Cerebral oxygenation in highlanders with and without high-altitude pulmonary hypertension

M. Furian¹,², T. D. Latshang¹, S. S. Aeschbacher¹, S. Ulrich¹, T. Sooronbaev³, E. M. Mirrakhimov³, A. Aldashev⁴ and K. E. Bloch¹

¹Pulmonary Division and Sleep Disorders Center, University Hospital of Zurich, Zurich, Switzerland
²Institute of Human Movement Sciences and Sport, Swiss Federal Institute of Technology, Zurich, Switzerland
³National Center for Cardiology and Internal Medicine, Bishkek, Kyrgyzstan
⁴Research Institute for Molecular Biology and Medicine, Bishkek, Kyrgyzstan

New Findings
• What is the central question of this study?
  Cerebral hypoxia impairs cognitive function and exercise performance and may result in brain damage. Residents at high altitude, in particular those with high-altitude pulmonary hypertension, are prone to hypoxaemia due to the exposure to reduced barometric pressure and impaired pulmonary gas exchange. Whether highlanders have a reduced cerebral oxygenation has not been studied.

• What is the main finding and its importance?
  We found that despite a reduced arterial oxygen saturation, healthy highlanders and even those with pulmonary hypertension have a similar cerebral oxygenation to healthy lowlanders, suggesting that compensatory mechanisms protect long-term residents at high altitude from cerebral hypoxia.

High-altitude pulmonary hypertension (HAPH), a chronic altitude-related illness, causes hypoxaemia and impaired exercise performance. We evaluated the hypothesis that haemodynamic limitation and hypoxaemia in patients with HAPH are associated with impaired cerebral tissue oxygenation (CTO) compared with healthy highlanders (HH) and lowlanders (LL). We studied 36 highlanders with HAPH and 54 HH at an altitude of 3250 m, and 34 LL at 760 m. Mean(±SD) pulmonary artery pressures were 34(±3), 22(±5) and 16(±4) mmHg, respectively (P < 0.05, all comparisons). The CTO was monitored by near-infrared spectroscopy along with pulse oximetry (peripheral arterial oxygen saturation, \( S_{pO_2} \)) during quiet breathing of room air (RA) and oxygen for 20 min each, and during hyperventilation with RA and oxygen, respectively. In HAPH, HH and LL breathing RA, \( S_{pO_2} \) was 88(±4), 92(±2) and 95(±2)%, respectively (P < 0.001, all comparisons), and CTO was similar in the three groups, at 68(±3), 68(±4) and 69(±4)%, respectively (n.s., all comparisons). Breathing oxygen increased \( S_{pO_2} \) and CTO significantly more in HAPH than in HH and LL. Hyperventilation (RA) did not reduce CTO in HAPH but did in HH and LL; hyperventilation (oxygen) increased CTO in HAPH only. Highlanders with and without HAPH studied at 3250 m had a similar CTO to healthy lowlanders at 760 m even though highlanders were hypoxaemic. The physiological response to hyperoxia and hypocapnia assessed by cerebral near-infrared spectroscopy suggests that healthy highlanders and even highlanders with HAPH effectively maintain an adequate CTO.
adoption may be of particular relevance because adequate cerebral oxygenation is essential for vital brain functions.

(Received 11 March 2015; accepted after revision 20 May 2015; first published online 23 May 2015)
Correspondence K. E. Bloch: Pulmonary Division, University Hospital Zurich, Ramistrasse 100, CH-8091 Zurich, Switzerland. Email: konrad.bloch@usz.ch

Introduction

Adequate oxygen delivery to the brain, an essential requirement for cognitive, executive and other vital cerebral functions, is controlled by several physiological mechanisms. Excessive alterations in cerebral perfusion during fluctuations in systemic blood pressure are prevented by adjusting the calibre of cerebral blood vessels, a mechanism termed cerebral autoregulation (CA; Paulson et al. 1972). Cerebral perfusion is also modulated in response to alterations in the partial pressures of oxygen (P\textsubscript{aO}\textsubscript{2}) and carbon dioxide (P\textsubscript{aCO}\textsubscript{2}), i.e. hypercapnia and hypoxia induce cerebral vasodilatation, while hypocapnia and hyperoxia induce vasoconstriction (Ainslie & Burgess, 2008; Willie et al. 2014). Impairment in control of cerebral perfusion can cause cerebral ischaemia, with potentially grave consequences (Roach & Hackett, 2001).

