Withstanding the flow

*Human cardiovascular control during postural challenges*

Truijen, J.

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Chapter 8

TRANSIENT INFLUENCE OF END-TIDAL CARBON DIOXIDE TENSION ON THE POSTURAL RESTRAINT IN CEREBRAL PERFUSION

R.V. IMMINK, J. TRUIJEN, N.H. SECHER, J.J. VAN LIESHOUT

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ABSTRACT

Background
In the upright position cerebral blood flow is reduced maybe because arterial carbon dioxide partial pressure ($P_{a,CO_2}$) decreases. We evaluated the time-dependent influence of a reduction in $P_{a,CO_2}$ as indicated by the end-tidal $P_{CO_2}$ tension ($P_{ET,CO_2}$) on cerebral perfusion during head-up tilt.

Methods
Mean arterial pressure, cardiac output, middle cerebral artery mean flow velocity (MCA $V_{mean}$), and dynamic cerebral autoregulation at supine rest and 70° head-up tilt were determined during free breathing and with $P_{ET,CO_2}$ clamped to the supine level.

Results
The postural changes in central hemodynamic variables were equivalent and the cerebrovascular autoregulatory capacity was not significantly affected by tilt or by clamping $P_{ET,CO_2}$. In the first minute of tilt, the decline in MCA $V_{mean}$ (10 ± 4 vs. 3 ± 4 cm s⁻¹; mean ± s.e.m; $P < 0.05$) and $P_{ET,CO_2}$ (6.8 ± 4.3 vs. 1.7 ± 1.6 mmHg; $P < 0.05$) was larger during spontaneous breathing than during isocapnic tilt. However, after two minutes in head-up position, the reduction in MCA $V_{mean}$ was similar (7 ± 5 vs. 6 ± 3 cm s⁻¹), although the spontaneous decline in $P_{ET,CO_2}$ was maintained ($P < 0.05$ vs. isocapnic tilt).

Conclusion
These results suggest that the potential contribution of $P_{a,CO_2}$ to the postural reduction in MCA $V_{mean}$ is transient, leaving the mechanisms for the sustained restrain in MCA $V_{mean}$ to be identified.
INTRODUCTION

When upright, middle cerebral artery mean flow velocity (MCA $V_{\text{mean}}$)$^{247, 249}$ and cerebral oxygenation$^{250}$ 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.$^{250}$

A low arterial carbon dioxide partial pressure ($P_{a,CO_2}$) reduces CBF by cerebral vasoconstriction$^{36}$ independently of cerebral autoregulation, known as the CO$_2$ reactivity of the brain circulation. Accordingly, one explanation for the postural decline in CBF is the concomitant reduction in $P_{a,CO_2}$ by an increase in pulmonary minute ventilation.$^{37, 38}$ Cardiac output (CO) also declines upon standing$^5$ and its distribution over the lungs changes$^{481}$ with an alteration in the ventilation perfusion ratio$^3$ and an overestimate of the postural reduction in the $P_{a,CO_2}$ by end-tidal $P_{CO_2}$ ($P_{ET,CO_2}$)$^{482, 483}$ In supine humans $P_{ET,CO_2}$ is an adequate reflection of $P_{a,CO_2}$ but when the postural reduction in MCA $V_{\text{mean}}$ is related to $P_{a,CO_2}$ rather than to $P_{ET,CO_2}$, it explains only about half of the postural decline in MCA $V_{\text{mean}}$.$^{3, 484}$

No data are available on the effects of $P_{CO_2}$ on CBF during adaptation to prolonged postural stress. We therefore evaluated the time dependent influence of $P_{a,CO_2}$ as indicated by $P_{ET,CO_2}$ to the decline in MCA $V_{\text{mean}}$ during head-up tilt to a $70^\circ$ position (HUT) testing the hypothesis that $P_{a,CO_2}$ as indicated by $P_{ET,CO_2}$ has an only temporary influence on the postural fall in cerebral perfusion. In order to identify an influence of the reduction of $P_{a,CO_2}$ on MCA $V_{\text{mean}}$ during orthostatic stress, this study clamped $P_{ET,CO_2}$ to the supine value.

