Sustained high-altitude hypoxia increases cerebral oxygen metabolism

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Submitted 7 June 2012; accepted in final form 21 September 2012

Smith ZM, Krizay E, Guo J, Shin DD, Scadeng M, Dubowitz DJ. Sustained high-altitude hypoxia increases cerebral oxygen metabolism. J Appl Physiol 114: 11–18, 2013. First published September 27, 2012; doi:10.1152/japplphysiol.00703.2012.—Acute mountain sickness (AMS) is a common condition occurring within hours of rapid exposure to high altitude. Despite its frequent occurrence, the pathophysiological mechanisms that underlie the condition remain poorly understood. We investigated the role of cerebral oxygen metabolism (CMRO2) in AMS. The purpose of this study was to test 1) if CMRO2 changes in response to hypoxia, and 2) if there is a difference in how individuals adapt to oxygen metabolic changes that may determine who develops AMS and who does not. Twenty-six normal human subjects were recruited into two groups based on Lake Louise AMS score (LLS): those with no AMS (LLS ≤ 2), and those with unambiguous AMS (LLS ≥ 5). [Subjects with intermediate scores (LLS 3–4) were not included.] CMRO2 was calculated from cerebral blood flow and arterial-venous difference in O2 content. Cerebral blood flow was measured using arterial spin labeling MRI; venous O2 saturation was calculated from the MRI of transverse relaxation in the superior sagittal sinus. Arterial O2 saturation was measured via pulse oximeter. Measurements were made during normoxia and after 2-day high-altitude exposure at 3,800 m. In all subjects, CMRO2 increased with sustained high-altitude hypoxia [1.54 (0.37) to 1.82 (0.49) μmol·g−1·min−1, n = 26, P = 0.045]. There was no significant difference in CMRO2 between AMS and no-AMS groups. End-tidal PCO2 was significantly reduced during hypoxia. Low arterial PCO2 is known to increase neural excitability, and we hypothesize that the low arterial PCO2 resulting from ventilatory acclimatization causes the observed increase in CMRO2.

ACUTE MOUNTAIN SICKNESS (AMS) is characterized by headache, in addition to gastrointestinal and neurological symptoms, sleep disturbance, and fatigue within 6–12 h of rapid exposure to hypoxia at high altitude (3). Despite being a common condition, the pathophysiological mechanisms of AMS remain poorly understood. Although AMS is a benign and self-limiting condition, it shares some clinical characteristics with high-altitude cerebral edema (18). The current consensus is that AMS and high-altitude cerebral edema may be part of the same spectrum of illness, and that increased brain parenchymal volume (i.e., cerebral swelling) is likely an etiological factor in both. Our laboratory previously found that increased cerebral blood flow (CBF) is a common outcome of ascent to high altitude (14), as is cerebral swelling (11), but neither were associated with a greater propensity to develop AMS. An alternate hypothesis for brain swelling and symptoms of AMS may relate to cerebral energy status. Kallenberg et al. (22) investigated changes in diffusion of brain water with magnetic resonance imaging (MRI) in subjects with uncomplicated hypoxia and with AMS. They found increased diffusion, suggesting vasogenic edema of a hydrostatic cause was evident during uncomplicated hypoxia, but found restricted diffusion, suggesting a cytotoxic process was evident when AMS was present. These findings support our hypothesis of altered energy status during AMS. We hypothesized that cerebral O2 metabolism may be reduced in the face of low oxygen availability, as found at high altitude, but that subjects who develop AMS may not be able to reduce their oxygen usage to the same degree as those who are resistant to AMS.

The purpose of this study was to test our hypothesis: 1) if cerebral oxygen metabolism changes in response to hypoxia, and 2) if there is a difference in how individuals adapt to oxygen metabolic changes that may determine who develops AMS and who does not.

We selected subjects into two distinct groups: those with no AMS, and those with unambiguous AMS following 2 days of sustained 90-Torr inspiratory PO2 high-altitude hypoxia. Using MRI, we quantified changes in CBF across cerebral gray matter and cerebral venous O2 saturation (SvO2) in the superior sagittal sinus. From these, we calculated resting cerebral metabolic rate of oxygen (CMRO2) to determine its impact on symptoms of AMS.

