Interaction of Carbon Dioxide and Sympathetic Nervous System Activity in the Regulation of Cerebral Perfusion in Humans

Jens Jordan, John R. Shannon, Andre Diedrich, Bonnie Black, Fernando Costa, David Robertson, Italo Biaggioni

Abstract—Recent studies suggest that activation of the sympathetic nervous system either directly or indirectly influences cerebrovascular tone in humans even within the autoregulatory range. In 6 healthy subjects (aged 29±4 years), we used transcranial Doppler sonography to determine cerebral blood flow velocity during sympathetic activation elicited through head-up tilt (HUT) and sympathetic deactivation through ganglionic blockade. PaCO₂ was manipulated through hyperventilation and CO₂ breathing (5%). With subjects in the supine position and during HUT, mean arterial pressure was not influenced by PaCO₂. During ganglionic blockade, mean arterial pressure decreased markedly with hyperventilation (∼13±1.9 mm Hg). Manipulation of sympathetic tone elicited only mild changes in cerebral blood flow (64±5.8 cm/s supine, 58±4.9 cm/s upright, and 66±6.2 cm/s during ganglionic blockade; P=0.07 by ANOVA). The slope of the regression between PaCO₂ and mean velocity was 1.6±0.18 cm/(s·mm Hg) supine, 1.3±0.14 cm/(s·mm Hg) during HUT, and 2.3±0.36 cm/(s·mm Hg) during ganglionic blockade (P<0.05). Spontaneous PaCO₂ and ventilatory response to hypercapnia were also modulated by the level of sympathetic activity. Changes in sympathetic tone have a limited effect on cerebral blood flow at normal PaCO₂ levels. However, the sympathetic nervous system seems to attenuate the CO₂-induced increase in cerebral blood flow. This phenomenon may indicate a moderate direct effect of the sympathetic nervous system on the cerebral vasculature. Furthermore, sympathetic activation tends to increase ventilation and thus can indirectly increase cerebrovascular tone. (Hypertension. 2000;36:383-388.)

Key Words: carbon dioxide • baroreflex • receptors, adrenergic • phenylephrine • sympathetic nervous system

The ability to assume the upright posture depends crucially on sufficient perfusion of the brain. Blood flow to the brain can be influenced through adjustments in systemic hemodynamics (ie, perfusion pressure) or through local vascular modulation (ie, cerebral autoregulation). Thus, impaired adjustment of systemic hemodynamics or disorders of regulation of cerebrovascular tone could contribute to cerebral hypoperfusion with standing. An example of the former is the profound orthostatic hypotension seen in autonomic failure patients, which leads to cerebral hypoperfusion as the decrease in blood pressure (BP) exceeds the autoregulatory capacity of the brain. On the other hand, the concept that impaired local regulation of cerebrovascular tone can also lead to cerebral hypoperfusion with standing is supported by recent findings in patients with orthostatic intolerance. These patients experience typical symptoms of cerebral hypoperfusion when they stand, and these symptoms are associated with excessive reductions in cerebral blood flow velocity despite maintenance of arterial BP. This cerebral vasoconstriction is attenuated either by interventions that blunt sympathetic activation or by α-adrenergic blockade. These observations suggest that activation of the sympathetic nervous system either directly or indirectly influences cerebrovascular tone in humans even within the autoregulatory range.

We therefore tested the hypothesis that in normal control subjects, activity of the sympathetic nervous system influences control of the cerebral circulation. We used head-up tilt (HUT) and complete Nₐ-Cholinergic blockade of autonomic ganglia to elicit sympathetic activation and deactivation, respectively. Because of the importance of arterial carbon dioxide concentrations (PaCO₂) on cerebral blood flow, we also explored the possibility that the effects of the autonomic nervous system on cerebral hemodynamics were mediated indirectly by changes in PaCO₂ levels or by modulation of the vascular effects of carbon dioxide. For this purpose we measured the relationship between PaCO₂ and cerebral blood flow at each level of sympathetic activity. We widened the range of PaCO₂ levels, using increased ventilation to induce hypocapnia and increasing inspiratory CO₂ to induce hypercapnia.
by guest on April 11, 2017 http://hyper.ahajournals.org/ Downloaded from

To limit the duration of HUT, we performed 2 tests with a recovery period of ~20 minutes in between. After baseline recordings in the supine position were taken for 6 minutes, subjects were tilted to 60° HUT. After stabilization of BP and HR, recordings were obtained for 6 minutes during normocapnic conditions. After this period, subjects either hyperventilated or were exposed to hypercapnic conditions.

