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Heat stress reduces cerebral blood velocity and markedly impairs orthostatic tolerance in humans

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Wilson, Thad E., Jian Cui, Rong Zhang, and Craig G. Crandall. Heat stress reduces cerebral blood velocity and markedly impairs orthostatic tolerance in humans. *Am J Physiol Regul Integr Comp Physiol* 291: R1443–R1448, 2006. First published June 8, 2006; doi:10.1152/ajpregu.00712.2005.—Orthostatic tolerance is reduced in the heat-stressed human. This study tested the following hypotheses: 1) whole body heat stress reduces cerebral blood velocity (CBV) and increases cerebral vascular resistance (CVR); and 2) reductions in CBV and increases in CVR in response to an orthostatic challenge will be greater while subjects are heat stressed. Fifteen subjects were instrumented for measurements of CBV (transcranial ultrasonography), mean arterial blood pressure (MAP), heart rate, and internal temperature. Whole body heating increased both internal temperature (36.4 ± 0.1 to $37.3 \pm 0.1^\circ\text{C}$) and heart rate (59 ± 3 to 90 ± 3 beats/min); $P < 0.001$. Whole body heating also reduced CBV (62 ± 3 to 53 ± 2 cm/s) primarily via an elevation in CVR (1.35 ± 0.06 to 1.63 ± 0.07 mmHg \cdot cm⁻¹ \cdot s); $P < 0.001$. A subset of subjects ($n = 8$) were exposed to lower-body negative pressure (LBNP 10, 20, 30, 40 mmHg) in both normothermic and heat-stressed conditions. During normothermia, LBNP of 30 mmHg (highest level of LBNP achieved by the majority of subjects in both thermal conditions) did not significantly alter CBV, CVR, or MAP. During whole body heating, this LBNP decreased MAP (81 ± 2 to 75 ± 3 mmHg), decreased CBV (50 ± 4 to 39 ± 1 cm/s), and increased CVR (1.67 ± 0.17 to 1.92 ± 0.12 mmHg \cdot cm⁻¹ \cdot s); $P < 0.05$. These data indicate that heat stress decreases CBV, and the reduction in CBV for a given orthostatic challenge is greater during heat stress. These outcomes reduce the reserve to buffer further decreases in cerebral perfusion before presyncope. Increases in CVR during whole body heating, coupled with even greater increases in CVR during orthostasis and heat stress, likely contribute to orthostatic intolerance.

hyperthermia; syncope; transcranial Doppler; cerebral vascular resistance

IN HUMANS, ORTHOSTATIC TOLERANCE is reduced during heat stress compared with normothermic conditions (1, 2, 19, 22, 37). In a recent study, 44% of participants could not complete a 10-min 60° head-up tilt after a mean increase in internal temperature of 0.8°C via whole body heating (42). Although mechanisms reducing 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 oxygenation (24, 26, 41).

The effects of whole body heating, and subsequent orthostasis, on cerebral vascular regulation remain unclear. Previous research suggests that both mild (8) and moderate (42) passive-

heat stresses decrease cerebral blood velocity (CBV) with little or no change in cerebral vascular resistance (CVR; 42). However, in the study in which CVR was calculated (42), there was a tendency for heat stress to increase cerebral vascular resistance, evidenced by a significant reduction in CBV coupled with the absence of a significant change in MAP. Thus the absence of an effect of whole body heating on cerebral vascular resistance in that study may be due to the relatively small number of subjects assessed resulting in a type II statistical error.

Accordingly, the first objective of this project was to test the hypothesis that whole body heat stress increases CVR, which contributes to the previously observed reduction in CBV (7, 42) in this thermal condition. Given that orthostatic intolerance is ultimately due to inadequate cerebral perfusion, it may be that the reduction in cerebral perfusion for a given orthostatic challenge is greater while subjects are heat stressed. Thus the second objective of this project was to test the hypothesis that during LBNP the decrease in CBV would be greater while subjects were heat stressed.