METHODS

Subjects

Twenty-six healthy, nonsmoking, sea level residents were recruited: 13 men [age 28 (9) yr] and 13 women [age 28 (8) yr]. Ethical approval for these studies was granted by the Human Research Protection Program of the University of California San Diego and conformed to the standards of the Declaration of Helsinki. Participants were informed of the experimental procedures and possible risks involved in the study, and written, informed consent was obtained before participation.

Study Design

MRI measurements were made at sea level of steady-state CBF and steady-state transverse relaxation in sagittal sinus blood (T2) (from which we calculated SvO2). Additional measurements were also made of hemoglobin (Hb) concentration, and hematocrit (Hct). From these measurements, we determined steady-state CMRO2. The measurements were repeated during sustained hypoxia following 2 days at altitude. For hypoxic exposure, subjects resided at high altitude at the White Mountain Research Station (3.800 m, inspiratory PO2 90 Torr). CMRO2, CBF, and arterial-venous O2 difference (A-V difference) were compared for AMS and no-AMS groups during normoxia and following sustained hypoxia. Pooled changes for normoxia vs. hypoxia across groups were also measured. In a subset of subjects, we also measured whole body resting oxygen consumption (VO2).
**Hypoxic Exposure**

Subjects spent two nights at altitude and then returned to San Diego for MRI. For each subject, the arterial O₂ saturation (SaO₂) achieved after 40 h of hypoxic exposure at altitude was maintained throughout the ~8 h of transportation and the MRI measurements. During transportation, this was via a venturi mask with variable %N₂ in the inspiratory port (to maintain consistent SaO₂ despite changing altitude and barometric pressure). Within the MRI scanner, subjects breathed a premixed 90-Torr hypoxic mixture (12.5% O₂, balance N₂) via a close-fitting low-dead space non-rebreathing mask (Hans Rudolph 7900/2600, Kansas City, MO). SaO₂ was intermittently monitored while resident at altitude and continuously monitored during transportation and MRI.

**AMS Groups**

To maximize potential physiological difference between subjects at altitude, the Lake Louise Score (LLS), an AMS self-report questionnaire (32), was used to divide subjects into two distinct groups: those with no symptoms of AMS (no-AMS group), and those with unambiguous AMS (AMS group). The Lake Louise AMS questionnaire is based on the responses regarding five different symptoms: headache, gastrointestinal symptoms, fatigue, dizziness, and difficulty sleeping. Each grade 0–3 in severity. Difficulty sleeping was not included as a criterion for AMS on the first night [to avoid confounds due to the rapid ascent (32)], but was scored on subsequent days. Subjects with an LLS ≥ 2, or with no headache, were considered AMS nonsufferers (no-AMS group). Those with an LLS ≥ 5 and a headache plus symptoms of nausea, fatigue, dizziness, or difficulty sleeping were considered unambiguous AMS suffersers (AMS group). Subjects with an intermediate score (3–4) and a headache were grouped into a third “intermediate” group and not used when comparing AMS vs. no-AMS, but were included in grouped analysis. LLS were determined in each subject on both day 1 and day 2 (each immediately following a night at altitude). The mean of these scores was used to characterize subjects into AMS and no-AMS groups.

**Physiological Measurements**

SaO₂ was measured and logged using a Nonin 3100 Wrist Pulse Oximeter (at altitude and during transportation) and a Nonin 8600FO MRI-compatible pulse oximeter (Nonin Medical, Plymouth, MN) (during MRI measurement) that was calibrated in each subject against an arterial oximeter (at altitude and during transportation) and a Nonin 8600FO Wrist Pulse Oximeter (Nonin Medical, Plymouth, MN) (during MRI measurement) that was calibrated in each subject against an arterial oximeter (at altitude and during transportation) and a Nonin 8600FO Wrist Pulse Oximeter (Nonin Medical, Plymouth, MN) (during MRI measurement). Hb concentration was determined from the arterial blood sample. Hb is expressed in units of molar concentration from a blood sample. Hct was determined from direct measurements of packed cell height in a capillary tube following centrifuging. To calculate the fractional Hb saturation (i.e., SvO₂ = Y × 100%), and parameters A and C are described in terms of quadratic fit parameters and the Hct thus:

$$A = a_1 + a_2 \cdot \text{Hct} + a_3 \cdot (\text{Hct})^2$$

$$C = c_1 \cdot \text{Hct} \cdot (1 - \text{Hct})$$

Venous T₂ relaxation, T₂ was measured in the Superior Sagittal Sinus using a TRUST (T2 relaxation under spin tagging) MRI technique (23) with single-shot spiral readout (TE = 2.8 ms, TR = 8 s, TI = 1.2 s, 4 echoes at effective TE 0, 40, 80, and 160 ms, 10-mm slice, 80-mm tag, 4.5 min). Images were acquired just superior to the torcula. T₂ relaxation times were found by fitting TRUST measurements within sagittal sinus, at the four TE to a monoeponential decay.