In healthy lowlanders ascending rapidly to high altitude, non-invasive near-infrared spectroscopy (NIRS) studies using sensors placed on the scalp revealed a considerable reduction in cerebral tissue oxygenation (CTO; Imray et al. 1998; Wilson et al. 2011; Rupp et al. 2014). Whether CTO is also reduced in lifelong residents at high altitude has not been studied, although this might elucidate mechanisms of chronic altitude adaptation and it may guide future research to identify targets for prevention and treatment of altitude-related illness associated with cerebral dysfunction (León-Velarde et al. 2005; Wilson et al. 2009; Vermeij et al. 2012).

High-altitude pulmonary hypertension (HAPH) is one particular type of chronic altitude-related illness affecting long-term residents at altitudes >2500 m (León-Velarde et al. 2005). It is characterized by an elevated pulmonary arterial pressure that leads to right heart overload and failure with hypoxaemia, dyspnoea, exercise intolerance, and eventually, premature death (Aldashev et al. 2002). As both hypoxaemia and haemodynamic impairment may reduce cerebral oxygen delivery and thereby predispose to cerebral hypoxia, the purpose of the present study was to evaluate the hypothesis that highlanders with HAPH have a reduced CTO and peripheral arterial oxygen saturation (S\textsubscript{aO}\textsubscript{2}) compared with healthy highlanders (HH) and lowlanders (LL). Moreover, we experimentally induced hypocapnia and hyperoxia, stimuli known to reduce cerebral perfusion (Ainslie & Ogoh, 2010; Willie et al. 2014), in order to test whether patients with HAPH would be more susceptible to such challenges than HH and LL in terms of CTO and cerebral tissue total haemoglobin concentration (totHb), a NIRS-derived measure of changes in cerebral blood volume (Ulrich et al. 2014).

Methods

Participants

Healthy highlanders and highlanders with HAPH, 16–80 years of age, both sexes, were recruited and studied at the Aksay health post (3250 m; barometric pressure 519 mmHg), Kyrgyzstan. Participants had to be of Kyrgyz ethnicity, born, raised and currently living at >2500 m. The diagnosis of HAPH was established by typical symptoms and a mean pulmonary artery pressure >30 mmHg in the absence of excessive erythrocytosis (haemoglobin concentration in females <19 g dl\textsuperscript{-1}, in males <21 g dl\textsuperscript{-1}) and other diseases that lead to hypoxaemia (i.e. such as cardiopulmonary diseases; León-Velarde et al. 2005). Healthy Kyrgyz lowlanders, 16–80 years of age, both sexes, living at <800 m were recruited and studied in Bishkek (760 m; barometric pressure 697 mmHg). Heavy smoking (>10 cigarettes day\textsuperscript{-1} or >25 pack-years) and pulmonary hypertension other than HAPH were exclusion criteria (Galié et al. 2009). This study was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained, and the ethics committee of the National Center of Cardiology and Internal Medicine, Bishkek, Kyrgyzstan, approved the study.

Design and interventions

Participants were studied in the supine position, breathing through a face mask equipped with a reservoir bag and a one-way exhalation valve. Room air [fractional inspired oxygen (F\textsubscript{iO}\textsubscript{2}) 0.21] delivered by a continuous positive airway pressure generator (REMstar; Philips Respironics, Zofingen, Switzerland) and oxygen (F\textsubscript{iO}\textsubscript{2} 1.0) at a flow rate of 10 l min\textsuperscript{-1} were administered in randomized order. After a 20 min baseline period, a 20 min recording took place with room air or oxygen, according to a randomized cross-over design. Participants were then instructed to hyperventilate until end-tidal partial pressure of carbon dioxide (P\textsubscript{ET,CO}\textsubscript{2}) was reduced by >10 mmHg. After a
period of at least 10 min of quiet breathing, which allowed the effects of hyperventilation or hyperoxia to be washed out, the procedure was repeated with the alternative gas mixture. Participants were blinded to the inhaled gas mixture. During the whole examination, participants were not allowed to sleep.

