Cerebrovascular Responses to Hypoxia and Hypocapnia in Ethiopian High Altitude Dwellers

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Background and Purpose—Cerebrovascular responses to hypoxia and hypocapnia in Peruvian altitude dwellers are impaired. This could contribute to the high incidence of altitude-related illness in Andeans. Ethiopian high altitude dwellers may show a different pattern of adaptation to high altitude. We aimed to examine cerebral reactivity to hypoxia and hypocapnia in healthy Ethiopian high altitude dwellers. Responses were compared with our previous data from Peruvians.

Methods—We studied 9 Ethiopian men at their permanent residence of 3622 m, and one day after descent to 794 m. We continuously recorded cerebral blood flow velocity (CBFV; transcranial Doppler). End-tidal oxygen (P_{ET}O_2) was decreased from 100 mm Hg to 50 mm Hg with end-tidal carbon dioxide (P_{ET}CO_2) clamped at the subject’s resting level. P_{ET}CO_2 was then manipulated by voluntary hyper- and hypoventilation, with P_{ET}O_2 clamped at 100 mm Hg (normoxia) and 50 mm Hg (hypoxia).

Results—During spontaneous breathing, P_{ET}CO_2 increased after descent, from 38.2 ± 1.0 mm Hg to 49.8 ± 0.6 mm Hg (P < 0.001). There was no significant response of CBFV to hypoxia at either high (−0.19 ± 3.1%) or low (1.1 ± 2.9%) altitudes. Cerebrovascular reactivity to normoxic hypocapnia at high and low altitudes was 3.92 ± 0.5%.mm Hg^{-1} and 3.09 ± 0.4%.mm Hg^{-1}; reactivity to hypoxic hypocapnia was 4.83 ± 0.7%.mm Hg^{-1} and 2.82 ± 0.5%.mm Hg^{-1}. Responses to hypoxic hypocapnia were significantly smaller at low altitude.

Conclusions—The cerebral circulation of Ethiopian high altitude dwellers is insensitive to hypoxia, unlike Peruvian high altitude dwellers. Cerebrovascular responses to P_{ET}CO_2 were greater in Ethiopians than Peruvians, particularly at high altitude. This, coupled with their high P_{ET}CO_2 levels, would lead to high cerebral blood flows, and may be advantageous for altitude living. (Stroke. 2008;39:336-342.)

Key Words: cerebrovascular responses ■ Ethiopia ■ high altitude ■ hypoxia

Individuals living permanently at high altitude must contend with chronic hypoxic hypoxia. Several compensatory mechanisms have evolved to enable these people to live and work in this inhospitable environment. In Andeans, these adaptations include raised hemoglobin concentrations with high hematocrits,2 large lung volumes,3 and blunted hypoxic ventilatory responses.1,4 In addition, our recent studies of healthy Peruvian high altitude dwellers (HA Peruvians) have demonstrated that they are hypoxic, hypocapnic, polycythemic (high packed cell volumes with normal plasma volumes), and have exceptionally high orthostatic tolerances.5,6 Peruvian altitude residents also have a high incidence of chronic mountain sickness (CMS), a maladaptation syndrome characterized by excessive hypoxia, abnormally high hematocrits, and various clinical manifestations including dyspnoea, insomnia, and symptoms of cerebral dysfunction.7 The incidence of CMS is dependent on altitude of residence; 28% of men living at 3510 m and 52% of men living at 4100 m in the Andes have CMS.8

It has emerged recently that Ethiopian altitude dwellers may use different adaptive strategies to hypoxia.9,10 Ethiopians living on high plateaux have lower hemoglobin levels and hence presumably lower hematocrits than Peruvians,1,11 and there are no reports of CMS in Ethiopians. The adaptations of Ethiopians may be more beneficial for high altitude living,9 which could explain the apparent absence of CMS in Ethiopia.

