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

**Rogier V. Immink,1,3 Jasper Truijen,2,3 Niels H. Secher,4,5 and Johannes J. Van Lieshout2,3**

*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*

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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.

When upright, middle cerebral artery mean flow velocity (MCA Vmean) (28, 36) and cerebral oxygenation (17) are lower than during supine 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).

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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).

The postural decrease in PaCO2, and the PETCO2–PaCO2 gradient. The postural change in PaCO2, and the PETCO2–PaCO2 gradient, was larger during supine rest and during 70° 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.
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 spon-

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**Fig. 1.** Protocol. A: determination of the change in arterial PCO₂ (PaCO₂) to end-tidal PCO₂ (PETCO₂) gradient [Δ(a-ET)PCO₂] directly after assuming the upright position (n = 6). B: determination to what level the PETCO₂ should be increased in the upright position, by using the CO₂ clamping contrivance, to reach a PaCO₂ that is comparable to the supine level (n = 4). C: spontaneous vs. isocapnic tilt (n = 10). Open bars indicate spontaneous breathing. Open to shaded bars indicate adjusting the clamping contrivance and creating the CO₂ clamp. Shaded bars indicate an adequate CO₂ clamped condition.

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**Fig. 2.** Experimental setup for the alveolar ventilation clamp. In the supine position, a continuous flow of pressurized air, adjusted to just below minute ventilation, supplies the alveolar ventilation clamp via a heater/humidifier. The pressurized air will be collected in a bag (solid arrows). During expiration (shaded arrows), the one-way valve (V₁) closes, and this forces the expiratory air into the rebreath tube. The air already present in the expiratory tube leaves the circuit via an one-way valve (V₂). During inspiration, V₁ opens and V₂ closes, and the collected pressurized air from the bag is inhaled. When the subject increases minute ventilation, the air pressure in the circuit tends to decrease, a low pressure spring valve (sV) opens, and carbon dioxide containing air from the rebreath tube (shaded) is inhaled (dotted arrows). For spontaneous ventilation, a valve in T₁ closes the inspiratory limb of the circuit, and the subject inhales room air (dashed arrow).
CO2 AND THE POSTURAL CEREBROVASCULAR RESPONSE

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 were analog-to-digital converted at 100 Hz and stored on hard disk for analysis, the subjects rested in a supine position on a tilt table to record 70° head-up during spontaneous breathing. Following instrumentation during HUT, 10 noninvasively instrumented subjects [3 women, 28 (range 21–36) yr, 74 (59–85) kg, 184 (175–198) cm] were tilted 70° head-up during spontaneous breathing. Following instrumentation, the subjects rested in a supine position on a tilt table to record baseline values for 5 min. After 5 min in the head-up position, the subjects were returned to supine and rested for 20 min. Thereafter, the tilt was repeated with the postural reduction in PETCO2 offset by using the clamping device (isocapnic tilt; Fig. 1C).

Arterial pressure was measured with a Finapres (model 5; the Netherlands Organization for Applied Scientific Research, Biomedical Instrumentation, TNO-BMI, Amsterdam). The cuff was applied to the midphalanx of the middle finger of the dominant hand placed at heart level and in the Finapres device; a built-in expert system (Physiocal) was operative to establish and adjust a proper volume clamp set point (9). Stroke volume (SV) was calculated from the blood pressure waveform using the model flow method, incorporating age, sex, height, and weight of the subjects (BeatScope 1.0 software; TNO TPD; Biomedical Instrumentation, Amsterdam, The Netherlands) (23). This technique tracks SV during moderate hypocapnia (∼PETCO2 = 30 Torr) induced by orthostatic stress (18). The proximal segment of the right MCA was insonated (Multidop X4, Sipplingen, Germany) through the posterior temporal ultrasound window (1). Once the optimal signal-to-noise ratio was obtained, the probe was covered with ultrasonic gel and secured with a headband (Mark 600, Spencer Technologies, Seattle, WA). PETCO2 was followed by a capnograph with the sample line mounted in the mouthpiece of the rebreathing device. The inspiratory PCO2 was increased to the preset PETCO2 until it was within 3 Torr of the supine value by the clamping device (isocapnic tilt; Fig. 1C).

The signals of finger blood pressure, the envelope curve of the transcranial Doppler spectrum, PETCO2, and a marker signal were analog-to-digital converted at 100 Hz and stored on hard disk for offline analysis. MAP and MCA Vmean were the integral over one heartbeat, HR was the inverse of the interbeat interval, and SVR was the ratio of MAP and Q, with SV, Q, and SVR expressed relative to supine rest. The cerebrovascular effects of PaCO2 were quantified as cerebral vascular resistance index from MAP and MCA Vmean, accounting for the difference in hydrostatic pressure between the site of blood pressure recording and MCA insonation (43).

Dynamic CA. Dynamic CA was determined by calculating the power spectra of pressure and velocity in the frequency domain from a 2-min episode of beat-to-beat data of MAP and MCA Vmean for supine and upright positions with spontaneous breathing and isocapnic with discrete Fourier transform, after spline interpolation with 4 Hz (22). Results were expressed as the integrated area in the low-frequency range (0.07–0.15 Hz). To examine the strength between low-frequency MAP and MCA Vmean, coherence signified that the two signals covary. The squared coherence function reflects the fraction of output power (MCA Vmean) that can be related to the input power (MAP). With squared coherence > 0.5 (35), the MCA Vmean to MAP phase lead and gain were obtained from the MAP to MCA Vmean cross spectrum. Phase was considered positive when MCA Vmean leads MAP.