Measurements

Near-infrared spectroscopy was performed using a NIRO 200NX device (Hamamatsu, Japan) emitting light at 735, 810 and 850 nm. Hamamatsu NIRO devices have been shown to track changes in cerebral tissue oxygenation accurately in comparison to measurements of cerebral tissue oxygen tension and jugular venous oxygen saturation (Al-Rawi et al. 2001; McLeod et al. 2003). Optodes were placed bilaterally, high on the forehead, 4 cm apart, and secured with adhesive tape (Ulrich et al. 2014). Concentrations of oxygenated ([O₂Hb]) and deoxygenated haemoglobin ([HHb]) were measured. The CTO was calculated as \([\text{O}_2\text{Hb}]/(\text{O}_2\text{Hb} + [\text{HHb}])\), and totHb as \([\text{O}_2\text{Hb} + [\text{HHb}])\). The NIRS data were recorded at 2 Hz in a polysomnography system (Alice 5; Philips Respironics, Zofingen, Switzerland), along with ECG, finger pulse oximetry and capnography of expired air (Capnocheck Sleep; Smiths Medical PM Inc., Waukesha, WI, USA). Data from the final 2 min during stable quiet breathing with \(F_{1,\text{O}_2} 0.21\) and 1.0, and from 10–15 s of hyperventilation, respectively, were analysed. Data from the two NIRS channels were averaged.

Haemoglobin concentration and blood gases were measured in a radial artery blood sample obtained during quiet breathing \((F_{1,\text{O}_2} 0.21);\) RapidPoint 405; Siemens, Zurich, Switzerland). Mean pulmonary artery pressure (mPAP) was derived by Doppler echocardiography (SonoSite MicroMaxx; SonoSite Inc., Bothell, WA, USA) from the acceleration time (AT) of maximal velocity of pulmonary artery outflow (Kitabatake et al. 1983), and spirometry (EasyOne; NDD, Zurich, Switzerland) was performed (Miller et al. 2005).

Statistics

Data are summarized as means ± SD. The normality of data distribution was verified with Shapiro–Wilk tests. Comparisons between groups were made by ANOVA followed by post hoc Scheffe multiple comparisons. Within-group comparisons were made with Student’s paired t tests or Wilcoxon signed ranks tests as appropriate. To evaluate effects of group membership (HAPH, HH, LL)

![Figure 1. Study flow chart, showing the three study groups, namely healthy lowlanders (LL), healthy highlanders (HH) and highlanders with HAPH](image)

Abbreviations: b/o, because of; COPD, chronic obstructive pulmonary disease; and HAPH, high-altitude pulmonary hypertension.
on CTO, multivariate regression analysis was performed with CTO as dependent and group membership, age, sex, $S_{P_{O_2}}$ and $P_{ET,CO_2}$ during room air breathing as independent variables. Further regression analyses were performed to evaluate the independent effect of mPAP on changes in CTO and totHb during hyperventilation and during breathing oxygen, respectively, while controlling for changes in $S_{P_{O_2}}$, $P_{ET,CO_2}$, age and sex. In addition,