Many of the symptoms of CMS are thought to be attributable to cerebral hypoxia,12 and possibly also hypocapnia. Hypoxia normally increases cerebral blood flow and hypocapnia causes marked decreases in flow.13 Because responses to hypocapnia are usually much greater than those to hypoxia,
at altitude the combined stimulus would reduce cerebral blood flow, and any adaptive changes could be of benefit for high altitude living. Abnormal adaptations of cerebral blood flow control may contribute to the CMS syndrome. We recently reported that cerebrovascular responses to hypoxia are impaired in Peruvians, and this impairment appears to be rapidly reversible on descent to low altitude. The response to hypocapnia during hypoxia, however, was greater at altitude. These changes would not appear beneficial for altitude living. Furthermore, we also showed that cerebrovascular responses to exogenous nitric oxide (NO, the proposed mediator of hypoxic vasodilatation) are different between Ethiopians and Peruvians, and may be related to fitness for life at high altitudes. However, the responses of the cerebral circulation to physiological changes in end-tidal oxygen (PETO2) and carbon dioxide (PETCO2) in Ethiopian high altitude dwellers are unknown. The aim of this study, therefore, was to examine the cerebrovascular responses to changes in PETO2 and PETCO2 in Ethiopian high altitude dwellers, and to compare them with those previously obtained in HA and CMS Peruvians. We hypothesized that responses would be different in Ethiopian high altitude dwellers, reflecting a different, and possibly more advantageous, pattern of cerebral adaptation to hypobaric hypoxia in these individuals.

**Methods**

**Subjects**

Studies were performed on 9 Ethiopian men at their resident altitude of 3622 m near Chennek in the Simen Mountains of Ethiopia (barometric pressure, P0 499 mm Hg). They were repeated the day after descent to the Tekkeze River Gorge (794m: P0 690 mm Hg). All subjects underwent a routine medical examination and medical history, and were apparently healthy and taking no medication. As part of subject characterization, we determined hematocrit (in quadruplicate from a peripheral venous sample), resting heart rates (EGC; Hewlett Packard, 78352C), and arterial oxygen saturations (SaO2; finger oximetry; Hewlett Packard) after a 30-minute supine rest period. CMS scores were determined using an internationally recognized scoring system, which assesses the 10 most common symptoms and signs of CMS. A CMS score ≥12 indicates the presence of CMS, with higher scores describing increased severity of disease. Written informed consent was obtained from all subjects. Ethical approval was granted by the Leeds Teaching Hospitals Research Ethics Committee and by the Federal Democratic Republic of Ethiopia, Ethiopian Science and Technology Commission National Ethics Review Committee. All studies were performed in accordance with the Declaration of Helsinki of the World Medical Association (2004).

**Procedure**

Subjects were asked to abstain from drinking alcohol and caffeine for 24 hours, and not to eat for at least 4 hours before testing. Studies were performed supine, after a 10-minute rest period. Throughout testing, beat-to-beat blood pressures were determined from the middle finger, supported at heart level (Portapres Model 2. TNO-TPD Biomedical Instrumentation). ECG and SaO2 were monitored continuously. We also determined middle cerebral artery blood flow velocity using the Doppler shift technique. The ultrasound probe was secured in position overlying the transcranial window with an angle of insolation as close to zero degrees as possible. Mean cerebral blood flow velocity (CBFV) was calculated off-line (T2-Dop, DWL Elektronische System GmbH, Sipplingen, Germany). Breath-by-breath PETO2 and PETCO2 were determined throughout. Subjects breathed through the mouthpiece for at least 10 minutes to allow recordings to stabilize before data collection.

**Cerebrovascular Responses to Hypoxia**

By adjusting the flow of inspiratory gases we clamped the subject’s PETCO2 at his own resting level throughout. PETO2 was initially clamped at approximately 100 mm Hg for 10 minutes, until steady-state was reached. We then adjusted the inspired gases to decrease PETO2 in a single step to approximately 50 mm Hg for 10 minutes, until steady-state was reached. Cerebrovascular responses were calculated as steady-state percentage changes in CBFV that occurred in response to the step decrease in PETO2 during isocapnia. Data were analyzed offline and represent averages of 2 respiratory cycles. Responses were normalized to allow for small differences in PETO2 between subjects and to allow for comparison of data obtained at different altitudes:

\[
\text{CBFV response} = \left(\frac{\text{change CBFV}}{\text{change PETO2 mm Hg}}\right) \times 50 \text{ mm Hg}
\]

