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Cutaneous Vascular Responses to Hypercapnia During Whole-Body Heating

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Abstract

Introduction—Hypercapnia may be encountered in lung disease as well as during situations involving rebreathing of previously expired air (e.g., occupational diving). Inhibitory effects of elevated arterial carbon dioxide partial pressure on the central nervous system may result in impaired thermoregulation. This study tested the hypothesis that in heat-stressed subjects, cutaneous vascular responsiveness [expressed as cutaneous vascular conductance (CVC)] would be reduced during hypercapnic exposure.

Methods—Four men and three women (mean $\pm$ SD; age: 35 ± 7 yr) rested supine while wearing a tube-lined suit perfused with 34°C water (normothermia). Following normothermic data collection, 50°C water was perfused through the suit to increase internal temperature approximately 1°C (whole-body heating). In both thermal conditions, a normoxic-hypercapnic (5% CO_2 , 21% O_2 , balance N_2) gas mixture was inspired while forearm skin blood flux (laser-Doppler flow-metry) was measured continuously and was used for calculation of CVC (skin blood flux/mean arterial pressure).

Results—End-tidal CO_2 increased similarly throughout hypercapnic exposure during both normothermic and whole-body heating conditions (7.9 ± 2.4 and 8.3 ± 1.9 mmHg, respectively). However, CVC was not different between normocapnia and hypercapnia under either thermal condition (normothermia: 0.42 ± 0.24 vs. 0.39 ± 0.21 flux units/mmHg for normocapnia and hypercapnia, respectively; heat stress: 1.89 ± 0.67 vs. 1.92 ± 0.63 flux units/mmHg for normocapnia and hypercapnia, respectively).

Discussion—Based on these findings, mild hypercapnia is unlikely to impair heat dissipation by reducing cutaneous vasodilation.

Keywords

thermoregulation; heat stress; skin blood flow; carbon dioxide

Individuals with lung disease may experience elevated arterial carbon dioxide tension (P_{aCO_2}) at rest and after exercise (6), the latter of which increases body temperature due to heat generation from muscle contraction. In addition to those with lung disease, recreational and occupational divers can experience hypercapnia (17). Some commercial diving operations involve exposure to water temperatures as high as 40°C (7,8,18), so hyperthermia can result.

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Hypercapnia may have the potential to impair heat dissipation by inhibiting central nervous system control of skin blood flow. Since each of the aforementioned populations may experience elevated body temperature during exertion, it is important to understand the effects of hypercapnia on heat dissipation mechanisms.

Mechanistic studies investigating effects of hypercapnia on hypothalamic neurons, purported to influence thermoregulation, have shown mixed results. In one study, exposure to inhaled carbon dioxide (CO₂) increased the firing rate of warm-sensitive neurons in anesthetized rats (15), while in two other studies in which rat preoptic brain slice preparations were exposed to high CO₂, the firing rate of preoptic neurons decreased (9,20). While mechanistic studies are useful in elucidating whether hypercapnia can modulate thermosensitive neuronal activity, it is also important to determine whether hypercapnia within a physiological range alters thermoregulatory effector responses in humans. However, human studies that have investigated the effects of hypercapnia on forearm and skin blood flows of normothermic subjects have also shown mixed results. Investigators who observed increased forearm blood flow after CO₂ inhalation attribute this response to a direct vasodilatory effect of CO₂ on local tissues that overrides centrally mediated vasoconstriction associated with CO₂ exposure (1). Conversely, Richardson et al. (13) showed that forearm blood flow increases during inhalation of CO₂, but only if sympathetic vasoconstriction is blocked, thereby indicating local dilatory effects of CO₂ are overridden by centrally mediated vasoconstriction associated with CO₂ exposure. Finally, data from Simmons et al. (14) suggest that vasodilation associated with hypercapnia is related either to a local effect of CO₂ in blunting the transduction of vasoconstriction or to vasoconstrictor withdrawal since they observed no evidence of vasodilation associated with hypercapnia when sympathetically mediated vasoconstriction was blocked. Taken together, the effects of elevated P_{aCO₂} cannot be clearly interpolated from these prior studies, so the effect of hypercapnia on cutaneous vasodilation associated with thermoregulation remains unclear. More importantly, no study has investigated the effect of hypercapnia on skin blood flow during heat stress, when appropriate cutaneous vasodilation is critical for heat dissipation, so it is uncertain whether hypercapnia affects skin blood flow under hot conditions.

