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Cerebrovascular responsiveness to steady-state changes in end-tidal CO₂ during passive heat stress

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Abstract

This study tested the hypothesis that passive heat stress alters cerebrovascular responsiveness to steady-state changes in end-tidal CO₂ (P_{ETCO₂}). Nine healthy subjects (4 men and 5 women), each dressed in a water-perfused suit, underwent normoxic hypocapnic hyperventilation (decrease P_{ETCO₂} ~20 Torr) and normoxic hypercapnic (increase in P_{ETCO₂} ~9 Torr) challenges under normothermic and passive heat stress conditions. The slope of the relationship between calculated cerebrovascular conductance (CBVC; middle cerebral artery blood velocity/mean arterial blood pressure) and P_{ETCO₂} was used to evaluate cerebrovascular CO₂ responsiveness. Passive heat stress increased core temperature (1.1 ± 0.2°C, *P* < 0.001) and reduced middle cerebral artery blood velocity by 8 ± 8 cm/s (*P* = 0.01), reduced CBVC by 0.09 ± 0.09 CBVC units (*P* = 0.02), and decreased P_{ETCO₂} by 3 ± 4 Torr (*P* = 0.07), while mean arterial blood pressure was well maintained (*P* = 0.36). The slope of the CBVC-P_{ETCO₂} relationship to the hypocapnic challenge was not different between normothermia and heat stress conditions (0.009 ± 0.006 vs. 0.009 ± 0.004 CBVC units/Torr, *P* = 0.63). Similarly, in response to the hypercapnic challenge, the slope of the CBVC-P_{ETCO₂} relationship was not different between normothermia and heat stress conditions (0.028 ± 0.020 vs. 0.023 ± 0.008 CBVC units/Torr, *P* = 0.31). These results indicate that cerebrovascular CO₂ responsiveness, to the prescribed steady-state changes in P_{ETCO₂}, is unchanged during passive heat stress.

Keywords

brain blood flow; hyperthermia; hypocapnia; hypercapnia

Orthostatic tolerance is reduced under heat stress, relative to normothermic, conditions (1,8, 19,40,41). Although mechanisms responsible for reduced orthostatic tolerance during heat stress are unclear, they are likely associated with factors that directly or indirectly affect cerebral perfusion pressure, cerebral blood flow, and thus cerebral oxygenation (20,24,38). Cerebral perfusion is very sensitive to changes in arterial carbon dioxide tension (PaCO₂), such that increases in PaCO₂ increase cerebral perfusion, whereas decreases in PaCO₂ decrease cerebral perfusion (16,36). Previously, our laboratory identified decreases in end-tidal carbon dioxide (P_{ETCO₂}; surrogate of PaCO₂) of ~2 Torr in response to whole body passive heat stress, as well as significant reductions in cerebral perfusion and cerebral vascular conductance (40,

41). Decreased cerebral perfusion would theoretically reduce the functional reserve by which cerebral blood flow can decrease further, before the onset of syncopal symptoms.

It is unlikely that the relatively small decrease in P_{ETCO_2} (i.e., ~2 Torr) in response to passive heat stress is the sole mechanism leading to the observed reduction in cerebral perfusion. However, this assumption is based on calculated cerebral vascular reactivity to changes in Pa_{CO_2} from normothermic individuals (31), which may be different relative to heat-stressed individuals. Consistent with this hypothesis, combined exercise and heat stress increased cerebral vascular reactivity to changes in P_{ETCO_2} relative to when subjects exercised while normothermic (30). It is important, however, to emphasize that cerebral vascular responsiveness to changes in Pa_{CO_2} may be very different when subjects are exercising in the heat relative to when they are passively heat stressed. If passive heating increases cerebral vascular responsiveness to changes in Pa_{CO_2} , similar to what occurs during active (i.e., exercise-induced) heating, this may partially explain greater than predicted decreases in cerebral vascular conductance and corresponding large decreases in cerebral blood flow to whole body heat stress (40). To that end, the effects of passive heat stress on cerebral vascular reactivity to changes in Pa_{CO_2} remain unknown, and thus the aim of this study was to test the hypothesis that passive heat stress enhances cerebrovascular responsiveness to steady-state increases and decreases in Pa_{CO_2} as indexed by P_{ETCO_2} .

