Voluntary suppression of hyperthermia-induced hyperventilation mitigates the reduction in cerebral blood flow velocity during exercise in the heat

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Tsuji B, Honda Y, Ikebe Y, Fujii N, Kondo N, Nishiyasu T. Voluntary suppression of hyperthermia-induced hyperventilation mitigates the reduction in cerebral blood flow velocity during exercise in the heat. Am J Physiol Regul Integr Comp Physiol 308; R669–R679, 2015. First published January 28, 2015; doi:10.1152/ajpregu.00419.2014.— Hyperthermia during prolonged exercise leads to hyperventilation, which can reduce arterial CO2 pressure (Paco2) and, in turn, cerebral blood flow (CBF) and thermoregulatory responses. We investigated 1) whether humans can voluntarily suppress hyperthermic hyperventilation during prolonged exercise and 2) the effects of voluntary breathing control on Paco2, CBF, sweating, and skin blood flow. Twelve male subjects performed two exercise trials at 50% of peak oxygen uptake in the heat (37°C, 50% relative humidity) for up to 60 min. Throughout the exercise, subjects breathed normally (normal-breathing trial) or they tried to control their minute ventilation (respiratory frequency was timed with a metronome, and target tidal volumes were displayed on a monitor) to the level reached after 5 min of exercise (controlled-breathing trial). Plotting ventilatory and cerebrovascular responses against esophageal temperature (Tes) showed that minute ventilation increased linearly with rising Tes during normal breathing, whereas controlled breathing attenuated the increased ventilation (increase in minute ventilation from the onset of controlled breathing: 7.4 vs. 1.6 l/min at +1.1°C Tes; P < 0.001). Normal breathing led to decreases in estimated Paco2 and middle cerebral artery blood flow velocity (MCAV) with rising Tes, but controlled breathing attenuated those reductions (estimated Paco2 −3.4 vs. −0.8 mmHg; MCAV −10.4 vs. −3.9 cm/s at +1.1°C Tes; P = 0.002 and 0.011, respectively). Controlled breathing had no significant effect on chest sweating or forearm vascular conductance (P = 0.67 and 0.91, respectively). Our results indicate that humans can voluntarily suppress hyperthermic hyperventilation during prolonged exercise, and this suppression mitigates changes in Paco2 and CBF.

Elevations in body temperature at rest (6, 12, 15, 40) and during exercise (4, 11–13, 17, 32, 39, 48) lead to increases in ventilation. For instance, an earlier study showed that during prolonged moderate exercise at a constant workload, core temperature and minute ventilation (VE) were maintained constant during the period from 10 min to 60 min of exercise in a thermoneutral environment, whereas both core temperature and VE increased progressively from 10 min of exercise to exhaustion in a hot environment (32). Because oxygen uptake and blood lactate concentrations remain relatively constant during such exercise and are similar under hot and thermoneutral conditions (18, 32), these results suggest that it is not metabolic factors, but the elevation in body temperature that mediates the increase in VE. During prolonged exercise, the elevation in core temperature, but not skin temperature (18, 46), leads to an increase in VE beyond what would be expected from metabolic demand.

When expressed as a function of esophageal temperature (Tes; an index of core temperature), VE reportedly increases during prolonged moderate exercise at 5–12 l/min per 1°C rise in Tes within the range of 37–40°C (11–13, 18, 32, 45, 46). This hyperthermia-induced increase in VE excessively eliminates CO2 from the body, reducing arterial CO2 pressure (Paco2) (hypocapnia) (18, 32). Because Paco2 has an important role in determining cerebral circulation (26), the hyperventilation-induced reduction in Paco2 can lead to a reduction in cerebral blood flow. It was previously observed, for example, that Paco2 and middle cerebral artery blood flow velocity (MCAV) declined during prolonged exercise in the heat (17, 32, 36), which implies cerebral blood flow was reduced. That implication has also been verified using the Kety-Schmidt technique (31). Moreover, when the hyperthermic hyperventilation-induced reduction in Paco2 was restored to eucapnia by inhaling hypercapnic air during prolonged moderate exercise, MCAV was also largely restored to normal (17, 36). On the basis of these findings, we speculate that if Paco2 can be maintained constant during exercise in the heat, the reduction in cerebral blood flow would be suppressed throughout the exercise. Although hyperthermic hyperventilation appears to be caused by involuntary respiratory control, humans can voluntarily control their ventilation. For instance, rapid cold stress-induced hyperventilation, and its resultant reductions in Paco2 and MCAV during ice-water immersion can reportedly be suppressed by voluntary control of breathing (29). However, it remains unclear whether humans can voluntarily suppress hyperthermic hyperventilation during prolonged exercise and, if so, whether the associated reductions in Paco2 and cerebral blood flow can be mitigated by this suppression.

Hypocapnia may also potentially affect thermoregulatory responses, such as sweating and skin vasodilation. For instance, voluntary hyperventilation-induced reductions in Paco2 at rest in the heat reportedly decrease sweating and skin blood flow (1, 9, 38) and increase core temperature (38), compared with normocapnic hyperventilation. Those findings suggest the two thermoregulatory responses ongoing during exercise in the heat may be suppressed by hyperthermic hyperventilation-induced hypocapnia. If so, suppression of hyperventilation and hypocapnia during exercise in the heat would be expected to increase sweating and skin blood flow, although that possibility has never been investigated.

In the present study, we examined whether humans can voluntarily suppress hyperthermic hyperventilation during prolonged exercise in the heat, and whether voluntary control of

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breathing can affect $P_{aCO_2}$, MCAV, and thermoregulatory responses, such as sweating and skin vasodilation.

