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Respiratory mechanics and cerebral blood flow during heat-induced hyperventilation and its voluntary suppression in passively heated humans

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Cerebral blood flow, hyperpnea, hyperthermia, voluntary control of breathing.

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Abstract
We investigated whether heat-induced hyperventilation can be voluntarily prevented, and, if so, how this modulates respiratory mechanics and cerebral blood flow in resting heated humans. In two separate trials, 10 healthy men were passively heated using lower body hot-water immersion and a water-perfused garment covering their upper body (both 41°C) until esophageal temperature (Tes) reached 39°C or volitional termination. In each trial, participants breathed normally (normal-breathing) or voluntarily controlled minute ventilation (VE) at a level equivalent to that observed after 5 min of heating (controlled-breathing). Respiratory gases, middle cerebral artery blood velocity (MCAV), work of breathing, and end-expiratory and inspiratory lung volumes were measured. During normal-breathing, VE increased as Tes rose above 38.0°C0.3°C, whereas controlled-breathing diminished the increase in VE (VE at Tes = 38.6°C: 25.6°C5.9 and 11.9°C1.3 L min−1 during normal- and controlled-breathing, respectively, P < 0.001). During normal-breathing, end-tidal CO2 pressure and MCAV decreased with rising Tes, but controlled-breathing diminished these reductions (at Tes = 38.6°C, 24.7°C5.0 vs. 39.5°C2.8 mmHg; 44.9°C5.9 vs. 60.2°C6.3 cm sec−1, both P < 0.001). The work of breathing correlated positively with changes in VE (P < 0.001) and was lower during controlled- than normal-breathing (16.1°C12.6 and 59.4°C49.5 J min−1, respectively, at heating termination, P = 0.013). End-expiratory and inspiratory lung volumes did not differ between trials (P = 0.25 and 0.71, respectively). These results suggest that during passive heating at rest, heat-induced hyperventilation increases the work of breathing without affecting end-expiratory lung volume, and that voluntary control of breathing can nearly abolish this hyperventilation, thereby diminishing hypocapnia, cerebral hypoperfusion, and increased work of breathing.

Introduction
Hyperthermia is known to cause cerebral hypoperfusion at rest (Fan et al. 2008; Fujii et al. 2008a; Low et al. 2008; Brothers et al. 2009; Nelson et al. 2011) and during exercise (Nybo and Nielsen 2001; Hayashi et al. 2011). This effect may cause elevations in brain temperature (Nybo et al. 2002) and central fatigue (Ross et al. 2012), which could contribute to the development of heat-related illness and to decreased exercise performance in the heat. Thus, reversal of the reduced cerebral blood flow during hyperthermia could reduce the risk of heat-related illness and improve exercise performance in the heat. Hyperthermia also leads to increases in minute ventilation (VE) at rest (Saxton 1975; Cabanac and White 1995; Fujii et al. 2015) and during exercise (White and Cabanac...
1996; Nybo and Nielsen 2001; Hayashi et al. 2011; Tsuji et al. 2012b). This hyperventilation results in excessive elimination of CO2 from the body, leading to reductions in arterial CO2 pressure (PaCO2) (hypocapnia). Moreover, the hyperventilation-induced hypocapnia contributes to cerebral hypoperfusion during hyperthermia at rest (Fujii et al. 2008a; Brothers et al. 2009; Nelson et al. 2011) and during exercise (Rasmussen et al. 2006; Hayashi et al. 2011). Thus, if one could suppress heat-induced hyperventilation, they may be able to substantially reverse hyperthermia-induced cerebral hypoperfusion.

We recently reported that, during prolonged exercise in the heat, heat-induced hyperventilation can be voluntarily suppressed using audiovisual feedback so that PaCO2 is maintained at the eucapnic level throughout the exercise (Tsuji et al. 2015). This largely reverses the heat-induced decreases in middle cerebral artery blood flow velocity (MCAV; an index of anterior cerebral blood flow) otherwise seen (Tsuji et al. 2015). However, whether heat-induced hyperventilation occurring during passive heating at rest can also be suppressed through voluntary control of breathing remains unknown. The heat-induced hyperventilation and the resultant hypocapnia at rest are three times greater than during exercise (Fujii et al. 2008b; Tsuji et al. 2012a). Because respiratory effort and dyspnea increases as the magnitude of ventilation suppression increases (Chonan et al. 1990), voluntarily suppressing hyperventilation and hypocapnia throughout passive heating at rest could be more challenging than during exercise.

Heat-induced hyperventilation is initiated during passive heating when core temperature exceeds ~38.0–38.5°C. Thereafter, VE increases at a rate of ~20–30 L min⁻¹ of V̇E per 1°C rise in core temperature (Cabanac and White 1995; Fujii et al. 2008b; Tsuji et al. 2012a). Although these features of hyperventilation have been extensively reported, available information on respiratory mechanics, such as lung volume and work of breathing during hyperthermia at rest remains unknown. During maximal incremental exercise accompanied by increases in core temperature, end-expiratory lung volume decreases below the resting level while tidal volume (V̇T) increases (Henke et al. 1988; Guenette et al. 2007). Heat-induced hyperventilation at rest is due to increases in both V̇T and respiratory frequency (f) (Gaudio and Abramson 1968; Baker et al. 1996; Fujii et al. 2008b; Tsuji et al. 2012a), though it remains uncertain whether the lung inflates or deflates more or less than normothermic resting levels. If heat-induced hyperventilation at rest is accompanied by changes in end-expiratory lung volume, work of breathing would be greater than expected, since work of breathing increases as the end-expiratory lung volume increases or decreases from the normal resting level (Butler and Arnott 1955).

