Cerebral vasoreactivity during hypercapnia is reset by augmented sympathetic influence

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Zhang P, Huang G, Shi X. Cerebral vasoreactivity during hypercapnia is reset by augmented sympathetic influence. J Appl Physiol 110: 352–358, 2011. First published November 11, 2010; doi:10.1152/japplphysiol.00802.2010.—Sympathetic nerve activity influences cerebral blood flow, but it is unknown whether augmented sympathetic nerve activity resets cerebral vasoreactivity to hypercapnia. This study tested the hypothesis that cerebral vasodilation during hypercapnia is restrained by lower-body negative pressure (LBNP)-stimulated sympathoexcitation. Cerebral hemodynamic responses were assessed in nine healthy volunteers [age 25 yr (SD 3)] during rebreathing-induced increases in partial pressure of end-tidal CO2 (PETCO2) at rest and during LBNP. Cerebral hemodynamic responses were determined by changes in flow velocity of middle cerebral artery (MCAV) using transcranial Doppler sonography and in regional cerebral tissue oxygenation (ScO2) using near-infrared spectroscopy. PETCO2 values during rebreathing were similarly increased from 41.9 to 56.5 mmHg at rest and from 40.7 to 56.0 mmHg during LBNP of −15 Torr. However, the rates of increases in MCAV and in ScO2 per unit increase in PETCO2 (i.e., the slopes of MCAV/PETCO2 and ScO2/PETCO2) were significantly (P ≤0.05) decreased from 2.62 ± 0.16 cm·s⁻¹/mmHg⁻¹ and 0.89 ± 0.10%/mmHg at rest to 1.68 ± 0.18 cm·s⁻¹/mmHg⁻¹ and 0.63 ± 0.07%/mmHg during LBNP. In conclusion, the sensitivity of cerebral vasoreactivity to hypercapnia, in terms of the rate of increases in MCAV and in ScO2, is diminished by LBNP-stimulated sympathoexcitation.

cerebral blood flow velocity; cerebral tissue oxygenation; cerebral vascular conductance; lower-body negative pressure; partial pressure of end-tidal carbon dioxide

CEREBRAL BLOOD FLOW (CBF), as indicated by middle cerebral arterial blood flow velocity (MCAV), decreases during orthostatic challenges, e.g., head-up tilt (HUT) (3, 12, 13, 19, 23) or lower-body negative pressure (LBNP) (6, 8, 21, 33, 40). This cerebral hypoperfusion results from baroreflex-mediated sympathoexcitation (12) and/or hyperventilation-induced hypocapnia (6, 24) during orthostasis. Jordan et al. (12) reported that increase in MCAV was enhanced after autonomic ganglionic blockade, presumably due to release of sympathetic nerve influence. However, Zhang et al. (40) found that LBNP-induced decrease in MCAV persisted after trimethaphan was administered to block the baroreflex-mediated sympathoexcitation, suggesting that sympathetic nerve activity is not the major mechanism for reduction of CBF during orthostasis. The question remained as to whether cerebral vasoreactivity to hypercapnia could be reset or the sensitivity of cerebral vasodilation is acutely altered by the baroreflex-stimulated sympathoexcitation during orthostasis.

Cerebral vasoreactivity is an indicator of the functional reserve of the cerebral circulation (2, 14, 36), which appears to be impaired in patients with diffuse atherosclerosis and subclinical endothelial dysfunction (37) and with lacunar infarctions (28). The purpose of the present study was to examine the impact of steady-state LBNP-elicited sympathoexcitation or hyperadrenergic state on sensitivity of cerebral hemodynamic responses to CO2 stimulation. LBNP is extensively applied to stimulate sympathetic nerve activity. Mild LBNP without significant tachycardiac response and systemic hypotension appreciably increases muscle sympathetic nerve activity assessed by microneurography (31, 32) and by norepinephrine measurements in plasma and tissue (7, 16). Our hypothesis was that the sensitivity of cerebral vasoreactivity to hypercapnia would be diminished if baroreflex-stimulated sympathetic nerve activity restrained cerebral vasodilation or modulated cerebral vasomotor tone.

