Cardiorespiratory and cerebrovascular responses to acute poikilocapnic hypoxia following intermittent and continuous exposure to hypoxia in humans

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Ainslie PN, Barach A, Cummings KJ, Murrell C, Hamlin M, Hellemans J. Cardiorespiratory and cerebrovascular responses to acute poikilocapnic hypoxia following intermittent and continuous exposure to hypoxia in humans. J Appl Physiol 102: 1953–1961, 2007. First published January 18, 2007; doi:10.1152/japplphysiol.01338.2006.—We tested the hypothesis that intermittent hypoxia (IH) and/or continuous hypoxia (CH) would enhance the ventilatory response to acute hypoxia (HVR), thereby altering blood pressure (BP) and cerebral perfusion. Seven healthy volunteers were randomly selected to complete 10–12 days of IH (5-min hypoxia to 5-min normoxia repeated for 90 min) before ascending to mild CH (1,560 m) for 12 days. Seven other volunteers did not receive any IH before ascending to CH for the same 12 days. Before the IH and CH, following 12 days of CH and 12–13 days post-CH exposure, all subjects underwent a 20-min acute exposure to poikilocapnic hypoxia (inspired fraction of O2, 0.12) in which ventilation, end-tidal gases, arterial O2 saturation, BP, and middle cerebral artery blood flow velocity (MCAV) were measured continuously. Following the IH and CH exposures, the peak HVR was elevated and was related to the increase in BP (r = 0.66 to r = 0.88, respectively; P < 0.05) and to a reciprocal decrease in MCAV (r = 0.73 to r = 0.80 vs. preexposures; P < 0.05) during the hypoxic test. Following both IH and CH exposures, HVR, BP, and MCAV sensitivity to hypoxia were elevated compared with preexposure, with no between-group differences following the IH and/or CH conditions, or persistent effects following 12 days of sea level exposure. Our findings indicate that IH and/or mild CH can equally enhance the HVR, which, by either direct or indirect mechanisms, facilitates alterations in BP and MCAV.

Cerebral blood flow velocity; ventilation; blood pressure

Ventricular acclimatization to hypoxia involves a progressive rise in ventilation (Ve) that, in turn, leads to a progressive rise in end-tidal P O2 (PETO2) and a fall in end-tidal P CO2 (PETCO2) (i.e., hypocapnia). Exposure to intermittent hypoxia (IH) (4, 19, 28, 35, 38, 48, 59), very mild (13, 14), or more severe hypoxia of high altitude (11, 17, 47, 51) results in an elevated ventilatory sensitivity to hypoxia. Typically, using isocapnic hypoxic testing, these studies have focused specifically on the role of the peripheral chemoreflex in the control of breathing following exposure to the various hypoxic paradigms and have not considered the potential role of cerebral blood flow (CBF) in modulating the ventilatory response to poikilocapnic hypoxia. During isocapnic hypoxia, changes in CBF appear to have no influence on the roll-off of the hypoxic ventilatory response (HVR) (57). Elevations in the sensitivity of CBF to acute variations in isocapnic hypoxia have been reported following a 5-day sojourn at 3,810 m (+34%; Ref. 26), following 48 h of continuous isocapnic and poikilocapnic hypoxic exposures (+103%; Ref. 46), and following 5 nights of hypoxia (+116%; Ref. 33). Despite these reports, the relative contributions of the effects of IH and continuous hypoxia (CH) on HVR and the concurrent change in CBF have not been studied in humans. This is somewhat surprising, given that CO2 highly influences CBF and that the magnitude of hypocapnia is largely determined by the magnitude of the HVR. Thus changes in CBF resulting from reduced arterial CO2 might have a critical role in stabilizing Ve during exposure to hypoxia (2, 54, 61). Furthermore, understanding how repeated exposures to different types of hypoxia affect both the ventilatory and cardiovascular responses to hypoxia could help understand the pathophysiology underlying health issues related to the chronic and/or intermittent hypoxemia, which occurs in a number of settings (e.g., altitude illness, obstructive and central sleep apnea, chronic obstructive pulmonary disease, carotid endarterectomy).