**Data Analysis**

CBF: Raw arterial spin-labeling data for each subject were corrected for T₁ relaxation of blood based on their measured SaO₂ (34). Images were corrected for cardio-respiratory physiological noise (31) and field inhomogeneities (29). Resting CBF was averaged across the 3.5 min of data collection in cerebral gray matter using a gray matter mask generated from a separate high-resolution fast spoiled gradient recalled echo T₁-weighted three-dimensional anatomical MRI (TE = 4.2 ms, TR = 10.1 ms, TI = 450 ms, bandwidth 20.83 kHz, field of view 25 × 25 × 16 cm, matrix 256 × 256 × 128, ~1 mm × 1 mm × 1.3 mm resolution, 5.5 min). Cerebral gray matter was automatically segmented using FAST (FMRIB Software Library, Oxford, UK).

SvO₂. Cerebral venous saturation was derived from the T₂ relaxation in superior sagittal sinus blood. Since T₂ measurements are dependent on the exact MRI method used, calibration data from the literature were found to be inadequate for the pulse sequences used (24). Calibration measurements were done on normative data from a separate group of normal volunteers (10 men, 11 women, age 30 ± 9 yr) using the same pulse sequence parameters detailed above. TRUST measurements of venous T₂, resting CBF, Hb concentration, and Hct were made in this normative calibration group.

In modeling the relationship between T₂ and SvO₂, we assumed the same simplified form of the Luz and Meiboom model (26) proposed by Golay et al. (16), but were able to further simplify it as follows:

$$\left(1 + C(1 - Y)^2\right)$$

where Y is the fractional Hb saturation (i.e., SvO₂ = Y × 100%), and parameters A and C are described in terms of quadratic fit parameters and the Hct thus:

$$A = a_1 + a_2 \cdot \text{Hct} + a_3 \cdot (\text{Hct})^2$$

$$C = c_1 \cdot \text{Hct} \cdot (1 - \text{Hct})$$

We used initial values of a₁, a₂, a₃, and c₁ from Lu et al. (24) as a starting value to optimize scaling parameters A and C for our studies. For each subject in the normative group, a₁, a₂, a₃, and c₁ were then used to calibrate their venous T₂ and measured Hct to generate a value of SvO₂ and hence calculate each subject’s CMRO₂ and oxygen extraction fraction (OEF) [calculation of CMRO₂ is described below, OEF was calculated from the relationship: OEF = (SaO₂ − SvO₂)/SaO₂]. We assumed a normal resting OEF of 0.4 and CMRO₂ of 1.6 μmol·g⁻¹·min⁻¹ for the normative group (19, 21, 27). The parameters a₁, a₂, a₃, and c₁ were then scaled from their starting values so that the average CMRO₂ and average OEF for the group corresponded to these expected literature values. This then defined the values of a₁, a₂, a₃, and c₁ for the 26 subjects in the current sustained hypoxia study (parameters used were a₁ = −18.6, a₂ = 110.8, a₃ = −104.8, c₁ = 341.7). These parameter values were then used to calculate SvO₂ for both normoxia and hypoxia from measured T₂ and Hct.

Cerebral oxygen metabolism. Cerebral O₂ metabolism was calculated using the Fick equation:

$$\text{CMRO₂} = \text{CBF} \cdot (\% \text{SaO₂} − \% \text{SvO₂})/100 \cdot [\text{Hb}]$$

CBF was calculated from the arterial spin labeled MRI measurements, SaO₂ from a pulse oximeter, SvO₂ from the venous T₂, and Hb concentration from a blood sample. Hb is expressed in units of molar...
equivalents of oxygen (10) carried per liter of blood when Hb is fully saturated, $S_{O_2}$, and $S_{Hb}$, in percentages, CBF in ml·100 ml$^{-1}$·min$^{-1}$, and $CMRO_2$ in μmol·g$^{-1}$·min$^{-1}$.