In this study, therefore, we examined whether one can voluntarily suppress heat-induced hyperventilation during passive heating at rest, and how this suppression modulates PaCO2 and MCAV. We hypothesized that voluntarily suppressing the heat-induced hyperventilation in healthy men, if possible, would largely alleviate hypocapnia and cerebral hypoperfusion, both of which occur during passive heating. We also evaluated how heat-induced hyperventilation and voluntary suppression of this response modulate respiratory mechanics, such as lung volume and the work of breathing.

Methods

Participants

Ten healthy males [age: 24 ± 2 years, height: 173 ± 4 cm, weight: 66 ± 8 kg] volunteered to participate in this study. The participants were nonsmokers and were taking no prescription medications. Written informed consent was obtained from each individual before his participation. The present protocol was approved by the Human Subjects Committee of the University of Tsukuba and conformed to the provisions of the Declaration of Helsinki.

Experimental design

Participants performed two trials wherein they were passively heated with or without controlling breathing. The experimental trials were conducted in a random order and were separated by at least 5 days. The participants were asked to abstain from strenuous exercise, alcohol, and caffeine for 24 h before the experimental testing. To standardize their hydration status, participants drank 500 mL water the night before the experiment and consumed a light meal and 500 mL water 2 h prior to the experiment.

Procedure

Participants arrived at the laboratory at 0830 h, and body weight was recorded after the voiding of urine. The participants then entered an environmental chamber (ambient temperature = 25°C, relative humidity = 50%) and put on a water-perfused garment that covered their upper body, except for the head, left forearm, and hands; the hands were sheathed in cotton gloves. The participants sat in a chair situated in a bath (water temperature = 35°C) filled with water up to their iliac crest. The water in the bath was also circulated through the water-perfused garment. After applying instrumentation, baseline measurements prior to heating (pre) were collected for 10 min while the
participants remained sitting. The temperature of the water in the bath, and thus the perfused garment, was then increased to 41°C and maintained at that temperature for the remainder of the experiment. The water temperature was controlled using a heater and was monitored using a thermocouple placed in the bath.

During heating, esophageal temperature ($T_{es}$) gradually increased from normothermia, and participants either breathed normally (normal-breathing trial) or managed to control $f$ and $V_T$, and therefore $V_E$, at the individual’s target level throughout the heating (controlled-breathing trial). The $V_T$ and $f$ values recorded 5 min into the heating, at which point stable low $f$ and $V_T$ values could be obtained, were used as target values for the controlled-breathing trial. The target $f$ was signaled using a metronome, while the target $V_T$ was indicated through visual $V_T$ feedback displayed on a monitor. After 10 min of heating, subjects began voluntarily controlling their breathing and continued until the end of heating. The heating was terminated when $T_{es}$ reached 39.0°C or at volitional intolerance, after which the participants were deinstrumented and postheating body weight was recorded.

The participants performed forced vital capacity measurements three times before the heating procedure. In addition, inspiratory capacity maneuvers were performed before and every 5 min during the heating; these maneuvers were used to estimate changes in lung volume.

**Measurements**

**Body temperature**

$T_{es}$ and skin temperature were recorded using copper-constantan thermocouples and recorded on a computer (Satellite K22, Toshiba, Japan) at 1-sec intervals via a data logger system (WE7000, Yokogawa, Japan). The thermocouple for measuring $T_{es}$ was inserted through the nasal passage to a distance equivalent to one-fourth of the participant’s height. The location of the probe in the esophagus was estimated to be posterior to the lower border of the left atrium (Wenger and Roberts 1980). Mean skin temperature was calculated from the skin temperatures at seven locations weighted as follows: forehead, 7%; forearm, 14%; hand, 5%; foot, 7%; lower leg, 13%; thigh, 19%; and chest, 35% (Hardy and Dubois 1938).

**Heart rate and blood pressure**

Heart rate was recorded every 5 sec using a heart rate monitor (Vantage NV, Polar, Finland). Blood pressure was measured from the upper right arm every 1 min using an automated sphygmomanometer (STBP-780, Nippon Colin, Japan). Mean arterial pressure (MAP) was calculated as the diastolic pressure plus one-third of the pulse pressure.

**Respiratory variables**

Inspired and expired gases were analyzed using a metabolic cart (AE310s, Minato Medical Science, Japan). The flow sensor was calibrated using an appurtenant calibration syringe able to deliver a fixed volume (2 L) of air. The O$_2$ and CO$_2$ sensors were calibrated with room air and reference gases of known concentration (O$_2$ 15%, CO$_2$ 5%, N$_2$ balance). $V_E$ and $V_T$ adjusted to BTPS, $f$, oxygen uptake (VO$_2$), carbon dioxide output (VCO$_2$), end-tidal CO$_2$ pressure ($P_{ETCO2}$), and respiratory exchange ratio were recorded breath-by-breath. To calculate the ventilatory mechanics (see Data Analysis for details), the flow signal was recorded via an A/D converter system (Power Lab 16/30, AD Instruments, Japan) at a sampling rate of 200 Hz.

