End-tidal carbon dioxide tension reflects arterial carbon dioxide tension in the heat-stressed human with and without simulated hemorrhage

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Brothers RM, Ganio MS, Hubing KA, Hastings JL, Crandall CG. End-tidal carbon dioxide tension reflects arterial carbon dioxide tension in the heat-stressed human with and without simulated hemorrhage. Am J Physiol Regul Integr Comp Physiol 300: R978–R983, 2011. First published February 9, 2011; doi:10.1152/ajpregu.00784.2010.—End-tidal carbon dioxide tension (PETCO2) is reduced during an orthostatic challenge, during heat stress, and during a combination of these two conditions. The importance of these changes is dependent on PETCO2 being an accurate surrogate for arterial carbon dioxide tension (PaCO2), the latter being the physiologically relevant variable. This study tested the hypothesis that PETCO2 provides an accurate assessment of PaCO2 during the aforementioned conditions. Comparisons between these measures were made: 1) after two levels of heat stress (N = 11); 2) during combined heat stress and simulated hemorrhage [via lower-body negative pressure (LBNP), N = 8]; and 3) during an end-tidal clamping protocol to attenuate heat-stress-induced reductions in PETCO2 (N = 7). PETCO2 and PaCO2 decreased during heat stress (P < 0.001); however, there was no group difference between PaCO2 and PETCO2 (P = 0.36) nor was there a significant interaction between thermal condition and measurement technique (P = 0.06). To verify that this nonsignificant trend for the interaction was not due to a type II error, PETCO2 and PaCO2 at three distinct thermal conditions were also compared using paired t-tests, revealing no difference between PaCO2 and PETCO2 while normothermic (P = 0.14) and following a 1.0 ± 0.2°C (P = 0.21) and 1.4 ± 0.2°C (P = 0.28) increase in internal temperature. During LBNP while heat stressed, measures of PETCO2 and PaCO2 were similar (P = 0.61). Likewise, during the end-tidal carbon dioxide clamping protocol, the increases in PETCO2 (7.5 ± 2.8 mmHg) and PaCO2 (6.6 ± 3.4 mmHg) were similar (P = 0.31). These data indicate that mean PETCO2 reflects mean PaCO2 during the evaluated conditions.

heat stress; orthostatic challenge; brain blood flow; carbon dioxide

ARTERIAL CARBON DIOXIDE TENSION (PaCO2) is a primary regulator of cerebral perfusion, with hypercapnia and hypocapnia inducing increases and decreases in cerebral blood perfusion, respectively (7, 23). Studies using end-tidal carbon dioxide tension (PETCO2) to estimate PaCO2 during passive heat stress (i.e., increase in internal temperature ~1.2–1.5°C) suggest that heat stress reduces PaCO2 ~4–8 mmHg (3, 5, 15, 26). A potential limitation to these studies is that the assumption is made that PETCO2 is an accurate surrogate for PaCO2, the latter being the physiologically relevant variable. In normothermic individuals, PETCO2 provides an accurate assessment of PaCO2 in supine, resting conditions (8, 9, 22). Upon assumption of the upright posture, however, there is a decrease in cardiac output that is accompanied by a ventilation/perfusion mismatch leading to much greater reductions in PETCO2 relative to PaCO2 (8, 9, 22). Thus, in this condition, there is a discrepancy between the values obtained from two measures of carbon dioxide tension such that reductions in PETCO2 overestimate reductions in PaCO2 (8, 9, 22). This issue has recently been minimized in normothermic individuals through the identification of a correction factor that can be used to predict PaCO2 from measures of PETCO2 (8). To our knowledge, however, there is no information regarding the relationship of PETCO2 to PaCO2 in individuals with elevated internal temperatures. This information is important because heat stress-induced reductions in PaCO2 likely contribute to reductions in cerebral blood flow (3, 5, 15, 26) and ultimately reduced orthostatic tolerance in this thermal condition (4, 12, 25). Because PETCO2 is commonly used as an index of PaCO2 in heat-stressed individuals (3, 5, 15, 26), it is important to identify the relationship between these variables in this thermal condition.

