Transient influence of end-tidal carbon dioxide tension on the postural restraint in cerebral perfusion

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Departments of 1Anesthesiology and 2Internal Medicine, Laboratory for Clinical Cardiovascular Physiology, and 3AMC Center for Heart Failure Research, Academic Medical Center, University of Amsterdam, Amsterdam; and 4Department of Anesthesiology and 5The Copenhagen Muscle Research Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Submitted 8 September 2008; accepted in final form 30 June 2009

Immink RV, Truijen J, Secher NH, Van Lieshout JJ. Transient influence of end-tidal carbon dioxide tension on the postural restraint in cerebral perfusion. J Appl Physiol 107: 816–823, 2009. First published July 2, 2009; doi:10.1152/japplphysiol.91198.2008.—In the upright position, cerebral blood flow is reduced, maybe because arterial carbon dioxide partial pressure (PaCO2) decreases. We evaluated the time-dependent influence of a reduction in PaCO2, as indicated by the end-tidal PCO2 tension (PETCO2), on cerebral perfusion during head-up tilt. Mean arterial pressure, cardiac output, middle cerebral artery mean flow velocity (MCA Vmean), and dynamic cerebral autoregulation at supine rest and 70° head-up tilt were determined during free breathing and with PETCO2 clamped to the supine level. The postural changes in central hemodynamic variables were equivalent, and the cerebrovascular autoregulatory capacity was not significantly affected by tilt or by clamping PETCO2. In the first minute of tilt, the decline in MCA Vmean (10 ± 4 vs. 3 ± 4 cm/s; mean ± SE; P < 0.05) and PETCO2 (6.8 ± 4.3 vs. 1.7 ± 1.6 Torr; P < 0.05) was larger during spontaneous breathing than during isocapnic tilt. However, after 2 min in the head-up position, the reduction in MCA Vmean was similar (7 ± 5 vs. 6 ± 3 cm/s), although the spontaneous decline in PETCO2 was maintained (P < 0.05 vs. isocapnic tilt). These results suggest that the potential contribution of PaCO2 to the postural reduction in MCA Vmean is transient, leaving the mechanisms for the sustained restraint in MCA Vmean to be identified.

blood pressure; cardiac output; cerebral blood velocity

WHEN UPRIGHT, MIDDLE CEREBRAL ARTERY MEAN FLOW VELOCITY (MCA Vmean) (28, 36) AND CEREBRAL OXYGENATION (17) ARE LOWER THAN DURING SUPIE REST, INDICATING THAT CEREBRAL BLOOD FLOW (CBF) IS REDUCED. THAT IS THE CASE, ALTHOUGH THE POSTURAL DECLINE IN MEAN ARTERIAL PRESSURE (MAP) AT THE LEVEL OF THE BRAIN IS MINIMAL, BECAUSE MAP AT HEART LEVEL INCREASES (17).

A LOW ARTERIAL CARBON DIOXIDE PARTIAL PRESSURE (PaCO2) REDUCES CBF BY CEREBRAL VASOCONSTRICTION (27) INDEPENDENTLY OF CEREBRAL AUTOREGULATION (CA), KNOWN AS THE CO2 REACTIVITY OF THE BRAIN CIRCULATION. ACCORDINGLY, ONE EXPLANATION FOR THE POSTURAL DECLINE IN CBF IS THE CONCOMITANT REDUCTION IN PaCO2, BY AN INCREASE IN PULMONARY MINUTE VENTILATION (10, 31). CARDIAC OUTPUT (Q) ALSO DECLINES ON STANDING (18), AND ITS DISTRIBUTION OVER THE LUNGS CHANGES (39) WITH AN ALTERATION IN THE VENTILATION-PERFUSION RATIO (21) AND AN OVERESTIMATE OF THE POSTURAL REDUCTION IN THE PaCO2, BY END-TIDAL PCO2 (PETCO2) (3, 7). IN SUPINE HUMANS, PETCO2 IS AN ADEQUATE REFLECTION OF PaCO2, BUT, WHEN THE POSTURAL REDUCTION IN MCA Vmean IS RELATED TO PaCO2 RATHER THAN TO PETCO2, IT EXPLAINS ONLY ABOUT ONE-HALF OF THE POSTURAL DECLINE IN MCA Vmean (21, 45).

No data are available on the effects of PCO2 on CBF during adaptation to prolonged postural stress. We, therefore, evaluated the time-dependent influence of PaCO2, as indicated by PETCO2, to the decline in MCA Vmean during head-up tilt to a 70° position (HUT), testing the hypothesis that PaCO2, as indicated by PETCO2, has an only temporary influence on the postural fall in cerebral perfusion. To identify an influence of the reduction of PaCO2 on MCA Vmean during orthostatic stress, this study clamped PETCO2, to the supine value.