Statistical Analysis

Data were analyzed with repeated-measures ANOVA of our primary outcome variables ($CMRO_2$, CBF, $PETCO_2$, $O_2$ delivery, A-V difference, $Sao_2$, $SvO_2$), with two grouping variables (AMS, sex) each at two levels (AMS, no AMS, male, female), and one repeated measure (normoxia, 2-day hypoxia) (StatView 5.0.1. SAS Institute, Cary, NC). This “paired” approach allowed each subject to act as his or her own control, which provided greater statistical power to detect small changes. Cohen’s effect size d and post hoc sample size were calculated using G*Power (G*Power 3.1.3, Heinrich Heine University, Dusseldorf, Germany). Data were expressed as means (SD). Changes were significant at $P < 0.05$ two tailed.

RESULTS

AMS

Of the 26 subjects recruited into the study, 13 developed criteria for AMS (LLS ≥ 5 and headache; 6 men, 7 women). A further 10 subjects met the criteria for no-AMS (LLS ≤ 2 or no headache; 6 men, 4 women). The remaining three subjects were characterized as intermediate. Results are summarized in Table 1.

We initially analyzed the 23 non-intermediate subjects in two groups. Subjects were grouped by LLS into AMS and no-AMS groups to highlight any physiological changes that accompany development of AMS symptoms (subjects with intermediate scores were omitted from this analysis). Differences between groups are plotted in Fig. 1. We investigated changes in $Sao_2$, $SvO_2$, $PETCO_2$, CBF, A-V difference, and $CMRO_2$ between AMS and no-AMS subjects following 2-days hypoxia. $Sao_2$ during hypoxia was lower in subjects with symptoms of AMS ($P = 0.047$). For all other measurements, there were no significant differences between the AMS and no-AMS groups.

Data were then pooled across the three groups (AMS, no-AMS, intermediate, $n = 26$) to examine the population response to sustained hypoxia. Subjects showed decreased $Sao_2$ [98.2 (0.7) to 83.2 (5.3)%; $P < 10^{-5}$] and $SvO_2$ [61.0 (7.8) to 49.3 (7.2)%; $P = 0.0005$] and increased ventilatory drive with reduced $PETCO_2$ [39.3 (3.1) to 32.0 (2.5) Torr; $P < 10^{-5}$], consistent with prolonged hypoxia.

There was a significant increase in $CMRO_2$ following 2 days of poikilocapnic hypoxia [1.54 (0.37) to 1.82 (0.49) μmol·g$^{-1}$·min$^{-1}$; $P = 0.045$]. Resting CBF also increased with prolonged hypoxia [51.3 (12.5) to 64.3 (16.1) ml·100 ml$^{-1}$·min$^{-1}$; $P = 0.0017$]. $O_2$ delivery showed moderated increases, but did not reach statistical significance [4.1 (0.9) to 4.5 (1.0) mmol·min$^{-1}$·l$^{-1}$; $P = 0.10$]. $Sao_2$-$SvO_2$ difference showed a trend toward decreasing with hypoxia [37.1 (8.1) to 33.9 (7.4)%; $P = 0.069$]. We observed variation in the rapidity of onset and recovery of AMS symptoms across subjects. Comparing symptoms on day 2 with day 1 at altitude, 5 subjects reported worsening symptoms, 12 reported improving symptoms, and 6 reported no significant difference. Linear regression showed no significant correlation between the time of onset of symptoms and the eventual changes in $CMRO_2$ ($r = 0.048, P = 0.82$).

Grouped responses to sustained hypoxia are summarized in Fig. 2.

To assess the impact of whole body $O_2$ metabolism ($\dot{V}O_2$) on cerebral $O_2$ metabolism, we simultaneously measured $V_\dot{O}_2$ in a subset of 14 subjects in normoxia and 5 subjects during hypoxia while in the MRI simultaneous with the $CMRO_2$ measurements. Results are shown in Fig. 3.

To observe sex differences in the measured parameters, subjects were also grouped into male and female groups. There was a significant main effect of sex for $PETCO_2$ and for CBF (results summarized in Table 1 and Fig. 4). Other measures were not significantly different between male and female subjects.