METHODS

Twenty healthy non-smoking subjects participated in this study at least two hours 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).

Arterial-to-end-tidal CO$_2$ pressure gradient

The postural change in $P_{a,CO_2}$ and the $P_{ET,CO_2}$ is correlated but the decrease in $P_{ET,CO_2}$ overestimates that in $P_{a,CO_2}$ ($\Delta P_{ET,CO_2} = -2.75 + 0.84 \Delta P_{a,CO_2}$).$^3$ Based on these data, we assumed that $P_{a,CO_2}$ was clamped when the $P_{ET,CO_2}$ was $\sim$3 mmHg below the supine value. To verify that assumption, in 6 male subjects (28 (23 – 34) year), 72 (60 - 88 kg), 182 (173 - 194 cm) $P_{a,CO_2}$ was sampled 4 respectively 2 min before assuming 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 (Figure 8.1A).$^{76, 142}$
We considered that invasive procedures increase the likelihood of (pre)vasovagal syncope during orthostatic stress with changes in CO and systemic vascular resistance (SVR) preceding manifest syncope.

In order to avoid exposing the subjects to these potentially confounding effects of invasive instrumentation, $P_{a,CO_2}$ was assessed non-invasively. To verify that approach, the steady-state $\Delta P(a\text{-}ET,CO_2)$ was determined twice in 4 male subjects (26 (22 – 30) year), 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. Subsequently, the inspired $P_{ET,CO_2}$ was increased by using a modified $P_{ET,CO_2}$ clamping device (see below) until $P_{a,CO_2}$ was equivalent to the supine value allowing for determination of $\Delta P(a\text{-}ET,CO_2)$ (Figure 8.1B)

For determination of $\Delta P(a\text{-}ET,CO_2)$, a cannula (1.1 mm ID, 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 $P_{a,CO_2}$, arterial O$_2$ pressure ($P_{a,O_2}$), O$_2$ saturation ($S_{a,O_2}$), and pH were obtained anaerobically in heparinised syringes and analysed immediately on an OSM-500 and ABL-3 apparatus (Radiometer, Copenhagen, Denmark) at 37° C. $P_{ET,CO_2}$, was followed by a
capnograph (Datex Normocap 200) with the sample line mounted in the mouthpiece of the rebreathing device.

$P_{ET,CO_2}$ clamping

To maintain the supine $P_{a,CO_2}$ during tilt we used a modified contrivance clamp developed by Banzett et al.\textsuperscript{489} 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 $P_{ET,CO_2}$ within ± 1 mmHg of the preset value.\textsuperscript{489} To reduce inspiratory pressure, the dimension of the flexible reservoir tube was modified to 7.5 cm ID 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 (Figure 8.2). The mouthpiece and nose clip needed to clamp $P_{ET,CO_2}$ were also used during spontaneous breathing to account for potential changes in breathing pattern and systemic hemodynamic variables. During spontaneous breathing, a valve closes the inspiratory limb of the clamp and allows for inhalation of room air. Prior to isocapnic tilt, the rebreathing loop device was opened when in the supine position. With the alveolar ventilation clamp in use, the amount of pressurized air provided was adjusted to just below supine minute ventilation. The $P_{CO_2}$ was considered clamped when, in the supine position, $P_{ET,CO_2}$ was equal to the value prior to HUT with spontaneous breathing (Figure 8.3).