METHODS

Subjects

Nine subjects (4 men and 5 women) participated in this study. The subjects' mean $\pm$ SD age, height, and weight were 34 ± 7 yr, 175 ± 9 cm, and 77 ± 14 kg, respectively. All subjects were healthy and free from cardiovascular, cerebrovascular, and metabolic diseases. Subjects refrained from alcohol consumption and exercise for 24 h, as well as caffeine consumption for 12 h, before the study. All study procedures were approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas. An institutionally approved written, informed consent was obtained from all participants before they enrolled in the study.

Experimental Protocol

Experiments were performed in a temperature-controlled laboratory ($26 \pm 1^\circ\text{C}$) in the morning or early afternoon, at least 2 h postprandial. Each subject was dressed in a water-perfused tube-lined suit (Med-Eng, Ottawa, Canada) that covered the entire body, except the head, face, hands, feet, and one forearm. This suit permitted the control of skin and core temperature by changing the temperature of the water perfusing the suit. After instrumentation, subjects rested in the supine position under normothermic conditions, during which time 34°C water was perfused through the suit. Following this resting period, 6 min of baseline data were collected. To achieve normoxic hypocapnia, subjects hyperventilated by breathing at a rate of 60 breaths/min for 30 s. This was followed by a 2-min recovery period. The subsequent normoxic hypercapnic challenge was performed by subjects inspiring a gas mixture of 5% CO_2 -21% O_2 -balance N_2 for 4–5 min followed by a 3-min recovery period. These challenges were repeated a minimum of 5 min after the end of the preceding challenge. Subjects were then exposed to a heat stress by perfusing 50°C water through the suit for a duration sufficient to increase core temperature $\sim 1.0^\circ\text{C}$. Once subjects had reached this target core temperature, the temperature of the water perfusing the suit was lowered to $\sim 44^\circ\text{C}$ to limit further increases in core temperature during the ensuing data collection periods. The aforementioned hypocapnic and hypercapnic challenges were then repeated in duplicate.

Instrumentation and Measurements

Core temperature was measured from an ingestible pill telemetry system (HTI Technologies, Palmetto, FL), that has previously been validated (27). The pill was ingested immediately on arrival at the laboratory. Mean skin temperature was measured via the weighted average of six thermocouples attached to the skin (37). Heart rate was obtained from an electrocardiogram (HP Patient Monitor, Agilent, Santa Clara, CA) interfaced with a cardiometer (CWE, Ardmore, PA). Continuous beat-by-beat arterial blood pressure was recorded from a digit using the Penaz method (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). Intermittent arterial blood pressure was also measured by auscultation of the brachial artery via electrophygmomanometry (SunTech, Raleigh, NC), and mean arterial blood pressure was calculated as one-third pulse pressure plus diastolic blood pressure. Skin blood flow was measured via laser-Doppler flowmetry using an integrating flow probe (MoorLAB Laser Doppler Perfusion Monitor, Moor Instruments, Wilmington, DE) attached to the forearm not covered by the water-perfused suit. Cutaneous vascular conductance was calculated from the ratio of laser Doppler flux to mean arterial blood pressure. Middle cerebral artery blood velocity (MCA V_{mean}) was continuously measured using transcranial Doppler ultrasonography. A 2-MHz Doppler probe (Multi-flow, DWL Elektronische Systeme, Singen, Germany) was adjusted over the temporal window until an optimal signal was identified. The probe was then fixed using a mold constructed of polyvinylsiloxane impression medium and held in place using a headband strap to prevent subtle movement of the Doppler probe. An index of cerebrovascular conductance (CBVC) was calculated from the ratio of MCA V_{mean} to mean arterial blood pressure, whereas an index of cerebrovascular resistance (CBVR) was calculated as the inverse of CBVC. Subjects were instrumented with a two-way valve breathing mouthpiece, from which P_{ETCO_2} , respiratory rate (VitalCap Capnograph Monitor, Oridion, Needham, MA), and minute ventilation were continuously measured (Parvo Medics True One 2400 Metabolic Measurement Systems, Sandy, UT). Oxygen saturation was measured using pulse oximetry (MicrO₂, Siemens, Danvers, MA).