DISCUSSION

In this study, we examined the changes in CBF and $CMRO_2$ during 2-days sustained hypoxia and correlated this with symptoms of AMS. Our primary finding was an increase in $CMRO_2$ following sustained hypoxia, which was present in all subjects. Comparing subjects with AMS and those with no AMS, there was lower $Sao_2$ in subjects with AMS, but no other significant physiological differences between the groups for $CMRO_2$ or any of the other measured parameters ($SV_\dot{O}_2$, $PETCO_2$, A-V difference, $O_2$ delivery). We also grouped subjects by sex to address if this may be a potential source of bias due to the difference in male and female subjects in the no-AMS group (men = 6, women = 4). There was no interaction of hypoxia acclimatization with sex ($P = 0.19$) or with AMS ($P = 0.86$) for the observed change in $CMRO_2$. Women showed a significantly higher CBF than men and a significantly lower $PETCO_2$. However, there were no sex-by-hypoxia interactions, and these findings did not bias our primary findings. We also observed increased CBF following hypoxia. In addition, arterial and venous $O_2$ content both showed significant decreases, but the A-V difference was not significantly different.

$CMRO_2$ accounts for ~15–20% of whole body $\dot{V}O_2$. To address if the change in $CMRO_2$ is reflective of a larger change in $V_\dot{O}_2$, we also measured $V_\dot{O}_2$ in a subset of subjects. This showed no significant $V_\dot{O}_2$ change. From this, we speculate that the $CMRO_2$ change during sustained hypoxia is not merely paralleling a change in $V_\dot{O}_2$, but rather could be under local cerebral control.

To maximize our ability to detect changes in cerebral physiology related to AMS, we only included those subjects with unambiguous AMS, or those with no AMS when assessing the impact of AMS on cerebral physiology ($n = 23$). To ensure that this approach did not bias our findings, we also analyzed the data with the intermediate group included ($n = 26$). For both approaches, there was no significant difference in $SV_\dot{O}_2$, $PETCO_2$, $O_2$ delivery, CBF difference in A-V $O_2$ content, or $CMRO_2$, between those subjects with AMS and those without AMS following sustained hypoxia (Table 1). There was a significant main effect of AMS for the changes in $Sao_2$ with sustained hypoxia when analyzed with only the AMS and no-AMS subjects ($P = 0.047$). This finding showed a trend when the intermediate group was included in the analysis ($P = 0.072$). Another issue that needs to be addressed is whether this study had adequate statistical power to support this conclusion. If there actually had been a significant difference in $CMRO_2$ between AMS and no-AMS groups ($P < 0.05$), post hoc power calculations reveal that between 2,256 and 10,236 subjects would be required to demonstrate it. Thus any effect of the elevated $CMRO_2$ on the propensity to develop AMS symptoms
is very small, and unlikely to be biologically relevant (similarly for other variables summarized in Table 1). Also, our approach to highlight potential CMRO₂ changes related to AMS by including only subjects with the extremes of AMS symptoms does not change these primary conclusions. An unexpected finding in this study was the increased resting CBF in the intermediate group (Table 1). Resting CBF tended to be lower in subjects who developed AMS symptoms than in those without (although this finding did not reach significance, \( P = 0.40 \)). If resting CBF is truly a correlate of AMS susceptibility, our expectation would be a continuum of CBF values, with the intermediate group does not fit with this model. Given the small number of subjects in the intermediate group (\( n = 3 \)\), unlikely to be biologically relevant (similarly for other variables summarized in Table 1). Also, our approach to highlight potential CMRO₂ changes related to AMS by including only subjects with the extremes of AMS symptoms does not change these primary conclusions. An unexpected finding in this study was the increased resting CBF in the intermediate group (Table 1). Resting CBF tended to be lower in subjects who developed AMS symptoms than in those without (although this finding did not reach significance, \( P = 0.40 \)). If resting CBF is truly a correlate of AMS susceptibility, our expectation would be a continuum of CBF values, with the intermediate group does not fit with this model. Given the small number of subjects in the intermediate group (\( n = 3 \)),
and the large range in CBF for these subjects, it seems more likely that this observation represents the biological variation in a very small sample rather than a true effect.

Another potential source of bias is the ordering of the measurements. For these studies, MRI measurements were made during normoxia first and during hypoxia second. This measurement order was introduced due to the ethical (and financial) imperative of selecting out subjects who were unsuitable for MRI exam before introducing additional risks or expense from the interventions (arterial blood samples, hypoxia, AMS, etc.). This has the potential to introduce a small bias in terms of familiarity with the scanner. Of the 26 subjects, 7 subjects had previously undergone multiple MRI scans (as part of other studies), and 19 were scanner naive. We observed no significant differences in MRI measurements between those familiar and those naive to MRI scanning. Thus prior familiarity with the scanner did not impact the MRI measurements of cerebral physiology changes. We anticipate that any additional effects of scanner familiarity induced by the fixed ordering of the normoxia/hypoxia measurements would not impact the measurements either.