**METHODS**

**Subjects**

Twelve healthy males [age 24 ± 3 years, height 172 ± 4 cm, weight 65 ± 6 kg, peak $O_2$ uptake ($V_{O2peak}$) 46.1 ± 3.4 ml·kg$^{-1}$·min$^{-1}$] volunteered to participate in this study. The participants were nonsmokers, and none was taking any medication. Written informed consent was obtained from each participant. The present procedure was approved by the Human Subjects Committee of the University of Tsukuba, and followed the provisions of the Declaration of Helsinki.

**$V_{O2peak}$ Test**

Each subject initially performed an incremental exercise test to exhaustion on a bicycle ergometer (818E, Monark, Sweden; customized for semirecumbent cycling) to determine $V_{O2peak}$. In an environmental chamber (Fujiika, Chiba, Japan) maintained at 25°C and 50% relative humidity, subjects first performed a light warm-up (30 W, 60 rpm) for 3 min, which was followed by a 1-min interval by an incremental exercise. The exercise began at a workload of 60 W, after which the load increased by 15 W every 1 min until exhaustion. Subjects pedaled at 60 rpm, and volitional exhaustion was defined as an inability to pedal at more than 50 rpm. Expired gas was analyzed using a metabolic cart (RM300i; Minato Medical Science, Japan). The flow sensor was calibrated using an apparatus to calibrate syringe able to blow a fixed volume (2 liters) of air. The $O_2$ and $CO_2$ sensors were calibrated with reference gases of known concentration ($O_2$ 15%-$CO_2$ 5%-N$_2$ balance). $V_{E}$, oxygen uptake ($V_{O2}$), and carbon dioxide output ($V_{CO2}$) were recorded at 60-s intervals.

**Experimental Design**

Once $V_{O2peak}$ was determined for each subject, on different days, the subjects performed two bouts of exercise in the heat, with or without controlled breathing. The experimental trials were conducted in random order and were separated by at least 5 days. Subjects were asked to abstain from strenuous exercise, alcohol, and caffeine for 24 h before the experimental testing. To standardize the hydration status, the subjects drank 500 ml of water on the night before the experiment and consumed a light meal and 500 ml of water 2 h before the experiment.

**Exercise Test in the Heat**

The subjects came to the laboratory at 8:30 AM and rested in an environmental chamber (ambient temperature = 25°C, relative humidity = 50%). During this time, a thermocouple for measuring $T_{es}$ was inserted through the nasal passage to a distance equivalent to one-fourth of the subject’s height. The location of the probe in the esophagus was estimated to be posterior to the lower border of the left atrium (47). The subjects then voided urine; body weight was recorded; a capsule for measuring sweat rate (SR) was attached to the left chest using collodion; and an ultrasound Doppler probe for measuring forearm blood flow (FBF) was attached to the arm. Thereafter, subjects moved to another environmental chamber (ambient temperature = 37°C, relative humidity = 50%, and wind speed <0.2 m/s), where they sat in a semirecumbent position in the chair of the cycle ergometer and rested for 30–40 min. During this time, a heart rate (HR) monitor, copper-constantant thermocouples for measuring skin temperature, a cuff (on the upper left arm), and electrodes for measuring arterial blood pressure, and a mask for measuring respiratory gas were attached. To measure forearm blood flow (FBF), a mercury-Silastic strain gauge (on the right forearm), a cuff for occlusion of venous blood flow (on the upper right arm), and a cuff for exclusion of hand blood flow (on the right wrist) were also attached.

Baseline resting measurements were performed while the subjects sat for another 10 min. The subjects then performed the cycle exercise at 50% of $V_{O2peak}$. Exercising at this intensity in the heat was previously shown to elicit gradual increases in $T_{es}$ and hyperventilation, while maintaining $V_{O2}$ and blood lactate concentrations (<2 mmol/l) virtually constant (18). This intensity can, thus, induce hyperthermic hyperventilation that is minimally influenced by metabolic factors. Throughout the exercise, the subjects breathed normally (normal-breathing trial), or they tried to maintain $V_{E}$ at the level reached after 5 min of exercise (controlled-breathing trial) by timing their respiratory frequency (f) using a metronome and attempting to match target tidal volume ($V_{T}$) values displayed on a monitor. The termination criteria for the exercise were 1) the exercise duration reached 60 min, 2) $T_{es}$ reached 39.0°C, or 3) the subject could no longer pedal at 60 rpm.