### Table 1. Characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Highlanders with HAPH</th>
<th>Healthy highlanders (HH)</th>
<th>Healthy lowlanders (LL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$ (females, %)</td>
<td>36 (16, 44%)</td>
<td>54 (21, 39%)</td>
<td>34 (12, 35%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 ± 10</td>
<td>39 ± 10$^*$</td>
<td>39 ± 11$^*$</td>
</tr>
<tr>
<td>Body mass index (kg m$^{-2}$)</td>
<td>28.7 ± 4.7</td>
<td>24.0 ± 3.9$^*$</td>
<td>25.6 ± 3.5$^+$</td>
</tr>
<tr>
<td>FEV$\text{I}$ (% predicted)</td>
<td>102 ± 13</td>
<td>106 ± 13</td>
<td>98 ± 11$^*$</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>27 (75)</td>
<td>37 (69)</td>
<td>23 (68)</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure by echocardiography (mmHg)</td>
<td>34 ± 3</td>
<td>22 ± 5$^*$</td>
<td>16 ± 4$^+$</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>115 ± 14</td>
<td>105 ± 12$^*$</td>
<td>119 ± 10$^1$</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75 ± 11</td>
<td>68 ± 9$^*$</td>
<td>76 ± 11$^1$</td>
</tr>
<tr>
<td>Haemoglobin concentration (g dl$^{-1}$)</td>
<td>16.3 ± 2.0</td>
<td>16.1 ± 2.0</td>
<td>14.7 ± 1.9$^+$</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$pH$</td>
<td>7.42 ± 0.03</td>
<td>7.43 ± 0.02$^*$</td>
<td>7.43 ± 0.04$^1$</td>
</tr>
<tr>
<td>$P_{aO_2}$ (mmHg)</td>
<td>56 ± 6</td>
<td>61 ± 8$^*$</td>
<td>79 ± 9$^1$</td>
</tr>
<tr>
<td>$S_{O_2}$ (mmHg)</td>
<td>86 ± 4</td>
<td>89 ± 3$^*$</td>
<td>95 ± 1$^1$</td>
</tr>
<tr>
<td>$P_{aCO_2}$ (mmHg)</td>
<td>32 ± 4</td>
<td>33 ± 4</td>
<td>38 ± 5$^1$</td>
</tr>
<tr>
<td>$P_{A-O_2}$ (mmHg)</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>10 ± 8$^1$</td>
</tr>
</tbody>
</table>

Values are means ± SD; $^*P < 0.05$ versus highlanders with HAPH; $^1P < 0.05$ versus healthy highlanders. Abbreviations: FEV$\text{I}$, forced expiratory volume in 1 s; HAPH, high-altitude pulmonary hypertension; $P_{A-O_2}$, alveolar–arterial $P_{O_2}$ difference (Crapo et al. 1999); $P_{aCO_2}$, arterial partial pressure of carbon dioxide; $P_{aO_2}$, arterial partial pressure of oxygen; and $S_{aO_2}$, arterial saturation of oxygen.

### Table 2. Effects of oxygen breathing and of hyperventilation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$F_{1, O_2}$ 0.21</th>
<th>$F_{1, O_2}$ 1.0</th>
<th>$F_{1, O_2}$ 0.21</th>
<th>$F_{1, O_2}$ 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highlanders with high-altitude pulmonary hypertension, $n = 36$, studied at 3250 m</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$S_{P_{O_2}}$ (%)</td>
<td>87.6 ± 4.3</td>
<td>97.6 ± 1.7$^*$</td>
<td>96.1 ± 1.8$^*$</td>
<td>98.1 ± 1.8$^*$</td>
</tr>
<tr>
<td>CTO (%)</td>
<td>68 ± 3</td>
<td>73 ± 3$^*$</td>
<td>68 ± 4</td>
<td>69 ± 5$^*$</td>
</tr>
<tr>
<td>$\Delta$totHb (μmol l$^{-1}$)</td>
<td>n.a.</td>
<td>−1.2 ± 1.7$^*$</td>
<td>−1.6 ± 3.5$^*$</td>
<td>−2.0 ± 3.5$^*$</td>
</tr>
<tr>
<td>$P_{ET,CO_2}$ (mmHg)</td>
<td>33 ± 5</td>
<td>31 ± 6$^*$</td>
<td>20 ± 4$^*$</td>
<td>20 ± 4$^*$</td>
</tr>
<tr>
<td>Healthy highlanders, $n = 54$, studied at 3250 m</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$S_{P_{O_2}}$ (%)</td>
<td>91.6 ± 2.2$^1$</td>
<td>98.5 ± 1.4$^+$</td>
<td>97.1 ± 1.7$^+$</td>
<td>98.8 ± 1.1$^*$</td>
</tr>
<tr>
<td>CTO (%)</td>
<td>68 ± 4</td>
<td>72 ± 5$^*$</td>
<td>66 ± 5</td>
<td>68 ± 5</td>
</tr>
<tr>
<td>$\Delta$totHb (μmol l$^{-1}$)</td>
<td>n.a.</td>
<td>−1.0 ± 1.9$^*$</td>
<td>−1.8 ± 2.8$^*$</td>
<td>−2.2 ± 2.8$^*$</td>
</tr>
<tr>
<td>$P_{ET,CO_2}$ (mmHg)</td>
<td>32 ± 5</td>
<td>32 ± 5</td>
<td>20 ± 3$^*$</td>
<td>20 ± 4$^*$</td>
</tr>
<tr>
<td>Healthy lowlanders, $n = 34$, studied at 760 m</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$S_{P_{O_2}}$ (%)</td>
<td>95.3 ± 1.8$^1$</td>
<td>98.6 ± 1.1$^+$</td>
<td>98.2 ± 1.0$^+$</td>
<td>99.0 ± 0.9$^1$</td>
</tr>
<tr>
<td>CTO (%)</td>
<td>69 ± 4</td>
<td>71 ± 5$^+$</td>
<td>65 ± 5$^+$</td>
<td>66 ± 5$^+$</td>
</tr>
<tr>
<td>$\Delta$totHb (μmol l$^{-1}$)</td>
<td>n.a.</td>
<td>−0.1 ± 1.1$^1$</td>
<td>−1.4 ± 1.7$^*$</td>
<td>−1.6 ± 1.6$^*$</td>
</tr>
<tr>
<td>$P_{ET,CO_2}$ (mmHg)</td>
<td>39 ± 3$^1$</td>
<td>38 ± 4$^1$</td>
<td>27 ± 4$^1$</td>
<td>27 ± 4$^1$</td>
</tr>
</tbody>
</table>