**Cerebrovascular Responses to Hypocapnia**

We assessed cerebrovascular reactivity to hypocapnia during normoxia (PETO2 100 mm Hg) and hypoxia (PETO2 50 mm Hg) at both altitudes. PETCO2 was decreased over a range of values by asking the subject to hyperventilate. Cerebrovascular responses were calculated from the linear regression of the relationship between PETCO2 and the percentage change in CBFV. Data were only included in the linear range and where the correlation coefficient describing the relationship was statistically significant. The gradient of the relationship was used as the measure of the vascular reactivity. Data were analyzed offline and represent averages of 2 complete respiratory cycles.

**Statistics**

All data are expressed as mean±SE. Within-group comparisons were performed using paired Student t tests. Comparisons with previously published data in Peruvian high altitude dwellers were performed using ANOVA with Tukey post-hoc tests. Correlations were examined using the Spearman correlation coefficient. Statistically significant was assumed at the level of P<0.05. NS denotes “not significant”.

**Results**

One subject declined to descend to low altitude for the repeat studies, and so was excluded from all analyses. No subject showed evidence of CMS. The mean CMS score was 0.13±0.1. The mean age was 36.0±1.4 years, height was 1.67±0.2 m, and weight 53.0±1.1 kg. Hematocrit was 48.4±1.8%.

When studied at high altitude, resting values of systolic and diastolic arterial pressure were 128±3.2/69±2.7 mm Hg and heart rate was 64.8±2.8 bpm. These values were not significantly different after descent (130±3.8/64±2.8 mm Hg and 64.3±1.9 bpm). At high altitude, resting SaO2 was 88±1.1%, PETO2 was 58.4±1.3 mm Hg, and PETCO2 was 38.2±1.0 mm Hg. After descent these values increased to 97±0.5%, 97.6±1.9 mm Hg and 49.8±0.6 mm Hg, all P<0.001.

**Cerebrovascular Responses to Hypoxia**

There was no significant effect of the hypoxic stimulus on blood pressure or heart rate. PETCO2 was effectively clamped at the subject’s resting level throughout. At the high altitude study it was clamped at 38.8±1.0 mm Hg and at low altitude it was 48.9±0.6 mm Hg.

There was no significant response of CBFV to hypoxia at either location. At high altitude it changed by −0.19±3.1% and at low altitude by 1.07±2.9%.
PETco2-CBFV gradients were significantly correlated. The studies either when performed under conditions of normoxia affected by hyperventilation during the high or low altitude (respectively). Blood pressures and heart rates were not significantly 15.9/H11006 14.5/H11006 14.5/H11006 0.4). Pprotocol or at any altitude (H11022/H11006/H11006/H11006 0.01). MAP. MAP was not significantly changed by the procedure 0.01 and 0.97 0.72%.mm Hg 3.1 mm Hg. 3.1 mm Hg and 6.7 11.9/H11006 2.80 0.52%.mm Hg 0.72%.mm Hg. During hyperventilation, changes in PETo2 increased by 29.4 1 at high altitude during normoxia and hypoxia, respectively, to eliminate possible effects of alterations in mean arterial pressure (MAP). During hyperventilation, changes in PETo2 were minimized by adjustments of the inspired gases. However, despite this, hyperventilation resulted in concomitant changes in PETo2. At high altitude PETo2 increased by 29.4±6.3 mm Hg and 11.9±1.5 mm Hg during normoxia and hypoxia, respectively, and at low altitude by 10.8±3.1 mm Hg and 6.7±3.1 mm Hg. Changes in PETo2 induced by hyperventilation were similar in all conditions (high altitude: 16.3±0.9 mm Hg and 14.5±1.3 mm Hg; low altitude: 16.5±1.0 mm Hg and 15.9±1.9 mm Hg, during normoxia and hypoxia respectively). Blood pressures and heart rates were not significantly affected by hyperventilation during the high or low altitude studies either when performed under conditions of normoxia or hypoxia.

