was on the effect of exercise-heat acclimation on ventilatory and cerebral blood flow responses to passive heat stress, had we included an orthostatic stress test, we would have been able to provide a more direct interpretation pertaining to whether partial alleviation of cerebral hypoperfusion after exercise-heat acclimation can improve orthostatic tolerance, as discussed below. Finally, we employed hot water immersion to increase body temperature. Such immersion can reduce blood pooling in the lower legs, which can ultimately change blood distribution and cardiovascular responses. We are not sure of the extent to which this water immersion affected our main results.

**Perspectives and significance.** Hyperthermia challenges cerebral circulation, as demonstrated by the present and previous studies (27, 28, 55). Because reducing cerebral blood flow can cause syncope (45), impaired orthostatic tolerance during hyperthermia and heat stroke may be attributable in part to a hyperthermia-induced reduction in cerebral blood flow. Our results indicate that short-term exercise-heat acclimation partially alleviates hyperthermia-induced cerebral hypoperfusion, which may be one of the mechanisms behind the observation that short-term exercise-heat acclimation improves orthostatic tolerance during hyperthermia (41).

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DISCLOSURES

REFERENCES