The purpose of the present investigation was to determine if normoxic hypercapnia differentially affects cutaneous vascular conductance (CVC) under normothermic and hyperthermic conditions. Based on the prior work of Simmons et al. (14), we hypothesized that CVC would be unchanged or slightly elevated during hypercapnic exposure while subjects are normothermic. Conversely, during whole-body heating, we hypothesized that hypercapnic exposure would decrease CVC because of reduced activity of preoptic hypothalamic neurons responsible for the elevated skin blood flow thermoregulatory effector response associated with an increase in core body temperature (20).

METHODS

Research Design

A repeated measures research design was used in which each subject was tested under the applied conditions. Subjects performed one normocapnic and two hypercapnic breathing trials while normothermic, and an additional set of normo/hypercapnic trials while heat-stressed. Normocapnic and hypercapnic breathing trials within each thermal condition were performed sequentially in order to minimize the duration of the study and the time subjects were heat stressed. Justification for this approach was the uncertainty of the necessary duration between trials had the hypercapnic trials been administered prior to the normocapnic trials. Hypercapnic trials within each temperature condition were separated by approximately 20 min and trials between temperature conditions were separated by approximately 60–90 min. All testing occurred in a temperate laboratory environment maintained at $26 \pm 1^\circ\text{C}$.

Subjects

Four men and three women participated in the study. The phase of the menstrual cycle was not controlled. The mean ($\pm$ SD) age, height, and body mass of the subjects were 35 ± 7 yr, 173.8 ± 10.0 cm, and 77.8 ± 15.3 kg, respectively. Participants were healthy and without known cardiovascular or metabolic diseases. Study approval was given by the institutional review boards at the University of Texas Southwestern Medical Center and at Presbyterian Hospital of Dallas, and subjects provided written informed consent prior to enrolling.

Protocol and Instrumentation

Subjects arrived at least 2 h postprandial, having refrained from exercise or consumption of alcohol during the previous 24 h and caffeine during the previous 12 h. Upon arrival, subjects swallowed an ingestible temperature-sensing pill (HQ Inc., Palmetto, FL) that has been validated previously (11). Electrocardiogram (ECG) electrodes were placed on the chest and thermocouples (Omega Engineering, Inc., Stamford, CT) were taped to the lateral calf, lateral thigh, lower back, lower abdomen, upper back, and chest for measurement of mean skin temperature ($\bar{T}_{sk}$) via the weighted average of the six sites (16). Subjects then put on a tube-lined water perfusion suit (Med-Eng, Ottawa, Canada) over shorts (and over a sports bra for the women). The suit covered the entire body except the feet, hands, face, head, and one forearm. Changing the temperature of the water perfusing the suit permitted control of skin and core temperatures.

Once clothed in the suit, subjects rested supine while being further instrumented. An integrating laser-Doppler flow probe (MoorLAB Laser-Doppler Perfusion Monitor, Moor Instruments, Wilmington, DE) was placed on the posterior side of the forearm not covered by the water-perfused suit to provide an index of skin blood flow. Additionally, a cuff for automated intermittent blood pressure measurement by auscultation of the brachial artery via electrophygmomanometry (SunTech, Raleigh, NC), was placed on the arm contralateral to the laser-Doppler flow probe. Mean arterial blood pressure (MAP) was calculated as:

$$\text{MAP} = 0.33(\text{SBP}) + 0.66(\text{DBP}),$$

where SBP = systolic blood pressure and DBP = diastolic blood pressure. Cutaneous vascular responses were indexed as CVC (calculated as the ratio of laser-Doppler flux to mean arterial blood pressure). In addition to absolute CVC, for both thermal conditions CVC during hypercapnia was normalized as a percent of CVC during normocapnia.