Data Analysis

Data were sampled at 50 Hz via a data-acquisition system (Biopac System, Santa Barbara, CA) and analyzed using a statistical software package (SigmaStat 3.11, Chicago, IL). Data from the last 60 s of the baseline period, the last 10 s of the hypocapnic hyperventilation, and the last 30 s of the hypercapnic challenge were used in the statistical analyses. Data from repeated trials within each thermal condition were averaged. The slope of the CBVC- P_{ETCO_2} relationship and the slope of the CBVR- P_{ETCO_2} relationship between baseline and the hypocapnic hyperventilation challenge and between baseline and the hypercapnic 5% CO₂ challenge were compared across thermal conditions using paired *T*-tests. CBVC, instead of cerebral blood velocity, was evaluated to examine the cerebrovascular responsiveness to changes in P_{ETCO_2} , thereby avoiding the potential confounding influence of changes in arterial blood pressure on cerebral blood velocity associated with hypo- and hypercapnic challenges (5). For the hypercapnic trial, mean arterial blood pressure measured from the brachial artery was used in the calculation of CBVC and CBVR. However, given the shorter duration of the hypocapnic trial (30 s), for these trials changes in arterial blood pressure were indexed from the Finometer. The changes (i.e., Δ) in blood pressure, P_{ETCO_2} , CBVC, and ventilation rate for the hypocapnic, as well as hypercapnic, challenges were compared between normothermia and heat stress conditions using paired *T*-tests. Differences in baseline thermoregulatory, cardiovascular, respiratory, and cerebral responses between normothermic and heat stress conditions were evaluated using a paired *T*-test. If a data set did not conform to a normal distribution, a Wilcoxon sign-ranks test was used instead of a paired *t*-test. Values are reported as means $\pm$ SD. *P* values of <0.05 were considered statistically significant.

RESULTS

Thermoregulatory, Cardiopulmonary, and Cerebral Responses to Heat Stress

Passive heat stress caused typical thermoregulatory and cardiovascular responses (see Table 1). The average increase in core and mean skin temperatures was 1.1 ± 0.2 and $3.7 \pm 0.6^\circ\text{C}$, respectively (both $P < 0.001$). Heart rate increased (39 ± 12 beats/min, $P < 0.001$), while mean arterial blood pressure was well maintained ($P = 0.36$). Forearm cutaneous vascular conductance increased approximately fourfold relative to preheat stress baseline. Heat stress decreased MCA V_{mean} (8 ± 8 cm/s, $P = 0.01$) and CBVC (0.09 ± 0.09 CBVC units, $P = 0.02$), while there was a tendency for a decrease in P_{ETCO_2} ($P = 0.07$). In addition, minute ventilation increased from 5.6 ± 1.6 to 7.7 ± 2.2 l/min ($P = 0.003$) during heat stress.

Arterial Saturation Responses to Hypo- and Hypercapnia

Oxygen saturation was unchanged during the hypo- and hypercapnic challenges, regardless of the thermal condition. Average responses for both thermal conditions were $98 \pm 1\%$ for the hypocapnic trials and $98 \pm 1\%$ for the hypercapnic trials, thereby confirming the normoxic nature of the procedures.