A representative example response of the cerebral circulation to hypocapnia during both hypoxia and normoxia in an Ethiopian subject at high altitude can be seen in Figure 1. All PETo2-CBFV gradients were significantly correlated. The mean correlation coefficients at the high and low altitude studies were 0.96±0.01 and 0.97±0.01 during normoxia and 0.95±0.01 and 0.93±0.02 during hypoxia.

The sensitivity of the cerebral circulation to hypocapnia during normoxia was similar at both altitudes (3.92±0.50%, mm Hg−1 at high and 3.09±0.44%.mm Hg−1 at low altitude). The sensitivity of the cerebral circulation to hypocapnia during hypoxia was 4.83±0.72%.mm Hg−1 at high altitude and 2.80±0.52%.mm Hg−1 after descent to low altitude. The sensitivity to hypocapnia during hypoxia was significantly greater at high altitude (P<0.01). To eliminate possible effects of alterations in mean arterial pressure (MAP) during hyperventilation on CBFV, we performed multiple regression analyses of CBFV, PETo2, and MAP. MAP was not significantly changed by the procedure and did not contribute significantly to CBFV during any protocol or at any altitude (P>0.4).

**Table 1. Subject Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Ethiopian</th>
<th>HA Peruvian</th>
<th>CMS Peruvian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altitude, m</td>
<td>3622</td>
<td>4338</td>
<td>4338</td>
</tr>
<tr>
<td>Barometric pressure, mm Hg</td>
<td>499</td>
<td>450</td>
<td>450</td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Age, years</td>
<td>36.0±1.4</td>
<td>39.0±2.3</td>
<td>42.2±1.6</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.67±0.2</td>
<td>1.60±0.1</td>
<td>1.63±0.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>53.0±1.1</td>
<td>65.3±2.0**</td>
<td>62.5±2.4**</td>
</tr>
<tr>
<td>CMS score</td>
<td>0.13±0.1</td>
<td>7.0±4.0</td>
<td>19.0±5.0**</td>
</tr>
<tr>
<td>Haematocrit, %</td>
<td>48.4±1.8†</td>
<td>52.8±1.3†</td>
<td>67.4±2.5</td>
</tr>
</tbody>
</table>

Significant difference from Ethiopians: **P<0.01; ***P<0.001. Significant difference from CMS Peruvians: †P<0.001. Data in Peruvians taken from references 5, 6, 13.

**Cerebrovascular Responses to Hypocapnia**

During hyperventilation, changes in PETo2 were minimized by adjustments of the inspired gases. However, despite this, hyperventilation resulted in concomitant changes in PETo2. At high altitude PETo2 increased by 29.4±6.3 mm Hg and 11.9±1.5 mm Hg during normoxia and hypoxia, respectively, and at low altitude by 10.8±3.1 mm Hg and 6.7±3.1 mm Hg. Changes in PETo2 induced by hyperventilation were similar in all conditions (high altitude: 16.3±0.9 mm Hg and 14.5±1.3 mm Hg; low altitude: 16.5±1.0 mm Hg and 15.9±1.9 mm Hg, during normoxia and hypoxia respectively). Blood pressures and heart rates were not significantly affected by hyperventilation during the high or low altitude studies either when performed under conditions of normoxia or hypoxia.

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To eliminate possible effects of alterations in mean arterial pressure (MAP) during hyperventilation on CBFV, we performed multiple regression analyses of CBFV, PETo2, and MAP. MAP was not significantly changed by the procedure and did not contribute significantly to CBFV during any protocol or at any altitude (P>0.4).

**Discussion**

This study revealed markedly different adaptations to high altitude living in Ethiopian highlanders compared with our recent reports in Peruvians. The principal findings of the present study are: (1) There was no evidence of CMS in Ethiopians as shown from their low CMS score; (2) The cerebral circulation of Ethiopians is completely insensitive to hypoxia, but reacts strongly to hypocapnia; (3) The relatively high PETo2 at high altitude implies that Ethiopians do not hyperventilate in response to hypoxia; (4) Ethiopians had higher SaO2 both at high and low altitudes, than Peruvians. These findings confirm previous suggestions that the Ethiopian pattern of adaptation to altitude may be beneficial for high altitude living.

