Cerebral blood flow during orthostasis: role of arterial \( \text{CO}_2 \)

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Serrador, J. M., R. L. Hughson, J. M. Kowalchuk, R. L. Bondar, and A. W. Gelb. Cerebral blood flow during orthostasis: role of arterial \( \text{CO}_2 \). Am J Physiol Regul Integr Comp Physiol 290: R1087–R1093, 2006. First published November 23, 2005; doi:10.1152/ajpregu.00446.2005.—Reductions in end-tidal \( \text{CO}_2 \) (\( \text{PETCO}_2 \)) during upright posture have been suggested to be the result of hyperventilation and the cause of decreases in cerebral blood flow (CBF). The goal of this study was to determine whether decreases in \( \text{PETCO}_2 \), reflected decreases in arterial \( \text{CO}_2 \) (\( \text{PaCO}_2 \)) and their relation to increases in alveolar ventilation (V\( \text{A} \)) and decreases in CBF. Fifteen healthy subjects (10 women and 5 men) were subjected to a 10-min head-up tilt (HUT) protocol. \( \text{PaCO}_2 \), V\( \text{A} \), and cerebral flow velocity (CFV) in the middle and anterior cerebral arteries were examined. In 12 subjects who completed the protocol, reductions in \( \text{PETCO}_2 \) and \( \text{PaCO}_2 \) (\(-1.7 \pm 0.5 \) and \(-1.1 \pm 0.4 \) mmHg, \( P<0.05 \)) during minute 1 of HUT were associated with a significant increase in V\( \text{A} \) (+0.7 \pm 0.3 l/min, \( P<0.05 \)). However, further decreases in \( \text{PaCO}_2 \) (\(-0.5 \pm 0.5 \) mmHg, \( P<0.05 \)), from minute 1 to the last minute of HUT, occurred even though V\( \text{A} \) did not change significantly (\(-0.2 \pm 0.3 \) l/min, \( P=\) not significant). Similarly, CFV in the middle and anterior cerebral arteries decreased (\(-7 \pm 2 \) and \(-8 \pm 2 \% \), \( P<0.05 \)) from minute 1 to the last minute of HUT, despite minimal changes in \( \text{PaCO}_2 \). These data suggest that decreases in \( \text{PETCO}_2 \) and \( \text{PaCO}_2 \) during upright posture are not solely due to increased V\( \text{A} \) but could be due to ventilation-perfusion mismatch or a redistribution of \( \text{CO}_2 \) stores. Furthermore, the reduction in \( \text{PaCO}_2 \) did not fully explain the decrease in CFV throughout HUT. These data suggest that factors in addition to a reduction in \( \text{PaCO}_2 \) play a role in the CBF response to orthostatic stress.

Transcranial Doppler; cerebral vasoconstriction; head-up tilt

It has been widely noted that orthostatic stress in humans decreases end-tidal \( \text{PCO}_2 \) (\( \text{PETCO}_2 \)) or arterial \( \text{PCO}_2 \) (\( \text{PaCO}_2 \)) (1, 4, 17, 27, 36, 38, 41). Because \( \text{PaCO}_2 \) is known to be critical in control of cerebral blood flow (CBF) (30), decreased \( \text{PaCO}_2 \) during tilt could play a role in orthostatic intolerance through inappropriate cerebral vasoconstriction. It has been hypothesized that hyperventilation in the upright posture reduces \( \text{PaCO}_2 \), compromising CBF and leading to syncope (27). One inherent problem with this previous work is the use of \( \text{PETCO}_2 \) to represent \( \text{PaCO}_2 \). Previous work has found that although, in the supine position, \( \text{PETCO}_2 \) is closely matched to \( \text{PaCO}_2 \), (i.e., \(~0.8 \) mmHg greater), the assumption of the upright posture resulted in the \( \text{PETCO}_2 \) being \(~2.9 \) mmHg lower than \( \text{PaCO}_2 \) (4).

No studies have directly measured alveolar ventilation (V\( \text{A} \)) and CBF during head-up tilt (HUT) and characterized their association to \( \text{PaCO}_2 \). On the basis of our previous findings that decreases in \( \text{PETCO}_2 \) did not relate to changes in minute ventilation (V\( \text{E} \)) (36), we hypothesized that \( \text{PaCO}_2 \) decreases would be attenuated compared with \( \text{PETCO}_2 \) and would not be the predominant factor in reduced CBF during HUT.

