Human cardiorespiratory and cerebrovascular function during severe passive hyperthermia: effects of mild hypohydration

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Fan J-L, Cotter JD, Lucas RA, Thomas K, Wilson L, Ainslie PN. Human cardiorespiratory and cerebrovascular function during severe passive hyperthermia: effects of mild hypohydration. J Appl Physiol 105: 433–445, 2008. First published May 15, 2008; doi:10.1152/japplphysiol.00010.2008.—The influence of severe passive heat stress and hypohydration (Hypo) on cardiorespiratory and cerebrovascular function is not known. We hypothesized that 1) heating-induced hypocapnia and peripheral redistribution of cardiac output (Q˙) would compromise blood flow velocity in the middle cerebral artery (MCAv) and cerebral oxygenation; 2) Hypo would exacerbate the hyperthermic-induced hypocapnia, further decreasing MCAv; and 3) heating would reduce MCAv-CO2 reactivity, thereby altering ventilation. Ten men, resting supine in a water-perfused suit, underwent progressive hyperthermia [0.5°C increments in core (esophageal) temperature (Tc) to +2°C] while euhydrated (Euh) or Hypo by 1.5% body mass (attained previous evening). Time-control (i.e., non-heat stressed) data were obtained on six of these subjects. Cerebral oxygenation (near-infrared spectroscopy), MCAv, end-tidal carbon dioxide (PETCO2) and arterial blood pressure, Q (flow model), and brachial and carotid blood flows (CCA) were measured continuously each 0.5°C change in Tc. At each level, hypocapnia was achieved through 3-min administrations of 5% CO2, and hypocapnia was achieved with controlled hyperventilation. At baseline in Hypo, heart rate, MCAv and CCA were elevated (P < 0.05 vs. Euh). MCAv-CO2 reactivity was unchanged in both groups at all Tc levels. Independent of hydration, hyperthermic-induced hyperventilation caused a severe drop in PETCO2 (−8 ± 1 mmHg/°C), which was related to lower MCAv (−15 ± 3%/°C; R² = 0.98; P < 0.001). Elevations in Q were related to increases in brachial blood flow (R² = 0.65; P < 0.01) and reductions in MCAv (R² = 0.70; P < 0.01), reflecting peripheral distribution of Q. Cerebral oxygenation was maintained, presumably via enhanced O2-extraction or regional differences in cerebral perfusion.

ELEVATIONS in body temperature at rest lead to hyperventilation and subsequent hypocapnia [i.e., reduction in partial pressure of end-tidal CO2 (PETCO2) of −3–12 mmHg per °C elevation in core temperature (Tc)] (44, 56)]. Since cerebral blood flow (CBF) is highly sensitive to hypocapnia (28, 52), heat-induced hyperventilation and related hypocapnia could severely reduce CBF. Related symptoms associated with hyperthermia, including nausea and cognitive decline, may be indicative of a compromised cerebral perfusion. Although the classical notion is that CBF is maintained over a range of blood pressure, it has more recently been established that CBF is also dependent on cardiac output (Q) (24, 36, 54; see Ref 47 for review). Thus, because heat-induced elevations in Q are redistributed to the skin to aid heat dissipation (41), such changes may further exacerbate the decline in CBF. Previous studies have, however, used only a one-step increase in Tc (3, 4, 12, 33, 48, 59), so relative changes in cardiorespiratory and cerebrovascular hemodynamics to a progressive passive increase in Tc have not been characterized.

Under normothermic conditions, respiratory-induced changes in the partial pressure of arterial carbon dioxide (PaCO2) play a major role in CBF regulation. Elevations in PaCO2 (hypocapnia) lead to vasodilatation of cerebral arterioles in the downstream bed and a subsequent increase in CBF, whereas a reduction in PaCO2 (hypocapnia) leads to vasoconstriction and a subsequent decrease in CBF. The cerebrovascular reactivity to changes in PaCO2 is between 2 and 5%/mmHg, with a greater reactivity in the hypercapnic range when compared with the hypocapnic range (38). Heat-induced changes in cerebrovascular CO2 reactivity might impact considerably on ventilation and the resulting degree of hypocapnia. For example, a lowering of cerebrovascular CO2 reactivity leads to less washout of hydrogen ions from central chemoreceptors (13, 60); such changes could potentially underlie the well-reported increases in the ventilatory response to CO2 at elevated body temperatures in humans (14, 56) and other mammals (7, 29). Conversely, if cerebrovascular CO2 reactivity is enhanced, as has been reported during hyperthermic exercise (40), this could lead to a greater reduction in CBF per mmHg reduction in PETCO2. In support of this possibility, blood flow velocity in the middle cerebral artery (MCAv) was reported to decline by −9% at a 1°C elevation in body temperature despite a 1–2 mmHg reduction in PETCO2 (58). Importantly, however, the influence of heat-induced changes in cerebrovascular CO2 reactivity over a range of body temperatures has not been reported.

An important issue during heat stress is hydration. In contrast to research on exercise-induced hyperthermia (34, 35, 40), few studies have controlled the critical role of hydration during passive heating. Studies have reported that dehydration induced an elevation in ventilation at rest during both normothermia (3) and hyperthermia (10), although this is not a universal finding (48). The latter study, however, provided evidence of a positive correlation between plasma osmolarity and ventilatory changes during passive heat stress when hypothenated but not euhydrated; unfortunately, PETCO2 data were

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not reported (48). Previous studies have found that increases in plasma osmolality through hypertonc saline infusion increase mean sympathetic nerve activity (17), and consequently elevate heart rate (HR) (5) in resting humans. Carter et al. (4) have previously investigated the effect of heat exposure and moderate levels of hypohydration (i.e., state of lowered total body water) on MCAv. In that study, measurements were carried out at least 2 h following heat exposure with one level of mild hyperthermia observed under hypohydrated condition (+0.5°C above baseline), while no elevations in Tc was observed in the euhydrated condition; unfortunately, cerebral oxygenation, CBF-CO2 reactivity, ventilation, Q, and peripheral blood flow were not measured. Thus, although no studies have examined the effects of hypohydration on cardiorespiratory and cerebrovascular function during progressive passive heat stress, it seems reasonable to expect that hydration might influence the degree of hyperventilation and the change in Q and, therefore, cerebral perfusion during heat stress.