METHODS

Twenty healthy, nonsmoking subjects participated in this study at least 2 h after a light meal without caffeine-containing beverages in a room maintained at 22°C. Following instrumentation, the subjects rested in a supine position on a tilt table to record baseline values after 10 min. The subjects received verbal and written explanation of the objectives of the study and techniques employed, including possible risks associated with the study, and they provided written, informed consent in accordance with the Declaration of Helsinki, as approved by the Institutional Ethical Committee (MEC 01/147).

PaCO2-to-PETCO2 gradient. The postural change in PaCO2, and the PETCO2 is correlated, but the decrease in PETCO2 overestimates that in PaCO2: \[ \Delta P_{\text{ET-CO2}} = -2.75 + 0.84 \Delta P_{\text{ACO2}} \] (21). Based on these data, we assumed that PaCO2 was clamped when the PETCO2 was ~3 Torr below the supine value. To verify that assumption, in six male subjects [28 (range 23–34) yr, 72 (60–88) kg, 182 (173–194) cm] PaCO2 was sampled for 2 min before the subjects assumed the upright position and during the early postural adaptation associated with characteristic and marked changes in blood pressure and heart rate (HR) at 30, 60, 90, and 120 s (Fig. 1A) (51, 57).

We considered that invasive procedures increase the likelihood of (pre)vasovagal syncope during orthostatic stress (11, 29, 47), with changes in Q and systemic vascular resistance (SVR) preceding manifest syncope (48, 55). To avoid exposing the subjects to these potentially confounding effects of invasive instrumentation, PaCO2 was assessed noninvasively. To verify that approach, the steady-state change in PaCO2 to PETCO2 gradient \( \Delta (\text{a-ET}) \text{PCO2} \) was determined twice in four male subjects [26 (22–30) yr, 74 (63–92) kg, 183 (171–188) cm], both after 5 min of supine rest and during 70° HUT with free breathing and when blood pressure and HR had stabilized (51, 57). Subsequently, the inspired PCO2 was increased by using a modified PETCO2 clamping device (see below) until PaCO2 was equivalent to the supine value allowing for determination of \( \Delta (\text{a-ET}) \text{PCO2} \) (Fig. 1B).

For determination of \( \Delta (\text{a-ET}) \text{PCO2} \), a cannula (1.1 mm inner diameter, 20 gauge) was introduced into the brachial artery of the non-dominant arm under local anesthesia (2% lidocaine) and connected to a pressure monitoring system (Hewlett Packard, Andover, MA). Blood samples for PaCO2, arterial O2 pressure (PaO2), O2 saturation
(SaO₂), and pH were obtained anaerobically in heparinized syringes and analyzed immediately on an OSM-500 and ABL-3 apparatus (Radiometer, Copenhagen, Denmark) at 37°C. PETCO₂ was followed by a capnograph (Datex Normocap 200), with the sample line mounted in the mouthpiece of the rebreathing device.

**PETCO₂ clamping.** To maintain the supine PaCO₂ during tilt, we used a modified contrivance clamp developed by Banzett et al. (5). This method uses a functionally variable dead space to maintain alveolar ventilation by applying a self-regulating partial rebreathing system that is independent of changes in breathing frequency and/or tidal volume and maintains PETCO₂ within ±1 Torr of the preset value (5).

To reduce inspiratory pressure, the dimension of the flexible reservoir tube was modified to 7.5-cm inner diameter by 100-cm stiff polystyrene tube, and we added a T-junction in the inspiratory limb of the clamping device to switch between spontaneous breathing and isocapnia (Fig. 2). The mouthpiece and nose clip needed to clamp PETCO₂ were also used during spontaneous breathing to account for potential changes in breathing pattern and systemic hemodynamic variables. During spont-
Supine rest. The cerebrovascular effects of PaCO₂ were quantified as contrivance. Steady-state PETCO₂ clamping was reached within 15 min offline analysis. MAP and MCA analog-to-digital converted at 100 Hz and stored on hard disk for offline analysis. MAP and MCA were recorded and verified by maintained PETCO₂ during hyperventilation. After adding CO₂ to inspired air in the upright position to increase PaCO₂ of 34 Torr, PETCO₂ was 38 ± 2 Torr, with a PETCO₂ of 2.5 Torr, respectively. In the first 2 min following HUT, PaCO₂ decreased to 40.4 ± 0.7, 41.7 ± 0.7, 40.6 ± 0.9, and 40.9 ± 1.3 Torr at 30, 60, 90 and 120 s, respectively whereas PETCO₂ decreased from 38 ± 1 Torr after 1 min to 37 ± 1 Torr after 2 min (Fig. 4).