Cerebral and Respiratory Responses to Hypo- and Hypercapnia

Hypocapnia—Respiratory rate was fixed at 60 breaths/min, so there was no difference in this variable during the hypocapnic trial between thermal conditions. The increase in ventilation in response to hypocapnic hyperventilation was also similar between normothermia and heat stress conditions (27.3 ± 20.4 vs. 29.2 ± 15.2 l/min, $P = 0.57$). There was no difference in the decrease in P_{ETCO_2} during the hypocapnic hyperventilation challenge between normothermia and heat stress conditions (19 ± 7 vs. 19 ± 4 Torr, $P = 0.98$; see Fig. 1). Blood pressure decreased during hyperventilation ($P = 0.05$), with no difference in the magnitude of the decrease between normothermia and heat stress conditions (7 ± 10 vs. 5 ± 8 mmHg, $P = 0.36$). Both MCA V_{mean} and CBVC significantly decreased during hyperventilation (both $P < 0.001$), with no difference in the magnitude of the reduction in CBVC expressed as ΔCBVC (normothermia: 0.17 ± 0.12 ; heat stress: 0.18 ± 0.09 CBVC units, $P = 0.85$, see Fig. 2A) or as percent change in CBVC from prehypocapnia baseline (normothermia: 21 ± 16 ; heat stress: $26 \pm 12\%$, $P = 0.30$, see Fig. 2B) between thermal conditions. The slope of the CBVC- P_{ETCO_2} relationship between baseline and hypocapnic hyperventilation was not affected by the heat stress (normothermia: 0.009 ± 0.006 ; heat stress: 0.009 ± 0.004 CBVC units/Torr, $P \pm 0.63$, see Fig. 1). When these data were expressed as CBVR (data not shown), there was a tendency for the slope of the CBVR- P_{ETCO_2} relationship between baseline and hypocapnic hyperventilation to be elevated by heat stress (normothermia: 0.02 ± 0.01 ; heat stress: 0.03 ± 0.01 CBVR units/Torr, $P = 0.06$).

Hypercapnia—The hypercapnic challenge did not alter respiratory rate in either normothermic (15 ± 4 to 16 ± 4 breaths/min, $P = 0.23$) or heat stress (17 ± 5 to 18 ± 5 breaths/min, $P = 0.80$) conditions. Ventilatory rate was significantly increased by hypercapnia by ~ 5 l/min ($P = 0.002$), with no significant difference in the magnitude of this increase between thermal conditions (normothermia: 4.9 ± 2.6 ; heat stress 5.3 ± 2.7 l/min, $P = 0.36$). There was also no difference in the increase in P_{ETCO_2} during the hypercapnic challenge, regardless of the thermal condition (normothermia: 8 ± 2 ; heat stress: 9 ± 2 Torr, $P = 0.11$; see Fig. 1). There was a slight, but nonsignificant, increase in blood pressure due to hypercapnia ($P = 0.33$), with no difference ($P = 0.63$) in the magnitude of this increase between normothermia (5 ± 5 mmHg) and heat stress (4 ± 6 mmHg) conditions.

Both MCA V_{mean} and CBVC significantly increased during hypercapnia (both $P < 0.001$), with no difference in the magnitude of the increase in CBVC expressed as ΔCBVC (normothermia:

0.18 ± 0.09 ; heat stress: 0.22 ± 0.10 CBVC units, $P = 0.68$, see Fig. 2A) or as percent change in CBVC (normothermia: 27 ± 11 ; heat stress: $31 \pm 17\%$, $P = 0.36$, see Fig. 2B) between thermal conditions. The slope of the CBVC- P_{ETCO_2} relationship between baseline and hypercapnia was not affected by the thermal condition (normothermia: 0.028 ± 0.020 ; heat stress: 0.022 ± 0.008 CBVC units/Torr, $P = 0.31$; see Fig. 1). Similarly, the slope of the CBVR- P_{ETCO_2} relationship between baseline and hypercapnia was unaffected by heat stress (normothermia: -0.04 ± 0.03 ; heat stress: -0.04 ± 0.03 CBVR units/Torr, $P = 0.93$).

DISCUSSION

The aim of this study was to test the hypothesis that passive heat stress alters cerebrovascular responsiveness to steady-state changes in CO_2 . Subjects underwent hypocapnic hyperventilation and hypercapnic 5% CO_2 challenges that reduced and increased P_{ETCO_2} , respectively, under normothermic and passive heat stress conditions. Despite significant reductions in MCA V_{mean} and CBVC, the slope of the relationship between CBVC and P_{ETCO_2} in the hypocapnic and hypercapnic ranges was not different between thermal conditions.