METHODS

Subjects. Healthy young subjects [6 men and 3 women, age 25.0 yr (SD 3.1) and body mass index 23.8 kg/m² (SD 3.8)] gave a written consent to participate in the study. The study protocol was approved by the Institutional Review Board for the Protection of Human Subjects at University of North Texas Health Science Center at Fort Worth. All volunteer participants were clinically confirmed to be free of cardiovascular, metabolic, renal, and pulmonary diseases. Before the experiment, the participants underwent laboratory orientation to familiarize them with the experimental procedure and measurements applied in the study.

Measurements. During the experiment, the subject’s heart rate (HR) was monitored from a standard electrocardiogram lead. Radial arterial pressure (ABP) was continuously measured by tonometry (Colin model 7000 Tonometry, San Antonio, TX). We (39) and others (15, 41) have shown this noninvasive ABP measurement to be highly correlated with ABP measured from intra-arterial catheter. Arterial O2 saturation (SaO2) was estimated by pulse oximetry (BIOPAC Oximeter, Santa Barbara, CA). MCAV was determined by transcranial Doppler (TCD) sonography using a 2-MHz probe (EZ-Dop DWL System, Singen, Germany) positioned over the left temporal window. Regional cerebral tissue oxygenation (ScO2) of the prefrontal cortex and regional forearm muscle oxygenation (SmO2) were monitored by near-infrared spectroscopy (NIRS, Somanetics, 4100 INVOS Cerebral Oximeter, Troy, MI) using sensors placed on the right side of the forehead and on the right brachioradialis, respectively. This NIRS technique has been validated, and the measured ScO2 is highly correlated with jugular venous oxygenation (9, 17). These measurements and the techniques of TCD sonography and NIRS have been applied in our studies (6, 8). Breath-by-breath inspired and expired fractions of O2 and CO2 were measured using a mass spectrometer (Perkin-Elmer, 1100 Medical Gas Analyzer, St. Louis, MO), which

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was calibrated against room air and gas containing 10% O₂ and 10% CO₂ balanced with N₂. Continuous partial pressure of transcutaneous CO₂ (PtCO₂) was determined by a Radiometer sensor placed on the subject’s ear lobe (TOSCA 500, Copenhagen). The sensor’s temperature was set and maintained at 42°C, which arterialized the local dermal capillary blood flow. This noninvasive continuous PtCO₂ is highly correlated with partial pressure of arterial CO₂ (PaCO₂) (4, 22, 26). Before each test, the PtCO₂ sensor was calibrated with TOSCA.

Fig. 1. Rebreathing-induced hypercapnia at rest. Top to bottom: partial pressure of transcutaneous CO₂ (PtCO₂), fractional CO₂, fractional O₂, blood flow velocity of middle cerebral artery (MCAV), cerebral tissue O₂ saturation (ScO₂), arterial O₂ saturation (SaO₂), arterial blood pressure (ABP), and heart rate (HR). There is a time delay in PtCO₂ response to the rebreathing procedure, although PtCO₂ parallels end-tidal CO₂ during a ramp hypercapnia. At the end of the rebreathing procedure, the inspired O₂ remained ≥21%.
commercial gas of a known CO2 concentration. Analog data were continuously digitized on-line at 250 Hz by a computer interfaced with a data-acquisition system (BIOPAC MP150, Santa Barbara, CA). Partial pressure of end-tidal CO2 (PetCO2) was calculated off-line from the product of ambient barometric pressure and the fraction of end-tidal CO2. Cerebral vascular conductance (CVC) was estimated from the ratio of MCAV to mean arterial pressure (MAP).