(a-ET)PCO₂ gradient during clamping. See Fig. 1B (n = 4). In the supine position, PaCO₂ and Pao2 were 41 ± 1 and 42 ± 1 Torr, respectively. During HUT with spontaneous breathing, ∆(a-ET)PCO₂ increased from 1.1 ± 0.4 to 3.8 ± 0.7 Torr, with a PETCO₂ of 34 ± 2 Torr and a PaCO₂ of 38 ± 2 Torr (P < 0.05). After adding CO₂ to inspired air in the upright position to clamp PaCO₂, 41 ± 2 Torr, PETCO₂ was 38 ± 2 Torr, with a ∆(a-ET)PCO₂ of 2.5 ± 0.4 Torr (Fig. 5). The CO₂ clamping procedure did not affect the PaO₂, SaO₂, or plasma pH.

Spontaneous breathing vs. isocapnic tilt. See Fig. 1C (n = 10). In the supine position, MAP was slightly lower than before isocapnic tilt (74 ± 4 vs. 77 ± 4 mmHg; P = 0.04), and that difference remained during HUT (87 ± 4 vs. 90 ± 4 mmHg; P = 0.04). The postural changes in HR (+21 ± 4 vs. +20 ± 4 beats/min), SV (−38 ± 3 vs. −36 ± 3%), Q (−20 ± 3 vs. −16 ± 3%), and SVR (+51 ± 8 vs. +44 ± 6%) after 2 min of HUT did not differ between spontaneous breathing and isocapnic tilt (Fig. 6). Before HUT, PETCO₂ was 44 ± 1 vs. 43 ± 2 Torr in the spontaneous breathing vs. the isocapnic
conditions. After 1 min in the spontaneous breathing HUT position, $\Delta_{PETCO2}$ stabilized at $6.8 \pm 4.3$ Torr. During isocapnic tilt, $\Delta_{PETCO2}$ was $-1.7 \pm 1.6$ Torr at 1 min, $-3.1 \pm 1.4$ Torr at 3 min, and stabilized after 5-min HUT at $-2.3 \pm 0.8$ Torr ($P < 0.05$ vs. spontaneous breathing). Resting MCA $V_{mean}$ was $64 \pm 5$ cm/s for both the spontaneous breathing and isocapnic tilted positions. After 1-min HUT, the postural re-
duction in MCA $V_{mean}$ for spontaneous breathing was larger ($10 \pm 4$ vs. $3 \pm 4$ cm/s; $P < 0.05$). However, from 2 min on,
this difference in postural reduction was no longer present ($8 \pm 1$ vs. $7 \pm 1$ cm/s; $P = 0.29$; Fig. 6). Changes in cerebrovascular resistance index were similar during spontaneous breathing $[1.17 \pm 0.06$ to $1.13 \pm 0.05$ mmHg$\cdot$(cm$\cdot$s$^{-1})^{-1}$] and isocapnic tilt $[1.23 \pm 0.06$ to $1.17 \pm 0.07$ mmHg$\cdot$(cm$\cdot$s$^{-1})^{-1}]$. Unaltered MAP-to-MCA $V_{mean}$ phase and gain across changes in $P_{CO2}$ indicated maintained CA (Table 1 and Fig. 7).

**DISCUSSION**

This study determined the temporal contribution of the postural decrease in $PETCO2$ on the decline in CBF velocity. Isocapnic tilting limited the postural reduction in MCA $V_{mean}$

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**Reference:**


![Fig. 4](http://jap.physiology.org/) Postural decrease is shown in $P_{CO2}$ vs. $PETCO2$ (solid line) in 6 subjects (means ± SE) in the early steady state of the head-up position. In the first 2 min following head-up tilt, $P_{CO2}$ did not change, whereas $PETCO2$ decreased to $37 \pm 1$ Torr after 2 min. Vertical dotted line indicates the onset of tilt.

![Fig. 5](http://jap.physiology.org/) Postural change in $P_{CO2}$ vs. $PETCO2$. Postural decrease is shown in $P_{CO2}$ vs. $PETCO2$ in 13 subjects (shaded circles; adapted from Ref. 21). The postural change are shown in $P_{CO2}$ to $PETCO2$ for 4 subjects unclamped (solid circles) and later clamped to maintain the $PETCO2$ (open circles).