Values are means ± SD; $^*P < 0.05$ versus quiet breathing, $F_{1, O_2}$ 0.21, in corresponding group; $^1P < 0.05$ versus highlanders with HAPH during corresponding intervention; and $^1P < 0.05$ versus healthy highlanders during corresponding intervention. Abbreviations: CTO, cerebral tissue oxygenation; $F_{1, O_2}$, fractional inspired oxygen; n.a., not assessed; $P_{ET,CO_2}$, end-tidal partial pressure of carbon dioxide; $S_{P_{O_2}}$, peripheral arterial oxygen saturation; and $\Delta$totHb, change in total haemoglobin concentration, a surrogate for cerebral blood volume, compared with quiet breathing at $F_{1, O_2}$ 0.21.
characteristics of HAPH, HH and LL matched for sex and age (within 5 years) were compared. A probability of $P < 0.05$ was considered statistically significant.

**Results**

Of 232 highlanders invited to participate, 105 declined, 37 were excluded due to co-morbidities, and 90 consented and were admitted. Of 39 LL invited to the study, four were excluded due to co-morbidity, and 35 consented and were admitted. One LL was excluded from analysis because of a technical failure (Fig. 1). Patients with HAPH were slightly older and had a higher body weight than HH and LL (Table 1). The HAPH patients were more hypoxaemic than HH. Both highlander groups were more hypoxaemic and had a lower $P_{aCO_2}$ than LL.

![Figure 2. Recording obtained in a healthy highlander in Aksay (3250 m)](image)

*Figure 2. Recording obtained in a healthy highlander in Aksay (3250 m)*  
*A*, pulse oximetry ($S_{PO_2}$); *B*, cerebral tissue oxygenation (CTO) measured by near-infrared spectroscopy; *C*, cerebral total haemoglobin concentration (totHb), a surrogate for cerebral blood volume, measured by near-infrared spectroscopy; *D*, capnography of expired air ($P_{expCO_2}$) was used for measuring end-tidal $P_{CO_2}$ ($P_{ET,CO_2}$ as a surrogate of arterial $P_{CO_2}$). The consecutive phases of the study include quiet room air breathing [fractional inspired oxygen ($F_{I,O_2}$) 0.21], followed by hyperventilation (HV), then quiet oxygen breathing ($F_{I,O_2}$ 1.0), followed by hyperventilation. Data analysis was performed on the final 2 min of the quiet breathing phase (QB) and at the end of HV. In participants randomized to room air first (as in the present example), a washin phase of at least 10 min on $F_{I,O_2}$ 1.0 was interposed before QB and HV measurements were made. In participants randomized to oxygen ($F_{I,O_2}$ 1.0) first (not shown), a washout period of at least 10 min was interposed before room air QB and HV measurements were made.
Breathing $F_{1,02}$ 1.0 (Fig. 4Aa–Da) increased CTO and $S_{PO_2}$ in all three groups with the greatest changes in HAPH, decreased totHb in HAPH and HH, and decreased $P_{ET,CO_2}$ in HAPH only.