**Measurements**

$T_{es}$ and skin temperatures were measured using copper-constantant thermocouples, recorded on a computer (ThinkPad A21p; IBM, Yokyo, Japan) at 1-s intervals via a data logger system (WE7000; Yokogawa, Japan), and averaged over 30 s. Mean skin temperature ($T_{sk}$) was calculated from the seven skin temperatures weighted to the following regional proportions: 7% forehead, 14% forearm, 5% hand, 7% foot, 13% lower leg, 19% thigh, and 35% chest (16). HR was recorded every 5 s using a heart rate monitor (Vantage NV; Polar Electro, Kempele, Finland) and was averaged over 30 s. Blood pressure was measured in the upper arm every 1 min using an automated sphygmomanometer (STBP-780; Nippon Colin, Komaki, Japan). Mean arterial pressure (MAP) was calculated as the diastolic pressure plus one-third of the pulse pressure. Expired gas was measured using the same analyzers used in the $V_{O2peak}$ test, and $V_{E}$, $V_{O2}$, $V_{CO2}$, and end-tidal $CO2$ pressure ($PEtCO2$), and respiratory exchange ratio were recorded breath-to-breath. Estimated $P_{aCO2}$ ($Paco_{2,estimated}$) was calculated using $PEtCO2$ and $VT$ using the equation of Jones et al. (24). MCAV was determined using the transcendental Doppler ultrasound technique (WAKI 1-TC; Atys Medical, Soucie-en-Jarrest, France). A 2-MHz Doppler probe was secured with a customized headband to the left temporal region, and the signal was collected at a rate of 45–60 min. Before the two exercise tests in the heat, preliminary examinations were carried out, and the position and angle of the probe that provided the optimal signal were determined, and pictures were taken. This picture information enabled us to obtain similar MCAV values at baseline between the two trials. Cerebral vascular conductance (CVC) was calculated as MCAV divided by MAP and expressed as cm·s$^{-1}$·100 mmHg$^{-1}$ for later analysis. SR was measured using the ventilated-capsule method. Dry nitrogen was supplied to the capsule (3.46 cm$^2$) at a rate of 1.5 l/min, and the humidity of the nitrogen gas flowing out of the capsule was measured using a capacitance hygrometer (HMP 45ASPF, Vaisala, Helsinki, Finland). FBF was measured using venous occlusion plethysmography with a mercury-Silastic strain gauge. The arm was elevated 10 cm above the heart level to facilitate venous return. Pressure in the venous occlusion cuff was set at 45 mmHg, and the circulation to the hand was excluded using a wrist cuff inflated to 220 mmHg. FBF was measured once or twice a minute after inflating the upper arm cuff. The strain gauge was calibrated using a cylinder and a 20-g weight before the experiment. Because it has been shown that there is little or no change in forearm muscle blood flow during whole body heating (7) and prolonged exercise (23), increases in FBF during heat stress were evaluated as increases in skin blood flow. Forearm vascular conductance (FVC) was calculated as FBF divided by MAP and expressed as ml·100 ml tissue$^{-1}$·1min$^{-1}$·100 mmHg$^{-1}$ for later analysis. Ratings of perceived exertion (RPE) were measured every 5 min using Borg’s scale. In four subjects, breathing effort was measured every 5 min using a 10-point scale (e.g., 1, very weak; 3, moderate; 5, strong; and 7, very strong).
**Statistical Analysis**

Two-factor repeated-measures ANOVA was used to analyze the time-dependent and core temperature-dependent data. For the former, the two factors were breathing trial (levels: normal breathing and controlled breathing) and time (0, 5, 10, 15, 20, 25, 30, 35, 40 min and end of exercise); for the latter, they were breathing trial (levels: normal breathing and controlled breathing) and relative T<sub>es</sub> level (levels: 0, 0.1, 0.2, 0.3, 0.5, 0.7, 0.9, and 1.1°C). After determination of the main effects, pairwise differences were identified using Bonferroni’s multiple-comparison test. All data are reported as means ± SD. Values of P < 0.05 were considered significant. All statistical analyses were performed using the SPSS statistics package (version 19.0, SPSS, Chicago, IL).

**RESULTS**

**Exercise Duration and Body Weight**

Exercise duration did not differ significantly between the normal-breathing and controlled-breathing trials (54.2 ± 7.9 vs. 55.4 ± 6.9 min; P = 0.19). Seven of the twelve subjects completed the 60-min exercise in both trials. Three of the remaining five subjects exercised for the same amount of time in each of the two trials, although they did not exercise for the full duration (40, 45, and 55 min, respectively). The exercise was terminated early because they could not continue pedaling at 60 rpm (RPE reached ∼18) in either trial. The final two subjects exercised for longer in the controlled-breathing trial than the normal-breathing trial (45 vs. 50 and 45 vs. 55 min). For one subject, the trials were terminated because of his inability to continue pedaling at 60 rpm (RPE reached ∼19); for the other, it was because his T<sub>es</sub> reached ∼39°C. Body weight at baseline (64.6 ± 5.7 vs. 64.8 ± 5.9 kg; P = 0.20) and after exercise (62.9 ± 5.7 vs. 63.1 ± 5.8 kg; P = 0.10), as well as the percent body weight lost (2.64 ± 0.58% vs. 2.62 ± 0.59%; P = 0.83), did not differ between the normal- and controlled-breathing trials.

**Time-Dependent Changes**

**Body temperature and ventilatory responses.** T<sub>es</sub> increased during exercise to 38.4 ± 0.4°C in both trials, and it did not significantly differ between trials (P = 0.68) (Fig. 1A). T<sub>sk</sub> also did not differ between trials (P = 0.46).