Once instrumented (~30 min after arrival), subjects rested supine for approximately 30 min under normothermic conditions (34°C perfused through the suit) while baseline data were collected. During the last 5 min of rest, subjects wore a nose clip and breathed through a mouthpiece for normocapnic baseline measurements. Then, the inspiratory side of the mouthpiece was switched to a bag containing a normoxic hypercapnic gas mixture (21% O_2 , 5% CO_2 , balance N_2). Subjects inhaled air from this bag for 4–5 min, followed by a 20-min recovery period, after which the hypercapnic challenge was repeated.

After the second hypercapnic exposure, subjects were heated by perfusing 50°C water through the suit for a period sufficient to increase core temperature about 1°C (typically 45–90 min). Once the target core temperature had been attained, the temperature of the water perfusing the suit was reduced to lessen further increases in core temperature during the subsequent data collection periods. Then, 5 min of normocapnic baseline measurements leading immediately to two trials of normoxic hypercapnic exposure, separated by 20 min, were repeated as before.

During normocapnia and hypercapnia, the peak end-tidal partial pressure of CO₂ (P_{ETCO_2}) was continuously monitored using a capnograph (VitalCap Capnograph Monitor, Oridion, Needham, MA) from expired air sampled through a line attached to the mouthpiece. Minute ventilation ($\dot{V}_E$) was continuously measured using a metabolic cart (PARVO Medics TrueOne 2400 Metabolic Measurement System, Sandy, UT). Heart rate (HR) was measured via the ECG (HP Patient Monitor, Agilent, Santa Clara, CA) interfaced with a cardiometer (Model CT-1000, CWE, Inc., Ardmore, PA). Blood oxygen saturation was measured via pulse oximetry (MicrO₂, Siemens Medical Electronics, Inc., Danvers, MA) of a finger.

Statistical Analyses

Data are presented as mean $\pm$ SD. All data, except $\dot{V}_E$, were sampled at 50 Hz and recorded using a data acquisition system (Biopac System, Santa Barbara, CA). The final 60 s of data during baseline and the final 30 s of data during hypercapnia were averaged and used in the data analysis. Data from duplicate trials within each thermal condition were averaged. Data were analyzed using SPSS v. 15.0 for Windows (SPSS, Inc., Chicago, IL). CVC responses between normocapnia and hypercapnia within each temperature condition were analyzed using paired samples *t*-tests. Two-way [thermal condition $\times$ inspired air condition (hypercapnia vs. normocapnia)] repeated measures analysis of variance (ANOVA) was used to test the significance of mean differences for other cardiovascular and respiratory variables. The Greenhouse-Geisser adjustment to degrees of freedom was used for all ANOVA tests, and when appropriate, paired samples *t*-tests (using the Bonferroni α adjustment to control family-wise error rate) were used to test for paired differences between thermal and inspired air conditions. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Whole-body heating increased core temperature (T_c) approximately 1°C ($P < 0.001$), while T_{sk} increased approximately 4°C ($P < 0.001$; Table I). HR increased 43 ± 14 bpm during heat stress and was also higher during hypercapnia in the normothermic condition ($P = 0.002$). Despite a significant increase in HR in the hypercapnic challenge during normothermia, there was no effect of hypercapnia on MAP regardless of thermal condition.

P_{ETCO_2} and $\dot{V}_E$ increased during hypercapnia under both thermal conditions (main effect of inspired air condition; $P < 0.001$ and $P < 0.002$ for P_{ETCO_2} and $\dot{V}_E$, respectively), but these increases were not different between thermal conditions (no thermal condition $\times$ inspired air condition interaction; Table I). During whole-body heating, however, $\dot{V}_E$ increased by ~ 2 L $\cdot$ min⁻¹ compared to normothermia (main effect of thermal condition; $P = 0.007$), while blood O₂ saturation was slightly but significantly reduced by 1–2% (main effect of thermal condition; $P = 0.027$, Table I). Despite this main effect, O₂ saturation was not different between normocapnia and hypercapnia exposures regardless of thermal condition.