To explore the influence of concurrent changes in the HVR following exposure to IH and/or CH upon CBF, the purposes of the present study were twofold. First, we examined the effects of 10–12 daily exposures to IH and/or a continuous 12-day exposure to mild hypoxia (1,560 m) on Ve, blood pressure (BP), and middle cerebral arterial blood flow velocity (MCAV) before, during, and after an acute 20-min poikilocapnic hypoxic exposure. Exposure to acute poikilocapnic hypoxia was selected to examine the interactive effects of hypocapnia and hypoxia on MCAV. Second, we monitored the same responses during the acute 20-min poikilocapnic hypoxic exposure following 12 days of recovery to examine whether there were any persistent effects of the intermittent and/or continuous interventions. Since an enhanced carotid body ventilatory chemosensitivity has been linked to an elevation in BP (3, 18, 30), muscle sympathetic nerve activity (37), and to a reduction in the sensitivity of MCAV to hypoxia (5), we hypothesized that the change in the HVR following the hypoxic interventions would be related to subsequent changes in BP and MCAV.

METHODS

Subjects. Fourteen healthy individuals (7 men and 7 women, aged 25 ± 4 yr (mean ± SD); body mass index 24 ± 4 kg/m²; and maximal oxygen consumption 57 ± 5 ml·kg⁻¹·min⁻¹) volunteered for this study, which was approved by the University of Otago’s Human Address for reprint requests and other correspondence: P. N. Ainslie, Dept. of Physiology, Univ. of Otago, Dunedin, New Zealand (e-mail: philip.ainslie@stonebow.otago.ac.nz).

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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. All subjects were sea level residents and had not spent time at altitude in the 6 mo before this study. Subjects maintained similar physical activities levels and diet during the study.

**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 outlined in Fig. 1. Measurements were completed at baseline, immediately following the IH, following the 12 days at altitude, and 12–13 days following altitude exposure (Fig. 1). Following 10 min of baseline measures, subjects received 20 min of hypoxia [inspired fraction of oxygen (FIO2) > 0.12] followed by a 4- to 5-min normoxic recovery. The subjects were 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. Seven subjects (3 men, 4 women) were randomly selected to complete 10–12 days of IH before ascending to mild altitude for a further 12 days. The other seven (4 men, 3 women) did not receive any IH before ascending to mild altitude for the same 12 days.

**IH intervention.** Subjects in the experimental group carried out 10–12 days of IH at sea level, in which they intermittently breathed hypoxic air delivered through a facemask [O2 Altitude Hypoxic Training System (Hypoxicator), Biomedtech] for 90 min 10–12 times over 12 days. IH was administered in a ratio of 5:5 (minutes of hypoxic air to minutes of ambient air), and the sessions took place at least 1–2 h before or after exercise training. The temporal and quantitative details of this IH protocol represent the standard IH treatment suggested for athletes, according to the manufacturer’s instructions, and is the protocol most frequently used by competitive athletes to improve performance (27). During the first 2–3 days, a target arterial oxygen saturation (SaO2) of 86–90% was maintained before reaching a SaO2 of 75–82% for the remaining sessions. The rationale for this protocol is purported to provide a hypoxic stimulus severe enough to induce acclimatization (27). The progressive decrease in FIO2 over the IH trial is to provide a maximal tolerable hypoxic stress by the end of the IH session but allow progressive acclimatization to minimize symptoms and improve tolerance. Peripheral O2 saturation was measured within the last 5-min “hypoxic” bout using a standard fingertip pulse oximetry clip, and the values were also recorded during the last minute of each hypoxic and normoxic step. Subjects ceased IH immediately before ascending to altitude.

**Altitude exposure.** Subjects in both groups stayed at mild altitude (1,560 m) for a period of 12 days. Morning heart rate, SaO2, body mass, and assessment of neurological symptoms typically associated with acute mountain sickness (AMS) and headache (see below) were recorded every morning at 7 AM throughout the study. With one exception, subjects were tested at the same time of day and within 8 h of descending from altitude.