Protocol. The experiment was conducted with the subject in the supine position with the lower body sealed in an airtight LBNP box at a room temperature of 24 ± 1°C. The subject wore a face mask throughout the experiment. The subject rested for ≥15 min after instrumentation, and then baseline HR, ABP, MCAV, SaO2, ScO2, SmO2, PetCO2, and PtCCO2 were recorded for ~3 min, followed by a rebreathing procedure (Fig. 1). During rebreathing the subject breathed into and out of a prefilled bag that contained ~10 liters of the mixed gas with ~3% CO2 and <40% O2 balanced with N2. This air mixture ensured that the fraction of inspired O2 remained above 21% at the end of the rebreathing procedure, which excluded hypoxic influence (Fig. 1). All subjects completed ≥6 min rebreathing except one who completed only 5 min rebreathing due to an equipment malfunction. After recovery from the rebreathing procedure, −15 Torr of LBNP was applied. While LBNP was maintained at −15 Torr, the cardiovascular, respiratory, and oxygenation data were collected for ≥2 min followed by the rebreathing-hypercapnia procedure superimposed on the mild, steady-state LBNP.

Data analyses. A section of 1-min continuous data before the rebreathing procedure at rest and during LBNP was averaged to provide control data. Data collected during 30-s interval of the rebreathing-elicited hypercapnia were averaged and plotted against the gradually increasing PetCO2 and PtCCO2. Control data at rest and during LBNP were compared by paired t-tests. Relationships of cerebral vascular conductance, MCAV, and cerebral tissue oxygenation with PetCO2 and PtCCO2 were analyzed by linear regression. All group data were reported as group mean ± SD. Values of P ≤ 0.05 were taken to indicate statistical significance. Statistic Analysis System software (SAS, Cary, NC) was used for the data analyses.

RESULTS

Table 1 summarizes the data at rest and during LBNP before the rebreathing-induced hypercapnia. LBNP at −15 Torr did not significantly change HR or blood pressure values. These similar cardiovascular data suggested a complete recovery from the prior rebreathing protocol. Mild steady-state LBNP induced modest hypocapnia prior to rebreathing, as indicated by significantly lower PetCO2 and PtCCO2 values, which was associated with a higher SaO2. LBNP effectively augmented sympathetic nerve activity, as indicated by lower cerebral vascular conductance and muscle O2 saturation. During the rebreathing procedure, PetCO2 gradually increased to 56.5 ± 3.7 and 56.0 ± 4.0 mmHg at rest and during LBNP, respectively. This hypercapnia during rebreathing was not confounded by hypoxia because inspired O2 was maintained ≥21% (Fig. 1) and SaO2 remained elevated throughout rebreathing at rest and with LBNP (Fig. 2). Although PtCCO2 was highly correlated with PetCO2, a delay of approximately 30–60 s in PtCCO2- assessed hypercapnia was observed during the rebreathing procedure, accompanied by a smaller magnitude of PtCCO2 response vs. that of PetCO2 (Fig. 2, bottom) during the rebreathing procedure at rest or during LBNP. Following the changes in PetCO2, PtCCO2 values similarly increased to 48.8 ± 3.7 and 48.3 ± 3.8 mmHg at rest and during LBNP, respectively.

The rebreathing-elicited hypercapnia stimulated tachycardic and hypertensive responses (Fig. 3). Neither the tachycardic response nor the hypertensive response in terms of unit increase in PetCO2 or PtCCO2 was statistically different at rest.
and during LBNP −15 Torr, suggesting a constant sensitivity of the chemoreflex-mediated systemic hemodynamic response.

However, the rates of increase in MCAV, CVC, and ScO2 per unit increase in CO2 were greater at rest than during LBNP (Fig. 4). Table 2 summarizes the slope data of MCAV/ΔTCCO2, CVC/ΔTCCO2, ScO2/ΔTCCO2, MCAV/ΔPETCO2, CVC/ΔPETCO2, and ScO2/ΔPETCO2. Nevertheless, the group slopes of ΔScO2/ΔCVC or ΔScO2/ΔMCAV were essentially identical at rest and during LBNP (Fig. 5).