Spontaneous breathing vs. isocapnic tilt

For determination of the time-dependent influence of a reduction in $P_{a,CO_2}$ on cerebral perfusion during HUT, 10 non-invasively instrumented subjects (3 women 28 (range 21-36 year), 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 $P_{ET,CO_2}$ offset by using the clamping device (isocapnic tilt; Figure 8.1C).
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.\textsuperscript{78} Stroke volume (SV) was calculated from the blood pressure waveform using the Model flow method incorporating age, gender, height, and weight of the subjects (BeatScope 1.0 software; TNO TPD; Biomedical

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Figure 8.2 Experimental set-up 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 (black arrows). During expiration (gray arrows), the one way valve ($V_1$) closes and this will force the expiratory air into the rebreath tube. The air already present in the expiratory tube leaves the circuit via an one way valve ($V_2$). During inspiration, $V_1$ opens and $V_2$ 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, and a low pressure spring valve (sV) opens and carbon dioxide containing air from the rebreath tube (grey) is inhaled (dotted arrows). For spontaneous ventilation, a valve in $T_1$ closes the inspiratory limb of the circuit and the subject inhales room air (dashed arrow).
Instrumentation; Amsterdam, The Netherlands). This technique tracks SV during moderate hypocapnia ($P_{ET,CO_2} = \sim 30$ mmHg) induced by orthostatic stress.\textsuperscript{5} The proximal segment of the right middle cerebral artery (MCA) was insonated (Multidop X4, Sipplingen, Germany) through the posterior temporal ultrasound window.\textsuperscript{490} 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). $P_{ET,CO_2}$ was followed by a capnograph with the sample line mounted in the mouthpiece of the rebreathing device. The inspiratory $P_{CO_2}$ was increased to the preset $P_{ET,CO_2}$ until it was within 3 mmHg of the supine value by the clamping contrivance. Steady-state $P_{ET,CO_2}$ clamping was reached within 15 min and verified by maintained $P_{ET,CO_2}$ during hyperventilation.

The signals of finger blood pressure, the envelope curve of the transcranial Doppler spectrum, $P_{ET,CO_2}$ and a marker signal were A/D converted at 100 Hz and stored on hard disk for off-line analysis. MAP and MCA $V_{mean}$ were the integral over one heartbeat, HR was the inverse of the interbeat interval, and SVR was the ratio of MAP and $CO_2$ with SV, CO and SVR expressed relative to supine rest. The cerebrovascular effects of $P_{A,CO_2}$ were quantified as cerebrovascular resistance index (CVRI) from MAP and MCA $V_{mean}$ accounting for the difference in hydrostatic pressure between the site of blood pressure recording and MCA insonation.\textsuperscript{491}

**Dynamic cerebral autoregulation**

Dynamic cerebral autoregulation (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 $V_{mean}$ in the supine and upright positions with spontaneous breathing and

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.3.png}
\caption{End-tidal carbon dioxide partial pressure ($P_{ET,CO_2}$) clamping. Representative example of the $P_{ET,CO_2}$ response in one subject to hyperventilation (black bar) during spontaneous breathing (Panel A) and with isocapnic clamp (Panel B).}
\end{figure}
isocapnia with discrete Fourier transform, after spline interpolation with 4 Hz. Results were expressed as the integrated area in the low frequency range (0.07 to 0.15 Hz). To examine the strength between low frequency MAP and MCA \( V_{\text{mean}} \) coherence signified that the two signals co-vary. The squared coherence function reflects the fraction of output power (MCA \( V_{\text{mean}} \)) that can be related to the input power (MAP). With squared coherence > 0.5, the MCA \( V_{\text{mean}} \) to MAP phase lead and gain were obtained from the MAP to MCA \( V_{\text{mean}} \) cross-spectrum. Phase was considered positive when MCA \( V_{\text{mean}} \) leads MAP.

**Statistical analysis**

Data were resampled at 0.1 Hz by polynomial interpolation, expressed as mean ± 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 non-parametric tests where appropriate and a \( p \) value <0.05 was considered to indicate a statistically significant difference.