The aim of this study was to examine the integrated changes in cardiorespiratory and cerebrovascular responses to passive hyperthermia and CO2 with and without hypohydration. We tested three novel hypotheses: first, in the supine position, that progressive heating-induced hypocapnia and redistribution of Q to the cutaneous vasculature would markedly compromise MCAv and cerebral oxygenation; second, that passive heating would lower the cerebral blood flow reactivity to CO2, thereby altering the steady-state ventilatory sensitivity to CO2; and third, that dehydration would exacerbate the hyperthermic-induced hyperventilation, leading to subsequent hypocapnia, further decreasing MCAv and cerebral oxygenation.

METHODS

Subjects

Ten healthy men [age 27 ± 7 (mean ± SD) yr; body mass 77 ± 6 kg; body mass index 24 ± 1 kg/m2] volunteered for this study, which was approved by the University of Otago Human Ethics Committee. Subjects were informed of the experimental procedures and possible risks involved in the study before their written consent was obtained. Subjects were not taking any medications, all were nonsmokers, and none had any history of cardiovascular, cerebrovascular, or respiratory disease.

Experimental Design

The experimental protocol is displayed in Fig. 1. As used in previous protocols (4, 9), subjects reported to the laboratory on seven or eight occasions: initially on three consecutive mornings before breakfast to establish baseline, near-nude body mass; on two evenings for dehydration intervention visits, each separated by at least 7 days; and two (n = 10) or three (n = 6) experimental trials in the morning (0700) following the dehydration intervention. Before each visit, participants were informed to abstain from alcohol, caffeine, and exercise in the 24 h before testing and to avoid consumption of a large meal 3–4 h prior. On arrival to the lab, the participants were instructed to void their bladder, and their near-nude body mass was recorded. The mean of the three morning near-nude body mass measurements (Wedderburn Scales, Dunedin; accuracy ±0.1 g) was used to calculate baseline body mass. During the evening dehydration interventions, participants ran on a treadmill [70–80% estimated maximal HR (HRmax)] in a hot, dry environment (40°C, 20% relative humidity, air velocity 4.4 m/s). Near-nude mass was measured every 15 min until the target body mass, a reduction of 2%, was reached. In a balanced (alternating) order, participants were then rehydrated to either their mean sympathetic nerve activity (17), and consequently ele-

baseline (Euh) or 1.5% hypohydration (Hypo), by drinking 150% or 38%, respectively, of the mass lost. In Hypo, participants were instructed to refrain from consuming fluid overnight before the experimental testing trial, to maintain 1.5% hypohydration (Fig. 1). Hydration status was also estimated the following morning from body mass and from urine specific gravity, in duplicate (hand refractometer, Atago, Tokyo, Japan). To examine the potential confounding effect of circadian rhythm in Tc, a subgroup (n = 6) of the participants completed a time-only control session (i.e., non-heat stressed).

Experimental Testing

A standardized breakfast was provided on each of the two experimental trials. On arrival to the laboratory at 0700, subjects were instructed to void their bladder before having body mass and height recorded.

The subjects were then instrumented in the supine position for at least 15 min before data collection. Data were recorded at each of five levels of body (esophageal) temperature: baseline, +0.5°C, +1.0°C, +1.5°C, and +2.0°C above baseline, if heat tolerance permitted. With the exceptions of 15 min before, and during, the experimental measurements, fluid was permitted ad libitum during the passive heating protocol. Tests of ventilatory and cerebrovascular reactivity comprised a 3-min baseline period in room air followed by 3 min of exposure to either hypocapnia following by 3 min of controlled hyperventilation to elicit a target level of hypocapnia (described below).

Measurements

Thermal measurements. Body temperature was controlled using a water-perfused two-piece suit that covered the trunk, arms, and legs. During heating, the tube network was perfused with water of ~48°C, at ~0.8 l/min. Flow was reduced at each 0.5°C increment in core temperature during data collection. Core temperature was measured using an esophageal thermistor (Thermistor 400 series, general purpose temperature probe, Mallinckrodt Medical). Skin temperature was
measured using insulated skin thermistors (Type EU, Grant Instruments, Cambridge, UK) at six right-side sites: 1) forehead; 2) chest, midway between the nipple and axilla; 3) scapula, medial from the inferior angle; 4) dorsal forearm, ~3 cm distal to the elbow; 5) front thigh, midway between patella and greater trochanter, and; 6) leg, widest part of the calf. Mean skin temperature was calculated from area weightings (24a). Core and skin temperatures were logged at 1-min intervals (Grant Instruments).

Monitoring equipment. Cerebral blood flow velocity was measured in the right middle cerebral artery using a 2-MHz pulsed Doppler ultrasound system (DWL Doppler, Sterling, VA) using search techniques described elsewhere (1) that was secured in place by a headband. The common carotid and brachial artery blood flows and diameters (20 mm proximal to the antecubital fossa) were measured using a high-resolution ultrasound system (Terason Ultrasound System, Teratech). Although MCAv is a reliable index of CBF (see Technological Considerations) during changes in end-tidal or arterial Pco2, we were not aware of any validation studies of MCAv measurements during progressive passive heat stress. Therefore, in 3 of the 10 subjects, carotid flow was also measured in the internal and external carotid arteries to 1) determine if changes in internal common carotid blood flow reflect the changes in MCAv; and 2) establish the extent of the redistribution of blood flow from the common carotid artery to the external carotid artery. HR was determined with a three-lead ECG. Beat-to-beat mean arterial blood pressure (MAP) was monitored using finger plethysmography (Fimometer, TPD Biological Medical Instrumentation). Stroke volume and cardiac output were calculated from the blood pressure waveform using the model-flow method, incorporating age, sex, height, and weight (BeatScope 1.0 software; TNO TPD; Biomedical Instruments); this method provides a reliable estimate of changes in cardiac output in healthy exercising humans (50), patients with septic shock (26), and patients undergoing cardiac surgery (25). It is not clear, however, if absolute measurements of Q by the model-flow method are valid during conditions of heat stress and hyponatremia; thus emphasis of these data are placed on the relative changes with passive heating. Likewise, although plethysmographic measurements correlate well with intra-arterial measurements during experimental manipulations of arterial pressure (37), the absolute values can sometimes be inaccurate; therefore, in addition to the absolute MAP recordings, all MAP data are normalized to the 3-min baseline preceding any intervention and are expressed as percent change from this baseline. Likewise, as used in other studies, MCAv was also expressed at both absolute and percent change from this baseline to enable the same relative comparison to other studies. Likewise, as used in other studies, MAP was also expressed as percent change from this baseline to enable the same relative comparison to other studies. MAP was also normalized to the 3-min baseline preceding any intervention and are expressed as percent change from this baseline.