**Esophageal and intraoral pressures**

To estimate the work of breathing, esophageal and intraoral pressures were measured using pressure transducers (Codman Microsensor, Codman), and were recorded on a computer (Satellite J72, Toshiba, Japan) at a sampling rate of 200 Hz via a digital manometer (TCB-500, Millar instruments) and A/D converter system (Power Lab 16/30, ADInstruments, Japan). The pressure transducer for esophageal pressure was inserted from the nasal passage to a distance equivalent to one-fourth of the height minus 9 cm, then was further inserted to the stomach, where pressure was changing from negative to positive. Thereafter, the probe was partially withdrawn to a point where the pressure read −1 to −10 cm H$_2$O. Another transducer for intraoral pressure was inserted into the oral cavity −3 cm away from the labium so as not to touch the tongue or hard palate. The pressure transducers were calibrated by immersing them in −38°C water to depths of 0, 10, 20, 30, and 40 cm.

**Cerebral blood flow velocity**

Middle cerebral artery blood velocity was measured using a transcranial Doppler ultrasound device (WAKI 1-TC, Atys Medical, France). A 2-MHz Doppler probe was secured with a customized headband to the left temporal region, and the signal was collected from a depth of 45–60 mm. Prior to the two experiments, the position and angle of the probe were predetermined and imaged using a digital camera. This enabled us to establish similar MCAV values at baseline in the two trials. Cerebral
vascular conductance (CVC) was calculated as MCAV divided by mean arterial pressure.

Other variables

The participants were instructed to rate the intensity of the sensation of difficulty in breathing (dyspnea) (Chonan et al. 1990) every 5 min using a 10-point scale (e.g., 1: very easy, 3: moderate, 5: hard, 7: very hard) in nine participants. Body weight was measured using a platform scale with an accuracy of ±10 g (Yamato scale, Japan) before and after the experiment.

Results

Heating duration and body weight

Heating duration did not differ between trials (normal- vs. controlled-breathing, 40.5 ± 6.9 vs. 39.5 ± 6.4 min, $P = 0.68$). Body weight losses over the course of the experiment were similar in the normal- and controlled-breathing trials (1.6 ± 1.0 vs. 1.4 ± 0.5% body weight loss, $P = 0.29$).

Time-dependent changes

Body temperatures, circulatory and respiratory responses

Time-dependent changes in body temperature, circulatory and respiratory variables are shown in Table 1 and Figure 1A. $T_{es}$ increased similarly during passive heating in both trials ($P = 0.61$, $\eta^2 = 0.001$ for a main effect of trial, Fig. 1A). The observed changes in mean skin temperature and heart rate were also similar in the two trials ($P = 0.91$ and 0.94, both $\eta^2 = 0.001$ for a main effect of trial, respectively). MAP was higher in the controlled-breathing than the normal-breathing trial after 30 min of heating ($P < 0.005$). MCAV was also higher in the controlled-breathing trial after 25 min ($P < 0.04$), and CVC was higher in the controlled-breathing trial at the end of heating ($P < 0.001$). A significant main effect of trial was detected for $V_{E}$, $P_{ETCO2}$, $P_{ETCO2}$, $VCO2$ and the respiratory exchange ratio ($P = 0.001, 0.01, 0.02, 0.001, <0.001, 0.004, and 0.03$; $\eta^2 = 0.10, 0.08, 0.06, 0.21, 0.23, 0.04,$ and 0.10, respectively) but not $VO2$ ($P = 0.94, \eta^2 = 0.001$). $V_{E}$ was lower in the controlled-breathing than the normal-breathing trial during the latter half of heating due to lower $V_T$ and $f$ (all $P < 0.04$). $P_{ETCO2}$ was higher in the controlled-breathing trial after 20 min of heating (all $P < 0.02$). Difficulty of breathing increased during the heating with no difference between trials ($P = 0.17, \eta^2 = 0.02$ for a main effect of trial).
Table 1. Time-dependent changes in circulatory and respiratory variables during normal-breathing and controlled-breathing trials.