**Incidence of CMS**

Based on data from the Andes, we would expect to see evidence of CMS in approximately 30% of our Ethiopian cohort. This was not the case, and Ethiopian CMS scores (0.13±0.1) were even lower than previously reported in healthy Peruvians (7.0±4.0). Our data are consistent with the lack of evidence of CMS based on hemoglobin levels and SaO2 reported in earlier population-based studies from the Ethiopian highlands, and suggests that Ethiopians are better adapted for high altitude living.

**Comparison of Responses in Ethiopians and Peruvians**

Responses in Ethiopians were compared with those previously reported in HA and CMS Peruvians, using the same methods, at their resident altitude of 4338 m, and the day after descent to near sea level (150 m). Subject characteristics can be seen in Table 1. The Peruvian subjects were resident at a slightly higher altitude. CMS scores were higher in CMS Peruvians than the other 2 groups, and were lowest in Ethiopians; all but 1 subject scored 0. Hematocrits were similar in Ethiopians and HA Peruvians, and lower than in CMS Peruvians.

**Resting Cardiovascular and Respiratory Parameters**

Resting cardiovascular and respiratory parameters for the 3 groups at high and low altitude are shown in Table 2. The tendency for higher blood pressures and faster heart rates in Ethiopians compared with Peruvians has been noted before and probably reflects altered cardiovascular autonomic regu-
implication in the different high altitude populations.10 $P_{ET}CO_2$ were reduced in Peruvians compared with Ethiopians at high altitude. $P_{ET}CO_2$ were reduced in Peruvians compared with Ethiopians, both at high and low altitude. There were increases in $P_{ET}CO_2$ after descent to low altitude only in Ethiopians. Sao2 were lower in CMS Peruvians than the other 2 groups when tested at high altitude. All groups had increases in Sao2 after descent to low altitude. However, Sao2 remained lower in CMS Peruvians than Ethiopians even at low altitude. The higher Sao2 and $P_{ET}CO_2$ in Ethiopians support the suggestion that they show enhanced adaptation to high altitude living.9 Respiratory adaptation patterns are discussed below.

Cerebrovascular Responses to Hypoxia and Hypocapnia
The cerebral circulation of Ethiopians is insensitive to hypoxia, unlike that of Peruvians13 (Figure 2). Hypoxia increased CBFV in Peruvians, but had no effect in Ethiopians. When retested after descent to low altitude, responses increased in Peruvians, but not in Ethiopians, who remained insensitive to hypoxia.

The cerebral circulation of Ethiopians was more reactive to hypocapnia than that of Peruvians,13,16 particularly when studied at high altitude and in conjunction with hypoxia (Figures 3 and 4).

Implications of These Results for Life at High Altitudes
For effective adaptation to high altitude living it would be advantageous to maximize oxygen delivery to the brain. Hypoxia increases CBFV, and thus increases oxygen delivery to brain tissue during hypoxic stress. Insensitivity to hypoxia, as seen in Ethiopians, may therefore appear disadvantageous to high altitude living. However, the hypoxic stimulus at a given altitude is much less in Ethiopians, because their Sao2 are not reduced as much as expected for the altitude (Table 1; see also Beall et al11). Furthermore, the cerebral circulation of Ethiopians is much more sensitive to changes in CO2 than oxygen, the vasodilatation to hypercapnia is greater in Ethiopians than Peruvians,13,16 and this is coupled with considerably higher $P_{ET}CO_2$ in Ethiopians than Peruvians. Taken together, this would promote marked cerebral vasodilatation in Ethiopians, and thus their responses appear to be advantageous.