Ventilatory and cerebrovascular reactivity to CO2. Hypercapnia was induced by switching the inspired gas from room air to 5% CO2 (in 21% O2 and N2 balance) for 3–4 min. Following the hypercapnia, subjects were permitted a brief recovery and were then instructed to increase their rate and depth of breathing to reduce PETCO2 to 16–18 mmHg. Verbal feedback was provided to assist subjects to reach and maintain the target levels of hyperventilation. The hypercapnic condition was always conducted first because prior hypocapnia (but not prior hypercapnia) may cause persistent cerebral vasodilatation, thus influencing the normal MCAv-CO2 response to hypercapnia (23).

Blood and urine analysis. Venous blood was obtained from an indwelling catheter located in a forearm antecubital vein. Following discard of the dead space in the catheter (~1 ml), blood samples (2 ml each) were procured and immediately analyzed for hemoglobin concentration ([Hb]) (Hemoximeter, OSM3 Radiometer, Copenhagen, Denmark) and hematocrit ratio (Hct) in triplicates. Blood for Hct was drawn into capillary tube and centrifuged for 5 min at 3,000 rpm (Hawksley Microcentrifuge, Sussex, UK) and read using a modified microcapillary tube reader (Damom/IEC Division, Needham Heights, MA); the measurement error was ±0.25%. The remaining blood samples were then centrifuged for 15 min (IEC refrigerated centrifuge, Needham Heights, MA). Plasma was then extracted and in −80°C until analysis for plasma osmolality. Plasma osmolality was measured in duplicate using vapor point depression (Osmometer, model Vapro5520, Wescor, Logan, UT). Urine specific gravity was obtained using a handheld refractometer (Hand Refractometer, Atago).

Calculation. Changes in plasma volume from baseline (ΔPV) were estimated from changes in Hct and [Hb] using the following equation (15):

\[
\% \Delta PV = 100\% \left(\frac{[Hb]_t}{[Hb]_b} \times \frac{[1 - Hct_t]}{[1 - Hct_b]}\right) - 100
\]

in which subscript t and b denote measurements at TC and at baseline, respectively. Hb is in grams per 100 milliliters, and Hct is a fraction.

Statistical and Data Analysis

All data were analyzed using SPSS statistical software (SPSS version 12.0.1, SPSS, Chicago, IL). To assess the mean difference between Euh and Hypo conditions, a simple paired-sample t-test was applied. To evaluate the extent of manipulation of core-body temperature, a two-way ANOVA of TC was conducted for condition (Euh and Hypo) and time. The effect of increase in TC on dependent measures was first assessed using repeated-measures ANOVA analysis, with two within factors: hydration (2 levels) and TC (5 levels). Since subject dropouts at higher TC were affecting the ability to carry out statistical analysis, repeated-measures ANOVA analysis was then repeated with four and three levels of TC: baseline, +0.5°C, +1°C, and +1.5°C; baseline, +0.5°C, and +1°C, respectively. Furthermore, dependent variables were also analyzed as a linear function of change in TC, with comparison of slopes between Euh and Hypo undertaken using paired-sample t-test. Post hoc t-test analysis of significant ANOVAs was performed to isolate the effect of hydration on dependent measures within subjects (paired). If significance was found with hydration status and temperature, paired t-test was then carried out at each temperature to identify the differences. Due to variances in individual participant dropout time between Euh and
Hypo, data were standardized so that if a participant lasted up to +2°C during Euh and only +1.5°C during Hypo, the data recorded during their +2°C stage would be excluded from statistical analysis. The slope of MCAv with PETCO2, MCAv with brachial artery blood flow, MCAv with Q, and Q with brachial artery blood flow was determined by the least squares linear regression analysis for group mean at each temperature. All data are expressed as means ± SD, and significance was set at the P < 0.05 level for each analysis.

RESULTS

Hydration and Heat Tolerance

The subjects’ body mass before experimental measurement was 1.5 ± 0.8% lower in Hypo than in Euh (P < 0.001). During the experimental testing day, the difference in precession body mass from the three previous baseline measures was −1.2 ± 0.5% in Hypo (P < 0.05) and 0.3 ± 0.9% in Euh (P = 0.21). Plasma osmolality was higher in Hypo (286 ± 5 vs. 280 ± 7 mmol/kg Euh; P < 0.05) during baseline. Urine specific gravity was also elevated in Hypo both before (1.027 ± 0.003 vs. 1.021 ± 0.004 Euh; P < 0.05) and following the experimental session (1.025 ± 0.002 vs. 1.010 ± 0.006 Euh; P < 0.01). Body mass dropped slightly across the experimental session in Hypo (−0.7 ± 0.8%; P < 0.05) but not in Euh (−0.2 ± 1.0%; P = 0.44), due to subjects consuming less ad libitum fluid during the experimental session (1.8 ± 0.6 vs. 2.9 ± 1.0 liters Euh; P < 0.001). Thus Hypo involved mild hydropenia and dehydration (i.e., process of losing body water), whereas Euh involved neither. During Euh, all 10 subjects tolerated a 1.5°C rise in TC, while only 8 of 10 subjects tolerated the entire +2°C protocol. In the Hypo trial, all 10 subjects tolerated a 1°C rise TC, while only 9 of 10 tolerated a 1.5°C rise and 7 of 10 tolerated the entire +2°C protocol. Typical symptomatic reasons for subject withdrawal were severe nausea, lightheadedness, and carpal-pedal spasm.