**Measurements of respiratory gas exchange.** Subjects breathed through a leak-free respiratory mask (Hans-Rudolph 8980, Kansas City, MO) attached to a one-way non-rebreathing valve (Hans-Rudolph 2700). Expiratory flow was measured using a heated pneumotach (Hans-Rudolph HR800). SaO2 was measured using pulse oximetry at the finger (model ML320). PETCO2 and PETO2 were sampled from a leak-free mask and measured by a gas analyzer (model CD-3A, AEI Technologies, Pittsburgh, PA). Ventilatory (flow, tidal volume, frequency) and gas values were displayed in real time during testing (PowerLab, ADI Instruments, Colorado Springs, CO). Expiratory volume was calculated using the integrated flow signal and the frequency of breathing. The ventilatory sensitivity to poikilocapnic hypoxia was calculated in two different ways (56), using the change (Δ) in Ve and the ΔPETO2 divided by the ΔSaO2 (i.e., ΔVe/ΔSaO2 and ΔPETO2/ΔSaO2, respectively). The use of the latter ratio, the ΔPETO2, for a given desaturation, has recently been suggested as a more sensitive marker of the poikilocapnic hypoxic response than Ve by improving the signal-to-noise ratio, apparently because small changes in Ve should cause relatively larger changes in PETO2, as dictated by the metabolic hyperbola (56).

**Measurements of CBF velocity and arterial BP.** CBF velocity in the right middle cerebral artery (MCAV) was measured using a 2-MHz pulsed Doppler ultrasound system (DLW Doppler, Sterling, VA) using search techniques described elsewhere (1). Beat-to-beat arterial BP was monitored using finger photoplethysmography (Finnometer, TPD Biomedical Instrumentation). All data, including respiratory gas exchange, were acquired continuously at 200 Hz using an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments, Colorado Springs, CO) interfaced with a computer and stored for subsequent analysis using commercially available software (Chart version 5.02, ADInstruments). The hypoxic cerebrovascular reactivity to poikilocapnic hypoxia was characterized in two different ways, using the percentage of ΔMCAV divided by the ΔSaO2 or ΔPETO2 (i.e., ΔMCAV/ΔSaO2 and ΔMCAV/ΔPETO2, respectively). Since the MCAV is relatively insensitive to hypoxia, but sensitive to ΔPCO2, the use of the ΔMCAV/ΔPETO2 index provides a means to assess the MCAV response to the related hypoxic-induced hypocapnia. The response of the mean arterial pressure (MAP) response to hypoxia was characterized by the ΔMAP per % decrease in SaO2.

**AMS and headache assessment.** All participants were asked to rate their cephalgia using a clinically validated visual analog scale (0–100 mm) incorporating hedonic descriptors (0 no headache, 10 mm mild headache, including a sensation of pressing or throbbing, 50 mm moderate-intensity headache, and 100 mm worst possible headache), as previously described (25). Neurological symptoms collectively ascribed to AMS were comprehensively examined using

Fig. 1. Overview of experimental protocol. Experimental subjects were tested 4 times at sea level: before intermittent hypoxic training (IH), immediately following cessation of IH training, immediately following descent from altitude, and 12 days after descent from altitude. MCAV, middle cerebral artery flow velocity; MAP, mean arterial pressure; HR, heart rate; SaO2, arterial oxygen saturation.
the Lake Louise (49) and Environmental Symptoms Questionnaires (50). AMS and headache were diagnosed if a subject presented with a total Lake Louise score (self-assessment + clinical scores) of $\geq 5$ points and an Environmental Symptoms Questionnaires cerebral symptoms score of $\geq 0.7$ points (8).

