The effect of oxygen on dynamic cerebral autoregulation: critical role of hypocapnia

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¹Department of Biomedical Engineering, Toyo University, Saitama; ²Department of Human Kinetics, Faculty of Health and Social Development, University of British Columbia, Okanagan, Kelowna, Canada; and ³Morinomiya University of Medical Sciences, Osaka, Japan; ⁴Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Osaka, Japan

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Ogoh S, Nakahara H, Ainslie PN, Miyamoto T. The effect of oxygen on dynamic cerebral autoregulation: critical role of hypocapnia. J Appl Physiol 108: 538–543, 2010. First published January 7, 2010; doi:10.1152/japplphysiol.01235.2009.—Hypoxia is known to impair cerebral autoregulation (CA). Previous studies indicate that CA is profoundly affected by cerebrovascular tone, which is largely determined by the partial pressure of arterial O₂ and CO₂. However, this impairment is profoundly affected by cerebrovascular tone, which is largely

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CEREBRAL BLOOD FLOW (CBF) is maintained relatively constant by a number of regulatory mechanisms during fluctuations in cerebral perfusion pressure (1). Although the CBF is regulated through the integration of numerous control mechanisms, cerebral autoregulation (CA) and the reactivity of the cerebral vasculature to changes in arterial blood-gas tensions likely provide the principle inputs of CBF regulation. Arterial PSCO₂ (Paco₂) is a powerful regulator of the cerebral vasculature; hypercapnia stimulates vessel dilation, increasing CBF, but attenuates dynamic CA (CA_d), while hypocapnia causes vessel constriction, a decrease in CBF, and improves CA_d (1). Hypoxia (10, 12, 35) and hypoxia (15) also influence both the cerebral and the systemic circulation. Acute hypoxia enhances muscle sympathetic discharge, cardiac output, skeletal muscle blood flow, and heart rate (HR), with little or no alteration in arterial blood pressure (ABP) (14). In the brain, isocapnic hypoxia causes cerebral artery dilation mediated by local metabolite production (e.g., adenosine) (36).

There have been a number of studies examining the influence of hypobaric and normoxic hypoxia on CA. Studies have suggested that there is CA impairment in both newcomers to high altitude (3, 18, 21) and in permanent high-altitude residents living above 4,000 m (19), particularly in the presence of acute mountain sickness (7, 34). During isocapnic hypoxia, studies have suggested that CA is either maintained (2) or impaired (17, 31). Differences in findings may be related to varying degrees of hypoxia (14 vs. 12 vs. 10%) and, importantly, the degree of subsequent hypocapnia. Because hypocapnia improves CA_d (1) and is a result of increased hypoxic ventilatory drive via the peripheral chemoreflex, it is difficult to separate the adverse effects of hypoxia per se on CA from the enhancing effects of hypocapnia. Therefore, the purpose of the present study was to examine the influence of hypoxia with and without consequent hypocapnia on both middle cerebral artery blood velocity (MCA V) and CA_d. Moreover, while the effects of hypoxia on CA have been partially explored (5, 17, 31), the effects of hyperoxia without concomitant changes in Paco₂ are unknown. Although Paco₂ has a marked effect on cerebral vascular tone, which defines CA_d (1, 24), this response is also influenced by arterial P0₂ (PaO₂). Therefore, investigation of the effect of hyperoxia on CA_d will also provide relevant clues regarding the mechanisms by which O₂ may affect dynamic CBF regulation. To address these questions, we compared MCA V and CA_d during isocapnic hypoxia, hypocapnic hypoxia, and isocapnic hyperoxia to identify the interactions between hypoxia and concomitant influence of hypocapnia on dynamic CBF regulation.