METHODS

Subjects. Fifteen subjects (7 men, 8 women) participated in this study; physical characteristics of male subjects were mean age of 34 ± 2 years, height of 178 ± 2 cm, and weight of 73 ± 5 kg; while female subjects had a mean age of 31 ± 2 years, height of 167 ± 2 cm, and weight of 60 ± 2 kg. Written informed consent was obtained from all participants before participating in this study. The protocol and informed consent were approved by the University of Texas Southwestern Medical Center and the Presbyterian Hospital of Dallas Human Institutional Review Boards.

Protocol 1. To determine the effect of heat stress on cerebral vascular variables, 15 subjects performed a total of 25 heat stresses. Eight subjects performed one heat stress, and to test the reproducibility of the responses, 7 subjects performed two heat stresses, and 3 of these 7 subjects each performed a third heat stress. During normothermia, thermoneutral water (35°C) was perfused through a high-density tube-lined suit (Carleton Technologies, Tampa Bay, FL). Whole body heating was performed until internal temperature increased ~ 0.6 – 1.0°C . This was accomplished by perfusing 46°C water through the tube-lined suit. Water temperature perfusing the suit was slightly reduced (to 44–45°C) for 10 to 15 min before data collection to decrease the rate of rise of internal temperature during the ensuing data collection period. Hemodynamic and thermal data were averaged during both normothermic and heat stress periods while the subjects rested quietly in the supine position.

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Protocol 2. To determine the effect of combined orthostatic and heat stresses on cerebral vascular variables, eight of the above participants (4 men, 4 women) were exposed to lower-body negative pressure (LBNP) while subjects were normothermic and at the end of the heat stress. Two-piece, water-perfused suits (upper and lower halves) were used for these subjects, thereby improving the seal of the LBNP chamber to the subject and reducing air leaking and associated skin cooling during LBNP. In both thermal conditions, after baseline measures, LBNP was applied for 3 min at 10, 20, 30, and 40 mmHg. LBNP was discontinued if signs or symptoms of syncope were observed (e.g., nausea, pallor, sudden decrease in heart rate and/or blood pressure, or a sustained decrease in systolic blood pressure <80 mmHg). A cumulative stress index was calculated by summing the product of duration and negative pressure at each gradation of LBNP tolerated by the subject (21).

Measurements. Heart rate was measured continuously from an electrocardiogram (SpaceLabs, Redmond, WA) interfaced to a cardiostomometer (CWE, Ardmore, PA). Arterial blood pressure was measured from the upper arm via electrospigmomanometry (Sun-Tech, Raleigh, NC) and at the finger via the Penaz method (Finapres Ohmeda, Englewood, CO). Mean arterial blood pressure (MAP) was calculated as 1/3 pulse pressure plus diastolic blood pressure. Trans-thoracic impedance [an index of central blood volume (4, 9)] was measured to determine whether a greater fluid shift occurred per level of LBNP between normothermia and heat stress in *protocol 2*. This measure was accomplished by passing a 50-kHz 400- μ A current between electrodes placed at the lateral neck at the approximate level of C7 and midaxillary line at the level of the xiphoid process (Biopac, Santa Barbara, CA).

CBV was measured from the middle cerebral artery via transcranial Doppler ultrasonography. A 2-MHz Doppler probe (DWL Elektronische Systeme, Sipplingen, 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 with a headband strap to prevent subtle movement of the Doppler probe. CVR was calculated by $\text{MAP}/\text{CBV}^{-1}$. End-tidal CO_2 (PET_{CO_2}) and respiratory rate were measured via nasal cannula (Criticare Systems, Waukesha, WI).