**Data and statistical analyses.** Because there were no statistical differences between men and women, data from the groups were combined for statistical analysis. The ventilatory, MCAV, and MAP responses to hypoxia were determined by the changes in mean $\dot{V}E$, MCAV, and MAP for the given change in $\text{SaO}_2$ every 5 min during hypoxia (time = $+5$, $+10$, $+15$, and $+20$). The ventilatory and MCAV sensitivity to $\text{PETCO}_2$ was also calculated as previously outlined. Peak $\dot{V}E$ and its time of occurrence were calculated as 1-min averages, centered on the visually identified time of maximal $\dot{V}E$. The associated change in MCAV and MAP was also recorded at this point. Likewise, the slope of the change in MCAV relative to $\text{PETCO}_2$ was determined at the same time point. To calculate the absolute and percent (%) change from baseline, data were averaged over the 5-min period of baseline immediately preceding any changes in $\text{FICO}_2$. All data were analyzed using the SPSS social statistics package (version 9, 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 were incorporated to examine the effects of time and state (hypoxia or normoxia) 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 $\pm$ SD.

**RESULTS**

**Subject compliance.** All of the seven subjects completed 10–12 days of exposure to IH. One subject did not complete day 7 of the IH breathing program, and one other did not conduct IH breathing on days 3 and 6; however, upon examination of the elevations in hypoxic ventilatory sensitivity following the 12-days of IH, one of these individuals showed the greatest increase, while the other showed the third greatest increase, indicating that missing 1 or 2 days of the IH breathing did not impact ventilatory sensitivity to hypoxia. Over the first 3 days of IH, when averaged over the last minute of hypoxia of each 5-min period, $\text{SaO}_2$ was maintained at an average of $88 \pm 2\%$ before being reduced to $78 \pm 3\%$ for the remaining days of exposure. One subject was unable to complete post-IH testing; this subject, however, did complete the continuous altitude exposure and was therefore included in the final related analysis. All participants ($n = 14$) completed testing immediately postaltitude; however, due to logistical difficulties, six participants (three women) from the IH group and five participants (two women) from the altitude-only group completed the testing session 12-day after CH exposure.

**Subjective symptomology.** All seven subjects in the IH group reported subjective symptoms (headache and mild nausea) of AMS and related headache following the first 4 days of IH ($P < 0.05$ vs. baseline; data not shown). The altitude-only group experienced mild symptoms (disturbed sleep and mild headache) of AMS and headache during the first 2 days of altitude exposure ($P < 0.05$ vs. IH group; Table 1). These symptoms were reflected in a lower $\text{SaO}_2$, during the first 2 days at altitude ($P < 0.05$ vs. IH group; Fig. 2). In other words, in the CH-only group, $\text{SaO}_2$ was lower during the first 2 days at altitude before returning to normal values, which was comparable to the IH group upon arrival at altitude.

**Baseline measurements.** As outlined in Table 2, there were no changes in resting cardiorespiratory or cerebrovascular variables following the IH or altitude exposure. Likewise, there were no between-group differences in heart rate or body mass at altitude, whereas $\text{SaO}_2$ was lower in the altitude-only group during the first 2 days at altitude ($P < 0.05$ vs. IH group; Fig. 2).

**Alterations in ventilatory, BP, and CBF responses to acute poikilocapnic hypoxia.** Changes in the ventilatory, BP, and MCAV responses to acute poikilocapnic hypoxia are depicted in Fig. 3. Following the IH and CH exposure, during acute poikilocapnic hypoxia during both peak and at the 5-min time point, there was an increase in $\dot{V}E$ and BP and a reciprocal decrease in $\text{PETCO}_2$ and MCAV ($P < 0.05$ vs. preexposure, Fig. 3). The lowered $\text{PETCO}_2$ and MCAV persisted for 10 min into the hypoxic test, whereas heart rate was elevated for the duration of the 20-min hypoxic test ($P < 0.05$ vs. preexposure, Fig. 3); these changes were similar whether subjects were exposed to IH and/or CH exposure; i.e., IH before CH did not

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**Table 1. Acute mountain sickness and headache scores monitored at sea level and altitude throughout the investigation in the intermittent hypoxia and altitude group**