Relatively few studies have addressed the changes in CMRO₂ during poikilocapnic hypoxia in the acute phase, and descriptions in the literature remain mixed. Cohen et al. (8) looked at CMRO₂ during isocapnic hypoxia and noted that CMRO₂ did not rise when arterial PCO₂ (PaCO₂) was clamped at baseline levels, which may be due to the neuromodulating effect of PaCO₂ discussed above. CMRO₂ has also been measured following several weeks of acclimatization to altitude (28). Under these prolonged conditions, it has been well described that early increases in CBF and or ventilatory hypocapnia tend to normalize, so it is not inconsistent that acute changes in CMRO₂ would also be reduced by 3 wk of acclimatization. Severinghaus et al. (33) made measurements of acute changes in CBF and CMRO₂ at 3,800-m altitude. They also noted an increase in CBF, but no significant change in CMRO₂ using a Kety-Schmidt technique. The reasons for the difference between their findings and the present study are not immediately obvious. The authors discussed the need to assume that CMRO₂ in each individual was not appreciably altered for their study. Whether this is a source of bias remains unclear. In addition, the sample sizes are different between the two studies (7 in Severinghaus’ series vs. 26 in the present one), which may also impact the ability to reject the null hypothesis. Bailey et al. (2) also used the Kety-Schmidt technique to measure CBF and calculated CMRO₂ as an incidental measurement while determining cerebral free radicals. They noted high CBF (94 ml·100 ml⁻¹·min⁻¹) and very high CMRO₂ (2.49 μmol·g⁻¹·min⁻¹) during 9 h of normobaric hypoxia. However, the significance of these elevated parameters was difficult to determine, as they also reported high CBF and CMRO₂ during normoxia.

Previous authors have addressed the ability of the vertebrate brain to reduce energy requirements in the face of decreased oxygen availability. Diving mammals are able to achieve impressive tolerance to hypoxia by managing oxidative stress (38). In humans, these effects are less clear. Sorensen et al. (35) found no difference in glucose metabolism or resting CBF in acclimatized high-altitude residents. In contrast, Hochachka
et al. (20) described lower glucose metabolism in habitually acclimatized high-altitude Andean natives compared with lowlanders. Extrapolating these results from habitually acclimatized individuals to hypoxia-naive subjects, as in this study, is difficult. However, we might hypothesize that CMRO₂ may stay constant or may, in fact, fall in the face of decreased O₂ availability during sustained hypoxia. At first sight, the elevation in CMRO₂ seems paradoxical, as it is unclear what biological advantage this response may have for an organism. It also raises the question whether the low arterial PO₂ (PaO₂) is the true control point for CMRO₂, or if other cerebral mediators, such as PaCO₂, play a more prominent role.

Previous studies looking at the relationship between PaCO₂ and CMRO₂ point toward a CMRO₂ dependence on PaCO₂, although the observed changes appear dependent on the exact experimental conditions and disease process present. Chen and Pike (7) measured significant increases in global CMRO₂ during hypocapnia compared with hypercapnia in normal human subjects. In a study in anesthetized dogs, Stoyka and Schutz (36) also noted increased CMRO₂ during increased-volume hyperventilation (but not when ventilation volume was not increased). A study of head injury patients and normal controls (9) found a more mixed picture, but overall global CMRO₂ increased with lower PaCO₂. However, in a study of patients with ischemic cerebrovascular disease, the response was variable, with one-half showing an increase and one-half a decrease in CMRO₂ during hyperventilation. To address if our data provided post hoc support for this PaCO₂ dependence, we used linear regression to examine the correlation between the decrease in PETCO₂ during hypoxia for each subject against their change in CMRO₂. This showed a negative relationship with greater increases in CMRO₂ occurring in those subjects with greater decreases in PETCO₂, although the correlation was not strong (r = 0.3). The influence of PaCO₂ on cerebral excitability has also been well described. Hypocapnia is known to increase neuronal excitability via adenosine receptors (13) and has been used clinically to induce or prolong seizures (1, 17). Poikilocapnic hypoxia is characterized by significant decreases in PaCO₂, and we postulated that the driving force behind the increased CMRO₂ may be the low PaCO₂ rather than the low PaO₂. The converse is also noted with increased low-frequency EEG power consistent with a low arousal state during hypercapnia (42).