Statistical analysis. Data were resampled at 0.1 Hz by polynomial interpolation, expressed as means ± SE, and changes over time and between spontaneous breathing and isocapnic tilt were examined by two-way ANOVA for repeated measures. Post hoc multiple comparisons were performed using the Holm-Sidak method. Differences in responses between body positions were examined by parametric or nonparametric tests where appropriate, and a P value < 0.05 was considered to indicate a statistically significant difference.

RESULTS

Effects of HUT on the (a-ET)PCO2 gradient. See Fig. 1A (n = 6). In the supine position at 4 and 2 min before HUT, PaCO2 was 42.8 ± 0.6 and 42.3 ± 0.7 Torr, and PETCO2 was 39 ± 1 and 40 ± 1 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, PETCO2 and PaCO2 were 41 ± 1 and 42 ± 1 Torr, respectively. During HUT with spontaneous breathing, Δ(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 Δ(a-ET)PCO2 of 2.5 ± 0.4 Torr (Fig. 5). The CO2 clamping procedure did not affect the PaO2, SæO2, 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

Fig. 3. PETCO2 clamping. Representative example is shown of PETCO2 response in one subject to hyperventilation (solid bar) during spontaneous breathing (A) and with isocapnic clamp (B).
conditions. After 1 min in the spontaneous breathing HUT position, PETCO2 stabilized at 6.8 ± 4.3 Torr. During isocapnic tilt, PETCO2 was 1.7 ± 1.6 Torr at 1 min, 0.7 ± 1.4 Torr at 3 min, and stabilized after 5-min HUT at −2.3 ± 0.8 Torr (P < 0.05 vs. spontaneous breathing). Resting MCA V_mean was 64 ± 5 cm/s for both the spontaneous breathing and isocapnic tilted positions. After 1-min HUT, the postural reduction in MCA V_mean for spontaneous breathing was larger (10 ± 4 vs. 3 ± 4 cm/s; P < 0.05). However, from 2 min on, this difference in postural reduction was no longer present (8 ± 1 vs. 7 ± 1 cm/s; P = 0.29; Fig. 6). Changes in cerebrovascular resistance index were similar during spontaneous breathing [1.17 ± 0.06 to 1.13 ± 0.05 mmHg·(cm·s^{-1})^{-1}] and isocapnic tilt [1.23 ± 0.06 to 1.17 ± 0.07 mmHg·(cm·s^{-1})^{-1}]. Unaltered MAP-to-MCA V_mean phase and gain across changes in Pco2 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.
only during the first minute of HUT, as the postural decline in MCA $V_{\text{mean}}$ was independent of PaCO$_2$ for the ~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

Table 1. Postural and carbon dioxide influence on dynamic cerebral autoregulation

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous Breathing</th>
<th>Isocapnic Breathing</th>
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<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
</tr>
<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$^3$·s$^{-1}$)·mmHg$^{-1}$·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$^3$·s$^{-1}$)·mmHg$^{-1}$</td>
<td>1.1±0.1</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>CVR$_i$, mmHg·(cm$^3$·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 (CVR$_i$) in the supine position and during 70° head-up tilt are given. *$P < 0.05$ vs. supine.

Fig. 7. Power spectra, MAP to $V_{\text{mean}}$ 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 Vmean follow cerebral 133Xe clearance (6, 44). Thus MCA Vmean 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 Vmean to those in CBF (46).

Posture and PaCO2. A tilt-induced reduction in MCA Vmean with PetCO2 clamped is reported (8). However, in that study, inequalities in MCA Vmean between the control state before isocapnic tilt vs. spontaneous breathing tilt precluded quantification of the contribution of Paco2 to the postural decrease in MCA Vmean. 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 Vmean 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 Delta EO2, 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). Kongstad and Grønå (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 heart level, cerebral venous pressure (VPCRB) rises linearly with end-expiratory airway pressure (52). However, when the head is elevated, VPCRB 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 VPCRB and supports that, in the upright position, a Starling resistor-type mechanism becomes operative (13, 52). 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 Q, 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 Q challenge CBF, and, although the postural reduction in cerebral perfusion may be limited by cerebral autoregulatory mechanisms, global CBF (42), MCA Vmean (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 Vmean assumed to reflect changes in cerebral vascular smooth muscle tone (33, 34). In the present study, CA was maintained across the changes in Paco2 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 Vmean declines in response to trigeminal ganglion stimulation (56) and increases following stellate ganglion blockade (20, 53). A relationship between CBF and Q was found by demonstrating that both the MCA Vmean and the near-infrared spectrophotometry determined cerebral oxygenation decrease in association with the postural reduction in Q (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 Vmean and cerebral oxygen increase when the standing position is supplemented by a leg muscle tensing maneuver that attenuates sympathetic activity by enhancing Q (54). Also, Q and MCA Vmean 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 Vmean, and the postural reduction in Q supports that Q is likely to have an independent influence on cerebral perfusion.

REFERENCES