<table>
<thead>
<tr>
<th>Group Phase</th>
<th>Intermittent Hypoxia Group</th>
<th>Altitude-only Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VAS, mm</td>
<td>ESQ-C, AU</td>
</tr>
<tr>
<td>Sea level</td>
<td>1 ± 0</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>Altitude (day)</td>
<td>1</td>
<td>3 ± 2</td>
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<tr>
<td></td>
<td>2</td>
<td>3 ± 1</td>
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<tr>
<td></td>
<td>3</td>
<td>2 ± 0</td>
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<tr>
<td></td>
<td>11</td>
<td>2 ± 1</td>
</tr>
<tr>
<td></td>
<td>Post-ALT</td>
<td>1 ± 1</td>
</tr>
<tr>
<td></td>
<td>12-post</td>
<td>0 ± 0</td>
</tr>
</tbody>
</table>

Values are expressed as means $\pm$ SD. VAS, visual analog scale; ESQ-C, Environmental Symptoms Questionnaire; AU, arbitrary units; LL score, Lake Louise Questionnaire; Post-ALT, after altitude; 12-post, 12 days after altitude. *Significant difference from hypoxic exposure vs. baseline and postaltitude exposure: $P < 0.05$. †Significant difference between intermittent hypoxia and altitude-only group for a given day: $P < 0.05$. 

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seem to change the related responses, in addition to that of CH alone. Before hypoxic exposure, the related changes in $\text{SaO}_2$ were reciprocal to that of $V_E$; that is, $\text{SaO}_2$ was elevated upon peak HVR and then declined progressively throughout the 20 min of poikilocapnic hypoxia. Following both IH and CH exposures, $\text{SaO}_2$ was elevated during the periods of heightening ventilatory response to the hypoxia (i.e., peak and 5-min time points) compared with preexposure values ($P < 0.05$). There were no persistent effects of the IH and/or the CH exposure 12 days following either intervention. The time for the change in peak $V_E$ in response to acute hypoxia exposure was not different between the groups or following the IH (pre-IH $73 \pm 34$ s; post-IH $68 \pm 39$ s; postaltitude $65 \pm 44$ s) or CH exposures (pre- $86 \pm 32$ s; postaltitude $83 \pm 39$ s). Following the IH and CH interventions, respectively, the peak HVR was elevated and was related to the increase in BP ($r = 0.66$ to $r = 0.88$; $P < 0.05$) and to a reciprocal decrease in MCAV ($r = 0.73$ to $r = 0.80$; $P < 0.05$; Fig. 4); such relationships were not evident before or 12 days following the hypoxic interventions (Fig. 4).

Alterations in ventilatory, BP, and CBF sensitivities to acute poikilocapnic hypoxia. Following the IH and continuous altitude exposure, the ventilatory sensitivity to poikilocapnic hypoxia (expressed as $\Delta V_E/\Delta \text{SaO}_2$) was elevated (Fig. 5); HVR sensitivity was also elevated at the 5-min time point before returning to baseline values at 10 min, where it was unchanged for the remaining 10 min of the hypoxic test. The magnitude of this increase in peak HVR sensitivity was related to the decrease in both $\text{PETCO}_2$ and MCAV following both the IH and continuous altitude exposures ($r = 0.56$–0.71; $P < 0.05$). In other words, those with the highest increase in peak HVR following the hypoxic intervention also showed the largest decrease in $\text{PETCO}_2$ and MCAV. There were also elevations in BP, heart rate (data not shown), and MCAV sensitivity to acute hypoxia at the peak and 5- and 10-min time points (Fig. 5).

When HVR sensitivity was computed as the change in $\text{PETCO}_2$ for the related change in $\text{SaO}_2$, there was a trend for an increase in peak response following the IH exposure (pre-IH $0.25$ to post-IH $0.32$ mmHg/$\text{SaO}_2$; $P = 0.07$). Similar trends were apparent following the CH exposures (preexposure $0.23$ to postexposure $0.31$ mmHg/$\text{SaO}_2$; $P = 0.09$). When the peak HVR sensitivity data from both the IH and CH group were included together following the continuous-altitude exposure, there was a significant increase in HVR sensitivity following the CH exposure (pre $0.24 \pm 0.9$ to post $0.31 \pm 1.1$ mmHg/$\text{SaO}_2$; $P < 0.05$). Following either IH or the CH interventions, apart from the time of the peak HVR, there were no differences in HVR at any time point (5, 10, 15, or 20 min) during the 20 min of poikilocapnic hypoxia. When MCAV sensitivity was expressed as the change in MCAV for the related change in $\text{PETCO}_2$, there were no significant differences in the peak response during the 20 min of poikilocapnic hypoxia between the two groups following the IH and CH exposures (IH group; pre-IH $2.6 \pm 1.6$%/Torr; post-IH $2.9 \pm 1.9$%/Torr; postaltitude $2.8 \pm 1.7$%/Torr) or following CH-only exposure (CH group only, pre-altitude $2.8 \pm 1.5$%/Torr; postaltitude $2.9 \pm 1.2$%/Torr). In other words, regardless of treatment, the response of MCAV to acute poikilocapnic hypoxia was proportional to the magnitude of the ensuing hypocapnia. There were no differences in either HVR or MCAV sensitivity index 12 days following the hypoxic exposure.