Methods

Subjects. Fifteen subjects (10 women and 5 men, averaging 25.3 yr of age (range 21–32 yr), 64.3 \pm 20.5 (SD) kg body wt, 174 \pm 9 cm) with no history of cardiopulmonary, renal, or other systemic disease participated in the study. Caffeine, alcohol, and heavy exercise were prohibited for 24 h before testing. All subjects provided signed consent to the experimental protocols, which had been approved by the Ethics Review Board at the University of Western Ontario.

Tilt testing. After providing a medical history, the subjects were placed in the supine position. Under local anesthesia (0.5–1 ml lidocaine), a 22-gauge catheter was positioned within the radial artery of the nondominant arm to allow blood sampling. Heart rate was obtained via standard three-lead electrocardiogram (Hewlett Packard), and beat-by-beat blood pressures were obtained through a finger photoplethysmograph (Finapres) maintained at heart level.

Cerebral flow velocities (CFV) in the middle and anterior cerebral arteries (CFV\(_{\text{MCA}}\) and CFV\(_{\text{ACA}}\)) were obtained with 2-MHz pulsed-wave transcranial Doppler (TCD) probes located over the temporal bones on each side (Medasonics CDS). For the MCA, the signal was range gated to a depth of 45–60 mm to ensure insonation of the M1 segment of the MCA according to standard techniques. For the ACA, gated depth was 60–75 mm. After the optimum signal was achieved, TCD probes were independently secured in place by headband devices.

Ventilatory data were collected via a face mask that allowed nasal and oral breathing. Expiratory and inspiratory gases (Random Access Mass Spectrometer, Marquette Electronics; Metabolic Cart, MedGraphics) and flow (ultrasonic flowmeter, Kou Consulting, Redmond, WA) were obtained throughout the collection period.

Subjects were supine throughout the instrumentation and stabilization period (55–65 min) and through 10 min of baseline data collection before they were passively tilted to an 85° upright position for 10 min or until the development of presyncopal symptoms. Previous research showed that ventilatory responses do not change between 5 and 20 min of tilt (1). Criteria for presyncope included any of the following: a sudden >25-mmHg drop of systolic pressure or >15-mmHg drop in diastolic pressure, a sudden and sustained >15-beat/min drop in heart rate, severe lightheadedness, and severe nausea or actual vomiting. After upright tilt, the subjects were returned to the supine position for a 10-min recovery period. Blood samples were drawn over 30-s periods during minutes 5, 7, and 9 of supine baseline; minutes 1, 2, 4, and 6, as well as the last minute, of HUT; and minutes 1, 4, and 9 of recovery.

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Data analysis. The analog CFVMCA, CFVACA, heart rate, and blood pressure signals were sampled simultaneously at 10 kHz. VA was determined from the VA equation (\( VA = VCO_2 \times 0.863/PaCO_2 \), where VCO2 is CO2 production), and physiological dead space was calculated from arterial and expired CO2 using the Bohr equation.

Blood pressure at the level of the MCA and ACA was estimated by subtraction of the hydrostatic gradient from the heart to the level of the TCD probe (\( BP_{brain} \)). Estimates of an index of regional cerebrovascular resistance (CVR) were calculated for the MCA and ACA as follows: \( CVR = BP_{brain}/CFV \). Because we assumed that intracranial pressure was unlikely to change greatly, \( BP_{brain} \) was used to reflect cerebral perfusion pressure (9). Previous work demonstrated that estimated CVR is a useful index of CVR in the upright posture (35).

Cerebrovascular data were assessed using repeated-measures ANOVA with Bonferroni’s post hoc analysis for multiple comparisons. Values were compared with baseline (mean of 3 supine values). Because our previous research demonstrated that CVF and PETCO2 continue to increase in the upright posture (36, 38), a comparison of minute 1 with the last minute of HUT was performed. To examine the relation between \( VA, PaCO_2 \), and CVF, correlations were obtained using Pearson’s product-moment analysis. Values are means ± SE. P \(<\) 0.05 was considered significant.

RESULTS

Fifteen subjects participated in the study: 12 (8 women and 4 men) were able to complete the HUT protocol, and 3 (2 women and 1 man) developed presyncopal symptoms. We were unable to obtain ACA signals from two (orthostatically tolerant) subjects.