Forearm skin blood flow was measured via laser-Doppler flowmetry using an integrating flow probe (Perimed, North Rayalton, OH). Cutaneous vascular conductance was indexed by dividing laser-Doppler flux by MAP and expressed as a percentage of baseline, with baseline being set as 100% of the normothermic value. Forearm sweat rate was measured via capacitance hygrometry (Viasala, Woburn, MA). Internal temperature was obtained at 10-s intervals via an ingestible pill telemetry system (HTI Technologies, Palmetto, FL). Mean skin temperature was measured via the weighted average of six thermocouples attached to the skin (38).

Data analysis. Data were acquired at a minimum of 50 Hz throughout experimental procedures by a data acquisition system (Biopac, Santa Barbara, CA). In *protocol 1*, paired *t*-tests were used to compare thermal and hemodynamic responses between normothermic and heat-stressed conditions. Subjects who underwent repeated heat stress trials were analyzed for repeatability via intraclass correlation coefficient and coefficient of variation techniques. In *protocol 2*, the last minute of baseline and each LBNP stage were analyzed during both thermal conditions. It was expected that not all subjects would complete all LBNPs in the heat stress condition. To address this challenge, data were statistically analyzed from the LBNP that the majority of subjects were able to complete. Using this approach, we reported data that are more conservative given that subjects who became presyncopal at lower LBNPs would have exhibited even more pronounced responses relative to subjects who were able to complete all LBNPs. These data were analyzed via two-way repeated-measures ANOVA. If a significant main effect or interaction was identified, Student-Newman-Keuls post hoc analysis was performed. The α -level

for all statistical analyses was set at 0.05. All values are reported as means \pm SE.

RESULTS

Protocol 1. Whole body heating increased skin temperature (34.1 ± 0.2 to $38.3 \pm 0.2^\circ\text{C}$; $P < 0.001$), which led to increases in internal temperature (36.4 ± 0.1 to $37.3 \pm 0.1^\circ\text{C}$; $P < 0.001$). MAP was unchanged as a result of the heat stress (84 ± 1 to 84 ± 1 mmHg; $P > 0.50$), whereas heart rate was elevated (59 ± 3 to 90 ± 3 beats/min; $P < 0.001$). PET_{CO_2} was reduced (42 ± 1 to 40 ± 1 mmHg; $P < 0.001$), and respiratory rate was slightly elevated (16 ± 1 to 18 ± 1 breaths/min; $P < 0.001$), during whole body heating. The heat stress significantly reduced CBV and increased CVR (Fig. 1). When data were analyzed from subjects who performed repeated trials, the reduced CBV response during whole body heating was similar between trials ($P > 0.50$), had a low coefficient of variation of the method error (9%), and had a high intraclass correlation coefficient ($r = 0.87$). These data indicate that whole body heating of this magnitude provides both stable and reproducible reductions in CBV.

Protocol 2. All subjects were able to complete the LBNP protocol during normothermia. However, only one of eight was