METHODS

Nine healthy, nonathletic men, age 22.7 ± 5.8 yr (mean ± SD), were recruited to participate in the study, as approved by the Human Subjects Committee of Morinomiya University of Medical Sciences (no. 004). Subjects were free of any known cardiovascular and pulmonary disorders and were not using prescribed or over-the-counter medications. Before the experiment, each subject gave informed, written consent and visited the laboratory for familiarization with the techniques and procedures. Subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for at least 24 h before the day of the experiment.
Measurements

All studies were performed at a room temperature between 23 and 24°C with external stimuli minimized. HR was monitored using a lead II electrocardiogram. ABP was monitored with tonometry (BP-608 Evolution II, Omron-Colin, Tokyo, Japan). This system utilizes an state-of-the-art multisensor array technology to detect pulse waves at the radial artery. The ABP system was calibrated from obtained arterial pulse waves by the auscultatory method before each condition. The MCA V was obtained by transcranial Doppler ultrasonography (TCD) (WAKI, Atys Medical, St. Genislaval, France). A 2-MHz Doppler probe was placed over the temporal window and fixed with an adjustable headband and adhesive ultrasonic gel (Tensive, Parker Laboratories, Orange, NJ). Arterial oxygen saturation (SaO2) was assessed at the ear using pulse oximetry (9900-MKII, Kohken Medical, Tokyo, Japan). Ventilatory responses were measured using an open-circuit apparatus. The subjects breathed through a face mask attached to a low-resistance one-way valve with a flowmeter. The valve mechanism allowed subjects to inspire room air or a selected gas mixture from a 200-liter Douglas bag containing 14% O2, 21% O2, or 40% O2 in 0% CO2 with nitrogen (N2) balance. The total instrumental dead space was 200 ml. Respiratory and metabolic data during the experiments were recorded by an automatic breath-by-breath respiratory gas analyzing system, consisting of a differential pressure transducer, sampler tube, filter, suction pump, and mass spectrometer (ARCO2000-MET, Arecosystem, Chiba, Japan). We digitized expired flow, CO2 and O2 concentrations, and derived tidal volume, minute ventilation, end-tidal Po2 (PETO2), and end-tidal PCO2 (PETCO2). Flow signals were computed to single-breath data and matched to gas concentrations identified as single breaths using the peak PETCO2, after accounting for the time delay in gas concentration measurements. The corresponding O2 uptake and CO2 output values for each breath were calculated from inspired-expired gas concentration differences, and by expired ventilation, with inspired ventilation being calculated by N2 correction. During each protocol, HR, ABP, minute ventilation, PETO2, PETCO2, and MCA V were recorded continuously at 200 Hz.

Experimental Protocol

On the experimental day, subjects arrived at the laboratory at least 2 h following a light meal. After instrumentation, the subjects were seated in a semirecumbent position (~45°) in a reclining seat and rested quietly for ~10 min, while wearing the face mask and breathing room air. After the resting period, each subject performed four randomly assigned respiratory interventions: 1) normoxia (21% O2); 2) hyperoxia (40% O2); 3) hypoxia (14% O2), each with volitionally controlled normal respiratory rate; and 4) hypoxia (14% O2) with hyperventilation. Full recovery was permitted between each intervention. Throughout the experimental interventions (interventions 1–3), subjects were instructed to adjust their resting respiratory pattern (14 breaths/min) to the sound of a metronome and the monitor showing each respiratory cycle, to avoid changes in PETCO2. During intervention 4, subjects were instructed to adjust breath at higher respiratory rate (16 respirations/min) to obtain a lower PETCO2 (29 ± 1 Torr; P < 0.001; Table 1). Eight minutes of baseline data were recorded with the subjects breathing the selected gas mixture with control respiration for each condition. Following the baseline at each condition, the thigh cuffs were inflated to more than the systolic pressure (>220 mmHg) for 3 min. After the 3 min of cuff inflation, the cuffs were deflated, and measurements were continued 2 min postdeflation to assess the CBF response to a rapid and transient drop in ABP to identify CAo. Previous investigations have indicated that, under resting conditions, the cuff occlusion-induced ischemia does not induce a muscle metaboreflex activation (29). All conditions were randomized and separated by a minimum of 20 min.