Changes in Cardiorespiratory and Cerebrovascular Variables at Baseline

Before heating onset, HR, V̇E, MCAv, and common carotid artery blood flow were higher in Hypo compared with Euh (P < 0.05; Table 1; Fig. 2). Furthermore, total peripheral resistance (TPR), cerebral vascular resistance (CVR), and common carotid artery resistance were lower in Hypo compared with Euh (all P < 0.05; Table 1). No other cardiorespiratory and cerebrovascular variables were changed by mild hydropenia (P > 0.05).

Passive Heating

The heating protocol was successful in elevating TC with no differences between the Hypo and Euh tests in the time required to reach each +0.5°C step (Fig. 3A). Likewise, mean skin temperature was elevated to ~34–35°C with no between-test differences (P > 0.05; Fig. 3B). During the control trial, TC and mean skin temperature were unchanged throughout the 6 h of experimental testing (P > 0.05; Fig. 3).

Table 1. Steady-state cardiorespiratory and cerebrovascular variables during thermoneutral baseline and with passive heating in euhydration and hydropenia condition during supine rest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>+0.5°C</th>
<th>+1.0°C</th>
<th>+1.5°C</th>
<th>+2.0°C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Euh</td>
<td>Hypo</td>
<td>Euh</td>
<td>Hypo</td>
<td>Euh</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>59 ± 9</td>
<td>61 ± 9 §</td>
<td>72 ± 9 §</td>
<td>72 ± 12 §</td>
<td>80 ± 11 §</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>83 ± 8</td>
<td>80 ± 11</td>
<td>69 ± 8 §</td>
<td>68 ± 6 §</td>
<td>64 ± 6 §</td>
</tr>
<tr>
<td>SV, ml</td>
<td>104 ± 12</td>
<td>114 ± 24</td>
<td>96 ± 17</td>
<td>98 ± 14</td>
<td>91 ± 15</td>
</tr>
<tr>
<td>Q, l/min</td>
<td>6 ± 1</td>
<td>7 ± 2</td>
<td>7 ± 2</td>
<td>7 ± 1</td>
<td>7 ± 1  §</td>
</tr>
<tr>
<td>TPR, mmHg·l−1·min−1</td>
<td>14 ± 2.7</td>
<td>12 ± 2</td>
<td>10.4 ± 1.5 §</td>
<td>9.8 ± 1.6 §</td>
<td>8.9 ± 1.7 §</td>
</tr>
<tr>
<td>BA diameter, cm</td>
<td>0.4 ± 0.0</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1 §</td>
<td>0.5 ± 0.1 §</td>
<td>0.5 ± 0.0 §</td>
</tr>
<tr>
<td>BA blood flow, ml·min</td>
<td>27 ± 10</td>
<td>31 ± 13</td>
<td>156 ± 55 §</td>
<td>135 ± 42 §</td>
<td>234 ± 92 §</td>
</tr>
<tr>
<td>BA resistance, mmHg·ml−1·min−1</td>
<td>3.6 ± 1.8</td>
<td>3.0 ± 1.1</td>
<td>0.5 ± 0.3</td>
<td>0.6 ± 0.2 §</td>
<td>0.3 ± 0.2 §</td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>7 ± 1</td>
<td>10 ± 3 &amp;</td>
<td>8 ± 2 §</td>
<td>11 ± 4 §</td>
<td>8 ± 1 §</td>
</tr>
<tr>
<td>f′, breaths/min</td>
<td>14 ± 3</td>
<td>15 ± 3</td>
<td>16 ± 3</td>
<td>16 ± 3</td>
<td>18 ± 5 §</td>
</tr>
<tr>
<td>PETCO2, mmHg</td>
<td>39 ± 6</td>
<td>40 ± 4</td>
<td>36 ± 3 §</td>
<td>37 ± 4 §</td>
<td>34 ± 3 §</td>
</tr>
<tr>
<td>VO2, ml·min</td>
<td>257 ± 59</td>
<td>276 ± 51</td>
<td>271 ± 55</td>
<td>272 ± 39</td>
<td>293 ± 59 §</td>
</tr>
<tr>
<td>VO2, l·min</td>
<td>313 ± 68</td>
<td>324 ± 47</td>
<td>327 ± 70</td>
<td>326 ± 43</td>
<td>334 ± 73 §</td>
</tr>
<tr>
<td>MCAV, cm/s</td>
<td>69 ± 10</td>
<td>77 ± 14 &amp;</td>
<td>65 ± 15</td>
<td>69 ± 15</td>
<td>60 ± 14 §</td>
</tr>
<tr>
<td>CBF, mmHg·cm−1·s</td>
<td>1.2 ± 0.2</td>
<td>1.1 ± 0.2 &amp;</td>
<td>1.1 ± 0.3</td>
<td>1.0 ± 0.3</td>
<td>1.1 ± 0.3 §</td>
</tr>
<tr>
<td>Cerebral oxygenation, %</td>
<td>71 ± 5</td>
<td>72 ± 5</td>
<td>72 ± 4</td>
<td>72 ± 4</td>
<td>72 ± 5 §</td>
</tr>
<tr>
<td>CCA diameter, cm</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.1 §</td>
</tr>
<tr>
<td>CCA blood flow, ml·min</td>
<td>296 ± 124</td>
<td>384 ± 143 §</td>
<td>484 ± 193 §</td>
<td>516 ± 152 §</td>
<td>468 ± 216 §</td>
</tr>
<tr>
<td>CCA resistance, mmHg·ml−1·min−1</td>
<td>0.3 ± 0.1</td>
<td>0.2 ± 0.1 §</td>
<td>0.2 ± 0.1</td>
<td>0.1 ± 0.1 §</td>
<td>0.2 ± 0.1 §</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD based on 1-min steady-state averaged data (n = 10). Cardiovascular variables: HR, heart rate; MAP, mean arterial blood pressure; SV, stroke volume; Q, cardiac output; TPR, total peripheral resistance; BA, brachial artery. Respiratory variables: Ve, ventilation; f′, tidal volume; PETCO2, end-tidal carbon dioxide; VO2, oxygen consumption. Cerebrovascular variables: MCAv, middle cerebral artery velocity; CBF, cerebral blood flow; CCA, common carotid artery. *Different from euhydration (Euh) (P < 0.05); †Different from Euh (P < 0.01); §Different from baseline (P < 0.05); ¶Different from baseline (P < 0.01).
Cardiorespiratory and Cerebrovascular Responses to Passive Heating