Cerebrovascular responses to hypoxia are attributable to NO-mediated vasodilatation.15 Ethiopians demonstrate altitude-dependent responses to exogenous NO donors, whereby responses at high altitude are robust, but at low altitude are small.9 Conversely, in Peruvians, responses to NO donors were small at high altitude and larger at sea level.9,16 In Peruvians, this increased cerebral sensitivity at low altitude is consistent with the increased response to hypoxia at low altitude.13 In Ethiopians there was no increase in reactivity to NO donors after descent,9 in fact the opposite occurred, and no increase in the responsiveness to hypoxia. However, the insensitivity to hypoxia at both high and low altitude, despite robust cerebral responses to exogenous NO donors in Ethiopians, especially at high altitude, suggests that this is not mediated by differences in NO responsiveness. It seems more

Table 2. Resting Supine Cardiorespiratory Variables in the Three Groups, Breathing Ambient Air, During High and Low Altitude Studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>High</th>
<th>Low</th>
<th>High</th>
<th>Low</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP, mm Hg</td>
<td>128±3.2</td>
<td>130±3.8</td>
<td>113.7±3.0</td>
<td>110.7±4.6†</td>
<td>117.2±2.6</td>
<td>115.1±3.6††</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>69±2.7</td>
<td>64±2.8</td>
<td>73.1±2.3</td>
<td>67.8±4.2</td>
<td>76.4±2.3</td>
<td>71.5±2.5*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>88±2.7</td>
<td>86±1.7</td>
<td>86.4±2.2</td>
<td>82.1±4.3</td>
<td>90.0±2.3</td>
<td>86.0±2.7</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>64.8±2.8</td>
<td>64.3±1.9</td>
<td>58.9±2.0</td>
<td>49.3±2.2††††</td>
<td>65.0±2.0</td>
<td>54.3±1.4†</td>
</tr>
<tr>
<td>$P_{ET}O_2$, mm Hg</td>
<td>58.4±1.3</td>
<td>97.6±1.9††††</td>
<td>50.4±1.2†††††</td>
<td>101.5±1.2***</td>
<td>45.5±1.0††††</td>
<td>103.1±1.2***†</td>
</tr>
<tr>
<td>$P_{ET}CO_2$, mm Hg</td>
<td>38.2±1.0</td>
<td>49.8±0.6***</td>
<td>27.3±1.2††††</td>
<td>25.7±1.2†††</td>
<td>27.8±1.5††††</td>
<td>28.0±1.4†††††</td>
</tr>
<tr>
<td>Sao2, %</td>
<td>88±1.1</td>
<td>97±0.5***</td>
<td>86±1.0</td>
<td>96±0.7***</td>
<td>82±1.2††††</td>
<td>94±0.7***††††</td>
</tr>
</tbody>
</table>

SAP indicates systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate; $P_{ET}O_2$, end-tidal oxygen levels; $P_{ET}CO_2$, end-tidal carbon dioxide levels; Sao2, arterial oxygen saturations. Data in Peruvians taken from references 5, 6, 13.

Significant difference between high and low altitude: *P<0.05; **P<0.01; ***P<0.001. Significant difference from Ethiopians: †P<0.05; ††P<0.01; †††P<0.001. Significant difference from CMS Peruvians: ‡P<0.05.

Figure 2. Cerebrovascular responses to normocapnic hypoxia. Responses are percentage changes in CBFV in response to a 50 mm Hg step decrease in $P_{ET}O_2$ while $P_{ET}CO_2$ levels were clamped at each subject’s own resting level. Unlike Peruvian altitude dwellers, the cerebral circulation of Ethiopians was insensitive to hypoxia both when tested at high and low altitude. Both HA and CMS Peruvians had significant increases in the cerebral response to hypoxia after descent to low altitude. Significant differences from high altitude shown by *P<0.01. Significant difference compared with Ethiopians shown by †P<0.01. Data in Peruvians taken from Norcliffe et al.10
likely, therefore, that there is a lack of NO release during hypoxia in Ethiopians. The mechanisms underlying this are uncertain but may involve differences in peripheral chemoreceptor oxygen sensitivity, signal transduction, or NO synthase.

