Alterations in cerebral autoregulation and cerebral blood flow velocity during acute hypoxia: rest and exercise

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Ainslie PN, Barach A, Murrell C, Hamlin M, Hellemans J, Ogoh S. Alterations in cerebral autoregulation and cerebral blood flow velocity during acute hypoxia: rest and exercise. Am J Physiol Heart Circ Physiol 292: H976–H983, 2007. First published September 29, 2006; doi:10.1152/ajpheart.00639.2006.—We examined the relationship between changes in cardiorespiratory and cerebrovascular function in 14 healthy volunteers with and without hypoxia [arterial O2 saturation (SaO2) ~80%] at rest and during 60–70% maximal oxygen uptake steady-state cycling exercise. During all procedures, ventilation, end-tidal gases, heart rate (HR), arterial blood pressure (BP; Finometer) cardiac output (Modelflow), muscle and cerebral oxygenation (near-infrared spectroscopy), and middle cerebral artery blood flow velocity (MCAV; transcranial Doppler ultrasound) were measured continuously. The effect of hypoxia on dynamic cerebral autoregulation was assessed with transfer function gain and phase shift in mean BP and MCAV. At rest, hypoxia resulted in increases in ventilation, progressive hypocapnia, and greater sympathetic activation (i.e., elevated HR and cardiac output); these responses were more marked during hypoxic exercise (P < 0.05 vs. rest) and were also reflected in elevation of the slopes of the linear regressions of ventilation, HR, and cardiac output with SaO2 (P < 0.05 vs. rest). MCAV was maintained during hypoxic exercise, despite marked hypocapnia (44.1 ± 2.9 to 36.3 ± 4.2 Torr; P < 0.05). Conversely, hypoxia both at rest and during exercise decreased cerebral oxygenation compared with muscle. The low-frequency phase between MCAV and mean BP was lowered during hypoxic exercise, indicating impairment in cerebral autoregulation. These data indicate that increases in cerebral neurogenic activity and/or sympathoexcititation during hypoxic exercise can potentially outbalance the hypocapnia-induced lowering of MCAV. Despite maintaining MCAV, such hypoxic exercise can potentially compromise cerebral autoregulation and oxygenation.

Hypocapnia; hypoxemia

An important protective feature of the cerebral circulation is the ability to maintain cerebral blood flow (CBF) over a wide range of cerebral perfusion pressures (36). At rest, lowering of arterial PCO2 (PaCO2) (hypocapnia) as a result of hyperventilation and elevations in sympathetic activation act to enhance cerebral autoregulation (i.e., by widening the cerebral autoregulation curve and causing a rightward shift, respectively), thus preventing cerebral hyperperfusion (36). During exercise, however, it has been shown that dynamic cerebral autoregulation was impaired by exhaustive exercise despite a hyperventilation-induced reduction in PaCO2, and likely exercise-induced elevations in sympathetic activation (35).

Acute hypoxia in resting and exercising humans results in an enhanced muscle sympathetic discharge, cardiac output, skeletal muscle blood flow, and increased heart rate with little or no alteration in mean arterial blood pressure (MAP) (15, 38). In the brain, the vasodilatory effects of acute hypoxia at rest tend to initially increase CBF; however, hypoxia-induced hyperventilation and subsequent hypocapnia lead to cerebral vasoconstriction, resulting in little change in CBF (3, 41). During exercise, however, it is not clear how acute hypoxia may alter CBF autoregulation. After prolonged exposure to high altitude, cerebral oxygenation has been reported to fall during submaximal exercise while blood flow velocity in the middle cerebral arterial (MCAV) was increased (23). A number of recent studies have indicated that cerebral autoregulation is impaired in conscious newcomers at high altitude (24, 45). Cerebrovascular responses to hypoxia and hypocapnia have also been shown to be impaired in high-altitude dwellers (33). Despite these findings from exposure to chronic hypoxia, we have discovered no published evidence to indicate whether dynamic cerebral autoregulation also becomes impaired during periods of acute hypoxia, either at rest or during exercise. Quantification of cerebral autoregulation with “static” methods obscures the fact that most of the challenges to cerebral perfusion originate from rapid shifts (i.e., within seconds) in cerebral perfusion. Loss of dynamic autoregulation may therefore be a more sensitive index of a threatened cerebral circulation than the standard static measures of cerebral autoregulation (7). Therefore, the aims of this investigation were to examine whether acute hypoxia alters CBF dynamics and autoregulation, assessed by using transfer function analysis, at rest and during exercise and to assess the integrative cardiorespiratory and cerebrovascular responses to acute hypoxia during rest and exercise. In light of the aforementioned observations, we tested two original hypotheses: first, that cerebral autoregulation would be impaired during resting conditions of acute hypoxia and would be further compounded during exercise and second, that acute hypoxia during exercise would result in sympathoexcitation (i.e., elevated cardiac output), thereby outbalancing the effects of hypoxia-induced hyperventilation and resultant lowering of PaCO2 on MCAV.