Figure 2 shows individual data for V<sub>E</sub>. Time-dependent changes in respiratory variables are shown in Table 1 and Figs. 3 and 4. In the normal-breathing trial, V<sub>E</sub> was higher than the 10-min value from 15 min to the end of the exercise (all P < 0.01), whereas it was maintained steady from 10 min throughout the controlled-breathing trial (all P > 0.21). Controlled breathing prevented the increases seen after 20 min of exercise in the normal-breathing trial (all P < 0.02) (Fig. 3A). In both trials, V<sub>T</sub> after 15 min did not differ from the level after 10 min of exercise (all P = 1.00). V<sub>T</sub> was higher in the controlled-breathing trial than in the normal-breathing trial from 15 min to the end of exercise (all P < 0.04) (Fig. 3B). f was higher than the 10-min value from 20 min to the end of exercise in the normal-breathing trial (all P < 0.01), whereas it remained constant in the controlled-breathing trial (all P = 1.00). f was lower in the controlled-breathing than the normal-breathing trial from 10 min to the end of exercise (all P < 0.01) (Fig. 3C). Both V<sub>E</sub>/V<sub>O</sub><sub>2</sub> and V<sub>E</sub>/V<sub>CO</sub><sub>2</sub> were higher from 20 min to the end of exercise than at 10 min in the normal-breathing trial (all P < 0.03), but controlled breathing prevented the increases seen in the normal-breathing trial (all P < 0.01) (Fig. 4, A and B). From 15 min to the end of exercise, PaCO<sub>2,estimated</sub> was lower than the level at 10 min in the normal-breathing trial (all P < 0.03) (Fig. 4C). In addition, PaCO<sub>2,estimated</sub> was higher in the controlled-breathing than the normal-breathing trial at 5 min and from 40 min to the end of exercise (all P < 0.02) (Fig. 4C). V<sub>O</sub><sub>2</sub> was slightly but significantly higher than the 10-min level from 15 min to the end of exercise in the normal-breathing trial (all P < 0.01) and was higher at the end of exercise than at 10 min in the controlled-breathing trial (P = 0.02). Moreover, V<sub>O</sub><sub>2</sub> was lower in the controlled-breathing trial than in the normal-breathing trial from 35 min to the end of exercise (all P < 0.04) (Fig. 4D). V<sub>CO</sub><sub>2</sub> was lower in the controlled-breathing trial than in the normal-breathing trial from 35 to 40 min (both P < 0.02). The respiratory exchange ratio remained <1.0 throughout the exercise in both trials, and it did not significantly differ between trials (P = 0.48).

**Cardiovascular and Cerebrovascular Responses**

There were no between-trial differences in HR or MAP during the exercise (P = 0.06 and 0.58, respectively). HR was higher from 15 min to the end of exercise than at 10 min in both trials (all P < 0.01), and MAP remained constant until the end of exercise in both trials (all P > 0.95) (Fig. 1, B and C). MCAV was lower from 20 min to the end of exercise than at 10 min in the normal-breathing trial (all P < 0.03), and there was no significant difference between trials (P = 0.91) (Fig. 1D). Changes in CVC were similar to those in MCAV. CVC was lower from 20 min to the end of exercise (60.5 ± 15.5 units) than at 10 min (70.9 ± 14.5 units) in the normal-breathing trial (all P < 0.02), whereas it remained at the 10-min value (68.4 ± 12.9 units) until the end of exercise (63.6 ± 14.3 units) in the controlled-breathing trial (all P = 1.00). There was no difference between trials (P = 0.86).

**Thermoregulatory Response**

After 10 min of exercise (normal-breathing vs. controlled-breathing: 11.8 ± 5.3 vs. 10.1 ± 4.3 units), FVC did not increase further throughout the rest of the exercise (16.6 ± 6.4 vs. 17.6 ± 8.1 units) in both trials (all P > 0.09), and there was no significant difference between trials (P = 0.91) (Fig. 5A). FBF also remained unchanged from the 10-min value (12.0 ± 5.0 vs. 10.3 ± 5.1 ml·100 ml tissue<sup>−1</sup>·min<sup>−1</sup>) to the end of the exercise (16.3 ± 6.8 vs. 17.6 ± 8.2 ml·100 ml tissue<sup>−1</sup>·min<sup>−1</sup>) in the normal-breathing and controlled-breathing trials (all P > 0.07), and it did not differ between trials (P = 0.73). Chest SR was higher from 15 min to the end of exercise (normal-breathing vs. controlled-breathing: 1.6 ± 0.6 vs. 1.7 ± 0.7 mg·cm<sup>−2</sup>·min<sup>−1</sup>) than at 10 min (1.1 ± 0.5 vs. 1.1 ± 0.4 mg·cm<sup>−2</sup>·min<sup>−1</sup>) in both trials (all P < 0.03), and there was no significant difference in SR between trials (P = 0.67) (Fig. 5B).

**RPE and Breathing Effort**

RPE was higher from 35 min to the end of exercise (17.6 ± 1.6) than at 10 min (normal-breathing vs. controlled-breathing: 13.1 ± 1.4 vs. 13.1 ± 1.2) (all P < 0.01) in the normal-breathing trial and was higher from 30 min to the end of exercise (16.8 ± 1.7) in the controlled-breathing trial (all P < 0.01).
RPE did not differ significantly between trials ($P = 0.48$), but at the end of the exercise, it tended to be lower in the controlled-breathing than the normal-breathing trial ($P = 0.082$) (Fig. 3D). Breathing effort scores ($n = 4$) did not significantly differ from the 10-min value (3.0 ± 0 and 3.3 ± 0.5) from 15 min to the end of exercise (60 min: 4.5 ± 1.3 and 5.5 ± 2.4) in the controlled-breathing and normal-breathing trials (all $P = 1.00$). The scores also did not differ between trials ($P = 0.49$).