The cerebral circulation of Ethiopians was more reactive to hypoxia than that of Peruvians, particularly when studied at high altitude and in conjunction with hypoxia. Given that the relationship between PETCO2 and CBFV is linear and highly significant, this suggests that, in addition to greater reductions in CBFV during hypocapnia, there would also be larger increases in CBFV during hypercapnia in Ethiopians. Peruvians had lower PETCO2 levels both at high and low altitude, and thus reduced sensitivity of the cerebral circulation to PETCO2 may be beneficial to minimize cerebral constriction during hyperventilation-induced hypocapnia. Ethiopians had markedly elevated PETCO2 both at high and low altitude. In this instance, increased sensitivity of the cerebral circulation may serve to maximize the cerebral vasodilatation induced by (relative) hypercapnia, and maintain CBFV and thus oxygen delivery during altitude-induced reductions in inspired oxygen. Indeed, the resting CBFV at high altitude in Ethiopians (58.9 ± 3.7 cm sec⁻¹) was greater than HA Peruvians (50.7 ± 4.5 cm sec⁻¹) and was markedly increased compared with CMS Peruvians (33.8 ± 2.8 cm sec⁻¹; P < 0.001). Resting CBFV was also reduced in CMS Peruvians compared with HA Peruvians (P < 0.01). The mechanisms underlying the different sensitivities to alterations in PETCO2 in these different altitude populations are uncertain, but may also be related to NO. Indeed, reduced cerebral reactivity to PETCO2 may be associated with endothelial dysfunction. The extreme polycythaemia in Peruvian subjects would be expected to lead to increased shear stress and possible endothelial damage, which could promote reduced cerebral sensitivity to PETCO2.

Thus, decreased sensitivity to hypoxia and increased sensitivity to hypocapnia in Ethiopians may serve to protect CBFV at altitude, and appears to represent further evidence of beneficial adaptations to high altitude living in Ethiopians. Given that the symptoms of CMS are thought to be ultimately attributable to cerebral hypoxia, these alterations in cerebral autoregulatory control, coupled with a higher CBFV and SaO₂, may explain the apparent lack of CMS on the Ethiopian plateau.

Respiratory Adaptations

Ethiopians do not appear to hyperventilate in response to hypoxia, as demonstrated by markedly elevated PETCO2 levels at high altitude, unlike Peruvians. After descent to low altitude, Ethiopians had further increases in PETCO2, whereas Peruvians continued to hyperventilate and PETCO2 did not increase. These findings are in direct contrast to previous reports that Peruvians with CMS have blunted hypoxic ventilatory responses, which is proposed to underlie their predisposition to CMS. Based on the PETCO2 levels, it appears that both groups of Peruvians actually chronically hyperventilate. Indeed, PETCO2 levels in HA and CMS Peruvians, both at their permanent high altitude residence and after 24 hours of normoxia after descent to sea level, are lower than those of Peruvians born and living at sea level. PETCO2 levels in Sherpa at 4243 m are intermediate to those of Peruvians and Ethiopians, and both Sherpa and Buddhist monks from the Himalayas are reported to use respiratory patterns similar to yoga breathing that help maintain higher SaO₂ and lower hematocrits. Furthermore, lowland dwellers acutely exposed to high altitude who practice slow yogic breathing maintain higher SaO₂ levels. It was proposed, therefore, that these slow diaphragmatic breathing techniques may be more efficient. The breathing patterns in the Ethiopian subjects are unknown, but could potentially explain some of the adaptive differences between these high altitude dwelling groups.

Not only do Peruvians hyperventilate in response to high altitude hypoxia, but they are also at increased risk of periodic breathing and apnoea, particularly during sleep, which may be attributable to their reduced cerebral reactivity to...
hypocapnia. Indeed, low baseline CBFV (as seen in Peruvian high altitude dwellers), is suggested to contribute to chronic hyperventilation via increased local stimulation of central chemoreceptors attributable to reduced perfusion and lack of clearance of $[H^+]$. 