Cardiovascular variables. HR and brachial artery blood flow were elevated at all stages of heating \((P < 0.05; \text{Table 1})\), while \(Q\) was increased at both +1°C and +1.5°C \((P < 0.05; \text{Table 1})\) but not at +2°C (Fig. 4A). Both TPR and brachial artery resistance were decreased at all stages of heating, while stroke volume (SV) remained unchanged. MAP was lower at +0.5°C, +1°C, and +1.5°C \((P < 0.05; \text{Table 1})\) and tended to be lower at +2°C \((P = 0.1; \text{Fig. 4E})\). Interestingly, both HR and MAP were higher in Hypo than Euh at +1°C \((P < 0.05; \text{Fig. 4})\) while brachial artery blood flow was lower at +2°C in Hypo than Euh \((P < 0.05; \text{Table 1})\).

Respiratory variables. \(V_{E}\) was elevated significantly at +0.5°C, +1°C, and +2°C \((P < 0.05; \text{Fig. 5A})\), mediated by an increase in \(f\) at +1°C and +2°C \((P < 0.05; \text{Table 1})\). \(P_{ETCO_2}\) was reduced during all stages of heating \((P < 0.05; \text{Fig. 5C})\). As with the HR and MAP responses, \(V_{E}\) was higher in Hypo than Euh at +1 \((P < 0.05)\) and +1.5°C \((P = 0.11; \text{Fig. 5A})\), which was mediated by higher \(V_t\) during Hypo at both +1°C and +1.5°C \((P < 0.05; \text{Table 1})\). Finally, both \(V_O_2\) and \(V_{CO_2}\) were elevated at +0.5°C, +1°C, and +1.5°C with no between-condition differences \((P < 0.05; \text{Table 1})\).

Cerebrovascular variables. \(MCAv\) was reduced at +1°C, +1.5°C, and +2°C \((P < 0.05; \text{Fig. 5E})\) and tended to be reduced at +0.5°C \((P = 0.11; \text{Fig. 5E})\). Meanwhile, common carotid artery blood flow was elevated at +0.5°C, +1°C, and +1.5°C \((P < 0.05; \text{Table 1})\). Interestingly, CVR, common...
carotid artery resistance, and cerebral oxygenation remained unchanged with heating ($P > 0.05$; Fig. 5, G and I; Table 1). There were no differences in cerebrovascular hemodynamics between Euh and Hypo during heating ($P > 0.05$). Finally, observations of internal and external carotid blood flows in three subjects showed a large increase in the external carotid artery blood flow ($1^\circ\text{C}: 146 \pm 23\%; 2^\circ\text{C}: 378 \pm 43\%; P < 0.01$), while no change was observed in blood flow to the internal carotid artery ($1^\circ\text{C}: P = 0.15; 2^\circ\text{C}: P = 0.31$).

**Blood variables.** During both Euh and Hypo conditions, plasma osmolality was reduced at $+1.5^\circ\text{C}$ ($P < 0.01$; Table 2). Meanwhile, hemoglobin concentration was elevated at $+1.5^\circ\text{C}$, and $+2^\circ\text{C}$ ($P < 0.05$; Table 2) under both Euh and Hypo conditions. Hematocrit ratio was higher at $+1.5^\circ\text{C}$ ($P < 0.01$; Table 2). There were no between-group differences in plasma volume with heating ($P > 0.05$).

**Relationship between cardiorespiratory and cerebrovascular variables.** The hyperthermic-induced reductions in $\text{PETCO}_2$ and MCAv showed a strong correlation in both Euh and Hypo ($R^2 = 0.98$, $P < 0.01$; $R^2 = 0.97$, $P < 0.001$ respectively; pooled data: $R^2 = 0.98$, $P < 0.0001$; Fig. 6). The MCAv responses during heating were also correlated with increases in $Q$ (Euh: $R^2 = 0.93$, $P < 0.05$; Hypo: $R^2 = 0.77$, $P < 0.05$; pooled data: $R^2 = 0.70$, $P < 0.01$; Fig. 7A). Finally, $Q$ was correlated with brachial artery blood flow during heating (Euh: $R^2 = 0.93$, $P < 0.05$; Hypo: $R^2 = 0.77$, $P < 0.05$; pooled data: $R^2 = 0.70$, $P < 0.01$; Fig. 7A).
Influence of progressive elevations in body temperature on monitored cardiorespiratory and cerebrovascular variables and markers of hydration. The decline in TPR with passive heating appeared to be attenuated in Hypo compared with Euh, while a greater decrease in cerebral oxygenation with passive heating was observed in Hypo compared with Euh ($P < 0.05$; Table 3). There were no hydration-related differences in heating-induced changes for any other variable ($P > 0.05$; Table 3).

Ventilatory and cerebrovascular reactivity to $\text{CO}_2$ during heating. There was no change in the sensitivities of either ventilation or cerebral blood flow to $\text{CO}_2$ during heating ($P > 0.05$; Fig. 8). Furthermore, there were no differences observed between Euh and Hypo for these variables throughout the experimental protocol ($P > 0.05$; Fig. 8).
The purpose of this study was to investigate the separate and interactive effects of progressive, severe passive heating and mild (1.5%) hypohydration on cardiorespiratory and cerebrovascular function in humans during supine rest. The major new findings were as follows.

1) In the absence of heat stress, hypohydration can elevate MCAv and blood flow in the common carotid artery; however, despite these changes at baseline, hypohydration had no effect on CBF during progressive heating.

2) Independent of hydration status, the severe reductions in MCAv with progressive hyperthermia can be accounted for by the reduction in PETCO₂ resulting from a hyperthermic-induced hyperventilation and potentially a redistribution of Q to the peripheral circulation.

3) Despite these large reductions in MCAv, cerebral oxygenation was maintained, presumably via an increased extraction of O₂ or regional changes in CBF.

4) Steady-state cerebral CO₂ reactivity was unchanged with progressive passive heating by 2°C, independent of hydration status, indicating that reduced CBF reactivity is not an important mechanism underlying hyperthermic-induced hyperventilation; conversely, potential elevations in CBF reactivity are not factors in further exacerbating the decline in CBF during hyperthermia.