|                          | Pre   | 5 min | 10 min | 15 min | 20 min | 25 min | 30 min | End of heating |
|--------------------------|-------|-------|--------|--------|--------|--------|--------|---------------|
| **Heart rate, beats min⁻¹** |       |       |        |        |        |        |        |               |
| Normal-breathing         | 66 ± 7| 69 ± 6| 83 ± 9†| 93 ± 10†| 104 ± 12†| 111 ± 12†| 118 ± 13†| 130 ± 15†    |
| Controlled-breathing     | 65 ± 5| 70 ± 6†| 85 ± 8†| 95 ± 11‡| 102 ± 10‡| 110 ± 9‡| 117 ± 9‡| 128 ± 9‡     |
| **Mean arterial pressure, mmHg** |       |       |        |        |        |        |        |               |
| Normal-breathing         | 91 ± 6| 91 ± 7| 92 ± 8 | 91 ± 7| 92 ± 6 | 90 ± 6 | 90 ± 5 | 89 ± 7       |
| Controlled-breathing     | 87 ± 7| 88 ± 6| 89 ± 6 | 90 ± 5| 92 ± 6 | 94 ± 8 | 96 ± 6*†| 98 ± 9*†     |
| **Middle cerebral artery blood flow velocity, cm sec⁻¹** |       |       |        |        |        |        |        |               |
| Normal-breathing         | 65.0 ± 5.2| 65.7 ± 5.9| 62.0 ± 4.9| 58.4 ± 5.5‡| 57.0 ± 5.1‡| 54.2 ± 6.3‡| 51.7 ± 8.4†| 43.5 ± 5.1†  |
| Controlled-breathing     | 65.4 ± 6.8| 64.4 ± 5.9| 61.4 ± 6.2†| 59.4 ± 8.7| 59.6 ± 6.4†| 59.7 ± 6.5*| 60.0 ± 6.0*| 60.5 ± 7.3*  |
| **Cerebral vascular conductance, cm sec⁻¹ mmHg** |       |       |        |        |        |        |        |               |
| Normal-breathing         | 0.72 ± 0.06 | 0.72 ± 0.08 | 0.69 ± 0.10 | 0.65 ± 0.09†| 0.63 ± 0.08†| 0.60 ± 0.09†| 0.58 ± 0.3* | 0.49 ± 0.08† |
| Controlled-breathing     | 0.75 ± 0.08 | 0.74 ± 0.07‡| 0.69 ± 0.08†| 0.66 ± 0.10‡| 0.65 ± 0.08‡| 0.64 ± 0.09‡| 0.64 ± 0.08‡| 0.63 ± 0.08*‡ |
| **Minute ventilation, L min⁻¹** |       |       |        |        |        |        |        |               |
| Normal-breathing         | 9.3 ± 0.8 | 10.1 ± 0.8 | 10.5 ± 1.3 | 10.9 ± 1.4 | 12.0 ± 1.3‡| 14.6 ± 3.5‡| 18.3 ± 6.7†| 26.7 ± 6.2†  |
| Controlled-breathing     | 9.6 ± 0.5 | 10.4 ± 0.9 | 11.0 ± 1.3 | 11.4 ± 2.0 | 11.0 ± 1.1*‡| 11.3 ± 1.7*‡| 11.3 ± 1.0*‡| 12.3 ± 1.7*‡ |
| **Tidal volume, mL**      |       |       |        |        |        |        |        |               |
| Normal-breathing         | 554 ± 57 | 553 ± 60 | 572 ± 79 | 587 ± 101 | 655 ± 137 | 755 ± 159†| 760 ± 166 | 920 ± 203†   |
| Controlled-breathing     | 545 ± 76 | 567 ± 92 | 582 ± 97 | 614 ± 126 | 597 ± 79 | 612 ± 84* | 626 ± 90* | 652 ± 75*‡   |
| **Respiratory frequency, breaths min⁻¹** |       |       |        |        |        |        |        |               |
| Normal-breathing         | 17 ± 2 | 18 ± 2 | 19 ± 4 | 19 ± 5 | 19 ± 5 | 20 ± 7 | 24 ± 8 | 30 ± 8‡      |
| Controlled-breathing     | 18 ± 3 | 19 ± 3 | 20 ± 4 | 19 ± 4 | 19 ± 4 | 19 ± 4* | 19 ± 4* | 19 ± 4*      |
| **End-tidal carbon dioxide pressure, mmHg** |       |       |        |        |        |        |        |               |
| Normal-breathing         | 37.7 ± 2.2 | 38.0 ± 2.2 | 37.8 ± 2.4 | 36.6 ± 2.7 | 36.8 ± 2.1 | 34.0 ± 3.3 | 31.2 ± 5.5 | 22.7 ± 4.2†  |
| Controlled-breathing     | 38.5 ± 2.3 | 37.6 ± 2.3 | 37.8 ± 2.3 | 38.0 ± 3.0 | 39.0 ± 2.6* | 39.3 ± 3.1* | 39.8 ± 2.5* | 39.3 ± 3.2*  |
| **Oxygen uptake, mL min⁻¹** |       |       |        |        |        |        |        |               |
| Normal-breathing         | 245 ± 33 | 257 ± 35 | 264 ± 42 | 278 ± 40† | 306 ± 43† | 326 ± 49† | 341 ± 43† | 358 ± 50†    |
| Controlled-breathing     | 250 ± 27 | 255 ± 32 | 269 ± 40 | 283 ± 43‡ | 303 ± 50‡ | 319 ± 55‡ | 337 ± 62‡ | 364 ± 56‡    |
| **Difficulty of breathing (n = 9)** |       |       |        |        |        |        |        |               |
| Normal-breathing         | 1.3 ± 0.8 | 1.7 ± 1.1 | 2.3 ± 1.2 | 3.1 ± 0.8† | 3.9 ± 1.1† | 4.9 ± 1.2† | 5.9 ± 1.8† | 6.8 ± 1.6†   |
| Controlled-breathing     | 1.2 ± 0.8 | 1.7 ± 0.8 | 2.6 ± 0.9 | 3.7 ± 0.9† | 4.7 ± 1.1† | 6.1 ± 1.7‡ | 6.7 ± 2.0† | 8.4 ± 2.5†   |

Values are means ± SD, n = 10 except for breathing effort.