METHODS

Subjects. Fourteen healthy individuals (6 men, 8 women; age 25 yr (4) [mean (SD)], body mass index 24 kg/m2 (SD 4), and maximal oxygen consumption 57 ml·kg⁻¹·min⁻¹ (5)) volunteered for this study.

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study, which was approved by the University of Otago’s Human Ethics Committee and conformed to the standards set by the Declaration of Helsinki. Subjects were informed of the experimental procedures and possible risks involved in the study, and written informed consent was obtained. Subjects were not taking any medication, all were nonsmokers, and none had any history of cardiovascular, cerebrovascular, or respiratory disease.

Experimental design. Subjects were instructed to abstain from exercise and alcohol 12 h before and not to eat a heavy meal or consume caffeine 4 h before experimental testing. A summary of the timing and experimental procedures performed during the study is provided in Fig. 1. Baseline control measurements were obtained in normoxia [inspired O2 fraction (FiO2) = 21%] and at selected time points in normobaric hypoxia during rest and exercise. During rest, after 10 min of baseline measures, subjects received 20 min of hypoxia (FiO2 = 12%) followed by a 3- to 4-min normoxic recovery. The subjects rested in a supine position in a darkened room and were instructed to close their eyes and to relax to reduce external stimuli that could affect respiration. After a 3- to 4-min warm-up, subjects then exercised on a cycle ergometer in the upright position at 60–70% of their maximal oxygen uptake. After 5–6 min of steady-state exercise, FiO2 was immediately reduced to 14% for 4–5 min, followed by a 3- to 4-min normoxic recovery. FiO2 levels at rest and during exercise were targeted to elicit an arterial O2 saturation (SaO2) of ~80%.

Measurements of respiratory gas exchange. Subjects breathed through a leak-free respiratory mask (Hans-Rudolph 8980, Kansas City, MO) attached to a one-way nonrebreathing valve (Hans-Rudolph 2700). Expiratory flow was measured with a heated pneumotach (Hans-Rudolph HR800). SaO2 was measured with pulse oximetry at the finger (model ML320). End-tidal PCO2 (PETCO2) and PO2 (PETCO2) were sampled from a leak-free mask and measured by a gas analyzer (model CD-3A, AEI Technologies, Pittsburgh, PA). Ventilatory and gas values (flow, tidal volume, frequency) were displayed in real time during testing (PowerLab, ADInstruments, Colorado Springs, CO). Expiratory flow was calculated with the integrated flow signal and the frequency of breathing. Changes in PETCO2 closely reflect changes in PacO2 at rest; however, during exercise, PETCO2 may significantly overestimate PacO2 (25). To account for this potential overestimation during exercise, and to provide a better reflection of PacO2 during exercise, PETCO2 values were adjusted for changes in tidal volume (25).

Measurements of CBF velocity and arterial BP. MCAV was measured with a 2-MHz pulsed Doppler ultrasound system (DLW Doppler, Sterling, VA) and search techniques described elsewhere (2). Beat-to-beat arterial BP was monitored with finger photoplethysmography (Finometer, TNO-TPD Biomedical Instrumentation). Cerebrovascular resistance (CVR) was calculated by dividing mean BP by MCAV. Heart rate, stroke volume, and cardiac output were calculated from the BP waveform with the Modelflow method, incorporating age, sex, height, and weight (BeatScope 1.0 software; TNO-TPD Biomedical Instrumentation); this method provides a reliable estimate of changes in cardiac output during exercise in healthy young humans (42). All data were acquired continuously at 200 Hz with an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments) interfaced with a computer. All data, including respiratory gas exchange, were sampled at 200 Hz and stored for subsequent analysis with commercially available software (Chart version 5.02, ADInstruments).