Data Analysis

Beat-to-mean arterial pressure (MAP) and mean MCA V (MCA Vmean) were obtained from each waveform. The cerebrovascular conductance index (CVCi) was calculated by dividing MCA Vmean by MAP and was used as an estimate of changes in cerebrovascular conductance. The derived CVCi during acute hypotension is not directly related to steady-state cerebrovascular conductance, because changes in the vascular compliance affect CBF (1). Control values of MAP, MCA Vmean, and CVCi were defined by calculating their means during the 4 s immediately before thigh-cuff release. Changes in MAP, MCA Vmean, and CVCi during cuff release were determined relative to their concomitant control values. At time 1.0–3.5 s from cuff release, the rate of change in CVCi is directly related to CAo (1). The rate of regulation (RoR) is calculated as an index of CAo (1).

\[
\text{RoR} = \frac{\Delta \text{CVCi/} \Delta T}{\Delta \text{MAP}}
\]

where \(\Delta \text{CVCi/} \Delta T\) is the slope of the linear regression between CVCi and time (T); and \(\Delta \text{MAP}\) was calculated by subtracting control MAP from MAP averaged during the interval from 1.0 to 3.5 s (1).

Statistics

Statistical comparison of variables and RoR were made utilizing a repeated-measures one-way analysis of variance. A Student-Newman-Keuls test was employed post hoc when interactions were significant. Statistical significance was set at P < 0.05, and results are presented as means ± SE. Analyses were conducted using SigmaStat (Jandel Scientific Software, SPSS, Chicago, IL).

Table 1. Steady-state cerebrovascular and cardiorespiratory variables during normoxia, hyperoxia, isocapnic hypoxia, and hypocapnic hypoxia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention 1: Normoxia</th>
<th>Intervention 2: Hyperoxia</th>
<th>Intervention 3: Hypoxia</th>
<th>Intervention 4: Hypocapnic Hypoxia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>65 ± 3</td>
<td>58 ± 8</td>
<td>68 ± 6</td>
<td>69 ± 3</td>
<td>0.347</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>85 ± 3</td>
<td>91 ± 4</td>
<td>85 ± 2</td>
<td>88 ± 5</td>
<td>0.243</td>
</tr>
<tr>
<td>MCA Vmean, cm/s</td>
<td>65 ± 3</td>
<td>62 ± 4</td>
<td>68 ± 4†</td>
<td>54 ± 4†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FIO2, %</td>
<td>20.7 ± 0.1</td>
<td>40.8 ± 0.1*</td>
<td>13.6 ± 0.1†‡</td>
<td>13.6 ± 0.1†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PETCO2, Torr</td>
<td>104 ± 1</td>
<td>245 ± 2*†</td>
<td>58 ± 1*†</td>
<td>67 ± 2*†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PETCO2, Torr</td>
<td>37 ± 1</td>
<td>36 ± 1</td>
<td>37 ± 1</td>
<td>29 ± 1†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>97.7 ± 1.3</td>
<td>99.6 ± 0.9*</td>
<td>88.9 ± 1.7*†</td>
<td>94.2 ± 2.3†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>8.8 ± 0.6</td>
<td>9.5 ± 0.5</td>
<td>9.6 ± 0.5</td>
<td>13.1 ± 0.6†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vt, ml</td>
<td>647 ± 22</td>
<td>694 ± 41</td>
<td>692 ± 46</td>
<td>843 ± 34†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RR, breathes/min</td>
<td>13.7 ± 0.8</td>
<td>13.9 ± 0.8</td>
<td>14.0 ± 0.8</td>
<td>15.6 ± 0.7†‡</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; MAP, mean arterial pressure; MCA Vmean, middle cerebral artery mean blood velocity; FIO2, fraction of inspired oxygen (O2); PETCO2, end-tidal PCO2; PETCO2, end-tidal PCO2; Ve, minute ventilation; Vt, tidal volume; RR, respiratory rate. *P < 0.05, different from normoxia; †P < 0.05, different from hyperoxia; ‡P < 0.05, different from isocapnic hypoxia.
RESULTS