Tes-Dependent Changes in Ventilatory, Cerebrovascular and Thermoregulatory Responses from the Start of Voluntary Control of Breathing

In the controlled-breathing trial, all of the subjects started the voluntary control of breathing after about 8 min of exercise. To examine its effect on ventilatory, cerebrovascular and thermoregulatory responses to increasing core temperature, we plotted $V_\text{E}$, $P_{\text{ACO}_2,\text{estimated}}$, MCAV, CVC, FVC, FBF, and SR against changes in $T_\text{es}$ from the onset of controlled breathing. $V_\text{E}$ was higher at $\pm 0.4–1.1^\circ \text{C}$ ($1.1^\circ \text{C}, 7.4 \pm 2.9 \text{ l/min}$) in the normal-breathing trial than at $\pm 0.1^\circ \text{C}$ (normal-breathing vs. controlled-breathing: 1.6 ± 1.4 vs. 0.3 ± 1.0 l/min) (all $P < 0.01$), whereas it remained unchanged at the $\pm 0.1^\circ \text{C}$ value until $\pm 1.1^\circ \text{C}$ (1.6 ± 2.9 l/min) in the controlled-breathing trial (all $P < 0.59$) (Fig. 6A). Consequently, $V_\text{E}$ was lower in the controlled-breathing than the normal-breathing trial at $\pm 0.1–1.1^\circ \text{C} T_\text{es}$ (all $P < 0.01$). $P_{\text{ACO}_2,\text{estimated}}$ was lower at $\pm 0.3–1.1^\circ \text{C}$ ($1.1^\circ \text{C}, -3.4 \pm 1.4 \text{ mmHg}$) than at $\pm 0.1^\circ \text{C}$ ($-0.6 \pm 0.6 \text{ mmHg}$) in the normal-breathing trial (all $P < 0.01$), but it remained nearly constant at the $\pm 0.1^\circ \text{C}$ value ($-0.1 \pm 0.7 \text{ mmHg}$) until $\pm 1.1^\circ \text{C}$ ($-0.8 \pm 1.5 \text{ mmHg}$) in the controlled-breathing trial (all $P > 0.26$). $P_{\text{ACO}_2,\text{estimated}}$ was higher in the controlled-breathing than the normal-breathing trial at $\pm 0.3–1.1^\circ \text{C} T_\text{es}$ (all $P < 0.02$) (Fig. 6B). MCAV was lower at $\pm 0.5–1.1^\circ \text{C}$ ($1.1^\circ \text{C}, -10.4 \pm 7.0 \text{ cm/s}$) than at $\pm 0.1^\circ \text{C}$

Fig. 1. Time-dependent changes in esophageal temperature (A), heart rate (B), mean arterial pressure (MAP; C) and middle cerebral artery blood velocity (MCAV; D) during normal-breathing and controlled-breathing trials. †$P < 0.05$ vs. the 10-min level in the normal-breathing trial. ‡$P < 0.05$ vs. the 10-min level in the controlled-breathing trial.

Fig. 2. Representative data showing time-dependent changes in minute ventilation during the normal-breathing and controlled-breathing trials. Symbols show 30-s averaged data.
Table 1. Time-dependent changes in respiratory breathing variables during the normal-breathing and controlled-breathing trials

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**Values are means ± SD.** 

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**DISCUSSION**

This study is, to the best of our knowledge, the first to investigate the effect of attempting to voluntarily suppress hyperthermic hyperventilation on $P_{ACO_2}$, CBF, and thermoregulatory responses during prolonged exercise in the heat. Our main findings are that 1) the hyperthermia-induced increase in $V_{E}$, which occurs spontaneously with rising core temperature during prolonged exercise in the heat, can be prevented in healthy men by controlling breathing with feedback about the ventilatory response; 2) $P_{ACO_2}$, estimated arterial carbon dioxide dioxide; $P_{ACO_2}$, estimated arterial carbon dioxide dioxide; $P_{ACO_2}$, oxygen uptake; $P_{ACO_2}$, carbon dioxide output. Normal, normal-breathing trial; Controlled, controlled-breathing trial. *P < 0.05 vs normal-breathing trial; †P < 0.05 vs. 10-min level in the normal-breathing trial; ‡P < 0.05 vs. 10-min level in the controlled-breathing trial.

(normal-breathing vs. controlled-breathing, $-0.7 ± 2.0$ vs. $± 1.6$ cm/s) in the normal-breathing trial (all $P < 0.01$), but it did not differ from the $+0.1°C$ value until $+1.1°C$ ($−3.9 ± 6.5$ cm/s) in the controlled-breathing trial (all $P > 0.31$). MCAV was higher in the controlled-breathing than the normal-breathing trial at $+0.5−1.1°C$ (all $P < 0.04$) (Fig. 6C). CVC was lower at $+0.5−1.1°C$ ($+1.1°C$, $−8.9 ± 6.8$ units) than at $+0.1°C$ ($−0.4 ± 3.7$ units) in the normal-breathing trial (all $P < 0.02$), whereas it did not differ from the $+0.1°C$ value (0.7 ± 2.5 units) until $+1.1°C$ ($−2.8 ± 7.3$ units) in the controlled-breathing trial (all $P > 0.39$). CVC was higher in the controlled-breathing than the normal-breathing trial at $+0.7−1.1°C$ (all $P < 0.04$) (Fig. 6D). FVC increased from $+0.1°C$ (1.5 ± 1.7 units) to $+0.7°C$ (3.7 ± 3.1 units) in the normal-breathing trial ($P = 0.03$) and from $+0.1°C$ (2.3 ± 2.8 units) to $+0.9−1.1°C$ ($+1.1°C$, 5.2 ± 3.0 units) in the controlled-breathing trial (both $P < 0.01$). FVC did not differ between trials ($P = 0.26$). FBF was also higher at $+0.7°C$ (3.7 ± 3.1 ml-100 ml tissue $^{-1}$ min$^{-1}$) in the normal-breathing trial ($P = 0.04$) and at $+0.9−1.1°C$ ($+1.1°C$, 4.7 ± 2.6 ml-100 ml tissue $^{-1}$ min$^{-1}$) in the controlled-breathing trial (both $P < 0.01$) than at $+0.1°C$ (normal-breathing vs. controlled-breathing, 1.5 ± 1.5 vs. 2.2 ± 2.8 ml-100 ml tissue $^{-1}$ min$^{-1}$). FBF did not differ between trials ($P = 0.47$). SR was higher at $+0.3−1.1°C$ ($+1.1°C$, normal-breathing vs. controlled-breathing: 0.5 ± 0.3 vs. 0.6 ± 0.3 mg·cm$^{-2}$·min$^{-1}$) than at $+0.1°C$ in both trials (both, 0.1 ± 0.1 mg·cm$^{-2}$·min$^{-1}$) (all $P < 0.01$), and it did not differ between trials ($P = 0.07$).