Cerebral and muscle oxygenation. Cerebral and muscle oxygenation were monitored with a commercially available near-infrared spectroscopy (NIRS) system (NIRO-300; Hamamatsu Photonics KK, Hamamatsu, Japan). A probe holder containing an emission probe and a detection probe was attached at the right side of the forehead with a distance of 5 cm between the probes. The methodology of this system was described previously (32). NIRO-300 measures the concentration changes of oxyhemoglobin (oxy-Hb), deoxyhemoglobin (deoxy-Hb), and total hemoglobin (t-Hb) with a modified Beer-Lambert law (4). It gives an absolute unit (micromoles per liter) for the changes in oxy-Hb, deoxy-Hb, and t-Hb by incorporating an optical path length. For assessment of muscle oxygenation, optodes were positioned on the middle portion of the right vastus lateralis muscle at the midthigh level and parallel with the long axis of the muscle. Similar to the brain, the optodes were housed in an optically dense plastic holder secured on the skin with tape to minimize extraneous light. In the brain and muscle, t-Hb, oxy-Hb, and deoxy-Hb were measured simultaneously every 1 s throughout the experiment and expressed as the magnitude of the change from the initial value. The deoxy-Hb signal was assumed to be a reliable estimator of the changes in tissue deoxygenation status (representing a mismatch between O2 delivery and O2 utilization) in the field of interrogation. All NIRS data were time aligned and simultaneously collected at 200 Hz along with the other aforementioned variables.

Cerebral autoregulation. The 3-min steady-state data segments were used for transfer function analysis to identify dynamic cerebral autoregulation at each condition. The beat-to-beat data of MAP and MCAV were then linearly interpolated and resampled at 2 Hz for spectral analysis (47). The transfer gain and phase shift reflect the relative amplitude and time relationship between the changes in MAP and MCAV over a specified frequency range. From the temporal sequences, the frequency-domain transforms were computed with a fast Fourier transformation algorithm. The transfer function H(f) between the MAP and MCAV signals was calculated as H(f) = Sx(f)/Sy(f), where Sx(f) is the autospectrum of the input signal (MAP) and Sy(f) is the cross-spectrum between the two signals. The transfer function magnitude H(f) and phase spectrum Φ(f) were calculated from the BP waveform with the Modelflow method, incorporating age, sex, height, and weight (BeatScope 1.0 software; TNO-TPD Biomedical Instrumentation); this method provides a reliable estimate of changes in cardiac output during exercise in healthy young humans (42). All data were acquired continuously at 200 Hz with an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments) interfaced with a computer. All data, including respiratory gas exchange, were sampled at 200 Hz and stored for subsequent analysis with commercially available software (Chart version 5.02, ADInstruments).
obtained from the real part \( H_0(f) \) and the imaginary part \( H_1(f) \) of the complex transfer function:

\[
H(f) = \left[ \left( \frac{H_0(f)}{\sqrt{H_0(f)^2 + H_1(f)^2}} \right) \right]^2 \\
\Phi(f) = \tan^{-1}\left( \frac{H_1(f)}{H_0(f)} \right)
\]