**DISCUSSION**

The three main novel findings of this study are as follows: 1) both IH and continuous exposure to mild altitude can lead to similar alterations in the cardiorespiratory and cerebrovascular responses to acute hypoxia, which are fully recovered within 12 days following exposure; 2) IH can promote acclimatization before exposure to continuous mild altitude, presumably caused by the enhanced carotid body sensitivity; 3) following the hypoxic interventions, the elevation in BP sensitivity to hypoxia was related to the heightened peak ventilatory response to hypoxia and resulted in a greater decrease in $\text{PETCO}_2$ and, consequently, MCAV.

**Ventilatory acclimatization to hypoxia.** In the present study, the alterations in ventilatory sensitivity to hypoxia, but unchanged air breathing end-tidal gases and $V_E$, is broadly consistent with previous reports following exposure to IH of similar duration (3, 18, 30, 37), or following 5 days of exposure.
to a small change in PETO2 (10 Torr below resting; Ref. 13). For changes in end-tidal gases to occur, it has been suggested that a significant degree of peripheral chemoreceptor stimulation is required (13). There were no persistent effects following 12 days of sea level exposure, indicating that the partial acclimatization from the IH and/or the altitude exposures were fully returned to preintervention values.

IH vs. CH exposure. Over the last decade, various paradigms of IH have been utilized and have provided experimental evidence that such exposures can provoke large changes in carotid body hypoxic chemosensitivity (3, 4, 18, 19, 28, 29, 41, 52). Consistent with the findings of the present study, previous work has shown that IH can reduce the incidence of AMS upon exposure to hypobaric hypoxia (9). That report indicated that IH can elicit similar perturbations in hypoxic drive to those following more chronic altitude exposures and can improve symptomology on initial altitude exposure at 4,300 m. The novel finding of the present study was that IH, although facilitating ventilatory acclimatization to hypoxia and improving initial symptomology, provides little persistent effects on acclimatization for more than the initial 2 days of exposure to mild altitude. It is also important to highlight that, as expected, the reported symptoms in the present study conducted at low altitude were small compared with those reported during severe AMS (8). For example, clinical headache associated with severe AMS is normally defined with a total Lake Louise score (self assessment + clinical scores) of ≥5 points and an Environmental Symptoms Questionnaire cerebral symptoms score ≥0.7 points (8). Whether there are differential cardiorespiratory and cerebrovascular responses following IH upon exposure to more severe altitude is possible, but remains to be clearly established, especially in relation to offsetting altitude illness.

The linkage between the ventilatory or cardiovascular responses following IH or CH exposure has been well reported (3, 18, 30, 37). Although the exact mechanisms that underlie such changes remain poorly understood, these findings indicate that such ventilatory and cardiovascular responses to hypoxia may have a common central origin (37). While the combined changes in ventilatory and cardiovascular hypoxic sensitivity have been shown previously, the linkage to similar changes in MCAV sensitivity following the hypoxic interventions to acute hypoxia is a novel finding. Following the hypoxic interventions, the peak decreases in MCAV are a consequence of the elevated peak ventilatory response to acute hypoxia, resulting in greater hypocapnia and, therefore, decrease in MCAV. The observation of similar changes in MCAV per change in PETCO2 following the hypoxic interventions would indicate that these changes are due to the resulting hypoxic-induced hypocapnia, rather than an intrinsic change in the response of the cerebrovascular bed to hypoxia. Following the peak ventilatory-induced reductions in MCAV, however, the relative transient cerebral hypoperfusion may have downstream effects on V̇E (see below).