Effects of Breathing Control on Ventilatory and Cerebrovascular Responses

Consistent with earlier studies in which $V_{E}$ increased linearly at $5−12$ l/min per $1°C$ rise in $T_{es}$ during prolonged moderate exercise (11−13, 18, 19, 32, 45, 46), we found that with normal breathing, $V_{E}$ increased at $8.0 ± 4.0$ l/min per $1°C$ rise in $T_{es}$. Several factors may contribute to the hyperventilation that occurs with progressive hyperthermia during prolonged exercise in the heat. Possible mechanisms include $I$)
Fig. 3. Time-dependent changes in minute ventilation (A), tidal volume (B), respiratory frequency (C), and ratings of perceived exertion (D) during the normal-breathing and controlled-breathing trials. *P < 0.05, normal-breathing vs. controlled-breathing. †P < 0.05 vs. the 10-min level in the normal-breathing trial; ‡P < 0.05 vs. the 10-min level in the controlled-breathing trial.

Fig. 4. Time-dependent changes in \( \dot{V}E/\dot{V}O_2 \) (A), \( \dot{V}E/\dot{V}CO_2 \) (B), estimated arterial CO\(_2\) pressure (\( PaCO_2 \text{estimated} \)) (C) and \( \dot{V}O_2 \) (D) during normal- and controlled-breathing trials. *P < 0.05, normal-breathing vs. controlled-breathing; †P < 0.05 vs. the 10-min level in the normal-breathing trial.
increased activity of respiratory pacemaker neurons due to elevation in the temperature of the medulla oblongata (44), 2) increased afferent input from group III and IV fibers with elevation in muscle temperature (20, 27), and 3) increased efferent output from the cerebral cortex (central command) (2). The hyperthermic hyperventilation appears to be caused by involuntary respiratory control. On the other hand, humans can voluntarily control ventilation, such as when they hold their breath. During prolonged moderate exercise in the heat, after marked increases at the start of the exercise, VT gradually declines while f gradually increases (12, 18, 45). In the present study, for the controlled-breathing trial, we instructed the subjects to maintain VT and f at the levels reached after 5 min of exercise throughout the remainder of the trial, and information about actual and target VT was fed back to subjects using a monitor. In addition, information about the target f was provided using a metronome. As a result, f and Ve were lower and VT was greater in the controlled-breathing trial than the normal-breathing trial (Fig. 3). As for the relationship between Te and Ve, Ve increased at 2.0 ± 2.8 l/min per 1°C rise in Te in the controlled-breathing trial, and it was maintained nearly constant after the onset of voluntary controlled breathing (Fig. 6A). Therefore, we suggest that even though hyperthermia during prolonged exercise in the heat acts to increase Ve, most healthy men can voluntarily suppress the hyperthermic hyperventilation.

Fig. 5. Time-dependent changes in forearm vascular conductance (A) and chest sweat rate (B) during normal breathing and controlled breathing trials. *P < 0.05 vs. the 10-min level in the normal-breathing trial. †P < 0.05 vs. the 10-min level in the controlled-breathing trial.

Fig. 6. Esophageal temperature-dependent changes in minute ventilation (A), PaCO2, estimated (B), MCAV (C), and CVC (D) during normal-breathing and controlled-breathing trials. *P < 0.05, normal-breathing vs. controlled-breathing. †P < 0.05 vs. 0.1°C in the normal-breathing trial. Change in each parameter (Δ) shows data collected after the start of the controlled breathing (after 8 min of exercise). The numbers adjacent to the symbols indicate the number of subjects remaining at the corresponding temperature.
It is possible that voluntary suppression of spontaneous hyperthermic hyperventilation could cause one to experience feelings of dyspnea. For example, it was previously observed that dyspnea increased when $V_E$ was voluntarily reduced to below the spontaneous level during exercise in a thermoneutral environment (35). In the present study, the breathing effort did not differ between trials for the four subjects in whom that parameter was measured; however, additional study using a larger sample will be needed to draw a conclusion about the effect of voluntary breathing control during hyperthermia on dyspnea. In addition, RPE did not differ between trials in the 12 subjects. Therefore, we think that although prolonged exercise in the heat results in an increase in perceived exertion, voluntary suppression of the hyperventilation has little effect on the perception.

Cerebral blood flow velocity reportedly decreases during hyperthermia at rest (3, 5, 8, 10, 28, 30) and during exercise in the heat (17, 32, 36). Consistent with earlier studies, we found that MCAV gradually declined with rising $T_{es}$ in the normal-breathing trial (Fig. 6C). Notably, controlled breathing attenuated the reduction in MCAV. This is the first reported observation that voluntary suppression of hyperthermic hyperventilation can be voluntarily suppressed, the elevation in core temperature, which leads to skin vasodilation, and the increase in cardiac output also affect cerebral blood flow responses.