The squared coherence function \( MSC(f) \) was estimated as \( MSC(f) = S_x(f)^2 / (S_x(f)S_y(f)) \), where \( S_x(f) \) is the autospectrum of changes in MCAV. The squared coherence function reflects the fraction of output power that can be linearly related to the input power at each frequency. Mean values of transfer function gain, phase, and coherence function were calculated in the very low (0.02–0.07 Hz), low (LF, 0.07–0.20 Hz), and high (0.20–0.30 Hz)-frequency ranges to reflect different patterns of the dynamic pressure-flow relationship (47). We used the LF range of each variable for the spectral analysis to identify dynamic cardiovascular and CBF regulation, because BP fluctuations in the LF (0.07–0.20 Hz) range are independent of the respiratory frequency and dampened by autoregulatory mechanisms (9). Thus, we used the LF spectral power of the mean value of transfer gain, phase, and coherence function to identify dynamic cerebral autoregulation at rest and during exercise with and without hypoxia. Cerebral autoregulation decreases the transmission effect of pressure on flow; therefore, an increased transfer function gain or decreased transfer function phase between pressure and flow can be interpreted as an increased effect of transmission, which suggests that dynamic cerebral autoregulation is impaired.

Data and statistical analyses. Because there were no statistical differences between men and women, data from the two groups were combined for statistical analysis. The ventilatory, MCAV, MAP, and NIRS responses to hypoxia were determined by linear regression between the mean ventilation, MCAV, MAP, and NIRS with \( \text{SaO}_2 \) (100 – \( \text{SaO}_2 \)) during the final averaged 60 s of each incremental step of hypoxia. Likewise, the slope of the change in MCAV relative to \( \text{PETCO}_2 \) was determined at the same time point. The relationship between these variables with \( \text{SaO}_2 \) or \( \text{PETCO}_2 \) was only considered acceptable when linearity (\( r > 0.7 \)) was demonstrated. To calculate the absolute and percent change from baseline, data were averaged over the 5-min period of baseline immediately preceding any changes in \( \text{SaO}_2 \). All data were analyzed with the SPSS social statistics package (version 9; SPSS, Surrey, UK). A Shapiro-Wilks test was applied to each dependent variable to mathematically assess distribution normality. Parametric and nonparametric equivalents of a two-way mixed ANOVA with one between (state: rest vs. exercise) and one within (normoxia vs. hypoxia) factor were incorporated to examine the effects of time and state on selected variables. Significance for all two-tailed tests was established at an \( \alpha \) level of \( P < 0.05 \), and data are expressed as means (SD).

RESULTS

General observations. The hypoxic stimulus produced comparable decreases in \( \text{SaO}_2 \); both at rest and during exercise (Table 1). Ventilation was elevated during hypoxic conditions at rest, which was reflected in parallel decreases in \( \text{PETCO}_2 \) and MCAV at each time point compared with baseline (\( P < 0.05 \); Table 1). The hypoxia-induced lowering of \( \text{PETCO}_2 \) at rest was related to the decline in MCAV (\( r = 0.87; P < 0.05 \)). During exercise, there was an increase in both MCAV and CVR (\( P < 0.05 \) vs. normoxic rest). These increases in MCAV were unaltered during hypoxia, despite marked hypocapnia at this time point (a shift from 44.1 ± 2.9 to 36.3 ± 4.2 Torr; \( P < 0.05 \); Figs. 2 and 3). No relationship was apparent between the lowered \( \text{PETCO}_2 \) and MCAV during hypoxic exercise (\( r = 0.2 \)). At rest, there was a slight increase in cardiac output during the early conditions of hypoxia (4–6 min and 10–12 min), which returned to baseline by 20 min. These increases in cardiac output were predominantly caused by an elevated heart rate since stroke volume was unchanged. During normoxic exercise, heart rate, stroke volume, MAP, and cardiac output were all elevated (\( P < 0.05 \) vs. normoxic rest; Table 1). Relative to normoxic exercise, hypoxic exercise caused an increase in heart rate and cardiac output while stroke volume and MAP were unchanged (Table 1).