**Hypocapnia and Hypercapnia**

A random breathing protocol lasting 6 minutes was used for hyperventilation-induced hypocapnia. Subjects’ breathing was paced by a graphic pattern on a computer screen that illustrated breathing duration breath by breath. Hypercapnia was elicited by giving 5% carbon dioxide over the open breathing circuit. Venous plasma catecholamines were determined in the supine position, during HUT, and during complete ganglionic blockade. Hypocapnia and hypercapnia were maintained for 6 minutes each.

**Complete Ganglionic Blockade**

Ganglionic blockade with trimethaphan (Cambridge Pharmaceuticals) was achieved as described previously.9,10 Bolus doses of phenylephrine were given during to assess completeness of blockade. Once complete ganglionic blockade was accomplished, a phenylephrine infusion was titrated to return BP to the baseline level.

**Transcranial Doppler Sonography**

The right middle cerebral artery (MCA) was insonated through the temporal window with a 2-MHz probe (Pioneer, EMD) that was maintained at a constant position by a headset. Pulsatility index (systolic–diastolic/mean velocity) was used as indicator of resistance.12 Cerebrovascular resistance index was calculated as mean BP divided by the corresponding mean flow velocity.13 At least 5 PaCO₂ values and the corresponding mean velocities during spontaneous breathing, hyperventilation, and hypercapnia were plotted for each subject and analyzed by linear regression analysis. This regression analysis was performed separately for the supine position, HUT, and ganglionic blockade. In each subject, the linear regression equation was used to adjust mean velocity to a PaCO₂ of 40 mm Hg.

**Statistical Analysis**

All data are expressed as mean±SEM. ANOVA testing for repeated measures was used for multiple comparisons. The Friedman test was used for comparison of nonparametric data. A value of $P<0.05$ was considered statistically significant.

**Results**

**Spontaneous Breathing**

Mean arterial pressure (MAP) in the supine position was 93±4.1 mm Hg and did not change with HUT (90±1.9 mm Hg). With trimethaphan, MAP decreased to 73±1.2 mm Hg ($P<0.01$). Phenylephrine at an infusion rate of 0.38±0.08 μg/min returned MAP to the baseline value before blockade (92±2.2 mm Hg) (Figure 2). HR increased from 66±2.8 bpm in the supine position to 83±1.6 bpm with HUT and to 78±3.1 bpm during ganglionic blockade ($P<0.001$). Compared with baseline values of subjects in the supine position, cardiac output changed ~22±3.0% during HUT ($P<0.01$), 16±4.9% ($P=NS$) during ganglionic blockade without phenylephrine, and 12±7.7% ($P=NS$) during ganglionic blockade with phenylephrine (Figure 3). Systemic vascular resistance increased 20±5.0% during HUT ($P<0.05$). With trimethaphan, systemic vascular resistance decreased profoundly by 33±3.4% ($P<0.01$). Phenylephrine attenuated the decrease in systemic vascular resistance (~7.0±6.4% compared with baseline; $P=NS$) (Figure 3).