**RESULTS**

*Effects of HUT on the arterial-to-end-tidal CO\(_2\) pressure gradient (Figure 8.1A; n=6)*

In the supine position at 4 and 2 min prior to HUT, \( P_{A,CO_2} \) was 42.8 ± 0.6 and 42.3 ± 0.7 mmHg, respectively, and \( P_{ET,CO_2} \) was 39 ± 1 and 40 ± 1 mmHg. In the first 2 minutes following HUT, \( P_{A,CO_2} \) decreased to 40.4 ± 0.7, 41.7 ± 0.7, 40.6 ± 0.9 and 40.9 ± 1.3 mmHg at 30, 60, 90 and 120 sec, respectively whereas \( P_{ET,CO_2} \) decreased from 38 ± 1 mmHg after 1 min to 37 ± 1 mmHg after 2 minutes (Figure 8.4).

![Figure 8.4 Arterial versus end-tidal carbon dioxide partial tension from supine to upright. Postural decrease in arterial carbon dioxide pressure (\( P_{A,CO_2} \): black circles) versus end-tidal carbon dioxide pressure (\( P_{ET,CO_2} \): black line) in 6 subjects mean ± SE in the early-steady state of the head up position. In the first 2 min following HUT, \( P_{A,CO_2} \) did not change whereas \( P_{ET,CO_2} \) decreased to 37 ± 1 mmHg after 2 min. Vertical dotted line indicates the onset of tilt.](image-url)
Arterial-to-end-tidal CO₂ pressure gradient during clamping (Figure 8.1B; n=4)

In the supine position, $P_{ET,CO_2}$ and $P_{a,CO_2}$ were 41 ± 1 and 42 ± 1 mmHg, respectively. During HUT with spontaneous breathing, $\Delta P_{(a-ET),CO_2}$ increased from 1.1±0.4 to 3.8±0.7 mmHg with a $P_{ET,CO_2}$ of 34 ± 2 mmHg and a $P_{a,CO_2}$ of 38 ± 2 mmHg ($P < 0.05$). After adding CO₂ to inspired air in the upright position to clamp $P_{a,CO_2}$ (41 ± 2 mmHg), $P_{ET,CO_2}$ was 38 ± 2 mmHg with a $\Delta P_{(a-ET),CO_2}$ of 2.5±0.4 mmHg (Figure 8.5). The CO₂ clamping procedure did not affect the $P_{a,O_2}$, $S_{a,O_2}$ or plasma pH.

Figure 8.5 Postural change in arterial vs. end-tidal carbon dioxide tension. Postural decrease in arterial carbon dioxide pressure ($P_{a,CO_2}$) vs. end-tidal carbon dioxide pressure ($P_{ET,CO_2}$) in 13 subjects (gray; adapted from ref.3) Black, the postural change in arterial to end-tidal carbon dioxide for 4 subjects unclamped (filled black circles) and later clamped to maintain the $P_{ET,CO_2}$ (open black circles).
Spontaneous breathing vs. isocapnic tilt (Figure 8.1C; n=10)

In the supine position, MAP was slightly lower than prior to 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 min⁻¹), SV (-38 ± 3% vs. -36 ± 3%), CO (-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 (Figure 8.6). Prior to HUT $P_{ET,CO_2}$ was 44 ± 1 vs. 43 ± 2 mmHg in the spontaneous breathing vs. the isocapnic conditions. After 1 min in the spontaneous breathing HUT position, $\Delta P_{ET,CO_2}$ stabilized at -6.8 ± 4.3 mmHg. During isocapnic tilt, $\Delta P_{ET,CO_2}$ was -1.7 ± 1.6 mmHg at 1 min, -3.1 ± 1.4 mmHg at 3 min and stabilized after 5 min HUT at -2.3 ± 0.8 mmHg (*P < 0.05 vs. spontaneous breathing). Resting MCA $V_{mean}$ was 64 ± 5 cm s⁻¹ for both the spontaneous breathing and isocapnic tilted
positions. After 1 min HUT, the postural reduction in MCA $V_{\text{mean}}$ for spontaneous breathing was larger ($10 \pm 4$ vs. $3 \pm 4$ cm·s$^{-1}$; $P < 0.05$). However, from 2 min on, this difference in postural reduction was no longer present ($8 \pm 1$ vs. $7 \pm 1$ cm·s$^{-1}$; $P = 0.29$; Figure 8.6). Changes in CVRi were similar during spontaneous breathing ($1.17 \pm 0.06$ to $1.13 \pm 0.05$ mmHg·cm$^{-1}$·s$^{-1}$) and isocapnic tilt ($1.23 \pm 0.06$ to $1.17 \pm 0.07$ mmHg·cm$^{-1}$·s$^{-1}$). Unaltered MAP-to-MCA $V_{\text{mean}}$ phase and gain across changes in $P_{CO_2}$ indicated maintained CA (Table 8.1 and Figure 8.7).