Table 1. Steady-state cerebrovascular and cardiorespiratory variables during normoxic and hypoxic rest and exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normoxic</th>
<th>Hypoxic 4–6 min</th>
<th>Hypoxic 10–12 min</th>
<th>Hypoxic 18–20 min</th>
<th>Normoxic</th>
<th>Hypoxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MCAV, cm/s</td>
<td>63.7 (14.5)</td>
<td>58.9 (9.1)*</td>
<td>59.7 (11.4)*</td>
<td>59.2 (13.5)</td>
<td>71.4 (17.8)*†</td>
<td>69.5 (17.1)*†</td>
</tr>
<tr>
<td>CVR, mmHg/cm²·s⁻¹</td>
<td>1.34 (0.393)</td>
<td>1.40 (0.38)</td>
<td>1.41 (0.42)</td>
<td>1.39 (0.40)</td>
<td>1.58 (0.58)*†</td>
<td>1.68 (0.52)*†</td>
</tr>
<tr>
<td>ΔOxy-Hb, mmol/l</td>
<td>0</td>
<td>-2.61 (1.86)</td>
<td>-3.40 (2.90)</td>
<td>-3.86 (3.55)</td>
<td>-12.7 (8.0)*†</td>
<td>-8.0 (6.3)*†</td>
</tr>
<tr>
<td>ΔDeoxy-Hb, mmol/l</td>
<td>0</td>
<td>36.2 (23.0)*</td>
<td>55.4 (36.5)*</td>
<td>65.7 (49.2)*</td>
<td>40.5 (32.5)*†</td>
<td>141.8 (51.7)*†</td>
</tr>
<tr>
<td>Δt-Hb, mmol/l</td>
<td>0</td>
<td>1.5 (2.1)</td>
<td>1.6 (2.0)</td>
<td>1.8 (2.6)</td>
<td>2.4 (3.4)</td>
<td>19.6 (11.8)*†</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>81.1 (10.3)</td>
<td>79.7 (13.4)</td>
<td>81.1 (13.5)</td>
<td>77.9 (12.4)</td>
<td>105.0 (22.8)*†</td>
<td>104.7 (30.4)*†</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>50.6 (7.1)</td>
<td>50.6 (12.3)*</td>
<td>55.6 (10.4)*</td>
<td>54.5 (9.0)*</td>
<td>138.6 (13.6)*†</td>
<td>153.7 (12.5)*†</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>99.0 (18.2)</td>
<td>95.3 (19.9)</td>
<td>98.9 (14.2)</td>
<td>97.7 (17.4)</td>
<td>116.6 (10.4)*†</td>
<td>119.8 (9.5)*†</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>5.0 (1.1)</td>
<td>5.5 (1.6)*</td>
<td>5.5 (1.2)*</td>
<td>5.2 (1.4)</td>
<td>16.5 (2.8)*†</td>
<td>18.9 (2.6)*†</td>
</tr>
<tr>
<td>ΔOxy-Hb, l/min</td>
<td>0</td>
<td>-1.06 (1.4)</td>
<td>-2.04 (2.44)</td>
<td>-2.5 (2.8)</td>
<td>-1.7 (6.0)</td>
<td>-4.4 (7.3)</td>
</tr>
<tr>
<td>ΔDeoxy-Hb, l/min</td>
<td>0</td>
<td>12.8 (15.0)</td>
<td>21.6 (24.5)</td>
<td>29.8 (28.6)*</td>
<td>59.3 (48.9)*</td>
<td>82.3 (49.8)*</td>
</tr>
<tr>
<td>Δt-Hb, l/min</td>
<td>0</td>
<td>1.0 (3.2)</td>
<td>1.8 (2.2)</td>
<td>2.2 (4.3)</td>
<td>3.8 (2.5)*†</td>
<td>3.9 (2.0)*†</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ventilation, l/min</td>
<td>5.1 (2.2)</td>
<td>6.2 (2.9)*</td>
<td>5.4 (1.7)*</td>
<td>5.3 (2.2)*</td>
<td>69.6 (20.6)*†</td>
<td>87.0 (23.0)*†</td>
</tr>
<tr>
<td>( \text{PETCO}_2 ), Torr</td>
<td>106.1 (4.2)</td>
<td>68.5 (13.4)*</td>
<td>61.5 (14.1)*</td>
<td>61.6 (15.1)*</td>
<td>105.2 (4.2)*†</td>
<td>74.4 (5.8)*†</td>
</tr>
<tr>
<td>( \text{PETCO}_2 ), Torr</td>
<td>41.9 (2.0)</td>
<td>38.7 (2.9)*</td>
<td>39.1 (3.0)*</td>
<td>39.4 (2.8)*</td>
<td>44.1 (2.9)*</td>
<td>36.3 (4.2)*†</td>
</tr>
<tr>
<td>( \text{SaO}_2 ), %</td>
<td>98.0 (9.0)</td>
<td>82.7 (2.6)*</td>
<td>81.9 (5.9)*</td>
<td>79.5 (6.1)*</td>
<td>96.8 (1.1)</td>
<td>80.0 (4.0)*†</td>
</tr>
</tbody>
</table>