The maintenance of cerebral perfusion is critical to avoid a loss of consciousness (20,24,38). Our laboratory has previously shown that passive heat stress reduces resting cerebral blood flow (40,41), primarily through decreases in CBVC (40). Furthermore, relative to when subjects are normothermic, the decrease in CBVC for a given orthostatic stress is enhanced under heat stress conditions (40). These combined responses are likely to be key mechanisms responsible for reductions in orthostatic tolerance in heat-stressed individuals, although the cause(s) by which heat stress alters cerebral vascular responses is not entirely clear. Given the close relationship between cerebral perfusion and PaCO_2 (16,36), decreases in PaCO_2 (as reflected by decreases in P_{ETCO_2}) that occur during heat stress alone and combined heat and orthostatic stress (40,41) could account for passive heat stress-induced reductions in resting cerebral blood flow and augmented decreases in CBVC during combined orthostatic and heat stress. However, based on the previously reported relationship that every 1-Torr change in PaCO_2 changes cerebral blood flow $\sim 3\%$ in the same direction under normothermic conditions (31), the decreases in P_{ETCO_2} that are evident during heat and combined heat and orthostatic stresses are not large enough to fully account for all of the decrease in cerebral blood flow. Such an assumption presumes that cerebral vascular reactivity to changes in PaCO_2 is unchanged by whole body heating, however. Consistent with that hypothesis, the slopes of the relationship between CBVC and P_{ETCO_2} were unchanged by the thermal condition of the subject, regardless of whether evaluation was during a hypocapnic or hypercapnic challenge. These findings strongly suggest that passive heat stress does not alter cerebral vascular reactivity to CO_2 . Given these observations, it is unlikely that the pronounced reduction in cerebral blood flow and decreases in CBVC associated with combined whole body heating and orthostatic stress are due entirely to changes in PaCO_2 , as reflected by P_{ETCO_2} .

A decrease in P_{ETCO_2} and CBVC in response to passive heating in the present study (see Fig. 1) suggests that the operating point of the CBVC- P_{ETCO_2} relationship was shifted. Although this shift was subtle, such a response may reduce the range by which further decreases in CBVC could occur in response to hypocapnia. Despite this, the magnitude of the change in CBVC (expressed as a percent change or ΔCBVC), in response to hypocapnia, was not different between thermal conditions. Similarly, in the hypercapnic range, where a shift in the operating point of the CBVC- P_{ETCO_2} relationship to a lower P_{ETCO_2} and CBVC would increase the CBVC range to hypercapnia, the increases in CBVC (expressed as a percent change or ΔCBVC) to the hypercapnic exposure were also the same between thermal conditions. Together, these observations suggest that a change in operating point of the CBVC- P_{ETCO_2} relationship per se does not affect the slope of the CBVC- P_{ETCO_2} relationship for the applied hypo-/hypercapnic stimuli.

Using similar techniques to manipulate P_{ETCO_2} relative to those used in the present study, Rasmussen and colleagues (30) reported that, when subjects exercised in a hot environment (40°C), cerebral vascular CO_2 reactivity was elevated relative to resting normothermic conditions. Rasmussen et al. (30) suggested that the observed increase in CO_2 reactivity, coupled with decreases in P_{ETCO_2} , provides a mechanistic basis for previously observed reductions in cerebral blood flow when subjects exercised in the heat (25,26). The most obvious reason for conflicting findings with respect to cerebral vascular CO_2 reactivity between the present study and that of Rasmussen et al. (30) is the absence of exercise in the present study. The increase in core temperature during the exercise heat stress trial of the study of Rasmussen et al. was greater than that observed during passive heating in the present study (~2 vs. 1°C), which may provide an additional explanation for the differences in the effects of the two types of heat stresses on cerebral vascular CO_2 reactivity. However, the subjects of Rasmussen et al. also completed an exercise trial under normothermic conditions (20°C) that caused an increase in core temperature of ~1°C, similar to that in the present study under passive heat stress conditions. Exercise in this thermal condition also increased cerebral vascular CO_2 reactivity relative to resting normothermic conditions. Together, these findings suggest that cerebrovascular responses during exercise, with or without accompanying elevated environmental temperature, are very different relative to that during passive heating. A number of studies have shown that, relative to resting conditions, ventilatory CO_2 sensitivity to a hypercapnic challenge (i.e., the change in ventilation in response to a change in P_{ETCO_2}) is increased during short-term aerobic exercise, independent of associated increases in core temperature (2,10,17,21,22,39). These studies support the hypothesis that exercise, independent of internal temperature, can alter responsiveness to CO_2 , although it is recognized that exercise-induced altered ventilatory responses to CO_2 are insufficient evidence to fully support the hypothesis that exercise itself can alter cerebrovascular responsiveness to CO_2 .

