Effects of High Altitude Exposure on Cerebral Hemodynamics in Normal Subjects

Aurélie Van Osta, BSc; Jean-Jacques Moraine, PhD; Christian Mélot, MD, PhD; Helmo Mairbäurl, PhD; Marco Maggiorini, MD, PhD; Robert Naeije, MD, PhD

Background and Purpose—Acute mountain sickness (AMS) may be an early stage of high altitude cerebral edema. If so, AMS could result from an alteration of dynamic autoregulation of cerebral blood flow resulting in overperfusion of capillaries and vasogenic cerebral edema.

Methods—We measured middle cerebral artery blood flow velocity (Vmca) by transcranial Doppler and arterial blood pressure by finger plethysmography at 490 m and 20 hours after arrival at 4559 m in 35 volunteers who had been randomized to tadalafil, dexamethasone, or placebo in a study on the pharmacological prevention of high altitude pulmonary edema. A dynamic cerebral autoregulation index (ARI) was calculated from continuous recordings of Vmca and blood pressure during transiently induced hypotension.

Results—Altitude was associated with an increase in a cerebral-sensible AMS (AMS-C) score (P<0.001) and with a decrease in arterial oxygen saturation (SaO2), whereas average Vmca or ARI did not change. However, at altitude, the subjects with the lowest ARI combined with the lowest SaO2 presented with the highest AMS-C score (P<0.03). In addition, a stepwise multiple linear regression analysis on arterial PCO2, SaO2, and baseline or altitude ARI identified altitude ARI as the only significant predictor of the AMS-C score (P=0.01). The AMS-C score was lower in dexamethasone-treated subjects compared with high altitude pulmonary edema–susceptible untreated subjects. Neither tadalafil nor dexamethasone had any significant effect on Vmca or ARI.

Conclusions—High altitude hypoxia is associated with impairment in the regulation of the cerebral circulation that might play a role in AMS pathogenesis. (Stroke. 2005;36:557-560.)

Key Words: autoregulation cerebral blood flow ultrasonography

The pathogenesis of acute mountain sickness (AMS) remains incompletely understood. A leading hypothesis relates AMS to early stages of brain edema that may progress in a proportion of subjects to high altitude cerebral edema. In this context, cerebral blood flow (CBF) would be expected to be a potential aggravating or contributing factor. However, reported CBF measurements in AMS have been inconsistent, with normal as well as increased values, and no clear relationship to AMS symptomatology. Lassen suggested that AMS could result rather from altered autoregulation of CBF, allowing for an overperfusion of cerebral capillaries and vasogenic cerebral edema. This notion was challenged recently by a study that showed that static cerebral autoregulation was similarly impaired in newcomers at high altitude and in high altitude resident Sherpas.

We took advantage of a study on the pharmacological prevention of high altitude pulmonary edema (HAPE) by tadalafil and dexamethasone to investigate CBF regulation during short-term high altitude exposure with variable AMS symptomatology. We measured dynamic cerebral autoregulation. Our hypothesis was that altitude exposure could alter dynamic cerebral autoregulation and arteriolar tone, thereby leading to capillary overperfusion and subclinical cerebral edema-related AMS symptomatology. Tadalafil is a phosphodiesterase-5 inhibitor used in the treatment of erectile dysfunction, which, if anything, could aggravate AMS in relation to cyclic GMP–related cerebral vasodilatation and associated headache. Dexamethasone is an effective treatment of vasogenic cerebral edema and, as such, has been successfully used for treatment of AMS.

Materials and Methods

Subjects
Thirty-five healthy volunteers (29 men and 6 women; 26 to 58 years of age; mean 40 years; weighing 74±6 kg [mean ± SD]) gave informed consent to the study, which was approved by the ethical committees of the University Hospital of Zürich and the University of Heidelberg. Twenty-six of them had at least 1 previous episode of
HAPE. Subjects had been recruited into a study on the effects of tadalafil, a phosphodiesterase-5 inhibitor, and dexamethasone on the prevention of HAPE. Tadalafil was expected to prevent HAPE through inhibition of hypoxic pulmonary vasoconstriction and associated increase in pulmonary capillary pressure and dexamethasone by an activation of respiratory epithelial sodium transport. This subject population was expected to present with a high incidence of AMS because HAPE often occurs in the presence of established AMS symptomatology.