CVC increased approximately 4.5-fold during whole-body heating (0.42 ± 0.24 to 1.89 ± 0.67 flux units/mmHg, $P = 0.001$). Absolute CVC was not affected by the hypercapnic challenge regardless of the thermal condition (normothermia: 0.42 ± 0.24 flux units/mmHg vs. 0.39 ± 0.21 flux units/mmHg for normocapnia and hypercapnia, respectively; $P = 0.198$; heat stress: 1.89 ± 0.67 flux units/mmHg vs. 1.92 ± 0.63 flux units/mmHg for normocapnia and hypercapnia, respectively; $P = 0.32$). Likewise, relative CVC, expressed as the ratio of CVC during hypercapnia to CVC during normocapnia and multiplied by 100, was similar ($P = 0.09$) for normothermia ($95.2 \pm 12.6\%$) and heat stress ($103.2 \pm 6.5\%$) conditions.

DISCUSSION

This study tested the hypothesis that a physiologically relevant hypercapnic challenge, via breathing 5% CO₂ (normoxic hypercapnia), would decrease CVC in passively heat-stressed subjects. Contrary to that hypothesis, CVC was not affected during the hypercapnic challenge while subjects were heat-stressed. Furthermore, the inspired hypercapnic challenge also did not alter CVC when subjects were normothermic.

The finding that CVC was unaffected by hypercapnia during normothermia is in contrast to a recent study by Simmons et al. (14). With a comparable increase in P_{ETCO₂} (~9 mmHg), they found that CVC increased approximately 10% from baseline. They concluded that cutaneous vasodilation from hypercapnia most likely stems from either withdrawal of vasoconstrictor tone (i.e., reduced sympathetic adrenergic impulses to skin) or impaired transduction of vasoconstriction (i.e., inhibited release of norepinephrine from sympathetic nerve endings and/or inhibited function of α -adrenergic receptors). The basis of those possible mechanisms originated from their finding of an absence of cutaneous vasodilation during hypercapnia when cutaneous sympathetic adrenergic activity was blocked via bretylium tosylate, coupled with findings from Gregor and Jänig (5) in cats showing decreased cutaneous sympathetic nerve activity concomitant with hypercapnia. Simmons et al. (14) further concluded that the reason the magnitude of cutaneous vasodilation attributable to hypercapnia was so small (i.e., ~10%) was likely because of a low level of basal sympathetic vasoconstrictor tone stemming from whole-body skin temperature being clamped at approximately 33°C. It is, perhaps, this same reasoning why in the present study there was an absence of an increase in CVC during hypercapnic exposure while subjects were normothermic since mean skin temperature was close to 35°C (Table I).

The present findings and those of Simmons et al. (14) also differ from those of Blair et al. (1), who reported decreases in forearm blood flow (comprised of muscle and skin) upon exposure to a comparable level of CO₂, while a related study showed no change in forearm blood flow with hypercapnia (13), similar to findings in the current study. Finally, the present findings are in agreement with a study on cats (19), in which no change in cutaneous blood flow occurred with hypercapnia. Inconsistencies in findings between studies of normothermic subjects/animals to hypercapnic exposure may originate from differences in the hypercapnic protocols (e.g., the concentration of CO₂ utilized), length of exposure, vasoconstrictor tone prior to the hypercapnic exposure, and differences inherent in comparing forearm blood flow relative to skin blood flow.

The reason for an absence of a CVC response to the hypercapnic challenge while subjects were hyperthermic is uncertain, although a few possibilities exist. One explanation hinges on the recent findings of Wright and Boulant (20). They found that hypercapnia per se does not affect the activity of hypothalamic warm-sensitive neurons, but rather acidosis that accompanies hypercapnia inhibits the activity of these neurons. They hypothesize that these warm-sensitive neurons initiate heat-dissipating responses (e.g., cutaneous vasodilation), such that acidosis that accompanies hypercapnia may ultimately contribute to heat illness by interfering with heat loss secondary to inhibition of warm-sensitive hypothalamic neurons. It is possible the hypercapnic stimulus in the present study was not sufficient to cause severe enough acidosis of the environment surrounding the warm-sensitive hypothalamic neurons. However, a previous study using a comparable stimulus (inhalation of 5–7% CO₂ for 5–10 min) demonstrated a significant increase in P_{aCO₂} of ~12 mmHg and significant acidosis (decrease in pH from 7.39 to 7.31) (13). This change in pH is comparable to that observed in rat preoptic thermosensitive neurons that showed decreased firing rate during exposure to high CO₂ (9). Although we did not measure arterial pH, based on the aforementioned research findings (9, 13), we speculate that arterial pH levels of subjects in the present investigation were lower

during hypercapnia, but whether this resulted in acidosis of the hypothalamic milieu remains uncertain. If acidosis associated with the hypercapnic challenge was insufficient to reduce the firing rate of the warm-sensitive preoptic anterior hypothalamic neurons, then reductions in CVC to the hypercapnic challenge would not be expected. Alternatively, regardless of the effect of hypercapnia or acidosis on the firing rate of warm-sensitive preoptic anterior hypothalamic neurons, these neurons may not be responsible for elevating skin blood flow in response to increased body temperature.