**DISCUSSION**

This study suggests that the sensitivity of cerebral vasomotor reactivity to hypercapnia is diminished during LBNP −15 Torr compared with the baseline response. Specifically, the data show that LBNP-augmented sympathetic nerve activity decreases the functional reserve of the cerebral circulation in response to CO2 stimulus.

*Evidence of sympathoexcitation during LBNP.* Orthostatic challenges stimulate adrenergic activity as indicated by increases in muscle sympathetic nerve activity (31, 32) and plasma norepinephrine (7, 16). Our previous study (5) confirmed that arterial plasma renin activity and norepinephrine concentrations were elevated by LBNP. In the present study, we observed that muscle tissue O2 saturation fell slightly but significantly during LBNP (Table 1). Since O2 demand (or metabolic rate during LBNP) in resting skeletal muscle was considered to remain constant, a decrease in the control SmO2 was most likely associated with a decrease in O2 delivery and/or blood flow, caused by the sympathoexcitation-stimulated peripheral vasoconstriction during LBNP. However, mild LBNP-stimulated sympathoexcitation did not significantly change either heart rate or systemic arterial pressure, indicating a limited disturbance in the systemic homeostasis.

During orthostatic challenge, cerebral hypoperfusion may result from baroreflex-mediated sympathoexcitation (12) and/or hyperventilation-induced hypocapnia (6, 24). This study revealed modest declines in PETCO2 and TCCO2 during LBNP before the rebreathing procedure. Furthermore, the LBNP-induced reduction of venous return or central hypovolemia could diminish cardiac output, which might influence the cerebral hemodynamic response. However, this central hypovolemic effect on the shift of cerebral perfusion was insignificant based on current (Table 1) and previous observations (8).

Furthermore, cerebral autoregulation in response to systemic hypotension was maintained during the LBNP-induced central hypovolemia (8). Shoemaker et al. (35) reported an increase in cardiac output (~1.1 l/min) during a rebreathing protocol with a change in PETCO2 from 40 to 58 mmHg. Collectively, these studies suggested that central hypovolemia during mild LBNP would not be a significant factor on the sensitivity of cerebral vasoreactivity.

*Effect of sympathoexcitation on cerebral vasoreactivity.* This study demonstrates that the cerebral hemodynamic responses, in terms of increases in CVC, MCAV, or ScO2 during the rebreathing-elicited hypercapnia, were less sensitive during LBNP than at rest. These results confirm the hypothesis that sympathoexcitation significantly diminishes the cerebrovascular sensitivity in response to hypercapnia during LBNP. This finding is complementary to a previous report (12) of augmented MCAV response to CO2 stimulus during ganglionic blockade. Collectively, these results show that the LBNP-activated sympathoexcitation modulated the sensitivity of the cerebral vasomotor response to hypercapnia during LBNP.

![Fig. 3. Responses of heart rate and mean arterial pressure during the rebreathing elicited hypercapnia at rest and during LBNP.](http://jap.physiology.org/content/journal/jappl/110/2/fig/3)

*Top:* rate of tachycardic response stimulated by CO2 is not significantly different at rest and during LBNP, i.e., 1.21 vs. 1.02 beats·min⁻¹·mmHg⁻¹ (P = 0.46) in terms of unit increase in partial pressure of transcutaneous CO2 (top left); 0.87 vs 0.79 beats·min⁻¹·mmHg⁻¹ (P = 0.69) in terms of unit increase in partial pressure of end-tidal CO2 (top right). *Bottom:* the magnitude of increase in mean arterial pressure during hypercapnia also is not statistically different at rest and during LBNP: i.e., 0.36 vs. 0.45 mmHg/mmHg (P = 0.37) in terms of unit increase in partial pressure of transcutaneous CO2 (bottom left); 0.25 vs. 0.35 mmHg/mmHg (r = 0.20) in terms of unit increase in partial pressure of end-tidal CO2 (bottom right). Data are group mean ± SD from 9 subjects.
cerebral vasoreactivity to hypercapnia. Nonetheless, a previous study (20) did not find a change in the cerebral vasoreactivity during LBNP. This difference might be related to a different hypercapnic protocol applied in the study (20). However, exercise-augmented sympathetic nerve activity did not alter (25) or even enhanced (30) cerebral CO2 reactivity. This discrepancy in the cerebral hemodynamic response is probably related to the exercise-elicited central command, as evident with significant tachycardia during mild to moderate exercise such as handgrip (1, 29) or leg cycling (25). This feedforward mechanism overrides the brain stem, which interferes with the chemoreflex and baroreflex. Furthermore, the exercise-induced increases in metabolic rate, blood plasma potassium, osmolality, and temperature may counteract the sympathetic influence on the systemic and cerebral vasomotor response (30).