Under normal (sea level) conditions, a decrease in O₂ delivery is usually accompanied by a rise in cerebral tissue PCO₂, thus this

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Fig. 2. Pooled physiological changes measured in 26 healthy, sea level residents during normoxia, and after 2-days sustained hypoxia at 90 Torr inspiratory PO₂ (3,800-m altitude). Values are means (1 SD). Dashed lines indicate the 95% confidence intervals. ***Decreases in SaO₂, SvO₂, and PETCO₂ with hypoxia were significant at \( P < 0.0001 \). CBF and CMRO₂ increased with hypoxia significant at **\( P < 0.01 \) and *\( P < 0.05 \), respectively. A-V difference showed a trend toward a small decrease with hypoxia (\( P = 0.06 \)).

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Fig. 3. Whole body oxygen consumption (\( \dot{V}O₂ \)) showed no significant increase with hypoxia. Dashed lines indicate 95% confidence interval. Values are means (1 SD).
response to limit CMRO₂ when PaCO₂ is increased is actually neuroprotective. Poikilocapnic hypoxia with both low PaO₂ and low PaCO₂ is a physiological state unique to hypoxic hypoxia, in which the “neuroprotective response” to the changes in CO₂ is actually the wrong response. Since tissue PO₂ (PtiO₂) is the balance point between O₂ delivery (from CBF and PaO₂) and O₂ consumption (from CMRO₂), then the low PaCO₂ will also tend to oppose any potential increase in CBF that would usually be driven by the low PaO₂. Thus the combination of a muted increase in CBF and a rise in CMRO₂ will have a combined effect in lowering PtiO₂ and is actually potentially neurotoxic. Since the PtiO₂ of the cerebral tissues is the common end point of CMRO₂, arterial oxygenation content, and CBF influences, this may prove to be a more important control point than the CMRO₂ alone for who develops AMS and who does not.

An emerging hypothesis from this study is the impact of PaCO₂ on CMRO₂ during poikilocapnic hypoxia. Other biochemical changes may also influence this. Cerebral glucose and lactate metabolism are also altered during hypoxia. Cerebral lactate production is increased during hypoxia (12), and the lactate may be used as an alternate carbohydrate source by neurons (6). The impact of this on CMRO₂ remains uncertain; during hypoglycemia, which stimulates lactate utilization by neurons, Lubow et al. (25) reported no increase in CMRO₂. Whether this is also the case during hypoxia warrants further investigation.

In the present study, we report increases in global CBF and CMRO₂ following sustained poikilocapnic hypoxia. Previous studies of cerebral reactivity observed differing regional cerebrovascular reactivity to isolated changes in O₂ (4) or CO₂ (5). Thus the actual CBF response to poikilocapnic hypoxia with decreases in both CO₂ and O₂ is likely to be more spatially heterogeneous than reported here. Since the local CMRO₂ will be impacted by local CBF, we hypothesize that CMRO₂ will also be regionally heterogeneous.

**Conclusion**

We observed a significant increase in CMRO₂ during sustained hypoxia at altitude, which we postulate is driven by the low PaCO₂ of ventilatory acclimatization to hypoxia. This was observed in all subjects, irrespective of the presence or time course of AMS symptoms, and is thus not a cause of AMS. These studies also draw attention to the potentially important role of PaCO₂ in modulating CMRO₂ and PtiO₂.

**ACKNOWLEDGMENTS**

The authors are grateful to G. Kim Prisk and Richard B. Buxton for helpful discussions.

**GRANTS**

This study was supported by National Institute of Neurological Disorders and Stroke Grants R01-NS053934 and R21-NS075812 (D. J. Dubowitz).

**DISCLOSURES**

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

**AUTHOR CONTRIBUTIONS**

Author contributions: Z.M.S., E.K., J.G., D.D.S., M.S., and D.J.D. performed experiments; Z.M.S., E.K., J.G., D.D.S., and D.J.D. analyzed data; Z.M.S. and D.J.D. interpreted results of experiments; Z.M.S. and D.J.D. prepared figures; Z.M.S. and D.J.D. drafted manuscript; Z.M.S., M.S., and D.J.D. edited and revised manuscript; Z.M.S., E.K., J.G., D.D.S., M.S., and D.J.D. approved final version of manuscript; D.J.D. conception and design of research.
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