Hyperventilation ($F_{1,02}$ 0.21; Fig. 4Ab–Db) reduced $P_{ET,CO_2}$ by >10 mmHg in all three groups. This did not change CTO in HAPH but decreased CTO in HH and LL; hyperventilation ($F_{1,02}$ 0.21) induced the greatest increase in $S_{PO_2}$ in HAPH followed by HH and LL, and it decreased totHb to a similar extent in all three groups.

Hyperventilation ($F_{1,02}$ 1.0; Fig. 4Ac–Dc) reduced $P_{ET,CO_2}$ by >10 mmHg in all three groups. Correspondingly, CTO was increased in HAPH, unchanged in HH and reduced in LL. The $S_{PO_2}$ increased in all three groups with greatest changes in HAPH, while totHb was reduced to a similar extent in all three groups.

Multivariate regression analysis did not reveal any significant association of CTO with HAPH, HH and LL when controlling for $S_{PO_2}$, $P_{ET,CO_2}$, age and sex (Table 3). In order to evaluate further the independent effect of pulmonary artery pressure on changes in CTO and on changes in totHb while controlling for changes in $S_{PO_2}$, $P_{ET,CO_2}$, age and sex, we performed multiple regression analyses on data from highlanders with and without HAPH. The change in CTO induced by hyperventilation was positively correlated with mPAP ($\beta = 0.201$, SE = 0.375, $P = 0.040$), i.e. the higher the mPAP, the greater the increase in CTO, while the change in CTO (increase) during hyperoxia was not significantly correlated with mPAP ($P = 0.947$) when controlled for several covariables (Table S1 in Supporting information). Changes in totHb during hyperventilation were not significantly correlated with mPAP ($P = 0.367$), but changes in totHb during hyperoxia were significantly correlated with mPAP ($\beta = 0.282$, SE = 0.034, $P = 0.042$) when controlling for covariables (Table S1).

In 57 age- and sex-matched participants, 19 HAPH, HH and LL, respectively, similar trends in CTO with interventions were seen to those in the entire groups (Tables S2 and S3).

**Discussion**

We studied cerebral and arterial oxygenation in Kyrgyz highlanders with HAPH and in healthy highlanders and lowlanders. Consistent with our hypothesis, $S_{PO_2}$ was significantly lower in highlanders suffering from HAPH compared with HH and LL. In contrast, CTO was similar in HAPH, HH and LL. These findings suggest that physiological adaptations defend CTO in highlanders with and without HAPH despite chronic hypoxaemia.

The finding of similar CTO measured at 3250 m in highlanders with and without HAPH in comparison to CTO measured in LL at 760 m were unexpected, because studies in healthy lowlanders acutely exposed
to hypoxia (Imray et al. 1998, 2003, 2005) and in lowlanders with obstructive sleep apnoea travelling to 2590 m (Ulrich et al. 2014) revealed significant reductions in CTO compared with values near sea level. The lack of a significant difference in CTO in highlanders compared with lowlanders in the present study suggests that in lifelong high-altitude residents adaptations took place that compensated for their reduced \( S_{\text{pO}_2} \), independent