Measurements

CBF velocity was estimated by the measurement of middle cerebral artery blood flow velocity (Vmca) at a depth of 50 to 55 mm using a 2-MHz pulsed transcranial Doppler (WAKI 2TC: Atys Medical). The ultrasonic transducer was positioned on the temporal window and fixed with a headband, allowing continuous recording without modification of the insonation angle. The right or left middle cerebral artery was insonated according to the best quality Doppler signal.

Arterial blood pressure (BP) was measured by finger plethysmography (Finapres BP Monitor; Ohmeda 2300). The CBF velocity and the arterial BP signals were sampled at 200 Hz using an analog/digital converter (RTI 800; Analog Devices) and stored on a personal computer for off-line computations. Arterial Pao2, arterial Pco2, and arterial oxygen saturation (SaO2) were measured with an automated blood gas analyzer (model ABL 5; Radiometer). Heart rate (HR) was measured on BP signals, which were continuously monitored.

Cerebral Autoregulation

A cerebral autoregulation index (ARI) was calculated in triplicate from continuously recorded Vmca and BP during an acute hypotension induced by the sudden release of bilateral thigh cuffs that had been kept inflated to a pressure of 30 mm Hg above systolic BP for 3 minutes as described previously. This maneuver allows for a decrease in mean BP by >15% for 20 to 30 s, during which, after an initial fall, Vmca smoothly returns back to baseline in 5 to 7 seconds. We calculated a dynamic rate of regulation, which expresses the rate of restoration of Vmca with respect to the decrease in mean BP, and derived an ARI using previously reported algorithm and software. The normal response of CBF to a fall in BP is a 20% correction per second, with a restoration to baseline in 5 seconds, yielding an ARI ≈ 5.11,12

AMS Assessment

The diagnosis and severity of AMS were established with use of a cerebral-sensitive (AMS-C) score of the Environmental Symptom Questionnaire, as proposed previously by Sampson et al.13 This self-report questionnaire consists of 67 questions, of which 11 are used to calculate the AMS-C score by multiplying the score of each question by a factorial weight. After that, the 11 products are added and the sum is multiplied by 0.1927. The influence of each question is then hidden for the examiner and the subject, making the assessment a very objective way to evaluate AMS. An AMS-C score of >0.7 establishes a diagnosis of AMS.

Study Protocol

Measurements were performed first at low altitude at the University Hospital of Zurich at 490 m (sea level), and then at 4559 m at the research laboratory hut Regina Margherita, on Monte Rosa (high altitude). One day before ascent, the study participants started taking one day before ascent, the study participants started taking a combination of tadalafil and dexamethasone. Tadalafil was expected to prevent HAPE by increasing cerebral blood flow and reducing cerebral edema, whereas dexamethasone was expected to prevent AMS by reducing cerebral edema. Subjects had been recruited into a study on the effects of high altitude on systemic and cerebral hemodynamics.

Table 1: Central Hemodynamic, Blood Gases, and Transcranial Doppler Variables in 35 Healthy Subjects at Sea Level and at High Altitude

<table>
<thead>
<tr>
<th></th>
<th>Sea Level</th>
<th>Altitude</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>76±20</td>
<td>85±12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sao2</td>
<td>97±1</td>
<td>79±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paco2, mm Hg</td>
<td>90±11</td>
<td>41±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paco2, mm Hg</td>
<td>40±2</td>
<td>30±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>137±20</td>
<td>137±26</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>81±12</td>
<td>82±17</td>
<td>NS</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>100±14</td>
<td>100±18</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic Vmca, cm/s</td>
<td>69±11</td>
<td>72±18</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic Vmca, cm/s</td>
<td>34±7</td>
<td>37±13</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Vmca, cm/s</td>
<td>49±8</td>
<td>52±14</td>
<td>NS</td>
</tr>
<tr>
<td>ARI</td>
<td>4.44±0.86</td>
<td>4.55±1.16</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are given as mean±SD.

ARI, HR, BP, Paco2, PaO2, and SaO2 were measured at sea level and on average 20 hours after arrival at high altitude.