Values are means (SD) based on 14 subjects. MCAV, middle cerebral artery flow velocity; CVR, cerebrovascular resistance; oxy-Hb, oxygenated hemoglobin; deoxy-Hb, deoxygenated hemoglobin; t-Hb, total hemoglobin; MAP, mean arterial pressure; HR, heart rate; \( \text{PETCO}_2 \), and \( \text{PETCO}_2 \)-end-tidal \( \text{PO}_2 \) and \( \text{PCO}_2 \), respectively; \( \text{SaO}_2 \), arterial oxygen saturation. *Different compared with normoxic rest (\( P \leq 0.05 \)); †different compared with hypoxic rest (\( P \leq 0.05 \)); ‡different compared with normoxic exercise (\( P \leq 0.05 \)).

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Differential alterations in cerebral and muscle oxygenation. The differential changes in t-Hb, oxy-Hb, and deoxy-Hb in brain and muscle are illustrated in Fig. 4. Hypoxia at rest provoked a gradual increase in cerebral deoxy-Hb, while cerebral oxy-Hb was decreased compared with muscle ($P < 0.05$; Table 1, Fig. 4). In the muscle, there was a slight elevation in t-Hb during exercise, which was unchanged during hypoxic exercise. Conversely, in the brain, there was a marked elevation in t-Hb during hypoxic exercise compared with the muscle and exercise without hypoxia ($P < 0.05$; Fig. 4). At rest, the lowered oxy-Hb in the brain was closely related to the lowered MCAV ($r = 0.75$; $P < 0.05$) during hypoxia, whereas no relationship was evident during the changes caused by hypoxia during exercise ($r = 0.01$).

Hypoxic sensitivities during rest and exercise. Cerebrovascular sensitivity to hypoxia was unchanged between rest and exercise; however, when expressed as the change in velocity per milligram of mercury change in PETCO$_2$, the sensitivity was abolished during exercise ($P < 0.05$; Table 2). During exercise, there was a greater increase in heart rate and cardiac output hypoxic sensitivity compared with rest ($P < 0.05$; Table 2). Likewise, ventilatory sensitivity to hypoxia was also elevated during exercise compared with rest.

Transfer function analyses. There was a decrease in the LF transfer function phase shift during hypoxic exercise, thus indicating an impairment in cerebral autoregulation ($P < 0.05$ vs. rest and normoxic exercise; Fig. 5). The LF coherence between MCAV and MAP was $>0.5$ at all measurement points (Fig. 4), reflecting a strong statistical reliability of the transfer analysis between input and output.

DISCUSSION

Our findings have revealed several novel observations. First, MCAV was maintained at a much higher level than expected for the given level of hypocapnia during hypoxic exercise. Second, the slope of the relationship between MCAV and PETCO$_2$ was abolished during exercise compared with rest, indicating that the cerebral circulation was less sensitive to hypocapnia during hypoxic conditions of exercise. Third, hypoxia during rest and exercise decreased cerebral oxygenation, whereas oxygenation was maintained in the muscle. Finally, cerebral autoregulation was maintained during hypoxia at rest but impaired during hypoxic exercise. The following discussion outlines the relevant evidence and limitations underlying these observations.