Cerebral blood flow is modulated via adjustments in systemic hemodynamics (e.g., perfusion pressure), through local vascular modulation (i.e., cerebral autoregulation, CO_2 responsiveness, etc.) (38) and could also be affected by sympathetic neural stimulation (3,12,15,29). Mean arterial pressure was not different between normothermic and heat stress conditions, indicating that the reduction in cerebral blood flow during heat stress was not due to changes in cerebral perfusion pressure. Recent research has also indicated that cerebral vascular conductance can change proportionally to changes in cardiac output, independent of blood pressure and Pa_{CO_2} (28,38). These findings suggest that cardiac output has the potential of changing cerebral blood flow, independent of changes in steady-state perfusion pressure. Although not measured in the present study, cardiac output can more than double during passive heat stress, which is necessary to support heat stress-induced increases in skin blood flow (34). We have observed increases in cardiac output between 2 and 4 l/min during passive heat stress, similar to that in the present study (i.e., ~1.1°C increase in internal temperature, unpublished observation). The directional differences in the change in cardiac output (i.e., increasing) relative to the change in cerebral blood flow (i.e., decreasing) with passive heating suggest that, although speculative, increases in cardiac output associated with heat stress may attenuate further reductions in cerebral blood flow had cardiac output not increased during heating. However, this conclusion must be made with the understanding that the distribution of cardiac output during heat stress (mostly to the skin) would be very different relative to the distribution of cardiac output when cardiac output was increased in normothermic subjects (28).

Passive heat stress causes pronounced elevations in sympathetic activity (32). Our laboratory and others have observed increases in muscle sympathetic nerve activity of ~90% and increases in skin sympathetic nerve activity of 300–600% during whole body heat stress (4,6–9,23). Reductions in splanchnic and renal blood flow also occur during passive heat stress (33,35), presumably through increases in sympathetic neural outflow (13,18). Less clear is whether

passive heating similarly increases cerebral sympathetic activity. If such an event occurs, this could lead to decreases in CBVC and subsequent reductions in cerebral perfusion, independent of direct effects of changes in P_{aCO_2} on the cerebral vasculature. Research using animal models has shown that increases in sympathetic activity can also alter the brain's autoregulatory curve by shifting it to the right (higher perfusion pressures) without changing resting cerebral blood flow (3,12,15,29). Thus, although speculative, it is conceivable that heat stress not only reduces cerebral perfusion, but causes such a shift in the cerebrovascular autoregulatory curve as is observed during hemorrhagic hypotension (11). These changes would further predispose the individual to orthostatic intolerance due to a reduction in the functional reserve to maintain cerebral blood flow during reductions in perfusion pressure, as our laboratory has previously demonstrated (40).

Limitations

In the present study, MCA V_{mean} was measured to reflect changes in cerebral blood flow. This assumption is only valid if the diameter of the insonated vessel remains constant. Measurements of MCA diameters in humans have shown that the diameters do not change during alterations in P_{ETCO_2} (14,36). Therefore, it is likely that alterations in MCA V_{mean} reflect changes in cerebral blood flow in the present study.