Figure 4. Physiological changes with interventions
Changes in physiological variables induced by different interventions in highlanders with high-altitude pulmonary hypertension (HAPH), healthy highlanders (HH) and healthy lowlanders (LL) in comparison to the baseline during quiet room air breathing (\( F_{\text{I,O}_{2}} 0.21 \)). Boxes with lines represent medians and quartiles of changes, whiskers represent the 10th and 90th percentiles, and dots represent individual values that fall outside the 10th–90th percentile range. \( \Delta \text{a}–\Delta \text{c} \), change in \( S_{\text{pO}_2} \) measured by pulse oximetry. \( \Delta \text{b}–\Delta \text{c} \), change in CTO measured by near-infrared spectroscopy. \( \Delta \text{c}–\Delta \text{c} \), change in total haemoglobin concentration (totHb), a surrogate for cerebral blood volume, measured by near-infrared spectroscopy. \( \Delta \text{da}–\Delta \text{dc} \), change in \( P_{\text{ET,CO}_2} \) measured by capnography. \( \Delta \text{a}–\Delta \text{da} \), changes with quiet oxygen breathing (\( F_{\text{I,O}_{2}} 1.0 \)). \( \Delta \text{b}–\Delta \text{db} \), changes with hyperventilation with room air (\( F_{\text{I,O}_{2}} 0.21 \)). \( \Delta \text{c}–\Delta \text{dc} \), changes with combined oxygen breathing (\( F_{\text{I,O}_{2}} 1.0 \)) and hyperventilation. A value of zero (horizontal line) in all panels represents no change from quiet room air breathing baseline (\( F_{\text{I,O}_{2}} 0.21 \)). Asterisks (*) indicate significant changes (\( P < 0.05 \)) from baseline of the corresponding group. Significant differences in changes between groups are marked with horizontal lines (\( P < 0.05 \)).
of whether they suffered from HAPH or not. The 95% confidence intervals of the differences in CTO between highlanders versus lowlanders indicate that differences as small as 2.8% could have been detected with high confidence.

In order to explore mechanisms that may have contributed to protecting the brain of highlanders from chronic hypoxia despite arterial hypoxaemia, we analysed the physiological responses to hyperoxia, hypocapnia and the combination of the two. Hyperoxia induced by breathing oxygen \( F_{1,2}O_2 = 1.0 \) resulted in an increased CTO in all three groups, but to a much greater extent in highlanders than in lowlanders, corresponding to the greater increase in \( S_{P_{O_2}} \) in highlanders starting from a lower baseline \( S_{P_{O_2}} \) (Table 2 and Fig. 3). The greater increase in CTO in highlanders than in LL during oxygen breathing was associated with a reduction in totHb, the measure of regional cerebral blood volume (Fig. 4). Given that \( P_{aO_2} \) is one of several factors that control cerebral blood flow during hypoxia (Ainslie & Ogoh, 2010), these findings are consistent with a reduction of cerebral blood flow related to the increase in \( P_{aO_2} \) by oxygen breathing in highlanders. Consistently, a reduced middle cerebral artery blood flow velocity during oxygen breathing has been reported in healthy subjects after rapid ascent to 3459 m (Watson et al. 2000; Imray et al. 2003).

Hyperventilation \( (F_{1,2}O_2 = 0.21) \) increased \( S_{P_{O_2}} \) in all three groups, but to a greater extent in highlanders than in LL, possibly favoured by a leftward shift of the oxygen–haemoglobin dissociation curve due to the more pronounced hypocapnia. Despite the rise in \( S_{P_{O_2}} \) during hyperventilation, CTO did not increase in HAPH and even decreased in HH and LL. Multiple regression analysis in highlanders confirmed a positive correlation between pulmonary artery pressure and changes in CTO during hyperventilation (Table S1), further corroborating that HAPH patients preserved cerebral oxygenation even when exposed to hypocapnia, a strong stimulus of cerebral vasoconstriction (Ainslie & Ogoh, 2010; Rangel-Castilla et al. 2010). Consistently, the cerebral totHb was reduced during hyperventilation in all three groups, although highlanders had a much lower \( P_{ET,CO_2} \) than lowlanders (Fig. 4). Contrary to the present findings in HH at 3250 m, healthy lowlanders acutely exposed to 3650 m in a previous study revealed no increase in CTO during hyperventilation, which may be related to a more pronounced hypoxaemia and hypocapnia at 3650 m compared with 3250 m, differences in the physiological response of unacclimatized lowlanders compared with highlanders, and to the smaller sample size \((n = 20)\) of the cited study (Imray et al. 2000).