### DISCUSSION

The purpose of this study was to investigate the separate and interactive effects of progressive, severe passive heating and mild (1.5%) hypohydration on cardiorespiratory and cerebrovascular function in humans during supine rest. The major new findings were as follows. 1) In the absence of heat stress, hypohydration can elevate MCAv and blood flow in the common carotid artery; however, despite these changes at baseline, hypohydration had no effect on CBF during progressive heating. 2) Independent of hydration status, the severe reductions in MCAv with progressive hyperthermia can be accounted for by the reduction in PETCO₂ resulting from a hyperthermic-induced hyperventilation and potentially a redistribution of Q to the peripheral circulation. 3) Despite these large reductions in MCAv, cerebral oxygenation was maintained, presumably via an increased extraction of O₂ or regional changes in CBF. 4) Steady-state cerebral CO₂ reactivity was unchanged with progressive passive heating by 2°C, independent of hydration status, indicating that reduced CBF reactivity is not an important mechanism underlying hyperthermic-induced hyperventilation; conversely, potential elevations in CBF reactivity are not factors in further exacerbating the decline in CBF during hyperthermia.

### Cardiorespiratory and Cerebrovascular Changes with Hypohydration at Normothermia

Consistent with previous reports during hypohydration, both HR (5) and ventilation (3) were elevated. Elevations in sym-
pathetic nerve activity (5, 17) and metabolism (30) associated with hypohydration are likely to underlie the increase in HR and maintenance of PetCO2 during increases in ventilation. An unexpected finding was a significant increase in MCAv (11 ± 11%; Fig. 2B) and blood flow in the common carotid artery (30 ± 26%) during Hypo (Fig. 2C). This observed increase in cerebral perfusion was mediated by proportional decreases in both CVR (−13 ± 16%) and common carotid artery resistance (−30 ± 22%; Table 1). Because the study design was randomized and elevations were apparent in both the MCAv and blood flow in the common carotid artery (measured independently), as well as related cardiovascular variables (higher HR and Q), it seems unlikely that these selective changes with hypohydration were due to artifact. The potential mechanisms that might underlie this finding are not known and warrant further investigation.

Effect of Hypohydration on Heat Tolerance

Severe hypohydration (7%) has been shown to significantly reduce heat tolerance during exercise in the heat, while mild levels (3 and 5%) have little (46) or no effect (8). The present study provides information on resting heat tolerance. Only 2 of the 10 subjects showed a reduced heat tolerance during Hypo; therefore, it seems that mild levels of hypohydration do not impact notably on heat tolerance during passive heat stress. While other changes might be anticipated with greater levels of hypohydration, or with greater heat stress, 1.5% hypohydration has been reported to impair exercise performance (16). In addition, this level of hypohydration is commonly observed in free living people (45, 61); thus the selective mild hypohydration has physiological relevance in terms of the effects of hypohydration on normal daily function during heat exposure.

Respiratory Changes During Passive Heating

As expected, although not previously established over a range of Tc, progressive passive heating induced hyperventilation and subsequent hypocapnia. The present study provided evidence that the threshold for heat-induced hyperventilation and resultant hypocapnia appears to be around +0.5°C and that the effect may be linear thereafter (Fig. 5C). These findings, independent of hypohydration (Fig. 6), further highlight the

Table 3. Sensitivity of cardiorespiratory and cerebrovascular variables to increasing body temperature in euhydrated and hypohydrated conditions during supine rest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Condition</th>
<th>Euh</th>
<th>Hypo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats·min^{-1}·°C^{-1}</td>
<td></td>
<td>18±6</td>
<td>19±5</td>
</tr>
<tr>
<td>MAP, mmHg/C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV, ml·°C</td>
<td></td>
<td>−8±4</td>
<td>−7±8</td>
</tr>
<tr>
<td>Q, l·min^{-1}·°C^{-1}</td>
<td></td>
<td>−13±7</td>
<td>−11±1</td>
</tr>
<tr>
<td>TPR, mmHg·l^{-1}·min^{-1}·°C^{-1}</td>
<td></td>
<td>−3±1</td>
<td>−2±1*</td>
</tr>
<tr>
<td>BA diameter, cm/°C</td>
<td></td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
</tr>
<tr>
<td>BA blood flow, ml·min^{-1}·°C^{-1}</td>
<td></td>
<td>90±30</td>
<td>114±52</td>
</tr>
<tr>
<td>BA resistance, mmHg·l^{-1}·min^{-1}·°C^{-1}</td>
<td></td>
<td>−2±1</td>
<td>−1±1</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ve, l·min^{-1}·°C^{-1}</td>
<td></td>
<td>3±2</td>
<td>6±6</td>
</tr>
<tr>
<td>Vt, ml/°C</td>
<td></td>
<td>0.1±0.1</td>
<td>0.1±0.2</td>
</tr>
<tr>
<td>f, breaths·min^{-1}·°C^{-1}</td>
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<td>6±5</td>
<td>4±2</td>
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<tr>
<td>PetCO2, mmHg/°C</td>
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<td>−8±5</td>
</tr>
<tr>
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<td>6±10</td>
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<tr>
<td>Vco2, ml·min^{-1}·°C^{-1}</td>
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<td>39±29</td>
</tr>
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<td>VO2, ml·min^{-1}·°C^{-1}</td>
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<td>18±15</td>
<td>23±12</td>
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<tr>
<td>Cerebrovascular</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MCAv, cm·s^{-1}·°C^{-1}</td>
<td></td>
<td>−10±7</td>
<td>−11±11</td>
</tr>
<tr>
<td>CVR, mmHg·cm^{-1}·s·°C^{-1}</td>
<td></td>
<td>0.1±0.2</td>
<td>0.1±0.2</td>
</tr>
<tr>
<td>Cerebral oxygenation, %/°C</td>
<td></td>
<td>−1±2</td>
<td>−2±3*</td>
</tr>
<tr>
<td>CCA diameter, cm/°C</td>
<td></td>
<td>0.0±0.1</td>
<td>0.0±0.0</td>
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<tr>
<td>CCA blood flow, ml·min^{-1}·°C^{-1}</td>
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<td>224±169</td>
<td>235±179</td>
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<tr>
<td>CCA resistance, mmHg·l^{-1}·min^{-1}·°C^{-1}</td>
<td></td>
<td>−0.1±0.1</td>
<td>−0.1±0.1</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma osmolality, mmol·kg^{-1}·°C^{-1}</td>
<td></td>
<td>−4±5</td>
<td>−4±5</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD of change per °C change in core (esophageal) temperature (Tc) for 10 participants. *Different from Euh (P < 0.05).
critical role of Pa\textsubscript{aCO\textsubscript{2}} in regulating MCA\textsubscript{v} during passive heat stress. Such marked heat-induced hyperventilation and reductions in CBF are clearly critical factors in the related symptoms (i.e., nausea and cognitive decline) associated with hyperthermia. The declines of MCA\textsubscript{v} (~32 ± 14%) are particularly noteworthy giving that reductions in MCA\textsubscript{v} of ~50% are required to induce syncope (55). Since Pa\textsubscript{aCO\textsubscript{2}} and MCA\textsubscript{v} would be further reduced in the upright position, such changes may underlie subsequent reports of collapse during adverse heat stress (4).