Plasma norepinephrine concentration was 1.2±0.10 nmol/L (198±18 pg/mL) in the supine position, 2.4±0.24 nmol/L (400±41 pg/mL) with HUT, and 0.57±0.094 nmol/L
(97±16 pg/mL) during ganglionic blockade (P<0.001 by ANOVA). Plasma epinephrine concentration increased from 76±11 pmol/L (14±2.0 pg/mL) in subjects in the supine position to 200±34 pmol/L (36±6.2 pg/mL) with HUT; with ganglionic blockade, plasma epinephrine concentration decreased to 49±15 pmol/L (9.0±2.7 pg/mL) (P<0.001 by ANOVA). Spontaneous Paco2 was 42±1.3 mm Hg supine, 41±1.5 mm Hg during HUT, and 43±1.4 mm Hg during ganglionic blockade (P<0.05) (Figure 2). Minute ventilation was 9.9±0.84 L/min supine, 10±1.3 during L/min during HUT, and 6.9±1.2 L/min during ganglionic blockade (P=0.08 by ANOVA).

At similar perfusion pressures, mean MCA velocity was 64±5.8 cm/s supine, 58±4.9 cm/s upright, and 66±6.2 cm/s during ganglionic blockade and phenylephrine (P=0.07 by ANOVA) (Figure 2). Mean MCA velocity during ganglionic blockade but without phenylephrine infusion was 61±5.9 cm/s (P=NS compared with baseline). Regional cerebrovascular resistance was 2.2±0.2 supine, 2.2±0.19 upright, and 2.0±0.19 during ganglionic blockade and phenylephrine (P=NS). Pulsatility index was 0.65±0.058 supine, 0.66±0.060 upright, and 0.57±0.039 during ganglionic blockade and phenylephrine (P=0.10). The differences in mean MCA velocity at different levels of sympathetic tone were decreased after adjustment to a Paco2 of 40 mm Hg (61±6.9 cm/s supine, 58±7.8 cm/s upright, and 62±5.1 cm/s during Nn-cholinergic blockade; P=NS).

Hyperventilation and Hypercapnia
With hyperventilation, Paco2 decreased to 26±1.2 mm Hg in the supine position, to 23±1.0 during HUT, and to 29±1.2 during ganglionic blockade (P<0.05 by ANOVA). The difference in Paco2 was explained by differences in minute ventilation (26±1.2 L/min supine, 29±1.2 L/min during HUT, and 21±3.3 L/min during ganglionic blockade; P<0.05 by ANOVA). Elevating inspiratory CO2 to 5% resulted in an increase of minute ventilation to 16±1.8 L/s while supine. This respiratory response to hypercapnia was enhanced during HUT, to 18±1.9 L/s. A blunted response was observed during ganglionic blockade (13.0±2.70 L/s) (P<0.05). The differences in respiratory response to 5% CO2 were associated with a trend for Pco2 to be smaller with sympathetic activation (47±1.5 mm Hg supine, 43±1.4 mm Hg during HUT, and 48±1.1 mm Hg during ganglionic blockade; P=0.09).

With subjects in the supine position, MAP changed 0.2±5.0 mm Hg with hyperventilation and 2.8±1.9 mm Hg during hypercapnia (P=NS). Similarly, hyper-
ventilation and hypercapnia did not change MAP during HUT (−3.6 ± 3.0 mm Hg during hyperventilation, −1.3 ± 3.6 mm Hg during hypercapnia). During complete ganglionic blockade, hypercapnia had no effect on MAP (5 ± 3 mm Hg; P = NS), but hyperventilation caused a decrease in MAP by 13 ± 1.9 mm Hg (P = 0.002). During ganglionic blockade there was a highly significant positive correlation between changes in MAP and changes in PaCO₂ (r = 0.86, P = 0.001) (Figure 4). HR increased during hyperventilation in the supine position (66 ± 2.8 bpm during normocapnia, 64 ± 3.2 bpm during hypercapnia, and 75 ± 2.8 bpm during hyperventilation; P < 0.01 by ANOVA). A similar increase was observed during HUT (83 ± 1.6 bpm during normocapnia, 83 ± 3.6 bpm during hypercapnia, and 99 ± 3.9 bpm during hyperventilation; P = 0.001 by ANOVA). The change in HR was attenuated during ganglionic blockade (79 ± 3.2 bpm during normocapnia, 77 ± 3.0 during hypercapnia, and 83 ± 3.5 bpm during hyperventilation; P = NS).