Ventilatory and blood gas responses. PETCO2 and PaCO2 were significantly reduced, whereas end-tidal PO2 was significantly increased throughout HUT (Fig. 1, Table 1). Although VE increased during HUT, VA was significantly elevated only in minute 1 of HUT (Fig. 1). The sustained increase in VE was due to an increase in physiological dead space (Table 1), inasmuch as tidal volume increased slightly (~10%) while breathing frequency did not change. Throughout HUT, there were no significant changes in O2 uptake (\( VO_2 \)) or \( VCO_2 \) (Fig. 2). Consistent with this lack of change in VA and VCO2, VA/VCO2 did not change during HUT (Fig. 2). The small reductions in VO2 were sufficient to cause VA/VO2 to increase transiently during minutes 1 and 2 of HUT and then return to supine levels.

On return of the subjects to the supine position, there was a significant increase in VE and VA associated with an increase in PETCO2 to greater than baseline levels but with a sustained reduction in PaCO2 (Fig. 1). This increase in ventilation was due to a transient increase in tidal volume during minute 1 of recovery without an associated change in breathing frequency, and dead space returned to baseline values (Table 1). This increased ventilation was associated with a significant increase in \( VO_2 \) and \( VCO_2 \), as well as a decrease \( VA/VO_2 \) (Fig. 2). VA/VCO2 remained unchanged.

Hemodynamic adjustments to HUT. HUT caused heart rate to increase significantly (Table 2) and \( BP_{brain} \) to decrease (Fig. 1) compared with the supine position. Heart rate and \( BP_{brain} \) returned to baseline levels during recovery, and heart rate was significantly below baseline during the last 5 min of recovery (Table 2). HUT caused a decrease in CFVMCA and CFVACA (Fig. 1). However, during minute 1 of HUT, only CFVACA decreased significantly.

Effect of prolonged orthostatic stress. After the initial decrease in CVF, there was a significant further decrease in CFVMCA (minutes 6–10) and CFVACA (minutes 4–10) during sustained HUT (Fig. 1). These decreases were associated with an increase in CVR in both vascular beds. Similarly, \( BP_{brain} \) increased after minute 1 of HUT.

To examine the effect of prolonged orthostatic stress, we examined the within-tilt (minutes 1–10 of HUT) response. After the initial decrease in CVF, there was a further significant decrease in CFVMCA and CFVACA within HUT (Fig. 3). This cerebral hypoperfusion during sustained HUT was associated
with an increase in the CVR index for ACA and MCA. Similarly, HUT was associated with a further decrease in PetCO₂ and PaCO₂ (Fig. 3). Neither Ve nor Va was significantly changed within HUT relative to the initial response.

Relation between ventilation, CO₂, and CFV. Because it has been proposed that increases in Va decrease PaCO₂, which in turn increases CVR and decreases CBF, we examined the relation among these variables within the 10 min of HUT. It did not appear that increases in Va considered in isolation could explain decreases in PaCO₂ from minutes 1 to 10 of HUT, because Va actually decreased from minutes 1 to 10 of HUT (P = nonsignificant) and PaCO₂ also decreased (Fig. 3).

We also examined the relation between changes in PaCO₂ within tilt and CFV changes. To ensure that significant relations in individuals were not obscured by the averaging process, we examined the relations between changes in PaCO₂ and CFV for each subject (Fig. 4). When we compared individual linear regressions with the expected change (3%/mmHg CO₂) (18), it did not appear that changes in PaCO₂ within tilt were the same for each breath comparing the change from the mean during minutes 10.25 to 10.75 of tilt (the same reference point at which the arterial sample was obtained). This analysis produced greater slopes [MCA = 1.7 ± 0.4%/mmHg (r² = 0.16 ± 0.05) and ACA = 1.3 ± 0.4%/mmHg (r² = 0.13 ± 0.05)]; however, they were still significantly lower than the expected ~3%/mmHg, suggesting that the reduced correlation was not due to limited data points.

Response of orthostatically intolerant subjects. Although the number of orthostatically intolerant subjects was insufficient for statistical analysis and comparison of the response with our orthostatically tolerant group, we have plotted the response of the three intolerant subjects (Fig. 5). These subjects demonstrated responses that were similar to those of our tolerant subjects. In all three subjects, an initial increase in Ve (not shown) and Va was followed by a decrease to below baseline levels (2 of 3 subjects). Similarly, they demonstrated decreases in PetCO₂ (not shown) and PaCO₂. Although they showed a similar initial drop in BPbrain, their pressure continued to drop and was significantly lower than that of our tolerant group at the end of HUT. CFVmca and CFVacca had similar temporal patterns but were significantly lower at the end of HUT. Interestingly, although all three subjects had typical presyncopal responses in pressure and flow (i.e., greatly reduced at presyncope), the proposed hyperventilation and hypocapnia were not consistently present. In two of the three subjects, Va was lower at presyncope than at baseline (+2.1, −1.4, and −1.1 l/min), and PaCO₂ changes from baseline to presyncope were not consistent with severe hypocapnia (−6.1, −0.6, and −4.5 mmHg).