The purpose of this study was to test the hypothesis that PETCO2 provides an accurate assessment of PaCO2 during a moderate heat stress and during a more severe heat stress sufficient to decrease PETCO2 (aim 1) as well as during a heat stress combined with an orthostatic challenge (aim 2). Lastly, restoration of PETCO2 to preperturbation baseline is often used to assess the role of carbon dioxide on various physiological responses (3, 9). This procedure relies on the assumption that clamping-induced increases in PETCO2 are accompanied by comparable increases in PaCO2, but this assumption has not been assessed in heat-stressed individuals. Therefore, aim 3 tested the hypothesis that PETCO2 accurately tracks PaCO2 when the heat stress-induced reductions in PETCO2 are attenuated through PETCO2 clamping.

METHODS

Eleven healthy normotensive subjects participated in this study. Average (mean ± SD) subject characteristics were as follows: age, 34 ± 12 yr; height, 172 ± 7 cm; and weight, 70 ± 7 kg. Subjects were not taking medications and were free of any known cardiovascular, metabolic, or neurological diseases. Subjects were informed of the purpose and risks of the study before providing their informed written consent. The protocol and consent were approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital Dallas. Subjects refrained from alcohol, caffeine, and intense exercise for 24 h before the study.
Instrumentation and Measurements

Following arrival to the laboratory, each subject swallowed a telemetry pill for the measurement of intestinal temperature (HQ, Palmetto, FL). Mean skin temperature was measured from the weighted average of six thermocouples attached to the skin (24). Each subject was fitted with a water-perfused tube-lined suit (Med-Eng, Ottawa, Canada) and was placed in a lower body negative pressure (LBNP) chamber, sealed at the iliac crest, while in the supine position. The suit covered the entire body except for the head, face, hands, one forearm, and feet and permitted the control of skin and internal temperatures by adjusting the temperature of the water perfusing the suit. Heart rate was continuously obtained from an electrocardiogram (HP Patient Monitor; Agilent, Santa Clara, CA) interfaced with a cardiotachometer (CWE, Ardmore, PA). A 20-gauge catheter was inserted in the radial artery of the nondominant arm using sterile techniques under local anesthesia. The cannula was connected to a pressure transducer (Maxxim Medical, Athens, TX) that was positioned at the level of the heart. This catheter was used for direct continuous assessment of heat-by-heat arterial pressure as well as for blood samples for subsequent analysis of PaCO₂.

Experimental Protocol

An outline of the entire experimental protocol is provided in Fig. 1. For all analyses, the alpha level was set at 0.05, and the results are reported as means ± SD.

Aim 1: PETCO₂ vs. PaCO₂ During Normothermia and Two Levels of Heat Stress

Following instrumentation, subjects rested quietly in the supine position while normothermic water (34°C) circulated through the suit. After a 10-min steady-state rest period, subjects were fitted with a nose clip and breathed room air through a mouth piece for 5 min while thermal, hemodynamic, and PETCO₂ (VitalCap Capnograph Monitor; Oridion, Needham, MA) data were collected during spontaneous respiration. During the last minute of this period, blood was obtained from the arterial catheter and stored in a heparinized syringe on ice until subsequent analysis of PaCO₂ was performed in triplicate (Gem Premier 3000; Instrumentation Laboratory, Lexington, MA). Following completion of normothermic data collection, heat stress began by circulating 49°C water through the suit. When internal temperature increased ~1.0°C above baseline temperature, the PETCO₂ and PaCO₂ measures were repeated (heat stress 1). Subjects continued to be heat stressed until PETCO₂ was reduced by at least 3 mmHg relative to normothermia. Once this decrease in PETCO₂ was attained, the temperature of the water circulating the suit was slightly decreased in an effort to attenuate the rate of rise in internal temperature, as well as further decreases in PETCO₂ at which point the PETCO₂ and PaCO₂ measures were repeated (heat stress 2).