**Table 8.1 Postural and carbon dioxide influence on dynamic cerebral autoregulation**

<table>
<thead>
<tr>
<th>Breathing</th>
<th>Spontaneous</th>
<th>Isocapnic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>supine</td>
<td>upright</td>
</tr>
<tr>
<td>MAP power (mm Hg$^2$·Hz$^{-1}$)</td>
<td>5.4 ± 1.6</td>
<td>15.1 ± 3.6$^*$</td>
</tr>
<tr>
<td>$V_{\text{mean}}$ power ((cm·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 (degrees)</td>
<td>48 ± 6</td>
<td>34 ± 6</td>
</tr>
<tr>
<td>Gain ((cm·s$^{-1}$·mmHg$^{-1}$)</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>CVRi (mmHg·cm$^{-1}$·s$^{-1}$)</td>
<td>1.17 ± 0.06</td>
<td>1.13 ± 0.05$^*$</td>
</tr>
</tbody>
</table>

*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 70º head up tilt. $^*$ $p < 0.05$ vs. supine. Values are mean ± SE.
DISCUSSION

This study determined the temporal contribution of the postural decrease in $P_{ET,CO_2}$ on the decline in cerebral blood flow velocity. Isocapnic tilting limited the postural reduction in MCA $V_{mean}$ only during the first minute of HUT as the postural decline in MCA $V_{mean}$ was independent of $P_{a,CO_2}$ for the ~4 mmHg $P_{CO_2}$ difference between the supine and the upright position. The data suggest that the postural decrease in MCA $V_{mean}$ coincides with, but is not explained by a reduction in $P_{a,CO_2}$ indicating that other factors dominate the reduction in MCA $V_{mean}$ during posture.

MCA $V_{mean}$ evaluated the postural and $P_{CO_2}$ related changes in cerebral perfusion assuming that changes in MCA $V_{mean}$ are representative for those in CBF. 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 changes in MAP within the physiological range appear to have negligible effects on the diameter of the insonated

Figure 8.7 Power spectra, and MAP to MCA $V_{mean}$ coherence, phase and gain during spontaneous breathing and isocapnia in the supine and upright position. Averaged power spectra of mean arterial pressure (MAP) and middle cerebral artery mean blood velocity (MCA $V_{mean}$) and MAP to MCA $V_{mean}$ coherence, phase and gain of 10 subjects ± SE during spontaneous breathing (black line) and isocapnia (grey line) in the supine position (upper panels) and upright (lower panels).
artery. 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. Also orthostatic stress, as simulated by lower body negative pressure, or changes in $P_{CO_2}$ do not alter the diameter of the MCA as assessed with magnetic resonance imaging and changes in $V_{\text{mean}}$ follow cerebral $^{133}$Xe clearance. Thus, MCA $V_{\text{mean}}$ increases in proportion to CBF and internal carotid flow, and constancy of the MCA diameter during postural stress relates changes in $V_{\text{mean}}$ to those in CBF.

Posture and $P_{CO_2}$
A tilt-induced reduction in MCA $V_{\text{mean}}$ with $P_{ET,CO_2}$ clamped is reported. However, in that study inequalities in MCA $V_{\text{mean}}$ between the control state prior to isocapnic tilt vs. spontaneous breathing tilt precluded quantification of the contribution of $P_{a,CO_2}$ to the postural decrease in MCA $V_{\text{mean}}$. 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.