Hyperoxia, Hypoxia, and Hypocapnic Hypoxia

During the four experimental conditions, PETO2 and PETCO2 were accurately controlled by the selected mix of inspired gases and control of respiratory pattern (Table 1). During the control intervention (intervention 1; 21% O2), PETO2 and PETCO2 were 104 ± 1 and 37 ± 1 Torr, respectively. In intervention 2 (40% O2), PETO2 was elevated to 245 ± 2 Torr (P < 0.001), whereas PETCO2 was well maintained at preintervention level (36 ± 1 Torr). Likewise, while hypoxia (intervention 3) decreased PETO2 to 58 ± 1 Torr (P < 0.001 vs. baseline), PETCO2 was maintained by voluntary control of respiration in the hypoxic (37 ± 1 Torr) condition. During intervention 4 (14% O2 with hyperventilation), voluntary hyperventilation decreased PETCO2 from 37 ± 1 to 29 ± 1 Torr. Compared with control, SaO2 was reduced during both isocapnic and hypocapnic hypoxia; however, the reduction in SaO2 was greater during the isocapnic hypoxic condition compared with the hypocapnic hypoxia condition (Table 1). During all interventions (interventions 2–4), there were no alterations in HR (P = 0.347) and MAP (P = 0.243). However, the isocapnic hypoxic intervention tended to increase MCA Vmean (4%; P = 0.237). In contrast, controlled hyperventilation during hypoxia decreased MCA Vmean (19%; P < 0.001). The CVCi increased at hypoxia and decreased at hypocapnic hypoxia condition (see Fig. 2).

Thigh Cuff Release During the Experimental Conditions

The release of the thigh cuffs elicited an acute decrease in ABP at all conditions. Changes in MAP with thigh deflation were −27 ± 3% (normoxia; intervention 1), −30 ± 2% (isocapnic hypoxia; 2), −28 ± 2% (isocapnic hypoxia; 3), and −27 ± 4% (hypocapnic hypoxia conditions; 4). There were no differences in the changes in MAP with each condition. As intended, these decreases in ABP were sufficient to evoke a transient decrease in MCA Vmean (1). As a reflection of CAd, changes in MCA Vmean were smaller (average 23%) from baseline compared with MAP in all conditions, particularly during the hypocapnic hypoxia condition (18 ± 3%, P < 0.001).

The RoR, an index of CAd, was calculated from the change in CVCi from 1 to 3.5 s (Fig. 1). Compared with normoxia, RoR was not altered with isocapnic hypoxia (0.321 ± 0.028/s; Fig. 2). Isocapnic hypoxia significantly attenuated RoR (0.202 ± 0.030/s; 27%, P = 0.043). In contrast, hypocapnic hypoxia increased RoR (0.444 ± 0.069/s) from normoxia (0.311 ± 0.054/s; +55%, P = 0.041).

DISCUSSION

The primary finding of the present study is that isocapnic hypoxia impairs CAd; however, mild hypocapnia counteracts this to improve CAd during hypoxia. These data indicate that, at least acutely, the respiratory chemoreflex may compensate for hypoxic-induced impaired in CAd through hyperventilation and consequent hypocapnia. That hypocapnia affected CAd even under conditions of hypoxia reinforces the idea that CBF control is influenced to a greater extent by Pco2 than by Paco2.

Hypocapnia leads to cerebral vasoconstriction, which attenuates the further fall of brain tissue Pco2, while hypercapnia causes cerebral vasodilation, limiting elevations in brain tissue Pco2. Changes in blood-gas concentrations modified dynamic CBF regulation (1, 24). For example, there was a significant inverse relationship between CAd and Paco2, indicating that the response rate of CAd is due to cerebral vascular tone as determined by levels of Pco2 (1). However, while hypoxia is a cerebral vasodilator, reflected in a rise in CBF in proportion to the severity of isocapnic hypoxia (6, 11), under normal conditions the hypoxia-induced activation of peripheral chemoreceptor activity leads to hyperventilation-induced lowering of Paco2 and subsequent cerebral vasoconstriction. Thus the cerebrovascular bed receives conflicting signals during exposure to acute hypoxia, which coincides with hypoxic ventilatory response and resultant hypocapnia (4). An important physio-
hyperventilation and subsequent reduction in arterial $P_{CO2}$ during acute (5 min) exposure to hypoxia ($F_{IO2}$ < 0.10; inspired PO$_2$ = 3–5 Torr), accompanied by cerebral vasodilation. In contrast, high cerebral vascular tone, induced via hypcapnia (1), improved CA$_d$. We found that CA$_d$ was improved by hyperventilation, even during hypoxia, which causes further cerebralvasoconstriction. Thus cerebral vascular tone may modify CA$_d$. However, heavy exercise (26), hypertensive patients (16), and orthostatic stress (38) impaired CA$_d$, despite a high cerebral vascular tone.