Data analysis for aim 1. Data were sampled at 50 Hz via a data-acquisition system (Biopac System, Santa Barbara, CA). For normothermia and both levels of heating, data during the 60-s period before the blood draw, for each respective thermal condition, were averaged, the exception being that PETCO₂ was averaged over the 30-s period when arterial blood was drawn. Hemodynamic data among the three conditions (i.e., baseline normothermia, heat stress 1, and heat stress 2) were analyzed via one-way repeated-measures ANOVA, followed by a Tukey post hoc analysis when a main effect was identified. Values of PETCO₂ and PaCO₂ were evaluated via a two-way repeated-measures ANOVA, with main factors of carbon dioxide measurement method and thermal condition. Comparisons between PaCO₂ and PETCO₂ measures, during the three thermal conditions, were also evaluated using the methods of differences as described by Bland-Altman (2). The Bland-Altman plot was subsequently analyzed by linear regression analysis to determine if the slope of the relationship was greater than zero, which would indicate that a proportional bias was present [i.e., difference between two methods changes as the average values from the two methods becomes smaller or larger (6, 14, 16)]. Furthermore, a fixed bias is present if the 95% confidence limit of the Bland-Altman plot does not include zero (14, 16). Lastly, a linear regression analysis was performed to further characterize the relationship between PaCO₂ and PETCO₂ measures during the three thermal conditions.

Aim 2: PETCO₂ vs. PaCO₂ During a Simulated Hemorrhage Challenge While Heat Stressed

Immediately after the PETCO₂ and PaCO₂ measures during moderate heating (i.e., heat stress 1), eight subjects were exposed to 4 min of ~30 mmHg LBNP. PETCO₂ and PaCO₂ were measured during the final minute of LBNP.

Data analysis for aim 2. Absolute values of PETCO₂ and PaCO₂ during the LBNP challenge were compared using a paired \(t\)-test as well as by linear regression analysis \((N = 8)\). In a subset of subjects \((N = 5)\), this level of LBNP was sufficient to further reduce PETCO₂ at least 2 mmHg below the heat stress value (i.e., pre-LBNP). In these individuals, the magnitude of the reduction in PETCO₂ and PaCO₂ during LBNP relative to the pre-LBNP values was compared using a paired \(t\)-test and linear regression analysis.

Aim 3: Does PETCO₂ Track PaCO₂ When the Heat Stress-Induced Reductions in PETCO₂, are Attenuated?

Immediately after the PETCO₂ and PaCO₂ measures during pronounced heating (i.e., heat stress 2), a subset of subjects \((N = 7)\) was exposed to a PETCO₂ clamping protocol. This was accomplished using a computer-controlled gas blender, sequential gas delivery, and rebreathing circuit (RespirAct; Thornhill Research, Toronto, Canada), which has been described in detail elsewhere (3, 10, 17–19). The RespirAct device was programmed to return PETCO₂ to tensions measured during normothermia while simultaneously maintaining normoxia via administration of a mixture of nitrogen, oxygen, and carbon dioxide gases in a closed-loop sequential rebreathing circuit. Once this was achieved, the aforementioned PETCO₂ and PaCO₂ measures were repeated.

Data analysis for aim 3. The magnitude of the increase in PETCO₂ and PaCO₂ during the clamping protocol relative to preclamped heat stress values was compared using a paired \(t\)-test and linear regression analysis.

RESULTS

Thermal and hemodynamic data. Before any thermal perturbations, internal and mean skin temperatures were 37.0 ± 0.4 and 34.5 ± 0.5°C, respectively. Heat stress 1 and
heat stress 2 increased mean skin temperature to 38.5 ± 0.6 and 38.7 ± 0.9°C, respectively (both variables \( P < 0.001 \) relative to normothermia), and the magnitude of this increase was similar between the two heat stress conditions \( (P = 0.66) \). Internal temperature was increased to 38.0 ± 0.5°C during heat stress 1 \( (P < 0.001 \) relative to normothermia) and was further elevated to 38.4 ± 0.4°C during heat stress 2 \( (P < 0.001 \) relative to normothermia and heat stress 1). Heart rate was increased from 63 ± 8 beats/min during normothermia to 102 ± 18 and 106 ± 14 beats/min during heat stress 1 and heat stress 2, respectively (both variables \( P < 0.001 \) relative to normothermia). Mean arterial pressure was reduced from a normothermic value of 89 ± 7 mmHg to 77 ± 7 and 76 ± 6 mmHg during heat