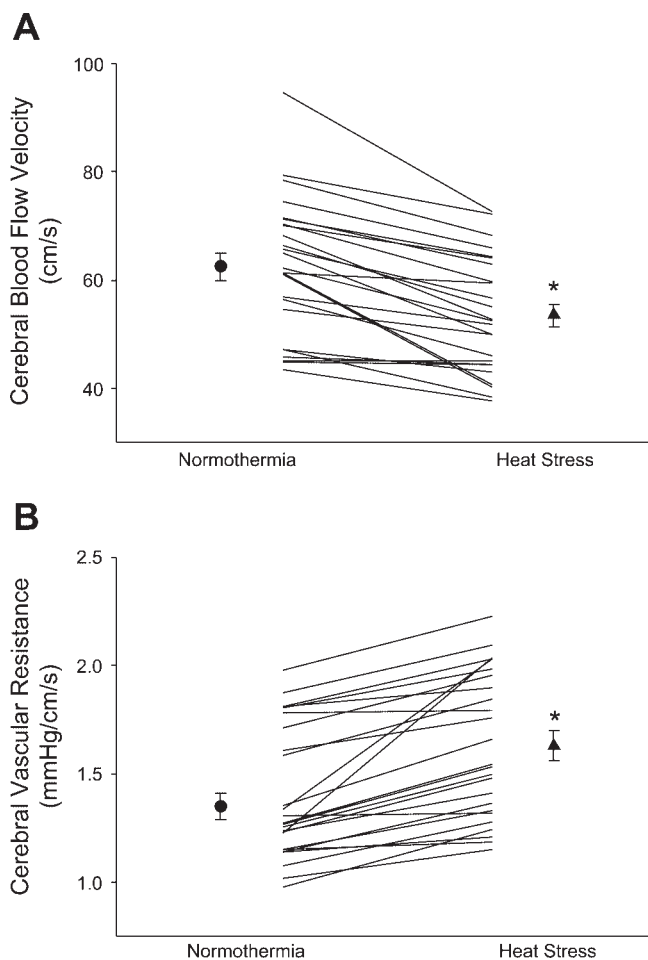


Fig. 1. Effects of whole body heating on cerebral blood velocity from the middle cerebral artery (A) and cerebral vascular resistance (B). The symbols with error bars denote mean responses, while lines denote individual responses. $*P < 0.001$.

able to complete the LBNP protocol during whole body heating without exhibiting presyncopal signs and/or symptoms. During combined LBNP and whole body heating, the number of subjects completing stages without presyncopal symptoms was as follows: 10 mmHg, 8 subjects; 20 mmHg, 8 subjects; 30 mmHg, 5 subjects; 40 mmHg, 1 subject. This resulted in the cumulative stress index significantly decreasing from 300 mmHg/min during normothermia to 188 ± 21 mmHg/min during whole body heating. Table 1 provides data for the five subjects (3 men, 2 women) who completed 30 mmHg LBNP without presyncopal symptoms in the heated condition. It is important to emphasize that if responses from all 8 subjects were included in Table 1, reported changes due to LBNP while heated would be even more pronounced. However, interpretation of such data would be challenging given the differing number of subjects at each LBNP during heat stress (e.g., 8 subjects at 10 and 20 mmHg but only 1 subject at 40 mmHg) relative to the number of subjects included in the analysis during normothermia (e.g., eight subjects for each LBNP). Before LBNP, there was a tendency for differences in baseline CBV, CVR, and PET_{CO_2} in these five subjects due to the heat stress, likely because of lower statistical power when compared with 15 subjects described above.

Heart rate significantly increased during LBNP; however, in normothermia the increase in heart rate occurred only at 40 mmHg LBNP, compared with significant increases in heart rate at 20 mmHg LBNP during whole body heating (Table 1). Similarly, MAP and PET_{CO_2} decreased at 40 mmHg LBNP during normothermia, while these variables significantly decreased at a lower LBNP during whole body heating (e.g., 20 mmHg and 30 mmHg, respectively; see Table 1). LBNP increased thoracic impedance (indicating a decrease in central blood volume), but the magnitude of this increase was unaffected by the thermal condition.

LBNP significantly decreased CBV during both normothermia and heat stress (Table 1). However, significant reductions in CBV occurred at an earlier LBNP during heat stress relative to normothermia (Fig. 2). During normothermia, LBNP did not alter CVR regardless of the level of negative pressure, while

LBNP during heat stress increased cerebral vascular resistance (Table 1). The combination of heat stress and LBNP resulted in greater increases in CVR compared with normothermia (Fig. 3). Together, these data clearly indicate that there were greater decreases in CBV and increases in CVR per gradation LBNP (i.e., 20 and 30 mmHg) during heat stress compared with normothermia.

DISCUSSION

The major findings of this study are that 1) whole body heating increases CVR leading to reductions in CBV, 2) combined heat and orthostatic stress causes further increases in CVR and accompanying greater reductions in CBV per gradation of LBNP relative to orthostatic stress in normothermia, and 3) whole body heating causes considerable decreases in orthostatic tolerance during LBNP. These results suggest that changes in the cerebral vasculature during heat stress likely contribute to reduced orthostatic tolerance.