Implications

**High altitude.** There have been a number of studies that have examined the influence of high altitude on CA. Studies indicate an impairment in CA (3, 18, 21) in both newcomers to high altitude and in permanent high-altitude residents living above 4,000 m (19), especially in the presence of acute mountain sickness (7, 34). These studies reported impairment in CA$_d$, despite the presence of marked hypoxemia, which is in contrast with those from the present study, where CA$_d$ was improved with the addition of hypoxemia. Differences in the experimental protocol (i.e., length of hypoxemic exposure), severity, and type of hypoxic exposure (i.e., simulated vs. high altitude) may underpin these different findings. Nevertheless, the possibility that those with a more vigorous hypoxic ventilatory responses at high altitude (and, therefore, greater degree of hypcapnia) may benefit from a better maintained CA$_d$ and, therefore, protection against acute mountain sickness (7, 34) warrants further study.

**Pathology.** Arterial hypoxemia is a common consequence of chronic lung and cardiac diseases. Little is known with respect to how CA$_d$ and CBF may be regulated in these disorders (4). However, transient drops in PaCO$_2$ are known to occur in a range of physiological (e.g., postural change, exercise) and pathophysiological (e.g., asthma, sleep apnea, congestive heart failure, anxiety attacks) situations. The possibility that such hypcapnia is of teleological relevance to offset hypoxic-induced impairment in CA$_d$ warrants further research.

**Methodological considerations.** A potential limitation of estimating MCA $V$ using TCD is that changes in the diameter of the insonated vessels could modulate MCA $V$ independently of flow. Numerous studies support the validity of MCA $V$ as an index of regional CBF (9, 23, 27, 30, 32, 33). Moreover, studies have shown that MCA diameter is relatively unchanged in the range of 23–60 Torr for PaCO$_2$ (13, 30, 33). However, evidence of unchanged MCA diameter during hypoxia is still less clear. Nevertheless, it is noteworthy that the observed MCA $V$ response during isocapnic hypoxia was comparable to
findings by Noth et al. (22), who have previously assessed the CBF response to isocapnic hypoxia using MRI (22). Consistent with this report, earlier studies (28) have used the Doppler power signal as an index of the cross-sectional area of the MCA diameter and have also reported that the diameter is unchanged during comparable hypoxia conditions. Collectively, these findings support the use of MCA V as a valid measure of CBF. In addition, TCD-determined blood flow velocity in large basal cerebral arteries (i.e., MCA) is widely used as an index of CBF and can identify a transient change in CBF (24).

A consequence of the hypoxic hypocapnia condition was that the hyperventilation caused a small rise in $P_{O_2}$ ($\approx 9$ Torr) and, therefore, $S_{aO_2}$. Nevertheless, alterations in $C_{Ad}$ occur at 15% $O_2$; some changes were also evident at 17% $O_2$ (17). Moreover, because of the alveolar-to-arterial $P_{O_2}$ gradient (normally $= 5$–8 Torr (5, 20)), $P_{O_2}$ would likely be $< 50$ Torr. Thus it would seem unlikely that the small increase in $P_{O_2}$ and, therefore, vasodilatory stimulus would alter our findings.

In summary, isocapnic hypoxia impairs $C_{Ad}$, whereas it is unchanged under conditions of isocapnic hyperoxia. In addition, hyperventilation-induced mild hypocapnia acts to improve $C_{Ad}$ during hypoxic conditions. It seems likely that, at least acutely, respiratory chemoreflex may compensate for hypoxia-induced impairment in $C_{Ad}$.

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DISCLOSURES

No conflicts of interest are declared by the author(s).

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