Fig. 2. Relationship between \( \text{PETCO}_2 \) and arterial carbon dioxide tension (\( \text{PaCO}_2 \)) during normothermia, as well as elevations in core body temperature of 1.0 ± 0.2°C (heat stress 1) and 1.4 ± 0.2°C (heat stress 2). Measures of \( \text{PETCO}_2 \) (white bars) and \( \text{PaCO}_2 \) (gray bars) were similar for each thermal condition \( (P \) values are from paired \( t \)-tests; \( A \)). The linear regression analysis \( (B) \) and the Bland-Altman plot \( (C) \) also revealed a close relationship between \( \text{PaCO}_2 \) and \( \text{PETCO}_2 \) within the three thermal conditions, which was particularly evident in the hypocapnic range \( (B \) and \( C \)). For the Bland-Altman plot, there was a small bias between measurement devices (bias, −0.4 mmHg) and 95% confidence limits of −4.2 and 3.4 \( (B) \).

Fig. 3. Relationship between \( \text{PETCO}_2 \) and \( \text{PaCO}_2 \) during combined lower body negative pressure (LBNP) and heat stress 1. Absolute \( \text{PETCO}_2 \) and \( \text{PaCO}_2 \) during LBNP while subjects were heat stressed were similar, as identified by a paired \( t \)-test \( (N = 8; A) \) and linear regression analysis \( (N = 8; B) \). Likewise, the magnitude of the reduction in \( \text{PETCO}_2 \) (5.3 ± 2.6 mmHg) and \( \text{PaCO}_2 \) (5.4 ± 4.2 mmHg) tensions to LBNP was similar, as identified by a paired \( t \)-test \( (N = 5; C) \) and linear regression analysis \( (N = 5; D) \), indicating that \( \text{PETCO}_2 \) tension accurately reflects \( \text{PaCO}_2 \) tension during these perturbations.
stress 1 and heat stress 2, respectively (both variables $P < 0.001$ relative to normothermia).

**Aim 1: PETCO2 Provides an Accurate Assessment of PaCO2 During Normothermia and Two Levels of Heat Stress**

The two-way repeated-measures ANOVA revealed a significant main effect of thermal condition in reducing carbon dioxide tension ($P < 0.001$); however, this reduction was similar between measurement techniques [main effect of carbon dioxide measurement technique (PETCO2 and PaCO2; $P = 0.36$)]. While not significant, there was a trend toward an interaction between thermal condition and measurement technique ($P = 0.06$). To verify that this nonsignificant trend was not due to a type II error, PETCO2 and PaCO2 values at each of the three thermal conditions were also compared using paired $t$-tests. The results were consistent with the two-way repeated-measures ANOVA in that there was no difference between PETCO2 and PaCO2 while normothermic ($P = 0.14$), during heat stress 1 ($P = 0.21$), and during heat stress 2 ($P = 0.28$; Fig. 2A). Linear regression analysis demonstrated a significant correlation between measures of PETCO2 and PaCO2 when the three thermal conditions were analyzed together ($r = 0.94, P < 0.001$; Fig. 2B). The Bland-Altman plot revealed a small bias (bias, $-0.4$ mmHg) between measures of PETCO2 and PaCO2 when the three thermal conditions were analyzed together (Fig. 2B). Neither a proportional ($r = 0.01, P = 0.94, \text{slope} = -0.004$) nor a fixed (95% confidence interval = $-4.2$ mmHg, 3.4 mmHg) bias was detected from the Bland-Altman plot (Fig. 2C).