Effect of an elevated HVR on CBF. Previous studies have shown that a heightened peripheral chemosensitivity response per se to be the major factor (3, 4, 18, 19, 28, 29, 41, 52) in elevating the HVR. Thus, in the present study, we suggest that the changes in MCAV may simply be a consequence of the elevated peak ventilatory response to acute hypoxia, resulting in greater hypocapnia and, therefore, decrease in MCAV. The observation of similar changes in MCAV per change in PETCO2, following the hypoxic interventions would indicate that these changes are due to the resulting hypoxic-induced hypocapnia, rather than an intrinsic change in the response of the cerebrovascular bed to hypoxia. Following the peak ventilatory-induced reductions in MCAV, however, the relative transient cerebral hypoperfusion may have downstream effects on V̇E (see below).
cerebral vasodilatation and constriction (54, 61), decreased peripheral input from hypocapnia (12), and decreased metabolic rate from hypoxia (58). From the present study, although carotid body sensitization likely dominates the enhanced HVR following IH/CH, it appears that the larger CO2 washout has a dominant effect on CBF, which could also have downstream effects on VE (54, 61). Following exposure to IH and or chronic hypoxia, the potential hypocapnia and reduction in MCAV may serve to preserve VE by preserving central H+ concentration in the face of hypoxia. More importantly, the reduction in CBF and its effects on central H+ concentration would preserve brain tissue pH.

Methodological considerations. The main limitations of our study include the use of transcranial Doppler ultrasound for the estimation of CBF and a single steady-state step of hypoxia to determine the ventilatory and cerebrovascular responsiveness to hypoxia. The majority of research suggests that there is little or no change in the cross-sectional area of the middle cerebral artery during conditions of hypercapnia and/or hypoxia; therefore, MCAV is a reliable index of CBF (20, 32, 53, 60). Although we only used one steady-state step of O2 for our reactivity calculations, our cardiorespiratory and cerebrovascular reactivity values are comparable with previous studies using one (56) or seven decrements in poikilocapnic PETO2 (5). Recent reports suggest that, although acute poikilocapnia hypoxia testing is more complicated than the commonly used isocapnic hypoxic tests due to the interactive effects of hypoxia and concomitant hypocapnia, they are more representative of the altitude environments, and the responses themselves are more readily assessed for their applied significance (56). Like many human-based studies, we suffered from a low sample size, especially as there were dropouts in the 12-day recovery phase of the design. Consequently, it is possible that our inability to identify significant changes 12 days follow relief of hypoxia reflects type II statistical errors due to the small number of subjects. Previous studies, however, indicate that the time course of acclimatization is comparable to the time course of “de-acclimatization” (3, 4, 13, 14, 28, 38); therefore, full recovery from the IH and very mild hypoxic stimulus is very likely. Furthermore, post hoc power calculations suggest that, given the very small difference between the means and the SD of the difference, the IH or mild CH exposures would need a sample size of >800 subjects to demonstrate a statistical

Fig. 4. Relationships between the peak change in the ventilatory response to hypoxia to the associated peak change in MAP (A) and the change in MCAV (B) before and following the IH and continuous hypoxic interventions. All measurements were conducted at sea level. These data indicate that the peak changes in the ventilatory response to hypoxia are closely related to the change in the peak MAP and MCAV responses following the IH and/or the continuous hypoxic exposure. *Significance, P < 0.05.

Fig. 5. MAP (A), MCAV (B), and the ventilatory (C) to acute poikilocapnic hypoxia before IH, following IH, altitude exposure, and a 12-day recovery (IH and altitude group; left column), and before and following altitude exposure and a 12-day recovery (altitude-only group; right column). All measurements were conducted at sea level. Values are expressed as means ± SD. †Significant difference between IH or altitude exposure vs. preexposure baseline: P < 0.05. *Significant difference between IH or altitude exposure vs. 12-day postexposure P < 0.01.