Statistical Analysis

Results are presented as mean (SD). The statistical analysis consisted in paired t tests to compare sea level and high altitude measurements and linear regression calculations. The normality of the distributions of the variables was checked using normal probability plot and the Wilk Shapiro test. A logit transformation (natural logarithm) was applied when the variable was not gaussian (AMS-C score). A multiple linear regression analysis was performed to determine the predictors of the AMS-C score. SaO2, PaCO2, baseline ARI, and altitude ARI were used as predictors in a model built using a backward elimination procedure. A P value <0.05 was considered significant to stay into the final model. The regression coefficients with their SEs are presented with the P value of the t test against 0.

Results

Thigh cuff release decreased mean BP by 25±11 mm Hg in normoxia and 18±9 in hypoxia (P<0.01). The resulting ARI calculation was not correlated to BP drop, but was inversely correlated to mean Vmca at sea level and at high altitude (r = −0.39, P<0.05, and r=−0.40, respectively). High altitude exposure was associated with an AMS-C score of 0.89±0.88.

The effects of high altitude on systemic and cerebral hemodynamics are presented in Table 1. Altitude increased HR, decreased SaO2, Paco2, and PaO2, but did not change BP, Vmca, and ARI.

When subgroups defined by 50% cut points for SaO2 and the AMS-C score were compared, altitude ARI in percentage of baseline was higher in the high-SaO2 group (118% versus 94%; P<0.03), whereas ARI was not different in the high–low–AMS-C score groups. However, the AMS-C score was higher at 1.54±1.20 in the combined low SaO2–low ARI group; P<0.05 compared with an AMS-C score of 0.36±0.36 in the high-Sao2–high-ARI group. The AMS-C scores of the high-Sao2–low-ARI and the low-Sao2–high-ARI groups were intermediate, respectively, at 0.74±0.75 and 0.9±0.76, and not different from the 2 other groups.

The results of the simple linear regression analysis to determine the slopes of the relationships between AMS-C...
The individual AMS-C scores disclosed ARI as the only significant independent predictor of the AMS-C score. The backward procedure of the multiple regression analysis are shown in Table 2. It is apparent that baseline ARI and altitude SaO₂ and PaCO₂ were not related to the AMS-C score. The backward procedure disclosed ARI as the only significant independent predictor of the AMS-C score (P=0.0107). The individual AMS-C scores and ARI measurements are shown in Figure 1. When the same procedure was applied to test the relationship between ARI and altitude SaO₂, PaO₂, and baseline ARI, only SaO₂ emerged as a significant predictor.

Two of the 35 subjects included in the present study and 3 other visitors of the Regina Margherita hut experienced severe AMS and HAPE requiring emergency treatment with oxygen, acetazolamide, nifedipine, or dexamethasone. In these subjects, there were parallel evolutions between ARI and AMS-C score (Figure 2).

There were no significant differences in BP, Vmca, or ARI between the tadalafil-, dexamethasone-, or placebo-treated subjects. However, the AMS-C score of the subjects taking dexamethasone was lower than in placebo controls (0.28±0.27 versus 1.38±1.17; P<0.05). The AMS-C score of tadalafil-treated subjects tended to be lower than in the controls (0.92±0.85 versus 1.38±1.17; P=0.062).

**Discussion**

The new finding of the present study is that AMS symptoms in subjects acutely exposed to high altitude appear to be related to an altered dynamic autoregulation of the cerebral circulation. Transcranial Doppler was used for the noninvasive and beat-by-beat estimation of CBF. This approach is based on the reasonable assumption that hypoxia or acute hypotension would not alter the diameter of the middle cerebral artery. Finger plethysmography was used for the noninvasive beat-by-beat estimation of cerebral arterial pressure. This approach is validated for the measurement of instantaneous relative changes, and as such, has been used previously for cerebral autoregulation studies and ARI computing.

Previous studies in normal subjects using the same methodology as in the present study reported a normal ARI of ~5, range from 3 to 7, for an average BP drop ranging from 15 to 28 mm Hg. Our normal subjects presented with a baseline ARI of 4.44 for an average cuff release–induced drop in BP on cuff release of 18 to 25 mm Hg, which is in keeping with these previous data. It is of interest that ARI was not correlated to BP drop, as reported previously as well. However, contrary to previous reports, we found an inverse correlation between ARI and Vmca at sea level and at high altitude, suggestive of a relative inhibition of cerebral autoregulation by higher blood flow velocities or decreased cerebral resistance.