*P < 0.05 versus normal-breathing trial.
†P < 0.04 versus prior to heating (pre) in the normal-breathing trial.
‡P < 0.05 versus pre in the controlled-breathing trial.
Respiratory mechanics

Time-dependent changes in respiratory mechanics are shown in Figure 1. Changes in end-expiratory and end-inspiratory lung volumes are presented in Figure 1B as percentages of forced vital capacity determined pre. End-expiratory and inspiratory lung volumes did not differ between trials ($P = 0.25$ and $0.71$, $\eta^2 = 0.03$ and 0.003 for a main effect of trial, respectively). End-expiratory lung volume increased slightly during heating, but did not significantly change as compared to preheating. In the normal-breathing trial, end-inspiratory lung volume had increased significantly after 25 min relative to preheating (all $P < 0.02$). The work of breathing increased from $13.0 \pm 8.9$ at pre to $59.4 \pm 49.5$ J min$^{-1}$ at the end of heating in the normal-breathing trial, whereas in the controlled-breathing trial it remained constant such that $16.1 \pm 12.6$ J min$^{-1}$ was recorded at the end of heating ($P = 0.01$, Fig. 1C). The work of breathing per $V_E$ was maintained nearly constant throughout the heating in either trial with no between-trial difference ($P = 0.49$ and 0.13, $\eta^2 = 0.04$ and 0.03 for main effects of trial and heating duration, respectively) (Fig. 1D). In addition, the work of breathing pooled across the normal- and controlled-breathing conditions correlated positively with $V_E$ ($r = 0.971$, $P < 0.001$) (Fig. 2).

$T_{es}$-dependent changes in ventilatory and cerebrovascular responses

We compared the ventilatory and cerebrovascular responses elicited by the similar rise in $T_{es}$ seen under the two conditions (Fig. 3). $V_E$ was lower in the controlled-breathing than normal-breathing trial at $T_{es} = 38.2–38.6^\circ$C...
Figure 3. Esophageal temperature-dependent changes in minute ventilation (A), end-tidal CO₂ pressure (B), middle cerebral artery blood flow velocity (C), and cerebral vascular conductance (D) during passive heating in the normal-breathing and controlled-breathing trials. Values are means ± SD. *P < 0.03, normal- versus controlled-breathing; †P < 0.04, versus 36.6°C in the normal-breathing trial; ‡P < 0.03, versus 36.6°C in the controlled-breathing trial.

Figure 4. Changes (Δ) in minute ventilation (A), end-tidal CO₂ pressure (B), middle cerebral artery blood flow velocity (C), and cerebral vascular conductance (D) occurring as Esophageal temperature was raised from 36.6°C to 38.6°C. Mean and individual data are presented in both the normal-breathing and controlled-breathing trials. Values are means ± SD. *P < 0.001, normal-breathing versus controlled-breathing.
(both $P < 0.02$). $P_{ETCO_2}$ was higher in the controlled-breathing trial at $T_{es} = 37.0^\circ C$ and 37.8–38.6$^\circ C$ (all $P < 0.01$). MCAV and CVC were higher in the controlled-breathing trial at $T_{es} = 38.2–38.6^\circ C$ (both $P < 0.03$) and 38.6$^\circ C$ ($P = 0.02$), respectively. Figure 4 illustrates the mean and individual data for the changes in $V_E$, $P_{ETCO_2}$, MCAV, and CVC from $T_{es} = 36.6^\circ C$ to 38.6$^\circ C$. Voluntary control of breathing diminished the increase in $V_E$ and decreases in $P_{ETCO_2}$, MCAV, and CVC observed in the normal-breathing trial at $T_{es} = 38.6^\circ C$ by 86 ± 19, 111 ± 36, 82 ± 31 and 58 ± 44%, respectively.

**Discussion**

This study examined whether heat-induced hyperventilation can be diminished through voluntary control of breathing, and, if so, how this affects respiratory mechanics, PaCO$_2$, and MCAV during passive heating. We demonstrated for the first time that heat-induced hyperventilation is accompanied by increases in the work of breathing chiefly due to increases in $V_E$ without a change in end-expiratory lung volume. This spontaneous hyperventilation elicited by passive heating can be nearly prevented by voluntary control of breathing, which attenuated largely the decreases in $P_{ETCO_2}$, MCAV, and CVC and the increases in the work of breathing that occurred during normal-breathing.

**Ventilatory and cerebrovascular responses during hyperthermia at rest**

Hyperthermia-induced hyperventilation is perhaps caused by elevations in the temperatures of the brain (Chai and Lin 1972; Boden et al. 2000) and carotid chemoreceptors (Chu et al. 2007; Fujii et al. 2008a). Consistent with previous studies (Cabanac and White 1995; Fujii et al. 2008b; Tsuji et al. 2012a), we found that there was a $T_{es}$ threshold for hyperventilation at 38.0 ± 0.3$^\circ C$ and that $V_E$ rose along with increasing $T_{es}$ at a rate of 30.4 ± 19.6 L·min$^{-1}$·$^\circ C$–$^{-1}$ in the normal-breathing trial. The increase in $V_E$ reached significance at >38.2$^\circ C$ $T_{es}$ (Fig. 3A), which is explained by increases in both $V_T$ and $f$ (Table 1) and is consistent with earlier findings (Gaudio and Abramson 1968; Baker et al. 1996; Fujii et al. 2008b; Tsuji et al. 2012a). The heat-induced hyperventilation is involuntary, but we demonstrated that the large portion of this response could be voluntarily suppressed. That is, the time- and $T_{es}$- dependent increases in $V_E$, $V_T$, and $f$ during normal-breathing were all suppressed (Figs. 3A and Table 1). Similarly, we recently reported that during prolonged exercise in the heat, most healthy men were able to suppress heat-induced hyperventilation by voluntarily controlling breathing (Tsuji et al. 2015). Healthy men thus appear able to voluntarily suppress heat-induced hyperventilation regardless of resting or exercising.