Mechanisms Underlying Different Patterns of Adaptation to Altitude

There are likely to be genetic differences that influence the pattern of altitude adaptation in different populations. One suggestion is that African altitude dwellers should be better adapted for high altitude living than South Americans because humans arrived in the Americas at a later date, and their migration to high altitude was delayed by lack of population pressures. Certainly, Africans seem to be well adapted to high altitude living, as seen from the absence of CMS. This is supported by our recent report that they had greater cerebrovascular responses to exogenous NO than Peruvians, which was suggested to be an index of fitness for altitude life. Consistent with this, many examples of genetic adaptation have been suggested, although actual genetic data are few because these adaptations are complicated quantitative traits affected by many different gene loci and are highly variable depending on age, sex, and other environmental factors.

Clinical Relevance

Stroke is the third most common cause of death in the USA. Central sleep apnoea is linked to both chronic hypoxia and stroke, and patients with recurrent transient ischemic attacks have reduced cerebral CO$_2$ reactivity. In addition, NO is implicated in cerebrovascular disease and stroke at sea level and likely mediates altered cerebral responses to hypoxia and hypocapnia. Thus, the alterations in cerebral reactivity to hypoxia and hypocapnia described in this study not only have great implications for the 100 million people living and working at high altitude and may be of relevance in the clinic with regard to hypoxic cardiovascular disease and stroke.

Limitations

The principle limitation of this study is that these field studies, carried out on 2 continents, preclude, because of constraints imposed by geography, exact matching of altitudes of residence. The Ethiopian high altitude studies were performed at a slightly lower altitude, and thus higher $P_H$, than the Peruvian studies, corresponding to an increased inspired oxygen tension ($PiO_2$) of approximately 10 mm Hg (Ethiopian $PiO_2$=94.9 mm Hg; Peruvian $PiO_2$=84.6 mm Hg). This would affect baseline end-tidal gas concentrations and may also have affected some of the blood and cardiovascular variables in the Ethiopian subjects. However, we feel that this is unlikely to fully explain the differences seen, particularly the absence of CMS in Ethiopians, because Andeans living at even lower altitudes (2700m, $PiO_2$=104 mm Hg) still have much higher CMS scores than the Ethiopians in this study. Furthermore, even after descent to near sea level, the Ethiopians still had consistently elevated $P_{ETCO_2}$ levels and SaO$_2$ compared with Peruvians, suggesting that differences in altitude alone cannot explain the different responses in the Ethiopian and Peruvian populations. Similarly, because of geographical constraints, the low altitude studies were not matched exactly for altitude. However, because the effects of altitude are not linear and are negligible below 1500 m, any differences in responses when restested after descent in Peruvians (150 m) and Ethiopians (794 m) could not be explained by this small altitude difference. Finally, as expected because of the altitude differences, the ambient temperature of the sea level studies, both in Peru and Ethiopia, was greater than the high altitude studies, and this could potentially influence the changes occurring after descent. The temperatures at comparable altitudes, however, were similar in Peru and Ethiopia.

Although the control of $P_{ETCO_2}$ was excellent throughout this study, the control of $P_{ETO_2}$ during the hyperventilation studies was technically more difficult, and $P_{ETO_2}$ tended to rise during these protocols. However, given that the cerebral circulation of our Ethiopians was insensitive to manipulation of $P_{ETO_2}$ this is not likely to have influenced our observations. In the Peruvian studies the control of both $P_{ETCO_2}$ and $P_{ETO_2}$ was excellent, and $P_{ETO_2}$ did not rise during hyperventilation.

Summary

We present further evidence for increased fitness for high altitude living in Ethiopian altitude dwellers. There was no evidence of CMS in Ethiopia, evidenced by increased SaO$_2$, and reduced hematocrit and CMS scores. The cerebral circulation of Ethiopians showed increased responsiveness to CO$_2$, but was insensitive to hypoxia. This is the opposite to that of Peruvians. Ethiopians did not hyperventilate in response to high altitude hypoxia, unlike Peruvians. Increased cerebral sensitivity to $P_{ETCO_2}$ coupled with high $P_{ETCO_2}$ levels, may help to protect cerebral perfusion in Ethiopians. These data have great implications for people living and working at high altitude and may be of relevance in the clinic with regard to hypoxic cardiovascular disease and stroke.

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Disclosures

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References


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