In the present study, the average ARI was not different between sea level and altitude. This is in contrast with previous reports of an impaired autoregulation in experimental animals in hypoxia and in healthy newcomers to high altitudes or high altitude residents. These discrepancies might be explained by compensatory enhancement of cerebral autoregulation by hypcapnia and by differences in methodological approach. The only available study showing similar decrease in cerebral autoregulation in high altitude newcomers and long-term residents did not consider the evolution of cerebral hemodynamics in relation to the quality of adaptation measured by an AMS score, and measured cerebral autoregulation in static conditions, with increases in BP induced by a phenylephrine infusion. Although static and dynamic cerebral autoregulation measurements have been shown to be well correlated, the agreement between both approaches in hypoxia is not known. Static cerebral autoregulation measurements require phenylephrine infusion. However, vascular reactivity to hypoxia may be affected by chronic as well as acute sympathetic influences and versa. Dynamic cerebral autoregulation measurements are performed without drug administration that might affect arteriolar tone, and within 5 seconds, thus preceding any possible vascular effect of decreased flow-induced sympathetic nervous system activation. Therefore, we believe that

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**TABLE 2. Multiple Linear Regression Analysis of Altitude ARI, Baseline ARI, SaO₂, and PaCO₂ as Predictors of AMS-C Score in 35 Healthy Volunteers Exposed to High Altitude**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td>SaO₂</td>
<td>−0.0489</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>Attitude</td>
<td>−0.4445</td>
<td>0.174</td>
</tr>
<tr>
<td></td>
<td>ARI</td>
<td>−0.3104</td>
<td>0.226</td>
</tr>
<tr>
<td></td>
<td>Baseline ARI</td>
<td>0.0315</td>
<td>0.087</td>
</tr>
<tr>
<td>Multivariable analysis</td>
<td>Attitude</td>
<td>−0.4445</td>
<td>0.174</td>
</tr>
<tr>
<td></td>
<td>ARI</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

P indicates significance of t tests of regression coefficients against 0.
dynamically measured ARI more closely reflects physiological cerebral autoregulation and is accordingly more likely related to AMS symptomatology.

In the present study, the subjects with the most severe AMS symptomatology tended to present with lower ARI, indicating altered dynamic cerebral autoregulation and decreased arteriolar tone, and this was significant despite concomitant hypcapnia. These changes could be a cause of increased capillary perfusion, increased filtration pressure, and resultant cerebral edema. Alternatively, cerebral edema related to other yet unknown direct effects of hypoxia⁴ could be a cause of secondary decrease in cerebral arteriolar tone and altered cerebral autoregulation. Although AMS and high altitude cerebral edema present at the extremes of a spectrum of clinical neurological manifestations of high altitude intolerance, with efficacy of dexamethasone therapy likely related to its effects on vasogenic cerebral edema in general,⁹ data available until now do not prove the existence of increased cerebral extravascular water content related to headache symptomatology in AMS.¹

It may be argued that the correlations between the AMS-C score and altitude ARI, although significant, were loose and accordingly not suggestive of a causal relationship. However, loose correlations could also be attributed to the variability of self-reporting questionnaire AMS manifestations¹³ and the inherent approximations of ARI estimates.¹¹ On the other hand, for the same reasons, it appears unlikely that AMS and ARI would be significantly correlated by chance.

Tadalafil would not be expected to affect AMS symptoms, except for an aggravation of headache that is a side effect of phosphodiesterase-5 inhibitors when used to treat erectile dysfunction.⁸ Sildenafil does not affect CBF velocity in normal subjects. Selective cerebral vascular effects are more likely related to its effects on increased capillary perfusion, increased filtration pressure, and resultant cerebral edema. Alternatively, cerebral edema related to other yet unknown direct effects of hypoxia could be a cause of secondary decrease in cerebral arteriolar tone and altered cerebral autoregulation.⁴ Although AMS and high altitude cerebral edema present at the extremes of a spectrum of clinical neurological manifestations of high altitude intolerance, with efficacy of dexamethasone therapy likely related to its effects on vasogenic cerebral edema in general, data available until now do not prove the existence of increased cerebral extravascular water content related to headache symptomatology in AMS.¹

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In conclusion, altitude exposure is associated with altered dynamic cerebral autoregulation in proportion to AMS symptomatology. This observation offers rationale for further clinical studies on the role of abnormal regulation of cerebral hemodynamics in the adaptation to high altitude.

Acknowledgments

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References

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