Limitations

A recognized limitation of the study is the inability to determine the effect of the hypercapnic stimulus on local CO₂ tension and acidosis of the hypothalamic environment. Additionally, we could not measure changes in firing rates of warm-sensitive neurons to the hypercapnic challenge or know what thermoregulatory responses, if any, these neurons effect. An additional limitation is that blood pH was not measured; however, even if it was measured it would not be clear whether changes in blood pH associated with the hypercapnic challenge would be representative of pH of the hypothalamic milieu.

Perspectives

Regardless of the presence or lack of change in CO₂ tension and acidosis of the hypothalamic milieu, an increase of ~8 mmHg in P_{ETCO₂} to the hypercapnic stimulus is within the physiological range encountered during rest and exercise conditions by someone with respiratory disease (2,10,12) or during diving operations (3,4). Therefore, our findings are directly applicable to situations involving the aforementioned populations/conditions, during which hyperthermia may be coupled with the exposed levels of hypercapnia. Under both the normothermic and heat stress conditions, CVC was unaffected by breathing a normoxic, 5% CO₂ gas mixture. Therefore, mild hypercapnic states, such as those encountered in the aforementioned conditions, are unlikely to impair heat dissipation by means of reducing cutaneous vasodilation.

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TABLE I

Responses during normothermia and whole-body heating while breathing room air or a normoxic hypercapnic gas mixture (5% CO₂, 21% O₂, balance N₂) (mean $\pm$ SD).

Variable	Normothermia		Whole-Body Heating		Statistical Main Effects from 2-way ANOVA
	Normocapnia	Hypercapnia	Normocapnia	Hypercapnia	
$\dot{V}_E$ (STPD, L $\cdot$ min ⁻¹)	5.8 $\pm$ 1.1	10.3 $\pm$ 2.4	7.7 $\pm$ 1.8	12.5 $\pm$ 1.7	*†
P _{ET} CO ₂ (mmHg)	41.7 $\pm$ 4.1	49.6 $\pm$ 3.5	39.4 $\pm$ 3.6	47.8 $\pm$ 3.0	†
Blood O ₂ saturation (%)	98.6 $\pm$ 1.4	99.1 $\pm$ 0.7	96.4 $\pm$ 1.7	97.1 $\pm$ 1.1	*
MAP (mmHg)	92.2 $\pm$ 6.3	98.0 $\pm$ 9.3	90.6 $\pm$ 6.7	93.3 $\pm$ 8.8	Significant interaction from 2-way ANOVA
HR (bpm)	54 $\pm$ 9	62 $\pm$ 10 [‡]	97 $\pm$ 17 [§]	96 $\pm$ 15 [§]	
T _c (°C)	36.9 $\pm$ 0.3	36.9 $\pm$ 0.3	38.0 $\pm$ 0.4	38.0 $\pm$ 0.3	*
T _{sk} (°C)	34.6 $\pm$ 0.4	34.6 $\pm$ 0.4	38.4 $\pm$ 0.4	38.4 $\pm$ 0.4	*

$\dot{V}_E$, minute ventilation; P_{ET}CO₂, peak end-tidal partial pressure of CO₂; MAP, mean arterial pressure; HR, heart rate; T_c, core temperature; T_{sk}, mean skin temperature.

* $P < 0.05$ whole-body heating vs. normothermia across both breathing conditions;

† $P < 0.05$ normocapnia vs. hypercapnia across both temperature conditions;

‡ $P < 0.05$ vs. normocapnia within the same thermal condition;

§ $P < 0.05$ vs. the value during the same breathing condition in normothermia.