During heat stress, CBV is reduced and CVR is elevated before orthostatic stress compared with normothermia. This observation suggests that heat stress reduces the reserve by which further reductions in CBV can occur before the onset of syncopal symptoms. The observed increase in CVR is in contrast to our previous findings in which we observed only a tendency for an increase in this variable during heat stress (42). Differences in these findings between studies are likely due to a lower subject number, and thus statistical power, in the prior study compared with the present study. Compounding these lower baseline (i.e., pre-LBNP) CBV values during heat stress are greater decreases in CBV per gradation of LBNP (see Fig. 3), together leading to greater reductions in orthostatic tolerance. The mechanism by which the same LBNP caused greater reductions in CBV during heat stress was likely due to a combination of greater reductions in cerebral perfusion pressure coupled with greater increases in CVR per gradation of LBNP relative to these responses during LBNP in normothermia (see Table 1).

Table 1. Effect of LBNP during normothermia and heat stress on cardiovascular and ventilatory parameters for the five subjects who completed 30 mmHg LBNP during whole body heating

Variable	Condition	Baseline	LBNP		
			10 mmHg	20 mmHg	30 mmHg
CBFV, cm/sec	Normothermia	55±5	55±5	54±5	55±6
	Heat stress	50±4	52±4	46±2*†‡	39±1*†‡
CVR, mmHg · cm ⁻¹ · s	Normothermia	1.55±0.16	1.52±0.15	1.50±0.13	1.50±0.18
	Heat stress	1.67±0.17	1.62±0.14	1.76±0.10*†‡	1.92±0.12*†‡
HR, beats/min	Normothermia	61±8	61±8	65±9	66±10
	Heat stress	91±8‡	96±9‡	107±11*†‡	117±12*†‡
MAP, mmHg	Normothermia	83±2	80±3	79±2	79±1
	Heat stress	81±3	81±2	80±3	75±3*
Zo, %change	Normothermia	—	0.9±0.5	1.9±0.9*	2.3±1.1*
	Heat stress	—	0.8±0.4	1.7±0.6*	2.4±0.8*
B _f , breaths/min	Normothermia	15±1	15±1	12±1*	12±1*
	Heat stress	18±2‡	16±1*†‡	14±1*†	13±2*
PET_{CO_2} , Torr	Normothermia	41±1	41±1	40±1	41±2
	Heat stress	39±1	39±2	37±2*†‡	35±2*†‡

Values are listed as means ± SE. HR, heart rate; MAP, mean arterial blood pressure; Zo, thoracic impedance; B_f, breathing frequency; PET_{CO_2} , end-tidal carbon dioxide; LBNP, lower body negative pressure. *Significant difference ($P < 0.05$) from baseline. †Significant difference ($P < 0.05$) from the preceding time point. ‡Significant difference ($P < 0.05$) between normothermia and heat stress.

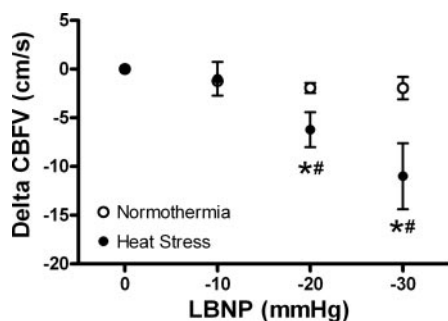


Fig. 2. Effects of normothermia and heat stress on the change in cerebral blood velocity (CBFV) during lower body negative pressure (LBNP). Baseline represents 0 mmHg LBNP. *Significant difference from baseline. #Significant difference from the previous LBNP. $n = 5$ given that only five subjects tolerated 30 mmHg LBNP while heat stressed. The three subjects who did not tolerate 30 mmHg LBNP were excluded from this figure to appropriately compare the paired and interactive effects of whole body heating and LBNP.