Recent research has shown that the relationship between cerebral blood flow and P_{ETCO_2} is curvilinear across a wide range of hypo- and hypercapnic levels (5,16). In the present study, linear regressions were used to assess the steady-state CBVC- P_{ETCO_2} relationship across the reported ranges of P_{ETCO_2} (~20 Torr below and ~9 Torr above normocapnic values), recognizing that changes in P_{ETCO_2} due to passive heat stress are well within this range. Consistent with the curvilinear nature of these responses (5,16), in the present study the slope of the CBVC- P_{ETCO_2} relationship was approximately threefold greater during the hypercapnic challenge relative to the hypocapnic challenge. It is for this reason that the slopes of the CBVC- P_{ETCO_2} relationships were separately analyzed between hypercapnic and hypocapnic trials. Furthermore, we were specifically interested in the hypocapnic response because of reductions in P_{ETCO_2} and P_{aCO_2} that occur during heat stress. Nevertheless, a nonlinear analysis of all of the data (i.e., baseline, hypocapnic, and hypercapnic exposures) via an exponential model, similar to that used by previous investigators (30), also showed an absence of a difference in cerebral CO_2 responsiveness between thermal conditions (normothermic: 0.019 ± 0.006 vs. heat stress: 0.021 ± 0.006 CBVC units/Torr, $P = 0.22$). Thus, based on the present findings, we are confident that, within the evaluated ranges of changes in P_{ETCO_2} , whole body heat stress did not affect cerebral vascular responsiveness to CO_2 . That said, we recognize the possibility that heat stress-induced changes in cerebral vascular responsiveness to CO_2 may occur had more pronounced hypercapnic and/or hypocapnic exposures been employed.

The mean decrease in P_{ETCO_2} in response to heat stress alone was 3 Torr ($P = 0.07$). However, these data were skewed by a subject who had a large decrease in P_{ETCO_2} (14 Torr) due to the heat stress that was well outside of the range of the decrease in P_{ETCO_2} of the other subjects (1–4 Torr). With the data from this subject excluded, a significant reduction in P_{ETCO_2} (1.6 ± 0.6 Torr; $P = 0.028$) was observed due to the heat stress, which is in line with data from our laboratory's prior study (40). According to work of Ringelstein et al. (31), a decrease in P_{ETCO_2} of 1.6 Torr "explains" a reduction in CBVC of ~4.5%. The average reduction in CBVC due to heat stress with this subject's data removed was almost double that predicted value (i.e., 8.4%; $P = 0.045$). Therefore, the predicted change in CBVC due to the decrease in P_{ETCO_2} associated with the heat stress was less than the actual change observed. This observation suggests that factor(s) other than just the decrease in P_{ETCO_2} contributes to the reduction in CBVC in response to passive heat stress.

In conclusion, despite a significant reduction in MCA V_{mean} and CBVC, relative to normothermia, the slope of the relationship between CBVC and P_{ETCO_2} during the hypocapnic and hypercapnic challenges was not affected by whole body passive heat stress. These results indicate that cerebrovascular CO_2 responsiveness, to the prescribed steady-state changes in P_{ETCO_2} and presumably PaCO_2 , is unchanged during passive heat stress.

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Fig. 1. Group mean ($\pm$ SD) cerebrovascular conductance responses at baseline (*middle* two points) and during hypocapnic and hypercapnic challenges under normothermic ($\bullet$) and heat stress ($\circ$) conditions.

Fig. 2.

Group mean ($\pm$ SD) absolute (A) and relative (B) changes in cerebrovascular conductance during hypocapnic and hypercapnic challenges under normothermic (NT; solid bars) and heat stress (HS; shaded bars) conditions. Regardless of how the data were expressed, there were no differences in the change in calculated cerebrovascular conductance between NT and HS conditions to these challenges. The increase and decrease, respectively, of endtidal CO₂ for the hypercapnic and hypocapnic challenges were not affected by the thermal condition of the subject (see text).

Table 1

Thermoregulatory, cardiovascular, respiratory, and cerebrovascular responses during normothermia and heat stress

	Normothermia	Heat Stress	<i>P</i>
Core temperature, °C	36.9±0.3	38.0±0.3	0.001
Mean skin temperature, °C	34.8±0.5	38.5±0.4	0.001
Heart rate, beats/min	56±9	95±15	0.001
Blood pressure, mmHg	91±6	89±6	0.363
Forearm CVC, AU/mmHg	0.65±0.68	2.32±0.86	0.003
Respiratory rate, breaths/min	14±4	17±5	0.063
End-tidal CO ₂ , Torr	42±4	39±3	0.073
MCA V_{mean} , cm/s	69±14	60±13	0.010
Cerebral vascular conductance, cm·s ⁻¹ ·mmHg ⁻¹	0.76±0.17	0.67±0.14	0.019

Values are means ± SD. CVC, cutaneous vascular conductance; AU, arbitrary units; MCA V_{mean} , middle cerebral artery blood velocity.