Figure 5 illustrates the relationship between changes in PaCO₂ and changes in mean cerebral blood flow velocity in the supine position, during HUT, and during ganglionic blockade. ANOVA testing showed that PaCO₂ explained a significant part of the variance of mean MCA velocity. There was a trend for PaCO₂ to have a different contribution to the variance of mean MCA velocity in the supine position, during HUT, and during ganglionic blockade (P = 0.1 by ANOVA). The slope of the regression between PaCO₂ and mean velocity was 1.6 ± 0.18 cm/(s · mm Hg) supine, 1.3 ± 0.14 cm/(s · mm Hg) during HUT, and 2.3 ± 0.36 cm/(s · mm Hg) during ganglionic blockade (P < 0.05 by ANOVA), indicating that the vasodilator effect of CO₂ is attenuated during HUT and augmented during ganglionic blockade. The r values for individual linear regressions ranged between 0.87 and 0.98, with P value < 0.05.

**Discussion**

Perfusion of the brain is tightly regulated through adjustment of cerebral perfusion pressure and changes in cerebrovascular tone. Systemic BP is the main determinant of cerebral perfusion pressure under most physiological conditions. The autonomic nervous system has a pivotal role in short-term BP control and prevents excessive fluctuations in cerebral perfusion pressure. Even if there are changes in cerebral perfusion pressure, these are compensated for by opposing local changes in cerebrovascular tone (cerebral autoregulation). This mechanism keeps cerebral blood flow relatively constant over a wide range of BP levels. The relationship between systemic BP and cerebral blood flow can be modulated by changes in arterial carbon dioxide concentration, a powerful cerebral vasodilator. The contribution of the autonomic nervous system to the regulation of cerebrovascular tone is imperfectly understood. Impaired autonomic control of the systemic or cerebral circulation, changes in arterial carbon dioxide concentration, or dysfunctional cerebral autoregulation could contribute individually or collectively to cerebral hypoperfusion in the upright posture. In the present study we manipulated sympathetic tone and arterial carbon dioxide concentration to characterize the interaction and integration of these components on cerebral perfusion pressure and systemic BP.

Changes in arterial carbon dioxide concentration elicit complex changes in systemic hemodynamics and thus cerebral perfusion pressure. These changes result from combination of direct vascular effects of carbon dioxide and reflex changes in sympathetic and parasympathetic tone. In the presence of intact sympathetic and parasympathetic control of the circulation, hyperventilation-induced hypocapnia is associated with a small or no decrease in MAP. Yet, forearm blood flow increases >2-fold. The decrease in systemic vascular tone is compensated for by an increase in cardiac output. The findings of our study show that in healthy young subjects reflex changes in autonomic nervous system activity are sufficient to maintain BP during hypocapnia and hypocapnia even in the upright posture. However, in autonomic failure patients and during ganglionic blockade, baroreflex-mediated regulation of sympathetic and parasympathetic tone is greatly impaired or even absent. Therefore, effects of vasodilators and vasoconstrictors are profoundly enhanced. Thus, modest increases in arterial carbon dioxide concentration elicit an increase in BP, while decreases in carbon dioxide concentration are associated with decreases in BP.

![Figure 5. Changes in mean cerebral blood flow velocity (vel mean) with changes in PaCO₂. Hypercapnia caused a profound increase in cerebral blood flow, while hypocapnia decreased cerebral blood flow.](image-url)
could conceivably decrease cerebral perfusion pressure in autonomic failure patients.

Patients with idiopathic orthostatic intolerance have symptoms on standing that suggest cerebral hypoperfusion and an excessive reduction in cerebral blood flow velocity despite the absence of significant orthostatic hypotension, which suggests cerebral vasoconstriction. However, in this study in healthy subjects, neither sympathetic activation elicited by HUT nor complete ganglionic blockade with or without concomitant phenylephrine infusion caused a clinically significant change in cerebral blood flow velocity. Thus, direct sympathetically mediated vasoconstriction of cerebral vessels alone is probably not sufficient to cause symptoms of cerebral hypoperfusion. The findings of our study might suggest, however, that sympathetic activation attenuates the increase in cerebral blood flow during hypercapnia.