**Cardiovascular Changes During Passive Heating**

The changes in cardiovascular variables observed in the present study are consistent with previous reports of significant increases in HR and Q with unchanged SV during passive heating in resting humans studies (18, 44, 59). The present study extends these previous findings by demonstrating that such changes develop relatively linearly with elevations in T\textsubscript{C} and that even during severe hyperthermia (+2°C), SV is still maintained. This lack of change in SV indicates that venous return is adequately maintained during heat stress, at least when supine. Rowell et al. (44) reported similar cardiovascular changes and observed a large reduction in right atrial pressure in hyperthermic humans. As Q and cutaneous blood flow increase during heat stress, cutaneous venous pressure is also elevated, coinciding with the reduction in right atrial pressure (43). The large pressure gradient between cutaneous postcapillary vessels and the right atrium facilitates the maintenance of venous return, and subsequently SV (43), at least when supine.

Findings from the present study indicate that Q increases at a rate of ~1.0 l/min per degree Centigrade rise in core temperature, which falls outside the range of previous reports of ~1.9–3.2 l/min per degree Centigrade rise (44, 59). Related differences in experimental design such as the rate and duration of heat exposure, methods to quantify Q, and site of core temperature measurement (esophageal temperature vs. right atrial blood and gastrointestinal) may underlie this variance in changes in Q with body temperature. Furthermore, unlike the previous studies (44, 58, 59), the present study controlled for the potential influence of hydration status both before and throughout heating. The increases in Q and decreases in TPR observed in the present study were likely due to elevation in cutaneous blood flow during heat stress, mediated by cutaneous vasodilation (41). This increase in cutaneous blood flow was reflected in the large increase (+630 ± 302 Euh; +897 ± 461% Hypo) in blood flow in the brachial artery (Fig. 4G), consistent with an early report of an increase in oxygen saturation in forearm venous blood during heat stress (41). Some (11, 58) but not all (12, 44) previous studies have found that MAP is maintained with passive heating independent of posture. Reduction in MAP indicates a mismatch between increases in Q and decreases in TPR during heat stress (44); thus data from the present study support the notion of a Q-TPR mismatch during heat stress, since significant reductions in MAP were observed at each of the 0.5°C elevations in body temperature.

**Cerebrovascular Changes During Passive Heating**

The present findings are consistent with previous reports of significant reduction in CBF in both resting (~9% (58, 59)) and exercising (34, 35, 40) hyperthermic humans. However, in contrast to previous studies (58, 59), which used a one-step passive heating protocol (+0.9°C gastrointestinal), the present study used four steps in T\textsubscript{C}, allowing investigation of the threshold T\textsubscript{C} at which CBF was reduced during heat stress. These data indicate that the T\textsubscript{C} elevation threshold of reduction in CBF occurred at around +1°C, although there was a tendency (P = 0.11) for reduced MCA\textsubscript{v} at +0.5°C, indicating that CBF may have been reduced at the same T\textsubscript{C} threshold as that of Pa\textsubscript{aCO\textsubscript{2}} during passive heating. This is further supported by the close correlation between these two measures (Fig. 6). Carter et al. (4) have previously shown that 3% hypohydration following heat exposure did not affect MCA\textsubscript{v} under mild hyperthermic condition (+0.5°C). However, because of the differences in experimental protocol between the present study and Carter et al. (4) (method of heating, timing of measurements, level of hydration, and the degree of hyperthermia), it is difficult to compare the findings. Taken together, while acknowledging that elevations in metabolism (Table 1) might promote elevations in MCA\textsubscript{v} (51), the present study indicates that the hyperthermic-induced reduction in MCA\textsubscript{v} is likely to be accounted for by two main factors: hyperthermic-induced hyperventilation and subsequent hypocapnic-induced cerebral vasoconstriction, and a redistribution of Q to the periphery.

Heat-induced hyperventilation and hypocapnic-mediated cerebral vasoconstriction. It was reported recently that reduction in CBF during supine passive heat stress was mediated by a significant increase in CVR (58). This finding is in contrast to those from the present study, in which no changes in CVR in Euh or Hypo (n = 20 trials) were apparent during any stages of passive heat. It is interesting to note that CVR tended to be lower in Hypo at +0.5°C (P = 0.096) compared with Euh, potentially indicating that hypohydration decreases CVR during mild hyperthermia and thermoneutrality (Table 1), but its effect is negated above +0.5°C. The present findings, in both Euh and Hypo, highlight a critical role of heat-induced hyperventilation and hypocapnic-cerebral vasoconstriction in mediating the decline in CBF (Fig. 6). Because CBF-CO\textsubscript{2} reactivity remained unchanged throughout the study (Fig. 8, A and B) and considering that the baseline CBF reactivity to CO\textsubscript{2} during hypocapnia accounts for a 2% drop in MCA\textsubscript{v} per mmHg drop in PET\textsubscript{CO\textsubscript{2}} (Fig. 8A), the observed reduction in MCA\textsubscript{v} (Euh: −30 ± 16%; Hypo: −34 ± 13%) with passive heating could be fully accounted by the decline in PET\textsubscript{CO\textsubscript{2}} (Euh: −16 ± 11 mmHg; Hypo: −17 ± 10 mmHg).