Previous work has documented that progressive increases in exercise intensity result in sympathoexcitation, leading to an enhanced proportional distribution of cardiac output to the active muscle and reducing the amount to the brain (18). Acute hypoxia may also augment both the heart rate and cardiac output response during exercise, although these alterations may not be solely mediated via sympathetic activation and circulating catecholamines acting on cardiac β-receptors (19). Since changes in cardiac output independent of MAP can affect MCAV (21, 22), one possibility is that the elevated cardiac output evoked by hypoxia during exercise outbalanced the hypocapnia-induced lowering of MCAV. In support of this, it has been shown that if the hyperventilation-induced hypocapnia achieved by cold-shock water immersion (12°C) was matched by voluntary hyperventilation either in warm air (24°C) or thermoneutral water (35°C), there was an even lower
MCAV (6). In other words, the MCAV seen during cold shock and/or hypoxic exercise seems to be higher than one would expect for a given level of PaCO2, suggestive of either increased cerebral neurogenic activity with an accompanying demand for increased CBF or systemic sympathetic-induced hypertension. Since there was no increase in BP during hypoxic exercise, systemic sympathetic-induced hypertension seems unlikely. Experimental work in animals provides additional evidence that total CBF can remain constant or slightly elevated during exercise despite arterial hypocapnia (10, 16). These studies suggest that the metabolic effects on cerebral vessels, secondary to regional increases in neuronal activity during exercise, can override the vasoconstrictor effects of hypocapnia. Our data are consistent with previous studies that have shown the slope (sensitivity) of the relationship between MCAV and PaCO2 to be markedly reduced during maximal exercise-induced hypocapnia compared with rest (34); these findings highlight the reduced influence of hypocapnia on the cerebral vessels during hypoxic exercise. Potentially, increases in cerebral neurogenic activity and/or sympathoexcitation (i.e., elevation in cardiac output) may outbalance the hypocapnia-induced lowering of MCAV, thereby resulting in the reduced influence of hypocapnia on the cerebral vessels during hypoxic exercise.

**Dynamic cerebral autoregulation.** It is well established that, at rest, hypocapnia, leading to constriction of cerebral vessels, and elevations in sympathetic activation help to resist increases of pressure, extending further the autoregulatory plateau (1). Our data seemingly indicate the opposite in that acute hypoxia during exercise reduced cerebral autoregulation despite the presence of hypocapnia and sympathoexcitation. These results, however, are consistent with the finding that dynamic cerebral autoregulation was impaired by exhaustive exercise despite a hyperventilation-induced reduction in PaCO2 (35). The mechanisms by which cerebral autoregulation becomes impaired in the presence of hypocapnia and/or sympathoexcitation remain to be established but are in broad agreement with recent reports of an impaired cerebral autoregulation in humans at high altitude (24, 45) and may be implicated, via capillary overperfusion, in the pathophysiology of altitude illness. Our results suggest that such impairment is also apparent over periods of acute hypoxia during exercise. Therefore, physical exercise, in addition to hypoxia, may be an important mediator in provoking the incidence of altitude illness (23, 45).

**Differential alterations in cerebral and muscle oxygenation.** Our results with simultaneously measured oxygenation in brain and muscle show that hypoxia during rest and exercise results in differential alterations in cerebral and muscle oxygenation. This finding is consistent with an earlier report of a significant “steal” of blood (as determined by NIRS) from the cerebral
Differential alterations in MCAV and cerebral oxygenation.

During hypoxia at rest, there was a strong relationship between the change in MCAV and the change in oxy-Hb ($r = 0.75; P < 0.05$), whereas no relationship was apparent during conditions of hypoxic exercise, where MCAV was maintained despite reduced oxy-Hb. Potential explanations for the apparent dissociation between the MCAV measurements and cerebral oxygenation during hypoxic exercise should also be considered. J) Since a change in the deoxy-Hb signal indicates a local mismatch between $O_2$ delivery and $O_2$ utilization (31), the maintained MCAV may be an attempt to meet, albeit inadequately, cerebral $O_2$ demand. Convergent data following exposure to high altitudes indicate that the decline in cerebral oxygenation during submaximal exercise may be attributed to a fall in $O_2$ delivery and/or a decrease in cerebral $O_2$ consumption (23).

