Cerebral blood flow during orthostasis: role of arterial CO₂

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Serrador, J. M., R. L. Hughson, J. M. Kowlachuk, R. L. Bondar, and A. W. Gelb. Cerebral blood flow during orthostasis: role of arterial CO₂. 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 PCO₂ (PETCO₂) 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 PETCO₂ reflected decreases in arterial PCO₂ (PaCO₂) and their relation to increases in alveolar ventilation (VA) and decreases in CBF. Fifteen healthy subjects (10 women and 5 men) were subjected to a 10-min head-up tilt (HUT) protocol. PaCO₂, VA, and cerebral flow velocity (CFV) in the middle and anterior cerebral arteries were examined. In 12 subjects who completed the protocol, reductions in PETCO₂ and PaCO₂ (−1.7 ± 0.5 and −1.1 ± 0.4 mmHg, P < 0.05) during minute 1 of HUT were associated with a significant increase in VA (+0.7 ± 0.3 l/min, P < 0.05). However, further decreases in PaCO₂ (−0.5 ± 0.5 mmHg, P < 0.05), from minute 1 to the last minute of HUT, occurred even though VA did not change significantly (−0.2 ± 0.3 l/min, P = not significant). Similarly, CFV in the middle and anterior cerebral arteries decreased (−7 ± 2 and −8 ± 2%, P < 0.05) from minute 1 to the last minute of HUT, despite minimal changes in PaCO₂. These data suggest that decreases in PETCO₂ and PaCO₂ during upright posture are not solely due to increased VA but could be due to ventilation-perfusion mismatch or a redistribution of CO₂ stores. Furthermore, the reduction in PaCO₂ did not fully explain the decrease in CFV throughout HUT. These data suggest that factors in addition to a reduction in PaCO₂ 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 PCO₂ (PETCO₂) or arterial PCO₂ (PaCO₂) (1, 4, 17, 27, 36, 38, 41). Because PaCO₂ is known to be critical in control of cerebral blood flow (CBF) (30), decreased PaCO₂ during tilt could play a role in orthostatic intolerance through inappropriate cerebral vasoconstriction. It has been hypothesized that hyperventilation in the upright posture reduces PaCO₂, compromising CBF and leading to syncope (27).

One inherent problem with this previous work is the use of PETCO₂ to represent PaCO₂. Previous work has found that, although in the supine position, PETCO₂ is closely matched to PaCO₂ (i.e., ~0.8 mmHg greater), the assumption of the upright posture resulted in the PETCO₂ being ~2.9 mmHg lower than PaCO₂ (4).

No studies have directly measured alveolar ventilation (VA) and CBF during head-up tilt (HUT) and characterized their association to PaCO₂. On the basis of our previous findings that decreases in PETCO₂ did not relate to changes in minute ventilation (VE) (36), we hypothesized that PaCO₂ decreases would be attenuated compared with PETCO₂ 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 ± 20.5 (SD) kg body wt, 174 ± 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 MCA and CFV 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, range 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 lightheadness, 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 CFV\textsubscript{MCA}, CFV\textsubscript{ACA}, heart rate, and blood pressure signals were sampled simultaneously at 10 kHz. \( V_\text{A} \) was determined from the \( V_\text{A} \) equation (\( V_\text{A} = V_\text{CO}_2 \cdot 0.863/P_\text{ACO}_2 \), where \( V_\text{CO}_2 \) is CO\(_2\) production), and physiological dead space was calculated from arterial and expired CO\(_2\) 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 (\( B\text{P}_{\text{brain}} \)). Estimates of an index of regional cerebrovascular resistance (CVR) were calculated for the MCA and ACA as follows: CVR = \( B\text{P}_{\text{brain}}/CFV \). Because we assumed that intracranial pressure was unlikely to change greatly, \( B\text{P}_{\text{brain}} \) 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). CFV was normalized to baseline (supine rest before HUT), because percent change has been shown to be the best reflection of changes in CBF (37). For comparison purposes, all beat-by-beat and breath-by-breath data were averaged over the 30-s periods in which blood samples were taken.