![Fig. 6](http://jap.physiology.org/) Carbon dioxide, cerebrovascular, and systemic hemodynamic responses to spontaneous breathing tilt and isocapnic tilt. Averaged tilt responses are shown of 10 healthy subjects ± SE. $PETCO2$, middle cerebral artery mean blood velocity (MCA $V_{mean}$), mean arterial blood pressure (MAP), heart rate (HR), and percent changes to supine of stroke volume (SV), cardiac output (Q), and systemic vascular resistance (SVR) during spontaneous breathing tilt (solid circles) and isocapnic tilt (open circles) are shown. Vertical dotted line indicates the moment of head-up tilt. Each dot represents the mean value of 10 s. $*P < 0.05$, spontaneous breathing vs. isocapnic.
only during the first minute of HUT, as the postural decline in MCA $V_{\text{mean}}$ was independent of PaCO$_2$ for the $\sim$4-Torr PCO$_2$ difference between the supine and the upright position. The data suggest that the postural decrease in MCA $V_{\text{mean}}$ coincides with, but is not explained by, a reduction in PaCO$_2$, indicating that other factors dominate the reduction in MCA $V_{\text{mean}}$ during posture.

MCA $V_{\text{mean}}$ evaluated the postural and PCO$_2$-related changes in cerebral perfusion, assuming that changes in MCA $V_{\text{mean}}$ are representative of those in CBF (6). This was the case, although transcranial Doppler monitors blood velocity rather than flow rate and changes in the diameter of the insonated vessel modulate velocity independently from flow. Yet the large cerebral arteries are conduit rather than resistance vessels, and

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<th>Spontaneous Breathing</th>
<th>Isocapnic Breathing</th>
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<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
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<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
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<tr>
<td>MAP power, mmHg$^2$.Hz$^{-1}$</td>
<td>5.4±1.6</td>
<td>15.1±3.6*</td>
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<tr>
<td>$V_{\text{mean}}$ power, (cm.$^\cdot$s$^{-1}$)$^2$.Hz$^{-1}$</td>
<td>7.3±2</td>
<td>20.5±4.3*</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.7±0.1</td>
<td>0.8±0.1*</td>
</tr>
<tr>
<td>Phase, °</td>
<td>48±6</td>
<td>34±6</td>
</tr>
<tr>
<td>Gain, (cm.$^\cdot$s$^{-1}$).mmHg$^{-1}$</td>
<td>1.1±0.1</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>CVRi, mmHg/(cm.$^\cdot$s$^{-1}$)$^{-1}$</td>
<td>1.17±0.06</td>
<td>1.13±0.05*</td>
</tr>
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Values are means ± SE. Low-frequency variability of mean arterial pressure (MAP power), mean middle cerebral artery blood velocity ($V_{\text{mean}}$ power), coherence, phase, gain, and cerebrovascular resistance index (CVRi) in the supine position and during 70° head-up tilt are given. *$P < 0.05$ vs. supine.

Fig. 7. Power spectra, MAP to MCA $V_{\text{mean}}$ coherence, phase, and gain during spontaneous breathing and isocapnia in the supine and upright position. Shown are averaged power spectra of MAP and MCA $V_{\text{mean}}$, and MAP to MCA $V_{\text{mean}}$ coherence, phase, and gain of 10 subjects ± SE during spontaneous breathing (solid line) and isocapnia (shaded line) in the supine position (top) and upright (bottom).
changes in MAP within the physiological range appear to have negligible effects on the diameter of the insonated artery (44). Observations during craniotomy reveal that the vessel diameter does not change during variations in MAP within a magnitude that surpasses the changes manifest in response to orthostasis (14). Also, orthostatic stress, as simulated by lower body negative pressure, or changes in PCO₂ do not alter the diameter of the MCA as assessed with magnetic resonance imaging (46) and changes in MCA V̇mean follow cerebral ⁴⁴CO₂ clearance (6, 44). Thus MCA V̇mean increases in proportion to CBF (24, 25, 44) and internal carotid flow (19), and constancy of the MCA diameter during postural stress relates changes in V̇mean to those in CBF (46).

**Posture and PCO₂.** A tilt-induced reduction in MCA V̇mean with PetCO₂ clamped is reported (8). However, in that study, inequalities in MCA V̇mean between the control state before isocapnic tilt vs. spontaneous breathing tilt precluded quantification of the contribution of PaCO₂ to the postural decrease in MCA V̇mean. A prerequisite for the present study was that the steady-state hemodynamic condition was comparable for spontaneous breathing and isocapnic tilt. These requirements were fulfilled apart from a small expected difference in MAP that did not change with posture (49).