2) Conversely, the change in both oxy-Hb and deoxy-Hb concentrations may reflect a decrease in regional blood flow, raising the possibility that discrete regions of the brain may respond differently during hypoxic exercise. In support of this notion, earlier research in animal models highlights the regional distribution of CBF during moderate-intensity exercise to the regions of the brain associated with integrating sensory input and motor output, cardiorespiratory control, and maintenance of equilibrium (8, 16). If the increase in blood flow is to meet metabolic demands (i.e., that of an increased motor cortex activation associated with exercise), this would explain the increase in flow despite the hypocapnia, especially given recent evidence that neurotransmitter release may act as a local vasodilator (5). This seems an especially plausible explanation since increases in flow and decreases in oxy-Hb were similar between normoxic and hypoxic exercise. Thus motor activation in both conditions resulted in similar responses despite differing levels of sympathoexcitation and cardiac output. Therefore, it seems reasonable to suggest that the decline in oxygenation levels in the NIRS-measured frontal cortex tissue area may be explained, at least in part, by hypoxic exercise-induced regional distribution of blood flow to this area that may not be reflected in the vicinity of the MCA.

3) Measurement of MCAV during exercise may not accurately reflect changes in actual blood flow (12, 29), possibly arising from an artifact from the increase in amplitude and frequency of the arterial pressure waveform (37) (see Technological considerations). However, we feel that the former is
unlikely, as our findings of a increase in MCAV of ~12% are broadly consistent with previous studies that estimated brain blood flow during submaximal exercise via carotid blood flow (17, 20) or by $^{133}$Xe clearance (43). Another important consideration is that the changes in cerebral oxy-Hb and deoxy-Hb during hypoxic exercise could primarily be related to volume shifts in the relationship between arterial and venous blood volumes; thus potential hypoxia-induced venodilation during exercise could explain the NIRS results (see Technical considerations).

Technological considerations. Cerebral NIRS has been shown to track changes in jugular venous bulb saturation in healthy volunteers under conditions of hypoxia (27) and has also been validated compared with PET scanning, with $^{133}$Xe washout methods, and with internal carotid artery stump pressures (46). Previous studies have shown that change in NIRS provides a good measure of the proportion of blood that is oxygenated; it does not, however, distinguish how much blood is in the arterial or venous part of the vascular bed (23). The proportion of total blood in the brain has been estimated to be 28% arterial and 72% venous (30). Since there were increases in t-Hb during hypoxic exercise, the changes in oxy-Hb and deoxy-Hb may be related primarily to volume shifts between the proportions of blood in the arterial or venous part of the cerebrovascular/muscular bed. We further acknowledge that NIRS measures only local (i.e., to one depth) oxygenation and, as highlighted in the present study, that discreet regions of the brain and/or muscle may respond differently during conditions of exercise and/or hypoxia.

The main assumption of transcranial Doppler ultrasound is that the relative changes in MCAV directly represent relative changes in the blood flow within this artery; however, the majority of research suggests that MCAV is a reliable index of CBF (11, 28, 40, 44). Calculation of CVR is complicated by unknown values of intracranial and venous pressures. During our resting conditions, since subjects were in a supine position, it is likely that the major determinant of cerebral perfusion pressure was MAP (39). Although the calculation of CVR in the upright position has been used extensively in previous studies, we acknowledge that MAP cannot be relied on to reflect cerebral perfusion pressure under all circumstances, especially in the upright posture. The effects of exercise and/or hypoxic stimulation on creating large changes in intrathoracic pressure, intracranial/venous pressures, and/or potentially cerebral blood volume may all additionally affect cerebral perfusion pressure.

Although both transfer function phase and gain are used as an index of dynamic cerebral autoregulation, changes in gain were not consistent with changes in phase in the present study. However, the phase estimate reflects the time relationship while the gain reflects the amplitude relationship between arterial blood pressure and MCAV. Therefore, it is possible that changes in gain are not associated with changes in phase. One possibility for why there were no changes in transfer function gain, as previously shown with exhaustive exercise (35), may be the combination of hypoxia with the nonexhaustive exercise having more of an differential influence on transfer function phase rather than gain.

In summary, our data indicate that elevations in cerebral neurogenic activity and/or sympathoeexcitation during hypoxic exercise can potentially outbalance the hypocapnia-induced lowering of MCAV. Despite maintaining MCAV, however, such hypoxic exercise can potentially compromise cerebral autoregulation and oxygenation.

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REFERENCES