The rate of increase in MCAV, CVC, and ScO2 per unit hypercapnia (i.e., mmHg increase in CO2) was smaller during LBNP; the relationship of the changes in ScO2 with MCAV or with CVC during the rebreathing procedure was unaltered by LBNP (Fig. 5). These results demonstrate that the response of cerebral tissue O2 saturation to hypercapnia is related to the change in cerebral O2 delivery (8, 36), and that an increase in ScO2 stimulated by hypercapnia reflects an increase in cerebral perfusion indicated by the changes in MCAV and CVC (Fig. 1). This observation demonstrates that cerebral tissue oxygenation depends on cerebral perfusion and their relationship was not affected by sympathetic nerve activity.

Implication of the study. Cerebral vasoreactivity is considered an indicator of the functional reserve of the cerebral circulation (2, 14, 36). An important clinical implication of the present study is that some physiological and pathological conditions, such as aging, hypertension, congestive heart failure, and obstructive sleep apnea, which are commonly associated with a heightened sympathetic nerve activity or hyperadrenergic activity, may diminish the functional reserve of cerebral hemodynamic responses to metabolic demand. This diminished cerebral vasoreactivity places these individuals at an increased risk for cerebral hypoperfusion and potentially compromises their physiological or cognitive function when cerebral tissue O2 demand increases. Our results suggest that prevention or treatment of a hyperadrenergic state may help improve the functional reserve of the cerebral circulation or the cerebral hemodynamic response.

Methodological considerations. Transcranial Doppler sonography measures blood flow velocity, which is affected by both blood flow and diameter of the vessel. As the blood vessel diameter was not measured, we could not compare CBF under the different conditions. On the other hand, diameters of cerebral vasoreactivity to hypercapnia. Nonetheless, a previous study (20) did not find a change in the cerebral vasoreactivity during LBNP. This difference might be related to a different hypercapnic protocol applied in the study (20). However, exercise-augmented sympathetic nerve activity did not alter (25) or even enhanced (30) cerebral CO2 reactivity. This discrepancy in the cerebral hemodynamic response is probably related to the exercise-elicited central command, as evident with significant tachycardia during mild to moderate exercise such as handgrip (1, 29) or leg cycling (25). This feedforward mechanism overrides the brain stem, which interferes with the chemoreflex and baroreflex. Furthermore, the exercise-induced increases in metabolic rate, blood plasma potassium, osmolality, and temperature may counteract the sympathetic influence on the systemic and cerebral vasomotor response (30).

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Table 2. *Slope data of cerebral hemodynamic response during hypercapnia*