We expected that combining the effects of hyperoxia and hypocapnia (hyperventilation), i.e. increasing the \( P_{aO_2}/P_{aCO_2} \) ratio (Ainslie & Ogoh, 2010; Lucas et al. 2011), would enhance the response compared with either stimulus alone. However, the reduction in totHb, suggesting a reduced cerebral blood volume due to reduced blood flow, was similar to that with hyperventilation or oxygen breathing alone (Fig. 4). Given that CTO increased in highlanders with HAPH during hyperventilation with oxygen, but decreased in LL despite a minor increase in \( S_{P_{O_2}} \), it seems that highlanders with HAPH experienced adaptations in the control of cerebral perfusion that defended CTO even during hypocapnia and hyperoxia. However, the measurements performed in the present study do not allow us to differentiate whether these adaptations were related to changes in cardiac output, cerebral perfusion, cerebral oxygen uptake or consumption, or combinations of these.

We measured CTO in the prefrontal cortex, which is important for cognitive function (Vermeij et al. 2012). We cannot exclude the possibility that other regions of the brain may have revealed different values of CTO and responses to blood gas changes. Systemic blood pressure was not continuously measured because no changes with hyperoxia (Becker et al. 1995) or hypocapnia (Rasmussen et al. 2007) were expected, and the conclusions on the CTO measurements are valid independent of potential blood pressure variations. Regression analysis (Table 3) and comparison of subgroups matched for age and sex (Tables S2 and S3) did not suggest that CTO varied between HAPH patients, HH and LL even when controlled for potential confounders.

Table 3. Predictors of cerebral tissue oxygenation in multivariate regression analysis

<table>
<thead>
<tr>
<th>Group (1 = LL, 2 = HH, 3 = HAPH)</th>
<th>( \beta )</th>
<th>SE</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( S_{P_{O_2}} ) room air (%)</td>
<td>0.094</td>
<td>0.608</td>
<td>0.430</td>
</tr>
<tr>
<td>( P_{ET,CO_2} ) room air (mmHg)</td>
<td>-0.086</td>
<td>0.097</td>
<td>0.404</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.170</td>
<td>0.065</td>
<td>0.057</td>
</tr>
<tr>
<td>Sex (1 = male, 2 = female)</td>
<td>-0.430</td>
<td>0.032</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>-0.431</td>
<td>0.585</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CTO, cerebral tissue oxygenation; \( P_{ET,CO_2} \), end-tidal partial pressure of carbon dioxide; \( S_{P_{O_2}} \), peripheral arterial oxygen saturation.
Conclusions

In this first investigation of cerebral oxygenation in highlanders, we found that CTO measured in highlanders with and without HAPH at 3250 m was similar to CTO measured in healthy lowlanders at 760 m despite the arterial hypoxaemia in highlanders. Moreover, the physiological response to hyperoxia and hypocapnia assessed by NIRS suggests that HH and even highlanders with HAPH having more pronounced hypoxaemia have effective mechanisms to maintain an adequate CTO and cerebral blood volume. This adaptation may be of particular relevance because an adequate cerebral oxygenation is essential for executive and other brain functions (Vermeij et al. 2012).

References


Imray CHE, Walsh S, Clarke T, Tiivas C, Hoar H, Harvey TC, Chan CWM, Forster PJG, Bradwell AR & Wright AD (2003). Effects of breathing air containing 3% carbon dioxide, 35% oxygen or a mixture of 3% carbon dioxide/35% oxygen on cerebral and peripheral oxygenation at 150 m and 3459 m. Clin Sci 104, 203–210.


**Author contributions**

M.F., K.E.B., T.S., A.A., T.D.L., S.S.A., S.U., T.S. and A.A. contributed to conception and design of the study, data acquisition, drafting and critical revision of the manuscript. E.M.M. contributed to conception and design of the study and critically revised the manuscript. All authors approved the final version to be published.

**Funding**

Grant support was provided by the OPO Foundation and the Lung League Zurich. Philips Respironics (Zofingen, Switzerland) and Siemens Healthcare Diagnostics AG (Zurich, Switzerland) contributed some of the measurement equipment.

**Supporting information**

**Table S1.** Predictors of changes in CTO and totHb in response to hypocapnia and hyperoxia in multivariate regression analysis of highlanders with and without HAPH.

**Table S2.** Characteristics of study participants matched for age (within 5 years) and gender.

**Table S3.** Effects of oxygen breathing and of hyperventilation in groups matched for age (within 5 years) and gender.

© 2015 The Authors. Experimental Physiology © 2015 The Physiological Society