Consistent with earlier studies (Fan et al. 2008; Fujii et al. 2008a; Low et al. 2008; Brothers et al. 2009; Nelson et al. 2011; Bain et al. 2013; Ogoh et al. 2014), in the normal-breathing trial MCAV and CVC decreased with rising $T_{es}$ as compared to normothermia (Figs. 3C and D). These reductions in MCAV and CVC were largely suppressed in the controlled-breathing trial, indicating that voluntary suppression of heat-induced hyperventilation negates the heat-induced reduction in cerebral blood flow. In the present study, voluntary breathing control reduced increases in $V_E$ occurring at $T_{es} = 38.6^\circ C$ by 86% and the decreases in $P_{ETCO_2}$, MCAV, and CVC by 111%, 82%, and 58%, respectively. Given that the pattern of $P_{ETCO_2}$ response was similar to those of the cerebral vascular variables (i.e., MCAV and CVC), it seems likely that the higher MCAV and CVC during voluntary breathing control were partially a consequence of altering PaCO$_2$. It should be noted that it is still debatable whether the reductions in MCAV during passive heating could be partially (Fujii et al. 2008a; Brothers et al. 2009) or entirely (Nelson et al. 2011; Bain et al. 2013) accounted for by the hyperventilation-induced decreases in PaCO$_2$. For instance, we recently reported that prevention of hypocapnia by CO$_2$ gas inhalation throughout passive heating resulted in a partial restoration of MCAV (~36% of total reduction) (Tsuji et al. 2018). Regarding the hypocapnia-independent factor(s), if at all, one potential candidate is MAP. MAP in the normal-breathing trial was maintained at the baseline level throughout the passive heating, though MAP in the controlled-breathing trial gradually increased with voluntary suppression of hyperventilation. Consequently, MAP was ~10 mmHg higher at the end of heating than at pre or during the normal-breathing trial, and CVC in the controlled-breathing trial decreased gradually compared to preheating (Table 1). This suggests that increases in cerebral perfusion pressure associated with elevated MAP may have contributed to the higher MCAV during controlled-breathing. The precise mechanism(s) underpinning the increases in MAP associated with voluntary suppression of breathing remain(s) elucidated.

Hyperventilation and hypoventilation both increase the sensation of dyspnea independently of PaCO$_2$, with a greater effect during hyperventilation (Chonan et al. 1990). We therefore assumed that heat-induced increases in $V_E$ would themselves lead to increases in dyspnea in the normal-breathing trial, and that the suppression of $V_E$ in the controlled-breathing would result in even greater increases in dyspnea. We found, however, that difficulty of breathing, an index of dyspneic sensation, similarly
increased during passive heating in both trials (Table 1). Thus, voluntary suppression of $V_E$ apparently does not cause further increases in feelings of dyspnea. It should be noted, however, that at the end of heating, difficulty of breathing tended to be higher in the controlled-breathing than in the normal-breathing trial ($P = 0.15$), with seven of nine participants showing a higher score during controlled-breathing. Taking these results into consideration, it seems reasonable to conclude that most healthy men can voluntarily suppress heat-induced hyperventilation despite a greater sensation of discomfort.

Although nine of the 10 participants were able to largely (77–104%) suppress the heat-induced hyperventilation, one individual was able to only partially (35%) suppress the response (Fig. 4). As a result, his $P_{E\text{CO}_2}$, MCAV, and CVC were also only partially restored (by 20, 23, and 20%, respectively). In this individual, by the end of heating, difficulty of breathing had increased to level 4 (somewhat hard) in the normal-breathing trial and to the maximum 10 (very, very hard) in the controlled-breathing trial. This suggests individuals who have strong sensation of dyspnea may not be able to greatly suppress heat-induced hyperventilation by voluntary control of breathing.

**Respiratory mechanics during hyperthermia at rest**

This is, to our knowledge, the first study to report on the respiratory mechanics during hyperthermia. The work of breathing gradually increased and reached ~60 J min$^{-1}$ as $V_E$ reached ~27 L min$^{-1}$ by the end of heating (Fig. 1C). By contrast, the work of breathing was maintained nearly constant throughout heating in the controlled-breathing trial, indicating that voluntary suppression of heat-induced hyperventilation markedly reduced the work of breathing. We also observed a significant correlative association between the work of breathing and $V_E$ (Fig. 2), which is consistent with previous findings (Milici-Emili and Petit 1960; Aaron et al. 1992a,b). The work of breathing–$V_E$ relation is also reportedly curvilinear when evaluated at the wide range of $V_E$ of ~30 to 150 L min$^{-1}$ (Milici-Emili and Petit 1960; Aaron et al. 1992a), but likely not at the low levels of $V_E$ as observed in the present study. In addition, the work of breathing per ventilation remained unchanged throughout heating regardless of trials, and it was similar in both trials (Fig. 1D). We therefore conclude that the increased work of breathing associated with heat-induced hyperventilation is mainly caused by the increase in ventilation per se.