Statistics. To examine the role of \( P_\text{ACO}_2 \) in the cerebrovascular response to HUT, only subjects who were able to complete the 10-min HUT without developing presyncopal symptoms were included for analysis. The effects of HUT on ventilatory, cardiovascular, and 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 CFV and PET\(_{\text{CO}_2}\) continue to increase throughout HUT (Fig. 1), Table 1). Although \( V_\text{A}/V_\text{O}_2 \) did not change during HUT (Fig. 2). The small reductions in \( V_\text{O}_2 \) were sufficient to cause \( V_\text{A}/V_\text{O}_2 \) 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 \( V_\text{E} \) and \( V_\text{A} \) associated with an increase in PET\(_{\text{CO}_2}\) to greater than baseline levels but with a sustained reduction in \( P_\text{ACO}_2 \) (Fig. 1). This increase in ventilation was due to a transient increase in tidal volume during \textit{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 \( V_\text{O}_2 \) and \( V_\text{CO}_2 \), as well as a decrease \( V_\text{A}/V_\text{O}_2 \) (Fig. 2). \( V_\text{A}/V_\text{CO}_2 \) remained unchanged.

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. PET\(_{\text{CO}_2}\) and \( P_\text{ACO}_2 \) were significantly reduced, whereas end-tidal \( P_\text{O}_2 \) was significantly increased throughout HUT (Fig. 1, Table 1). Although \( V_\text{E} \) increased during HUT, \( V_\text{A} \) was significantly elevated only in \textit{minute 1} of HUT (Fig. 1). The sustained increase in \( V_\text{E} \) 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 \( O_2 \) uptake (\( V_\text{O}_2 \)) or \( V_\text{O}_2 \) (Fig. 2). Consistent with this lack of change in \( V_\text{A} \) and \( V_\text{CO}_2 \), \( V_\text{A}/V_\text{O}_2 \) did not change during HUT (Fig. 2). The small reductions in \( V_\text{O}_2 \) were sufficient to cause \( V_\text{A}/V_\text{O}_2 \) to increase transiently during minutes 1 and 2 of HUT and then return to supine levels.

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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 producing the expected change in CFV for most subjects: MCA mean slope $= 0.9 \pm 0.7$/mmHg ($r^2 = 0.30 \pm 0.07$) and ACA mean slope $= -0.6 \pm 0.5$/mmHg ($r^2 = 0.32 \pm 0.07$). To ensure that this lack of correlation was not the result of a limited range of CO2 values, we performed linear regressions on breath-by-breath PETCO2 with the associated mean flow velocities 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 $[\text{MCA} = 1.7 \pm 0.4$/mmHg ($r^2 = 0.16 \pm 0.05$) and ACA $= 1.3 \pm 0.4$/mmHg ($r^2 = 0.13 \pm 0.05$)], 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 CFVACA had similar temporal patterns but were significantly lower at the end of HUT. Interestingly, although all three subjects had typical presyncope-like 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.

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**Table 1. Ventilatory response to HUT**

<table>
<thead>
<tr>
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<th>Supine</th>
<th></th>
<th>HUT</th>
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<th>Recovery</th>
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<tr>
<td></td>
<td>7.5 min</td>
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<td>14.5 min</td>
<td>16.5 min</td>
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<tr>
<td>PtETCO2 mmHg</td>
<td>106±1</td>
<td>112±2</td>
<td>108±2</td>
<td>108±2</td>
<td>109±2</td>
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<tr>
<td>Vt, ml</td>
<td>482±35</td>
<td>538±28</td>
<td>543±39</td>
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<tr>
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<td>f, breaths/min</td>
<td>17±1</td>
<td>16±1</td>
<td>15±1</td>
<td>16±1</td>
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</tr>
</tbody>
</table>

Values are means ± SE. PtETCO2, end-tidal PO2; Vt, tidal volume; Vd, dead space; f, breathing frequency. Supine values represent mean of 30-s periods during which arterial blood samples were obtained while the subjects lay supine; head up tilt (HUT) and recovery data are mean values over 30-s periods during which arterial samples were obtained. Alveolar ventilation (VA) was calculated from Vt, Vd (determined by the Bohr equation), and breathing frequency. Significantly different from supine. *$P < 0.05$; †$P < 0.005$. 