**Aim 2: PETCO2 Provides an Accurate Assessment of PaCO2 During a Simulated Hemorrhage Challenge While Heat Stressed**

A paired $t$-test revealed no difference between absolute values of PETCO2 (31.4 ± 7.2 mmHg) and PaCO2 (31.8 ± 7.0 mmHg) during LBNP while subjects were heat stressed ($P = 0.61$; Fig. 3A). This finding was supported by linear regression analysis which revealed a significant correlation between absolute values of PETCO2 and PaCO2 during LBNP ($r = 0.96, P < 0.001$; Fig. 3B). Likewise, a paired $t$-test revealed that the magnitude of the reduction in PETCO2 (5.3 ± 2.6 mmHg) and PaCO2 (5.4 ± 4.2 mmHg) in the subset of subjects ($N = 5$) who exhibited decreases in PETCO2 during LBNP was also similar ($P = 0.89$; Fig. 3C), which was further confirmed by linear regression analysis ($r = 0.93, P = 0.02$; Fig. 3D).

**Aim 3: The Magnitude of the Increase in PETCO2 and PaCO2 During a PETCO2 Clamping Procedure is Similar in Heat-Stressed Subjects**

The PETCO2 clamping procedure was successful at returning PETCO2, which decreased during heat stress 2, to normothermic levels (normothermia: 38 ± 4 mmHg; heat stress preclamp: 31 ± 5 mmHg; heat stress clamp: 38 ± 5 mmHg; $P < 0.001$ between heat stress values, whereas there was no difference between normothermia and heat stress + clamp values; $P = 0.97$). Importantly, the magnitude of the increase in PaCO2 that occurred during this clamping procedure was similar to the increase in PETCO2 ($P = 0.31$; Fig. 4A). This finding was confirmed by linear regression analysis ($r = 0.86, P = 0.01$; Fig. 4B).

DISCUSSION

PETCO2 is reduced in individuals with an elevated internal temperature, and the reduction in PETCO2 is exacerbated when this thermal stress is combined with an orthostatic challenge (3, 15, 26). These physiological occurrences likely contribute to decreases in cerebral perfusion and thus the reduction in orthostatic tolerance that occur during heat stress (1, 4, 11–13, 25). The precise understanding of the relationship between carbon dioxide tension and the cerebral vasculature is dependent on the assumption that PETCO2 accurately reflects PaCO2, the latter of which is the physiologically relevant variable. The current results indicate that PETCO2 provides an accurate noninvasive index of PaCO2 during normothermic conditions, differing degrees of heat stress, and during a simulated hemorrhage challenge combined with heat stress. Furthermore, the magnitude of the increase in PaCO2 upon returning PETCO2 to normothermic levels (i.e., the PETCO2 clamping protocol) is similar to that of PETCO2. These data suggest that PETCO2 provides an accurate assessment of PaCO2 under the testing...
conditions without the added cost and risk of arterial catheterization.

In normothermic supine resting individuals, $\text{PETCO}_2$ provides an accurate reflection of $\text{PaCO}_2$ (8, 9, 22), which is consistent with the present data (Fig. 2, A, B, and C). That said, a discrepancy in the relationship between these variables has been reported following the assumption of the upright posture in normothermic individuals, such that reductions in $\text{PETCO}_2$ are greater than $\text{PaCO}_2$ (8, 9). This response is due to changes in distribution of blood flow throughout the lungs secondary to postural reductions in cardiac output, which subsequently alters the ventilation-perfusion ratio (8). In the current study, subjects were exposed to a simulated orthostatic challenge during heat stress conditions by LBNP. Unlike what is observed during normothermia (8, 9), the present results indicate that $\text{PETCO}_2$ is similar to $\text{PaCO}_2$ during the LBNP challenge (Fig. 3, A and B), and, furthermore, the magnitude of the reductions in $\text{PETCO}_2$ and $\text{PaCO}_2$ during this challenge are similar (Fig. 3, C and D). While speculative, it is possible that differing normothermic and heat stress responses to an orthostatic stress are related to the differences in cardiac output between thermal conditions. Cardiac output was not measured in the current study; however, values of 10–13 l/min have been reported during similar degrees of heat stress (20, 21, 26). The imposed LBNP during heat stress reduces cardiac output by ~3 l/min (26), resulting in final cardiac outputs of ~7–10 l/min. In contrast, during an orthostatic challenge in normothermic conditions, cardiac output is reduced by ~1.5 l/min (26), resulting in a final cardiac output of ~4 l/min. Thus it is possible that, despite greater reductions in cardiac output during LBNP while heat stressed, the prevailing cardiac output (i.e., ~7–10 l/min) and thus blood flow distribution throughout the lungs remains sufficient to maintain similarities between measures of $\text{PETCO}_2$ and $\text{PaCO}_2$, relative to when cardiac output has been reduced to ~4 l/min during LBNP while normothermic.