Effects of Breathing Control on Thermoregulatory Responses and Oxygen Uptake

Time- and $T_{es}$-dependent changes in FVC, FBF, and chest SR were unaffected by voluntary control of breathing. Robinson and King (38) reported that when subjects voluntarily hyperventilated for 1 h at rest in the heat, hand blood flow was reduced due to hyperventilation-induced hypocapnia, compared with normocapnia achieved through inspiration of CO$_2$ gas during the hyperventilation. In addition, hyperventilation-induced hypocapnia reportedly resulted in a decrease in SR during the same hyperventilation at rest in the heat (1). By contrast, Simmons et al. (42) found that increasing PaCO$_2$ to 5 mmHg above normal led to an increase in forearm skin vascular conductance at rest under thermoneutral conditions. The explanation for the difference in the effect of PaCO$_2$ on the thermoregulatory responses between the present and previous studies could be the level of PaCO$_2$. The relatively small difference in PaCO$_2$ observed in the present study (2 mmHg) may have had little effect on the thermoregulatory response during exercise in the heat. Alternatively, or in addition, the difference in effect may reflect the fact that PaCO$_2$ during exercise in the normal-breathing trial hardly decreased to below the baseline resting level. In that regard, we analyzed the relationships between changes in PaCO$_2$, estimated from baseline rest to $T_{es} = +1.1^\circ$C in the normal-breathing trial (1.23 to 4.0 mmHg; in six subjects, PaCO$_2$, estimated dropped below baseline), as well as the between-trial differences in SR, FVC, and FBF at given $T_{es}$ levels. We found that there was no significant correlation between the PaCO$_2$, estimated and SR ($P = 0.29$), FVC ($P = 0.51$), or FBF ($P = 0.46$). Moreover, there was no correlation in the six subjects in whom PaCO$_2$, estimated decreased to below the baseline resting level (all $P > 0.29$). These findings suggest that even though PaCO$_2$ decreased during the normal-breathing trial dropped below the baseline resting level, the thermoregulatory response was not decreased, compared with the controlled-breathing trial. Nevertheless, further studies will be required to clarify to what extent a decline in PaCO$_2$ to below the baseline resting level can affect the thermoregulatory response during exercise in the heat. Another possibility is that the elevation in core temperature, which leads to skin vasodilation and sweating, masked the hypocapnia-induced reduction in the thermoregulatory response. A previous study reported that voluntary hyperventilation-induced hypocapnia diminished the increase in forearm skin blood flow normally seen with a 0.6°C rise in $T_{es}$, but not the increase seen with a 1.0°C rise (9). In the present study, because $T_{es}$ had already reached about 38°C when the controlled breathing produced a significant difference in PaCO$_2$, compared with normal breathing, the
high core temperature may have suppressed the effect of hypocapnia on the thermoregulatory response.

Our finding that \( \dot{V}O_2 \) was slightly but significantly lower in the controlled-breathing trial than the normal-breathing trial after 30–45 min of exercise suggests that the suppression of hyperthermic hyperventilation results in a decrease in \( \dot{V}O_2 \) during exercise in the heat. Because subjects performed the same cycle exercise in both trials, as reflected by the cadence and load measured in some subjects, we think the \( \dot{V}O_2 \) needed and \( O_2 \) consumed in the active muscles was the same in both trials. One possible explanation for the decrease in \( \dot{V}O_2 \) in the controlled-breathing trial is there was a reduction in \( O_2 \) consumed in the respiratory muscles, i.e., the reduction in \( \dot{V}E \) observed in the controlled-breathing trial reduced the work of breathing. However, in light of the relationship between \( \dot{V}E \) and the work of breathing reported by Johnson et al. (22), it seems unlikely that the difference in \( \dot{V}E \) seen with voluntary control of breathing adequately explains the observed difference in \( \dot{V}O_2 \). Another possible explanation for the decreased \( \dot{V}O_2 \) may be related to an effect of hypocapnia on metabolism. Karetzky and Cain (25) reported that \( \dot{V}O_2 \) increased with decreasing \( PaCO_2 \) when inspiration of four different \( CO_2 \) gas concentrations during voluntary hyperventilation at rest produced different \( PaCO_2 \) levels, although \( \dot{V}E \) was unchanged.

Further research will be needed to identify the cause of the reduction in \( \dot{V}O_2 \) related to suppression of \( \dot{V}E \) during prolonged exercise in the heat.

Limitations

One subject could not voluntarily suppress hyperventilation, such that \( \dot{V}E \) similarly increased at 6.7 and 8.7 l/min per °C rise in \( T_{es} \) in the controlled-breathing and normal-breathing trials, respectively. We included this subject in all data analyses, but it is important to note that excluding the subject did not greatly affect our statistical results. Given a similar increase in \( \dot{V}E \) between trials, it is not surprising that this subject exhibited equivalent decreases in \( PaCO_2\)_{estimated} and MCAV in response to rising \( T_{es} \) in both trials (controlled-breathing vs. normal-breathing, \( PaCO_2\)_{estimated}: \(-3.8 \text{ vs. } -4.7 \text{ mmHg/°C}; \) MCAV \(-13.5 \text{ vs. } -17.3 \text{ cm/s per °C}). Other physiological responses in this subject, including the thermoregulatory response, were comparable to the other subjects. We do not know why this subject was unable to control his breathing, but importantly, this fact suggests that it is difficult for some individuals to control their breathing during exercise in the heat. Notably, the exercise duration was 5 min longer in the controlled-breathing trial than normal-breathing trial, which is perhaps attributable to the lower RPE observed during the controlled-breathing trial.