**DISCUSSION**

These data demonstrate three important findings: 1) postural hypocapnia was a common occurrence, 2) progressive decreases in CFV during HUT were due to increased CVR index, and 3) beyond minute 1 of tilt, there was no clear relation between changes in PaCO₂ and CFV.

CFVmca has been found to decrease with upright tilt (13, 17, 27, 38) and lower body negative pressure (LBNP) (6, 22). Concomitant with this decrease in CBF is a drop in PetCO₂ (6, 17, 22, 27, 38). Because it is well known that a decrease in PaCO₂ results in an increase in CVR (30), we investigated the possibility that the hypocapnia associated with orthostatic stress might be the cause of the cerebral hypoperfusion during 10 min of HUT.
Postural hypocapnia. Our observation of significant reductions in PETCO2 (−2.6 ± 0.6 mmHg) and PaCO2 (−1.6 ± 0.6 mmHg) during HUT is consistent with values reported previously (1, 4) during the development of postural hypocapnia. The decrease in PETCO2 in the upright posture has been attributed to hyperventilation (27), but the transient responses of ventilation and gas exchange with movement to the upright posture are complex. In minute 1 of HUT, the significant (−8%) increase in V˙A was associated with a significant increase in V˙A/V˙O2 but no change in V˙A/V˙CO2. The finding for V˙A/V˙O2 is consistent with a reduction in venous return with HUT (7, 23) that would also reduce total delivery of CO2 to the lungs. However, the small increase in V˙A together with the small, but nonsignificant, increase in V˙A/V˙CO2 indicates that some CO2 stores of the body were excreted in minute 1 of HUT, contributing to the reduction in PaCO2. Also supporting the idea that changes in whole body blood flow distribution might play a role in postural hypocapnia, Anthonisen and Milic-Emili (2) found that the decrease in PaCO2 did not occur when the tilt was performed while subjects were submerged in water to the xiphoid process to prevent venous pooling. Similarly, Gisolf et al. (12), using a theoretical model, demonstrated that decreases in cardiac output were responsible for −20% of the decrease in PETCO2 during standing.

Beyond minute 1 of HUT, V˙CO2 did not change significantly. The very small (−4%) increase over baseline values was similar to previous reports of unchanged or slightly increased V˙CO2 during HUT (1, 4, 24–26, 43). The tendency for V˙A/V˙CO2 to be elevated throughout HUT is consistent with reports of increased VA for some (1, 4), but not all (4, 16), subjects. The significant increase in total V˙E above supine baseline was a consequence of increased dead space ventilation as observed previously (4), with no change in breathing frequency (3, 26).

Table 2. Circulatory response to HUT

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>HUT</th>
<th>Recovery</th>
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<tbody>
<tr>
<td></td>
<td>7.5 min</td>
<td>10.5 min</td>
<td>14.5 min</td>
</tr>
<tr>
<td>CFVMA, cm/s</td>
<td>64.4±3.9</td>
<td>62.0±3.3</td>
<td>61.7±3.5*</td>
</tr>
<tr>
<td>CFVACA, cm/s</td>
<td>62.1±3.3</td>
<td>58.1±3.3*</td>
<td>57.0±3.6†</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>92±5</td>
<td>88±6*</td>
<td>93±5</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>60±2</td>
<td>75±3†</td>
<td>73±3†</td>
</tr>
</tbody>
</table>

Values are means ± SE. CFVMA and CFVACA, cerebral flow velocity in middle and anterior cerebral arteries; MAP, mean arterial pressure; HR, heart rate. See table 1 footnote for further explanation. Significantly different from supine. *P < 0.05; †P < 0.005.
nisms other than hyperventilation were involved. Whereas PaCO2 had a large initial decrease and then slowly declined, CFV showed a progressive decrease (Fig. 1). Comparison of the change in PaCO2 and PETCO2 during HUT on an individual basis showed no consistent trend. We did not see the expected −3% decrease in CFV per mmHg decrease in PETCO2. Similarly, if we examine the change in PETCO2 from minute 1 to the last minute of HUT, slopes were −1.5%/mmHg, i.e., one-half of the expected values. Thus the role of PaCO2 in the decrease in CBF during orthostatic stress must be questioned.