It is widely recognized that autoregulation is important in controlling CBF during perturbations that change perfusion pressure (31). It is interesting to note that increased CVR during LBNP, while subjects were heat stressed, is in contrast to what would be expected for cerebrovascular autoregulation. That is, given that perfusion pressure was reduced by LBNP in heat-stressed subjects, cerebrovascular autoregulation would dictate reductions in CVR to maintain flow, which is in contrast to the observed increases in this variable. This observation suggests that heat stress impairs cerebrovascular autoregulatory capabilities. In contrast to this hypothesis, Doering et al. (7) reported an increase in the autoregulation index after a hypotensive challenge during heat stress compared with responses during both normothermia and cold stress. Two important methodological differences exist between the present study and that of Doering et al. (7). First, Doering et al. (7) used a single brief hypotensive challenge, vs. a sustained and graded orthostatic stress used in this study. Second, the current study used a greater thermal stress, which resulted in pronounced increases in internal temperature, mean skin temperature, heart rate, cutaneous vascular conductance, and sweat rate. In the cited study (7), cerebral autoregulation was assessed after internal temperature was elevated only $\sim 0.4^{\circ}\text{C}$ and there were no reports of mean skin temperature, heart rate, or thermoregulatory effector responses (e.g., skin blood flow and sweat rate). Therefore, it is difficult to directly compare these studies. Nevertheless, it is possible that slight increases in internal temperature may not affect or may improve cerebrovascular autoregulation, while a greater heat stress impairs this response and contributes to heat-related syncope.

Heat stress increases sympathetic nerve activity to kidneys, muscle, and skin (34). Orthostatic stress is also a potent activator of the sympathetic nervous system (20). Sympathetic stimulation during a hypotensive episode has previously been identified to cause vasoconstriction of cerebral blood vessels (10, 23). Thus a component of the increase in CVR during heat stress alone, and combined with LBNP, could be due to sympathetically mediated cerebral vasoconstriction. Compounding identified changes in CBV and CVR during heat stress, is that increases in sympathetic activity may cause a rightward shift of the cerebrovascular autoregulation curve (31). A rightward shift would move the operating point to a

location closer to the steep descending portion of the curve, resulting in greater reductions in cerebral blood flow per change in perfusion pressure. The possibility that these sympathetically mediated events alter cerebrovascular control in heat stress subjects warrants further investigation.

MAP was not significantly different between normothermia and heat stress trials and was maintained during low levels of LBNP in both conditions. Recent evidence suggests that despite similar MAP, central blood volume can affect CBV during orthostasis (40). To account for the potential of greater decreases in central blood volume during whole body heating, we measured thoracic impedance as an index of central blood volume (4, 9). There were no significant differences in the change in thoracic impedance during LBNP between normothermia and heat stress. A second cardiovascular parameter that can also alter CBV is cardiac output (30). Although we did not measure cardiac output in this study, previous results from our laboratory have identified increases in cardiac output during heat stress and similar decreases in cardiac output during head-up tilt between normothermia and heat stress (42). Thus it is doubtful that differences in central blood volume or cardiac output contributed appreciably to differences in CBV responses observed in this study.

PET_{CO_2} decreased during whole body heating and continued to decrease during subsequent LBNP. These decreases in PET_{CO_2} paralleled increases in CVR and likely contribute to the reduction in cerebral perfusion, given the observed strong relationship between decreases in PET_{CO_2} and decreases in CBV (16, 36). It has been proposed that in resting humans every 1 Torr change in Pa_{CO_2} changes cerebral blood flow $\sim 3\%$ in the same direction (33). Using this calculation with the present data, we found that a significant component, but not all, of the elevation in CVR can be accounted for by the decrease in Pa_{CO_2} . Nybo and Nielsen (29) determined that during an exercise-heat stress, the decrease in PET_{CO_2} accounted for approximately one-half of the reduction in CBV, but the other half was likely due to other mechanisms. Followup studies have identified increases in CO_2 reactivity (32) and strong relations between Pa_{CO_2} and global cerebral blood flow (28) during exercise in the heat. However, responses during an exercise-heat stress paradigm may be very different relative to passive heating