We also showed that end-expiratory lung volume was maintained at normothermic levels throughout the passive heating in both trials (Fig. 1B). This suggests that end-expiratory lung volume is unaffected by elevations in the core temperature of ~2.5°C and the resultant heat-induced hyperventilation, and that voluntary suppression of the hyperventilation does not affect the lung volume. Butler and Arnott (1955) previously reported that the work of breathing increases with decreases or increases in end-expiratory lung volume from the normal level, though such an effect of lung volume level on the work of breathing may not have occurred in the present study. Furthermore, it is well known that exercise decreases end-expiratory lung volume below the resting level (Henke et al. 1988; Guenette et al. 2007), though the present result infers that there is little linkage between this reduction in end-expiratory lung volume and the elevation in core temperature observed during exercise.

We previously reported slight but significant decreases in $V_O_2$ with voluntary suppression of the gradual increase in $V_E$ during prolonged exercise in the heat (Tsuji et al. 2015). This suggests that hyperthermia-induced hyperventilation increases the work of breathing, and thus the oxygen cost (though we did not measure that in the work). Unlike in our earlier report (Tsuji et al. 2015), we found in the present study that $V_O_2$ did not differ between the two trials (Table 1), suggesting that $V_E$ is unaffected by hyperthermia-induced hyperventilation during passive heating. Assuming a 1-L increase in $V_E$ leads to an approximately 1.2 mL increase in $V_O_2$ under resting conditions (Lorenzo and Babb 2012), the difference in $V_E$ between the normal- and controlled-breathing trials at the end of heating (~13 L min$^{-1}$) would increase $V_O_2$ by about 16 mL, which appears to be too small to accurately detect. Another possible explanation for the disparate findings is the different levels of $V_E$. A prior study reported that the work of breathing increases exponentially with increases in $V_E$, whereas respiratory muscle $V_O_2$ increases linearly with increases in the work of breathing (Aaron et al. 1992a). This implies that the effects of suppressing $V_E$ on the work of breathing and respiratory muscle $V_O_2$ are more pronounced during exercise, which is accompanied by higher $V_E$ levels, than during passive heating, where $V_E$ is low. Furthermore, it is worth mentioning that increases in the work of breathing can activate the muscle metaboreflex in the respiratory muscles, leading to locomotor muscle vasoconstriction. However, an earlier study reported that this response is only observed when exercise intensity is greater than 75% $V_O_2_{\text{max}}$ during which the levels of ventilation, and thus the work of breathing, are substantially elevated (Dempsey et al. 2006). Because breathing levels are much lower during hyperthermia at rest than during intense exercise, it seems unlikely that a robust blood distribution associated with increased work of breathing occurred during the passive hyperthermia at rest in the
present study. However, future study is warranted to directly test this possibility.

**Limitation**

The present study and our earlier one (Tsuji et al. 2015) used a protocol in which participants controlled both $f$ and $V_T$ as much as possible with the aid of feedback. However, it remains uncertain whether individuals can voluntarily suppress hyperthermia-induced hyperventilation without feedback for either $f$ or $V_T$, or both. We also do not know whether suppression of hyperthermia-induced hyperventilation, with and without feedback, differentially modulates $\text{PaCO}_2$, cerebral blood flow, and the work of breathing. We also used MCAV as an index of cerebral blood flow, though a recent magnetic resonance imaging study reported that MCA diameter decreased by 4% when $\text{P}_{\text{ETCO}}$ decreased from 36 to 23 mmHg (Coverdale et al. 2014). This is in contrast to earlier reports that the diameter was unchanged by decreases in $\text{P}_{\text{ETCO}}$ to ~25 mmHg (Giller et al. 1993; Serrador et al. 2000). It is therefore possible that we underestimated the magnitude of the MCAV reduction in the normal-breathing trial, though MCAV in the controlled-breathing trial reflected blood flow without an effect of diameter. In addition, it remains unclear whether hyperthermia itself modulates MCA diameter independently of hypocapnia.

**Perspectives and significance**

Decreases in $\text{PaCO}_2$ and cerebral blood flow during hyperthermia reportedly lead to increases in brain temperature (Nybo et al. 2002) and central fatigue (Ross et al. 2012). Ross et al. (2012) reported that the decrease in cortical activation seen during passive heating is related to heat-induced hypocapnia and subsequent cerebral hypoperfusion. Our results suggest these detrimental effects can be mitigated somewhat through voluntary control of breathing that restores $\text{PaCO}_2$. Additional research will be required to test this possibility, however. Nonetheless, voluntary control of breathing could be an effective countermeasure to suppress hypocapnia and cerebral hypoperfusion during hyperthermia, along with the previously reported whole-body skin cooling (Wilson et al. 2002; Lucas et al. 2010).

**Conclusion**

In summary, heat-induced hyperventilation during passive heating is accompanied by increases in the work of breathing reflecting increases in ventilation, per se, and occurs without changing end-expiratory lung volume. This hyperventilatory response can be greatly suppressed in healthy young men through voluntary control of breathing with ventilatory feedback, mitigating the increased work of breathing and decreased arterial CO$_2$ pressure and cerebral blood flow velocity observed during normal-breathing.

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**Conflict of Interest**

None declared.

**References**

Aaron, E. A., B. D. Johnson, C. K. Seow, and J. A. Dempsey. 1992a. Oxygen cost of exercise hyperpnea: measurement. J. Appl. Physiol. 72:1810–1817.

Aaron, E. A., C. K. Seow, B. D. Johnson, and J. A. Dempsey. 1992b. Oxygen cost of exercise hyperpnea: implications for performance. J. Appl. Physiol. 72:1818–1825.