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significance with this magnitude of difference. Finally, it is unfortunate that the potential influence of ovarian hormones could not be controlled for during the study. To partly mitigate this problem, with the exception of the 12-day recovery measures due to the small sample size, we conducted gender analysis at all points where possible. These results indicate no apparent gender differences between the groups during rest or hypoxia and comparable interindividual variability between genders. Although there have been reports of a lack of influence of menstrual cycle phase on ventilatory responses at altitude (10), arterial Pco2 can vary across the menstrual cycle (2–8 Torr), which may impact on CBF. Currently, however, the associated changes in ovarian hormones and their potential influence on the cerebrovascular responses to hypoxia are not understood.

Implications. Despite the potential use of IH in improving ventilatory acclimatization, our findings confirm previous reports of IH leading to a linkage in elevations in BP (3, 18, 30), potentially mediated by an elevated sympathetic response to hypoxia (22, 37). It has recently been shown that, following 10 days of IH [1 h of hypoxia (SaO2, 80%) per day], the rise in muscle sympathetic nerve activity burst frequency was related to the change in HVR, suggesting that these sympathetic and ventilatory responses may have common central origin (37). In relation to the present study, potential hypoxic-induced elevations in sympathetic nerve activity may underlie the apparent elevation in heart rate and BP during acute hypoxia following the IH and/or the continuous altitude exposure. The extent to which IH may be of benefit to autonomic or respiratory diseases characterized by low ventilatory drive, such as familial dysautononia (15), asthma, and chronic bronchitis (7, 16, 23), may, therefore, be limited by potential adverse effects on the cardiovascular system.

In the present study, we attribute the changes in MCAV to hypoxia-induced hypocapnia rather than an intrinsic change in the response of the cerebrovascular bed to hypoxia. However, there are several instances in the literature where vessels of animals (45) and humans (21, 43) are affected directly by hypoxia. The latter studies in humans are based on systemic vascular endothelial function in patients with obstructive sleep apnea, a disorder characterized by reoccurring episodes of apnea and hypopnea, and lead to sudden increases in arterial BP and sympathetic nerve activity (36). These changes are likely responsible for the high prevalence of cardiovascular (42, 55) and cerebrovascular morbidity (40, 62) in patients with obstructive sleep apnea and have been associated with endothelial dysfunction (24, 31, 34). To the best of our knowledge, only one study in humans has monitored the possible implications of daily exposures to either short-duration IH (12% O2 separated by 5 min of normoxia for 1 h, for 10 days) or long-duration IH (30 min of 12% O2, for 10 days) on cerebrovascular function (18). Findings from this study indicate that, following exposure to short-duration IH, compared with pre-exposure, there was a small lowering of ~2% in cerebral tissue oxygen index (as monitored using spatially resolved spectroscopy) in response to acute progressive isocapnic hypoxia. Since MCAV was not monitored in this study, and conditions of isocapnic hypoxia were maintained, it is difficult to compare the findings with those of the present study. Importantly, however, two recent studies have reported that decreases in cerebral tissue oxygen index, as assessed using spatially resolved spectroscopy, of ~13% (6) or ~20% (39) are required to reach a “threshold” of cerebral ischemia (<=40% decrease in MCAV from baseline); therefore, it seems unlikely that small change in cerebral tissue oxygen index reflects a maladaptation from the short-duration IH exposure. Likewise, in the present study, it would also seem equally unlikely that small reductions in MCAV following the hypoxic interventions would influence cerebral oxygen supply. Differences in experimental design, species, and intensity and duration of hypoxic intervention (44) may, in part, account for the discrepancy between the present findings and those reported previously, especially in animal models. Whether these alterations in cerebrovascular responses in humans are simply a consequence of alternations in ventilatory sensitivity or could in any way be pathological, potentially compromising vascular function, is worthy of future investigation.

In summary, our findings indicate that both IH and continuous exposure to mild altitude can elevate the ventilatory response to acute hypoxia, which, by either direct or indirect mechanisms, facilitates alterations in BP and MCAV.

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