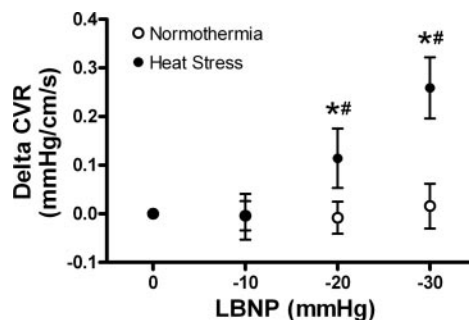


Fig. 3. Effects of normothermia and heat stress on the change of cerebral vascular resistance (CVR) during LBNP. Baseline represents 0 mmHg LBNP. *Significant difference from baseline. #Significant difference from the previous LBNP. $n = 5$ given that only five subjects tolerated 30 mmHg LBNP. The three subjects who did not tolerate 30 mmHg LBNP were excluded from this figure to appropriately compare the paired and interactive effects of whole body heating and LBNP.

because during exercise, variables such as ventilation rate, cardiac output (heart rate and stroke volume), and systolic blood pressure are elevated to a greater extent relative to during passive heating (6, 17, 29, 39). Given these data, it is difficult to directly compare exercise-heat and passive-heat stress conditions with respect to the impact of changes in P_{aCO_2} on the control of CVR and cerebral perfusion.

Comparative observations also have identified decreases in brain and spinal cord blood flow (assessed via microspheres) during heat stress in panting, but not nonpanting, species (12–14). This indicates that high respiratory frequencies that result in decreases in P_{aCO_2} can be influential in the decrease in brain blood flow during heating. Our data identify significant increases in respiration frequency and decreases in P_{ETCO_2} during heat stress. However, some caution must be made given the small increase in respiratory rate observed in the current subjects relative to panting species, such as the canine, which can respire over 300 times per minute (15). Nevertheless, it is clear that P_{ETCO_2} and P_{aCO_2} play an important, but not solitary causatory role, in orthostatic intolerance in humans (18, 35) and that increasing inspiratory CO_2 can improve orthostatic tolerance in a number of conditions (3, 27).

Limitations. Whole body heating reduces central venous pressure 3–4 mmHg (5, 25). In the present experiment, central venous pressure was not measured, although changes in this variable are expected to follow those previously observed. Given that perfusion pressure is the pressure gradient between arterial and venous circulatory regions, a reduction in venous pressure during heat stress results in a slight increase in perfusion pressure despite a lack of change in arterial pressure. However, if actual perfusion pressure (i.e., arterial-venous pressure) had been used to calculate CVR, then even greater increases in vascular resistance would have been identified during heat stress. Thus the limitation of not accounting for venous pressures in the calculation of vascular resistance does not affect the interpretation of the heat stress results.

In the current study, middle cerebral artery velocity was used as an index of cerebral blood flow. We recognize that velocity is representative of flow only if the diameter of the vessel remains unchanged. In support of this concept, investigators directly measured the middle cerebral artery diameter in humans and found that the diameter of this large vessel was either not changed or was only minimally affected by changes in MAP and P_{ETCO_2} (11, 36). Thus it is likely that changes in CBV reported in the present investigation reflect changes in cerebral blood flow.

In summary, heat stress dramatically reduces orthostatic tolerance in humans. Whole body heating reduces CBV and increases CVR during nonorthostatic and orthostatic conditions. Additionally, heat stress resulted in greater decreases in CBV and increases in CVR during LBNP compared with normothermia. These cerebral vascular changes occurred in combination with decreases in P_{ETCO_2} and presumably increases in cerebral sympathetic activity, indicating potential mechanisms for the observed cerebral vasoconstriction under these conditions. Collectively, compromised cerebral perfusion contributes to the reduction in orthostatic tolerance during heat stress.

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