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**Fig. 2. Changes in CO2 production (VCO2), O2 uptake (VO2), VA/VCO2, and VA/VO2 during HUT. Values are means ± SE. *Significant different from mean baseline values, $P < 0.05$.**
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 V˙A 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

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<thead>
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<th>Supine</th>
<th>HUT</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.5 min</td>
<td>10.5 min</td>
<td>11.5 min</td>
</tr>
<tr>
<td>CFV_{MCA}, cm/s</td>
<td>64.4±3.9</td>
<td>62.0±3.3</td>
<td>61.7±3.5</td>
</tr>
<tr>
<td>CFV_{ACA}, 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>
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Values are means ± SE. CFV_{MCA} and CFV_{ACA}, cerebral flow velocity in middle and anterior cerebral arteries; MAP, mean arterial pressure; HR, heart rate. See table 1 footnote for further explanation. *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 decreased (Fig. 1). However, examination of the temporal response during the tilt demonstrated a disparity between the changes in PaCO2 and CFV. 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 CFV 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 (18). 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 CFVMCA and CFVACA during 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 change 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 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, in the development of syncope in healthy individuals, in previous work, voluntary hyperventilation during supine LBNP was found to produce significant hypocapnia, dramatic reductions in CFVMCA, 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 cerebrohypoperfusion in patients and subjects who become or-
thostatically intolerant (15, 28, 29, 40). Similarly, we found greater decreases in $CFV_{ACA}$ than in $CFV_{MCA}$ during HUT, although they were not significant ($P = 0.056$). However, this was not the case in the three subjects who became presyncopal in this study, because they demonstrated significantly reduced end-tilt $CFV_{MCA}$ (70.6 ± 6.3%) and $CFV_{ACA}$ (71.9 ± 8.3%) without a relative frontal hyperperfusion (i.e., greater reduction in $CFV_{ACA}$). However, because only three subjects became presyncopal, it is possible that a larger number would have shown a frontal cerebral hyperperfusion.

**Limitations.** It must be considered that the relation between ventilation, hypocapnia, and cerebrovascular tone during HUT is different between healthy volunteers, as studied in the present and previous experiments (22, 38), and patients who are chronically thostatically intolerant (27). Also we must consider that blood samples were drawn over 30-s periods. Because presyncopal symptoms may appear rapidly, it is possible that an increase in $V_A$ in the last 15 s of HUT was not detected. However, examination of $V_e$ on a breath-by-breath basis during the same period did not demonstrate a discordant increase.

A primary limitation of TCD evaluations is the assumption that MCA diameter at the point of insonation is not changing. In a recent examination of this issue, Serrador et al. (37) used MRI measures of MCA diameter combined with TCD measures of CFV during LBNP and various levels of PET$_{CO_2}$. Although CFV changed considerably in response to the experimental manipulations, no change in MCA diameter at the M1 segment was found. Other work examined the lower limit of cerebral autoregulation using a combination of ganglionic blockade and LBNP to create hypotension. These studies found significant correlations between CBF (using $^{133}$Xe) and mean flow velocity: $r^2 = 0.60$ (19) and $r^2 = 0.73$ (20).

Finally, to estimate CVR, we must assume that intracranial pressure changes are minimal. Recently, Dawson et al. (9) found that internal jugular venous pressure decreased from ~10 to ~5 mmHg in the transition from the supine to the seated position. If intracranial pressure were to decrease ~5 mmHg throughout tilt, the increase in CVR would be ~5% greater, suggesting that we underestimated the increase in CVR. To minimize the possible effect of increased pulsatility in finger measures of blood pressure, mean pressure was used to calculate CVR (35).

The present study has documented development of postural hypocapnia through reductions in $P_{aCO_2}$ and $PET_{CO_2}$ during HUT. We have shown, however, a dissociation between the fall in $P_{aCO_2}$ and the decline in cerebral mean flow velocity. These observations suggest that other mechanisms, in addition to the decline in $P_{aCO_2}$, are responsible for the increase in CVR and the reduction in cerebral flow during HUT.

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