Association between the initial postural decline in PaCO₂ and MCA V̇mean was suggested by Cencetti et al. (10), expressing PaCO₂ as PetCO₂. For the supine position, changes in PetCO₂ correlated with those in PaCO₂ (58). However, in the upright position, ventilation increases with a reduction in lung perfusion and a gravitational blood pressure gradient over the lung (15). In upright humans, distribution of lung ventilation and perfusion by gravity (40) overestimate the postural decrease in PaCO₂ by the PetCO₂ (3, 7, 21, 45). Accordingly, applying the Δ(a-ET)PCO₂, we considered PaCO₂ to be clamped when PetCO₂ decreased by 3 Torr during posture.

**Posture and critical closing pressure.** Adaptation of CBF to orthostatic stress is conceptually linked to critical closing pressure (CrCP) (38). In the rabbit, the relationship between CrCP and intracranial pressure is linear, and CrCP decreases with arterial hypotension (38). Königst and Gränäde (26) demonstrated in the cat an increase in venous pressure not to influence tissue pressure for as long as venous pressure remains below tissue pressure. Only when pressures are equal does the collapse of the outflow vein disappear, and the two pressures increase in parallel (26). The implication is that, for as long as there is a venous outflow resistance, the effect of venous pressure on intracranial pressure is minimal. Accordingly, with the head at head level, cerebral venous pressure (V̇PCRB) rises linearly with end-expiratory airway pressure (52). However, when the head is elevated, V̇PCRB is affected only by a large increase in central venous pressure. Thus jugular venous collapse serves as a resistance to the transmission of central venous pressure to V̇PCRB and supports that, in the upright position, a Starling resistor-type mechanism becomes operative (13, 32). These observations are consistent with the fact that the CrCP is under the influence of the cerebral venous outflow pressure and a variable venous outflow resistance (4, 26). CO₂ has a significant influence on cerebral vessels and CBF independent of CA (1, 37). In humans, CrCP cannot be assessed directly, and it remains uncertain whether a small decline in PaCO₂ modifies CrCP.

**Posture and cerebral perfusion.** CBF remains relatively stable over a range of blood pressure (1, 50). Assumption of the upright position affects venous return and Q̇, whereas MAP at the level of the heart is maintained by a sympathetically mediated increase in SVR (16). In the upright position, the cerebral arteries are positioned above the heart, and their perfusion pressure is reduced (41). Both the position of the cerebral circulation and the reduction in Q̇ challenge CBF, and, although the postural reduction in cerebral perfusion may be limited by cerebral autoregulatory mechanisms, global CBF (42), MCA V̇mean (28, 36), and cerebral oxygenation (17) decrease. CA is also affected by the basal vascular tone. Aaslid et al. (2) demonstrated a relationship between PaCO₂ and CA, with a strong influence of PaCO₂ on MCA V̇mean assumed to reflect changes in cerebral vascular smooth muscle tone (33, 34). In the present study, CA was maintained across the changes in PCO₂ associated with posture change. Autonomic neural control of the cerebral circulation is tonically active (33). Evidence for sympathetic control of the cerebral circulation in humans was identified by demonstrating that CBF and, in parallel, MCA V̇mean declines in response to trigeminal ganglion stimulation (56) and increases following stellate ganglion blockade (20, 53). A relationship between CBF and Q̇ was found by demonstrating that both the MCA V̇mean and the near-infrared spectrophotometry determined cerebral oxygenation decrease in association with the postural reduction in Q̇ (44). This reduction in cerebral perfusion takes place even though MAP increases (54), further indicating an important role of sympathetic activation for regulation of CBF (44). In support, both MCA V̇mean and cerebral oxygenation increase when the standing position is supplemented by a leg muscle tensing maneuver that attenuates sympathetic activity by enhancing Q̇ (54). Also, Q̇ and MCA V̇mean change concordantly with, respectively, volume expansion and depletion (12, 32). Evidence for an influence of autonomic neural activity on cerebral hemodynamics in humans is the finding that noradrenaline plasma kinetic measurements across the brain reflect cerebrovascular sympathetic activity (30).

This study suggests that the partial contribution of PaCO₂ to the postural reduction in cerebral perfusion is limited to the first minute of tilt. This finding indicates that, after this first minute, other factors than PaCO₂ dominate the postural reduction in MCA V̇mean, and the postural reduction in Q̇ supports that Q̇ is likely to have an independent influence on cerebral perfusion.

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