Bain, A. R., K. J. Smith, N. C. Lewis, G. E. Foster, K. W. Wildfong, C. K. Willie, et al. 2013. Regional changes in brain blood flow during severe passive hyperthermia: effects of $\text{PaCO}_2$ and extracranial blood flow. J. Appl. Physiol. 115:653–659.

Baker, J. F., R. C. Goode, and J. Duffin. 1996. The effect of a rise in body temperature on the central-chemoreflex ventilatory response to carbon dioxide. Eur. J. App. Physiol. Occup. Physiol. 72:537–541.

Boden, A. G., M. C. Harris, and M. J. Parkes. 2000. The preoptic area in the hypothalamus is the source of the additional respiratory drive at raised body temperature in anaesthetised rats. Exp. Physiol. 85:527–537.

Brothers, R. M., J. E. Wingo, K. A. Hubing, and C. G. Crandall. 2009. The effects of reduced end-tidal carbon dioxide tension on cerebral blood flow during heat stress. J. Physiol. 587:3921–3927.

Butler, J., and W. Arnott. 1955. The work of pulmonary ventilation at different respiratory levels. Clin. Sci. (London) 14:703–710.

Cabanac, M., and M. D. White. 1995. Core temperature thresholds for hyperpnea during passive hyperthermia in humans. Eur. J. Appl. Physiol. 71:71–76.

Chai, C. Y., and M. T. Lin. 1972. Effects of heating and cooling the spinal cord and medulla oblongata on thermoregulation in monkeys. J. Physiol. 225:297–308.

Chonan, T., M. B. Mulholland, M. D. Altose, and N. S. Cherniack. 1990. Effects of changes in level and pattern of breathing on the sensation of dyspnea. J. Appl. Physiol. 69:1290–1295.
Chu, A. L., O. Jay, and M. D. White. 2007. The effects of hyperthermia and hypoxia on ventilation during low-intensity steady-state exercise. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292:R195–R203.

Cohen, J. 1988. Statistical power analysis for the behavioral sciences, 2nd ed. Lawrence Erlbaum, Hillsdale.

Coverdale, N. S., J. S. Gati, O. Opalevych, A. Perrotta, and J. K. Shoemaker. 2014. Cerebral blood flow velocity underestimates cerebral blood flow during modest hypercapnia and hypocapnia. J. Appl. Physiol. 117:1090–1096.

Dempsey, J. A., L. Romer, J. Rodman, J. Miller, and C. Smith. 2006. Consequences of exercise-induced respiratory muscle work. Respir. Physiol. Neurobiol. 151:242–250.

Fan, J. L., J. D. Cotter, R. A. Lucas, K. Thomas, L. Wilson, and P. N. Ainslie. 2008. Human cardiorespiratory and cerebrovascular function during severe passive hyperthermia: effects of mild hypohydration. J. Appl. Physiol. 105:433–445.

Fujii, N., Y. Honda, K. Hayashi, N. Kondo, S. Koga, and T. Nishiyasu. 2008a. Effects of chemoreflexes on hyperthermic hyperventilation and cerebral blood velocity in resting heatd humans. Exp. Physiol. 93:994–1001.

Fujii, N., Y. Honda, K. Hayashi, H. Soya, N. Kondo, and T. Nishiyasu. 2008b. Comparison of hyperthermic hyperpnea elicited during rest and submaximal, moderate-intensity exercise. J. Appl. Physiol. 104:998–1005.

Nybo, L., and B. Nielsen. 2001. Middle cerebral artery blood velocity is reduced with hyperthermia during prolonged exercise in humans. J. Physiol. 534:279–286.

Nybo, L., N. H. Secher, and B. Nielsen. 2002. Inadequate heat release from the human brain during prolonged exercise with hyperthermia. J. Physiol. 545:697–704.

Otis, A. B., W. O. Fenn, and H. Rahn. 1950. Mechanics of breathing in man. J. Appl. Physiol. 2:592–607.

Tsuji, B., Y. Honda, Y. Ikebe, N. Fujii, N. Kondo, and T. Nishiyasu. 2015a. Effect of initial core temperature on hyperthermic hyperpnea during prolonged submaximal exercise in man. J. Appl. Physiol. 119:304–311.

Tsuji, B., Y. Honda, N. Fujii, N. Kondo, and T. Nishiyasu. 2015b. Voluntary suppression of hyperthermia-induced hyperventilation during prolonged submaximal exercise in man. J. Appl. Physiol. 119:1034–1043.

Tsuji, B., Y. Honda, Y. Ikebe, N. Fujii, N. Kondo, and T. Nishiyasu. 2015. 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.
Tsuji, B., D. Filingeri, Y. Honda, T. Eguchi, N. Fujii, N. Kondo, et al. 2018. Effect of hypocapnia on the sensitivity of hyperthermic hyperventilation and the cerebrovascular response in resting heated humans. J. Appl. Physiol. 124:225–233.

Wenger, C. B., and M. F. Roberts. 1980. Control of forearm venous volume during exercise and body heating. J. Appl. Physiol. 48:114–119.

White, M. D., and M. Cabanac. 1996. Exercise hyperpnea and hyperthermia in humans. J. Appl. Physiol. 81:1249–1254.

Wilson, T. E., J. Cui, R. Zhang, S. Witkowski, and C. G. Crandall. 2002. Skin cooling maintains cerebral blood flow velocity and orthostatic tolerance during tilting in heated humans. J. Appl. Physiol. 93:85–91.