Despite differences in $\text{PETCO}_2$ and $\text{PaCO}_2$ during normothermic head up tilt (8, 9), Immink et al. (9) reported that the magnitude of increase in both of these variables was similar when $\text{PETCO}_2$ was clamped at the pretilt level. Additionally, using the same clamping device as in the current study, Ito et al. (10) recently reported that the accuracy of $\text{PETCO}_2$, as an estimate of $\text{PaCO}_2$, was sustained in seated normothermic individuals across a wide range of hypocapnic and hypercapnic stimuli. The present findings are in agreement with the cited findings given that the magnitude of the increase in $\text{PETCO}_2$ and $\text{PaCO}_2$ was similar during the clamping protocol (Fig. 4, A and B).

Considerations/Limitations

While not significant, there was a trend toward an interaction between the thermal condition and measurement technique in aim 1 ($P = 0.06$). This is most likely the result of a slightly greater decrease in $\text{PaCO}_2$ ($8.8 \pm 4.6$ mmHg) during heat stress 2 relative to the decrease in $\text{PETCO}_2$ ($7.2 \pm 4.2$ mmHg). Nonetheless, when paired comparisons were made at each thermal condition, the measures of CO$_2$ were similar regardless of the measurement technique (Fig. 2).

The Bland-Altman plot in Fig. 2C depicts the relationship of the difference between the two measurement techniques (y-axis) and the average between the two techniques (x-axis) during resting normothermia and two levels of heat stress. This plot further reveals a close relationship between measures of $\text{PETCO}_2$ and $\text{PaCO}_2$, as demonstrated by a small measurement bias of ~0.4 mmHg. A proportional bias exists if the slope of the relationship between the difference of two measurements and the mean of the two measurements is significantly different from zero [i.e., the difference between the two methods changes as the average values from the two methods becomes smaller or larger (6, 14, 16)]. In the current study, a proportional bias was not detected ($r = 0.01$, $P = 0.94$, slope $-0.004$). That being said, it appears that the relationship between the $\text{PETCO}_2$ and $\text{PaCO}_2$ weakens at higher CO$_2$ tensions as indicated by a wider dispersion of data points with respect to the measurement bias (in both the positive and negative direction). Therefore, it is possible that greater differences would be identified if comparisons between carbon dioxide measurement methods were evaluated in the hypercapnic range.

Perspectives and Significance

In conclusion, absolute $\text{PETCO}_2$ and $\text{PaCO}_2$ were similar during normothermic conditions, differing degrees of heat stress, as well as during LBNP combined with heat stress. Furthermore, the heat stress-induced reductions in $\text{PETCO}_2$ and $\text{PaCO}_2$ were of similar magnitude, and subsequent further decreases in $\text{PETCO}_2$ and $\text{PaCO}_2$ imposed by LBNP were also of a similar magnitude. Based on these findings, $\text{PETCO}_2$ measures can be used to estimate $\text{PaCO}_2$ during heat stress studies that use the imposed perturbations. These findings are important to the clinical community who are interested in the impact of changes in carbon dioxide concentration on physiological responses, and to researchers who do not have access to skilled personnel necessary for arterial catheter placement and to the subjects by reducing the risks associated with experimentation where estimates of $\text{PaCO}_2$, are needed.

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DISCLOSURES

No conflicts of interest are declared by the authors.

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