**Redistribution of cardiac output during passive heat stress.** As mentioned, there is a positive relationship between Q and CBF at normothermia during rest and exercise (22, 36). In the present study, during progressive heat stress, there was an inverse relationship between the reductions in MCA\textsubscript{v} and heat-induced elevations in Q (Fig. 7A), potentially reflecting selective redistribution of Q to the peripheral circulation to aid heat dissipation during hyperthermia (41). Consistent with this possibility was the observed relationship between the elevations in brachial blood flow and Q, such changes, independently of hydration at the levels tested here, likely reflect peripheral distribution of Q to the skin to aid heat dissipation (Fig. 7B) (59). Collectively, it seems that marked heat-induced hypocapnia and peripheral redistribution of Q might further compound the decline in CBF.
Cerebral Oxygenation During Hyperthermia

In contrast to our original hypothesis, and independent of hydration, cerebral oxygenation was not impaired as the result of reduced CBF during heat stress (Fig. 5J). Two possibilities may explain this maintained oxygenation. 1) Despite the reductions in MCAv, cerebral oxygen delivery could be maintained by elevations in oxygen extraction. Despite a smaller vascular bed in the brain compared with the muscle, the brain has a greater ability to increase its arteriovenous O₂ difference and therefore maintain a constant local O₂ delivery (20). 2) The decline in MCAv but maintained frontal cerebral oxygenation might reflect a regional distribution of CBF. Nunneley et al. (33), using positron-emission tomography (PET), found significant increases in regional cerebral metabolism and subsequent increase in blood flow in the hypothalamus, thalamus, corpus callosum, cingulated gyrus, and cerebellum in heat stressed humans (+1.5°C rectal). In addition, that study also reported reduced regional cerebral activity during heat stress, particularly in the occipital and sublobar lobe (33), which is predominately supplied by the middle cerebral artery (27). Unfortunately, due to technical difficulties, it was not possible to measure global changes in cerebral metabolism during heat stress (33), so the roles of altered extraction or distribution of perfusion could not be adequately evaluated.

Unchanged CBF and Ve-CO₂ Reactivity

Changes in cerebral blood flow, and cerebrovascular reactivity to CO₂, play important roles in ventilatory control (60); reductions in CBF reduce [H⁺] washout from the brain, which subsequently increases [H⁺] for a given PaCO₂ presented at the level of the central chemoreceptor, thereby enhancing ventilatory drive (60). If heat-induced hyperventilation leads to a reduction in CO₂ reactivity of CBF, it provides a possible mechanism where relatively larger changes in [H⁺] could be presented to the central chemoreceptors and therefore exacerbate hyperthermic-induced hyperventilation and elevations in the previously reported ventilatory responsiveness to CO₂ in humans (14, 56) and other animals (7, 29). The present findings (Fig. 8, A and B), however, clearly show that steady-state cerebral CO₂ reactivity was unchanged with progressive heating, independent of hydration status, indicating that reduction in CBF reactivity is not an important mechanism underlying hyperthermic-induced hyperventilation. Furthermore, the unchanged CBF-CO₂ reactivity is not a factor in further exacerbating the decline in CBF during hyperthermia; thus, the recent report of enhanced cerebral CO₂ reactivity during hyperthermic exercise (40) reflects an additional influence from exercise rather hyperthermia per se. Collectively, the influence of hyperthermia alone seems to override the normal chemical control of breathing with hypercapnia, although other factors such as blood-borne metabolites or increased firing of group III and IV afferents in skeletal muscle with elevations in body temperature (21) might also influence ventilation.

Technological Considerations

There are three important technological considerations in our study. First, although we used Doppler ultrasound to measure flow velocity, rather than blood flow, in the MCA, the majority of research indicates that MCAv is a reliable index of CBF (19, 53). Recent data from our laboratory indicate that changes in MCAv during related changes in arterial blood gases are closely related to the changes in global CBF, as estimated from direct measurements based on the Fick principle (38). However, it is important to mention that while MCAv is a reliable index of regional CBF, local changes in the respiratory center may differ. For example, if the changes in MCAv do not reflect changes in the posterior circulation supplying the medulla, then this could potentially explain the lack of influence of MCAv on ventilatory sensitivity to CO₂. Furthermore, in the present study, the reductions in MCAv and elevations in common carotid artery blood flow were reflected in a preferential distribution of blood to the external carotid artery rather than the internal carotid artery. Time constraints limited these internal and external carotid artery blood flow measurements to only three subjects, so inferential statistical analyses of this perfusion distribution should be examined with caution. Second, cerebral NIRS has been shown to track changes in jugular venous bulb saturation in healthy volunteers under conditions of hypoxia (39) and has also been validated against PET scanning (42), ¹³³Xe washout methods (49), and internal carotid artery stump pressures (57). It should be acknowledged, however, that NIRS measures only local (i.e., to one depth) oxygenation and that discreet regions of the brain may respond differently during hyperthermia (33). Furthermore, heat stress could induce a volume shift between the proportions of blood in the arterial or venous part of the cerebrovascular beds, thereby influencing the accuracy of the NIRS measurement of cerebral tissue oxygenation. Finally, because the experiments spanned from 0700 to 1400, the results, in part, could be influenced by circadian influences acting to elevate body temperature. This possibility, however, was ruled out by inclusion of a control group to confirm that there were no significant changes in body temperature over the experimental testing period (Fig. 3), presumably caused by the supine posture suppressing Tc (31) and thus offsetting the circadian effect.

In summary, independent of hydration, severe passive hyperthermia induced in the supine position causes marked hyperventilation and subsequent hypocapnia, and a distribution of Q to the periphery to aid heat loss. While both these factors may act to compromise cerebral perfusion, and potentially underlie neurological symptoms associated with severe heat stress in humans, cerebral oxygenation was maintained, presumably via enhanced O₂ extraction or regional differences in cerebral perfusion. In the absence of heat stress, however, hypohydration at rest can elevate both increases in MCAv and blood flow in the common carotid artery. The mechanism(s) underlying these changes warrant further investigation.

REFERENCES