Another subject who exercised longer in the controlled-breathing trial was able to suppress his hyperventilation, as reflected by the lower \( \dot{V}E \) response to rising \( T_{es} \) (controlled-breathing vs. normal-breathing, \(-2.4 \text{ vs. } 6.5 \text{ l/min per °C}), which, in turn, suppressed the decrease in \( PaCO_2\)_{estimated} (0.6 vs. \(-1.6 \text{ mmHg/°C}). Nonetheless, MCAV decreased similarly in the two trials (\(-8.8 \text{ vs. } -8.2 \text{ cm/s per °C}), and we do not know the reason. We also found greater FVC and SR responses to rising \( T_{es} \) and a lower rate of rise in \( T_{es} \) (2.5 vs. 3.3°C/h) in the controlled-breathing trial than the normal-breathing trial. Because this subject ended both trials early when his \( T_{es} \) reached 39°C, the longer exercise duration may be due to the slower rate of rise in \( T_{es} \). The physiological responses seen in these two subjects did not necessarily correspond to the overall effect of breathing control in this study; i.e., voluntary breathing suppressed the decrease in MCAV and had little effect on thermoregulatory response. We will need to clarify the connection between exercise performance, physiological responses, and psychological effects during voluntary control of breathing during exercise in the heat.

We used transcranial Doppler ultrasound to measure MCAV, after which the blood flow velocity was used as an index of anterior cerebral blood flow. Although these data could be affected by changes in MCA diameter (e.g., vasoconstriction), it was previously demonstrated that MCA diameter is not affected by hyperventilation-induced reductions in PETCO2, down to about 25 mmHg (14, 41). Therefore, we think our observed MCAV levels were unaffected by hyperthermic hyperventilation-induced decreases in PaCO2, to about 38 mmHg, which was the level seen at the end of exercise in the normal-breathing trial.

To voluntarily suppress hyperthermic hyperventilation, we used a protocol in which subjects worked to control both \( f \) and \( VT \) with feedback from a metronome and a monitor. Although most of the subjects were able to suppress the hyperventilation, we do not know whether the same would be true with feedback for only \( f \) or \( VT \), or without feedback, and, in turn, the effect of breathing control on \( PaCO_2 \), and cerebral blood flow. Additional investigation will be needed to determine the impact of the method by which hyperthermic hyperventilation is suppressed during exercise and its effect on physiological responses and perception.

Because we used only male subjects, it remains unclear whether females can voluntarily suppress hyperthermic hyperventilation during exercise in the heat. An earlier study that tested young females reported that \( \dot{V}E \) increased by \(-10 \text{ l/min per °C rise in } T_{es} \) (19), which is comparable to the males in the present study. Given this similarity, it seems likely that females are able to voluntarily suppress hyperthermic hyperventilation, although this will need to be confirmed in the future. We will also need to directly evaluate how voluntary suppression of hyperthermic hyperventilation alters thermoregulatory and MCAV responses in females.

Perspectives and Significance

Our findings indicate that voluntary suppression of spontaneous hyperthermic hyperventilation during prolonged moderate exercise in the heat diminishes the reductions in \( PaCO_2 \), and MCAV otherwise seen. The decrease in cerebral blood flow seen during exercise in the heat reportedly does not impede cerebral metabolism because brain oxygen uptake is maintained or increased irrespective of the reduced flow (31, 43). On the other hand, brain temperature may increase due to the resultant reduction in heat exchange in the brain (33). Thus, restoration of \( PaCO_2 \), and cerebral blood flow through voluntary control of breathing may have the beneficial effect of mitigating the increase in brain temperature during prolonged exercise in the heat.

Despite the restoration of MCAV by voluntary breathing control, we found no change in RPE. It appears that largely preventing the decrease in cerebral blood flow during pro-
longed exercise in the heat had little or no effect on perceived effort. Consistent with that finding, Rasmussen et al. (37) reported that during prolonged moderate exercise in the heat, RPE was not reduced, and decreases in alertness, estimated on the basis of electroencephalogram activity, were unchanged when P_ACO2 and MCAV were temporarily restored through CO2 inhalation. Continuous CO2 inhalation-induced restoration of P_ACO2 and MCAV throughout prolonged exercise in the heat also reportedly does not affect RPE (17). Further research will be needed to assess the significance of the voluntary suppression of hyperthermic hyperventilation during prolonged exercise in the heat.

Conclusion

In summary, hyperthermia-induced increases in V_E were prevented by voluntary breathing control in healthy men, and P_ACO2 and MCAV responses to rising core temperature were higher in controlled-breathing than normal-breathing trials. These results suggest that healthy men can voluntarily suppress hyperthermic hyperventilation during prolonged exercise in the heat and that this suppression can diminish changes in P_ACO2 and cerebral blood flow.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

Author Contributions

Author contributions: B.T., Y.I., N.F., and T.N. edited and revised manuscript; B.T., Y.H., Y.I., and N.K. performed experiments; B.T., Y.H., and N.F. designed research; B.T., Y.I., and N.F. prepared figures; B.T. drafted manuscript; B.T., Y.H., and N.F. helped to revise the manuscript. All authors reviewed the manuscript.

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