Decreased arterial carbon dioxide tension due to augmented ventilation seems to contribute to the postural increase in cerebrovascular tone, at least in subgroups of idiopathic orthostatic intolerance patients. Our study suggests that the association between sympathetic activation and decreased cerebral blood flow is in part explained by changes in ventilation and corresponding changes in arterial carbon dioxide concentration. Sympathetic activation elicited by HUT increased ventilation and decreased PaCO₂, whereas the opposite occurred during the sympathoinhibition of ganglionic blockade. Moreover, the respiratory response to increased inspiratory carbon dioxide concentration was augmented during HUT and attenuated with complete ganglionic blockade. Increased sympathetic activation in patients with idiopathic orthostatic intolerance may contribute to hyperventilation-induced hypocapnia and thereby indirectly elevate cerebrovascular tone. The effect of sympathetic activity on respiration might be mediated through sympathetic efferents innervating the carotid bodies. An alternative explanation for the relationship is a modulatory effect of afferent nerve traffic from pulmonary stretch receptors on sympathetic neurons in the brain stem mediated through central connections between respiratory and sympathetic neurons.

The findings of this study may have clinical implications in patients with impaired orthostatic tolerance. Patients who do not respond to conventional treatments might benefit from interventions that modulate the ventilatory response to upright posture or prevent the effect of increased ventilation on cerebrovascular resistance (e.g., acetazolamide).

Potential limitations of our experimental approach should be considered. First, transcranial Doppler sonography is widely used to detect acute changes in cerebral perfusion. However, it actually measures cerebral blood flow velocity rather than cerebral blood flow. Blood flow velocity is directly related to blood flow only if the diameter of the insonated blood vessel remains constant. A moderate change in vessel diameter would translate into a substantial change in blood flow. It is reassuring that the diameter of the MCA changes little with hemodynamic perturbations. Second, ganglionic blockade produced substantial changes in systemic hemodynamics, with a significant decrease in BP and therefore cerebral perfusion pressure. We used phenylephrine infusion to restore cerebral perfusion pressure to baseline levels. Phenylephrine attenuated the decrease in systemic vascular resistance elicited by ganglionic blockade and did not lead to a significant reduction in cardiac output. Phenylephrine might have a mild direct effect on cerebral blood vessels, which is unlikely given the small infusion used in this study. The infusion rate of phenylephrine was kept constant during hyperventilation and during hypercapnia. Thus, carbon dioxide–induced changes in cerebral perfusion could be assessed in the absence of baroreflex-mediated changes in autonomic nervous system activity.

We conclude that, during ganglionic blockade, hyperventilation-induced hypocapnia causes a profound decrease in arterial BP, while hypercapnia increases BP. These effects of carbon dioxide are normally masked by the baroreflex. In contrast, changes in sympathetic tone did not have a major effect on cerebral blood flow at normal PaCO₂ levels. However, the sympathetic nervous system seems to attenuate the carbon dioxide–induced increase in cerebral blood flow. This phenomenon may indicate a moderate direct effect of the sympathetic nervous system on the cerebral vasculature. Furthermore, the level of sympathetic activity influenced the respiratory response to hypercapnia as well as the level of PaCO₂ achieved at a given concentration of inspiratory carbon dioxide. In hyperadrenergic states such as idiopathic orthostatic intolerance, the symptoms of cerebral hypoperfusion on standing may be related to a combination of increased ventilation causing hypocapnia and increased sensitivity of cerebral vessels to decreased arterial carbon dioxide concentration.

Acknowledgments
This study was supported in part by National Institutes of Health grants HL-56693 and RR00095.

References


Interaction of Carbon Dioxide and Sympathetic Nervous System Activity in the Regulation of Cerebral Perfusion in Humans

Jens Jordan, John R. Shannon, Andre Diedrich, Bonnie Black, Fernando Costa, David Robertson and Italo Biaggioni

Hypertension. 2000;36:383-388
doi: 10.1161/01.HYP.36.3.383

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/36/3/383

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/