<table>
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<tr>
<th></th>
<th>Baseline</th>
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<th>−15 Torr</th>
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<th>Baseline vs. −15 Torr,</th>
<th>P Value *</th>
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<tr>
<td></td>
<td>Slope</td>
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<td>r</td>
<td>Slope</td>
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<tr>
<td>MCAV/PtcCO2, cm·s⁻¹·mmHg⁻¹</td>
<td>3.38 ± 0.18</td>
<td>0.0001</td>
<td>0.88</td>
<td>1.90 ± 0.24</td>
<td>0.0001</td>
<td>0.61</td>
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<tr>
<td>CVC/PtcCO2, U/mmHg</td>
<td>0.026 ± 0.003</td>
<td>0.0001</td>
<td>0.64</td>
<td>0.017 ± 0.003</td>
<td>0.0001</td>
<td>0.53</td>
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<tr>
<td>ScO2/PtcCO2, %/mmHg</td>
<td>1.13 ± 0.12</td>
<td>0.0001</td>
<td>0.67</td>
<td>0.83 ± 0.09</td>
<td>0.0001</td>
<td>0.66</td>
</tr>
<tr>
<td>MCAV/PetCO2, cm·s⁻¹·mmHg⁻¹</td>
<td>2.62 ± 0.16</td>
<td>0.0001</td>
<td>0.83</td>
<td>1.68 ± 0.18</td>
<td>0.0001</td>
<td>0.67</td>
</tr>
<tr>
<td>CVC/PetCO2, U/mmHg</td>
<td>0.020 ± 0.003</td>
<td>0.0001</td>
<td>0.61</td>
<td>0.013 ± 0.002</td>
<td>0.0001</td>
<td>0.52</td>
</tr>
<tr>
<td>ScO2/PetCO2, %/mmHg</td>
<td>0.89 ± 0.10</td>
<td>0.0001</td>
<td>0.66</td>
<td>0.63 ± 0.07</td>
<td>0.0001</td>
<td>0.64</td>
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Slope data include the estimate of the SD of the slopes. *Baseline vs. −15 Torr P value indicates significant difference in the slopes between baseline and LBNP."
Conduit vessels, such as the middle cerebral artery, are reported to be relatively constant in response to changes in CO2 and LBNP (34), so the measured responses of MCAV should provide a reliable index of changes in CBF. Although NIRS is a common technique applied to monitor regional tissue oxygenation (9, 18, 27), it cannot differentiate the oxyhemoglobin contents within the various vessels of the region. However, the hemoglobin volume in the venous bed or capacitance vessels is predominant compared with that within the arterial bed or resistance vessels (38). Thus the tissue oxygenation is more related to a change in the venous oxyhemoglobin, and ScO2 has been validated to be significantly correlated with jugular venous oxygenation (9, 17). We believe that NIRS is able to measure the response of ScO2. Breath-by-breath PetCO2 and continuous PtCCO2 were applied to monitor the rebreathing-elicited hypercapnia. However, these indirect changes in PCO2 could differ from PaCO2 or pH in the cerebral tissue. Nonetheless, in healthy subjects without circulatory or respiratory disease, a breath-by-breath measured continuous response in PetCO2 or PtCCO2 should faithfully reflect the change in PaCO2 (or tissue pH) during a ramp hypercapnia at rest or during steady-state orthostatic challenge (10, 11). Furthermore, the study outcome was the same whether the cerebral vasoreactivity data were plotted against the changes in PetCO2 or PtCCO2 during the rebreathing-elicited hypercapnia (Table 2). The order of the rebreathing tests at rest and during LBNP was not randomized. However, neither the control cardiovascular data (Table 1) nor the response or the change in arterial O2 saturation and CO2 (Fig. 2) were different with and without LBNP. Furthermore, the sensitivity of the chemoreflex-stimulated tachycardia and hypertensive responses remained constant at rest and during LBNP (Fig. 3). We postulated that the residual effect of the prior breathing protocol at rest on the chemoreceptor and the systemic hemodynamic and respiratory functions during LBNP should be insignificant. Therefore, the difference in cerebral vasoreactivity to hypercapnia at rest and during LBNP was not due to the order of the rebreathing tests.

Conclusion. The present study suggests that the orthostasis-stimulated sympathoexcitation diminishes the sensitivity of cerebral vasoreactivity, in terms of the magnitude of the responses in MCAV, CVC, and ScO2 during hypercapnia. Our results provide evidence that pathological and physiological conditions associated with a heightened sympathetic nerve activity diminish the functional reserve of the cerebral circulation or the cerebral hemodynamic response during CO2 stimulation.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

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