Association between the initial postural decline in $P_{a,CO_2}$ and MCA $V_{\text{mean}}$ was suggested by Cencetti et al. expressing $P_{a,CO_2}$ as $P_{ET,CO_2}$. For the supine position, changes in $P_{ET,CO_2}$ correlated with those in $P_{a,CO_2}$. However, in the upright position, ventilation increases with a reduction in lung perfusion and a gravitational blood pressure gradient over the lung. In upright humans, distribution of lung ventilation and perfusion by gravity overestimate the postural decrease in $P_{a,CO_2}$ by the $P_{ET,CO_2}$. Accordingly, applying the $\Delta P(a-ET),CO_2$ we considered $P_{a,CO_2}$ to be clamped when $P_{ET,CO_2}$ decreased by 3 mmHg during posture.

Posture and critical closing pressure
Adaptation of CBF to orthostatic stress is conceptually linked to critical closing pressure (CrCP). In the rabbit, the relationship between CrCP and intracranial pressure is linear and CrCP decreases with arterial hypotension. Kongstad and Grände 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 the collapse of the outflow vein disappears and the two pressures increase in parallel. 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 ($VP_{CRB}$) rises linearly with end-expiratory airway pressure. However, when the head is elevated, $VP_{CRB}$ 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 $VP_{CRB}$ and supports that in the upright position, a Starling resistor-type mechanism becomes operative. These observations are consistent with that the CrCP is under the influence of the cerebral venous outflow pressure and a variable venous outflow resistance. CO$_2$ has a significant influence on cerebral vessels and CBF independent of CA. In humans, CrCP cannot be assessed directly and it remains uncertain whether a
small decline in $P_{a,CO_2}$ modifies CrCP.

*Posture and cerebral perfusion*

CBF remains relatively stable over a range of blood pressure. Assumption of the upright position affects venous return and CO, whereas MAP at the level of the heart is maintained by a sympathetically mediated increase in SVR. In the upright position, the cerebral arteries are positioned above the heart and their perfusion pressure is reduced. Both the position of the cerebral circulation and the reduction in CO challenge CBF, and although the postural reduction in cerebral perfusion may be limited by cerebral autoregulatory mechanisms, global CBF, MCA $V_{\text{mean}}$, and cerebral oxygenation decrease. CA is also affected by the basal vascular tone. Aaslid et al. demonstrated a relationship between $P_{a,CO_2}$ and CA with a strong influence of $P_{a,CO_2}$ on MCA $V_{\text{mean}}$ assumed to reflect changes in cerebral vascular smooth muscle tone. In the present study, CA was maintained across the changes in $P_{CO_2}$ associated with posture change. Autonomic neural control of the cerebral circulation is tonically active. Evidence for sympathetic control of the cerebral circulation in humans was identified by demonstrating that CBF, and in parallel MCA $V_{\text{mean}}$, declines in response to trigeminal ganglion stimulation and increases following stellate ganglion blockade. A relationship between CBF and CO was found by demonstrating that both the MCA $V_{\text{mean}}$ and the near-infrared spectrophotometry determined cerebral oxygenation decrease in association with the postural reduction in CO. This reduction in cerebral perfusion takes place even though MAP increases, further indicating an important role of sympathetic activation for regulation of CBF. In support, both MCA $V_{\text{mean}}$ and cerebral oxygenation increase when the standing position is supplemented by a leg muscle tensing manoeuvre that attenuates sympathetic activity by enhancing CO. Also, CO and MCA $V_{\text{mean}}$ change concordantly with, respectively, volume expansion and depletion. 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.

This study suggests that the partial contribution of $P_{a,CO_2}$ 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 $P_{a,CO_2}$ dominate the postural reduction in MCA $V_{\text{mean}}$ and the postural reduction in CO supports that cardiac output is likely to have an independent influence on cerebral perfusion.