Further questioning of the specific link between PaCO2 and CFV derives from our previous work in which we maintained PETCO2 at supine levels during upright tilts but did not eliminate the reduction in CBF (5). However, maintaining PETCO2 during 45° tilt did eliminate the decrease in CFV (10), indicating that a greater orthostatic stress was required to elicit a tilt-related decrease in CFV unrelated to postural hypocapnia.

If reductions in PaCO2 do not explain the progressive fall in CFV at the end of HUT, other mechanisms must be examined. The concurrent increase in CVR indicates that the time-dependent fall in CFV was due to cerebral vasoconstriction.

Although part of this constrictive response might have been the result of an appropriate autoregulatory response to the −6% increase in BPbrain during tilt, it seems unlikely that autoregulation would reduce CFV under conditions where BPbrain was −20 mmHg lower than in the supine posture. Altered cerebrovascular control unrelated to changes in PETCO2 has been reported during LBNP following bed rest (44) and parabolic flight (38). In addition, a paradoxical cerebral vasoconstriction in healthy (5, 6, 22, 38) and orthostatically intolerant (13, 14) individuals has been reported during postural stress and LBNP. However, our previous work (38), as well as that of others (8, 21), showed that cerebral autoregulation remains intact during HUT in healthy subjects, suggesting that decreases in perfusion pressure were unlikely to be the cause of the decrease in cerebral flow. Similarly, analysis of transfer function gain between CFV and blood pressure found no decreases in perfusion pressure were unlikely to be the cause of the decrease in cerebral flow. Similarly, analysis of transfer function gain between CFV and blood pressure found no changes in gains during tilt in these subjects (data not shown). Other possible causes may be increased sympathetic outflow to the brain (34), activation of vestibular or other central mechanisms (38, 42), endocrine-related changes such as angiotensin (33), changes in cardiac output (41), or as yet undetermined mechanisms.

The role of PaCO2, or cerebral vasoconstriction in the development of orthostatic intolerance is poorly understood. Previous research has suggested a role for PaCO2 (27) and cerebral vasoconstriction (13). In the three subjects who became presyncopal in this study, only two demonstrated significant decreases in PaCO2 (Fig. 5). Even in these subjects, decreases in CFV at the end of HUT were again approximately double that predicted from changes in PaCO2. Consistent with this minimal role for PaCO2, cerebral vasoconstriction remains intact during HUT in healthy subjects, suggesting that decreases in perfusion pressure were unlikely to be the cause of the decrease in cerebral flow. Similarly, analysis of transfer function gain between CFV and blood pressure found no changes in gains during tilt in these subjects (data not shown). Other possible causes may be increased sympathetic outflow to the brain (34), activation of vestibular or other central mechanisms (38, 42), endocrine-related changes such as angiotensin (33), changes in cardiac output (41), or as yet undetermined mechanisms.

The cerebrovascular response to the upright posture. Regardless of the mechanism, a decrease in PaCO2 should result in a decrease in CBF (30). Despite this, during HUT, CFV in healthy individuals, in previous work, voluntary hyperventilation during supine bed rest was found to produce significant hypocapnia, dramatic reductions in CFV, and large increases in CVR without concurrent hypotension or syncope (22). Similarly, we previously found that addition of inspired CO2 extends the time to presyncope but does not prevent it (5). These data suggest that although postural hypocapnia may contribute to cerebral hypoperfusion, it does not appear to be a primary cause of orthostatic intolerance.

Interestingly, several previous studies noted a frontal cerebral hypoperfusion in patients and subjects who become or-
CVR (35). In finger measures of blood pressure, mean pressure was used to calculate CVR. To minimize the possible effect of increased pulsatility greater, suggesting that we underestimated the increase in mmHg throughout tilt, the increase in CVR would be seated position. If intracranial pressure were to decrease to the decline in PaCO2, are responsible for the increase in CVR. These observations suggest that other mechanisms, in addition to experimental manipulations, no change in MCA diameter at the M1 segment was found. Other work examined the lower limit of arterial blood velocity and end-tidal P02 in the hypocapnic range in humans. Circulation 95: 129–137, 2003.


