Acute mountain sickness is not related to cerebral blood flow: a decompression chamber study

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Acute mountain sickness is not related to cerebral blood flow: a decompression chamber study. J. Appl. Physiol. 86(5): 1578–1582, 1999.—To evaluate the pathogenetic role of cerebral blood flow (CBF) changes occurring before and during the development of acute mountain sickness (AMS), peak mean middle cerebral artery flow velocities (V̇MCA) were assessed by transcranial Doppler sonography in 10 subjects at 490-m altitude, and during three 12-min periods immediately (SA1), 3 (SA2), and 6 (SA3) h after decompression to a simulated altitude of 4,559 m. AMS cerebral scores increased from 0.16 ± 0.14 at baseline to 0.44 ± 0.31 at SA1, 1.11 ± 0.88 at SA2 (P < 0.05), and 1.43 ± 1.03 at SA3 (P < 0.01); correspondingly, three, seven, and eight subjects had AMS. Absolute and relative V̇MCA at simulated altitude, expressed as percentages of low-altitude values (%V̇MCA), did not correlate with AMS cerebral scores. Average %V̇MCA remained unchanged, because %V̇MCA increased in three and remained unchanged or decreased in seven subjects at SA2 and SA3. These results suggest that CBF is not important in the pathogenesis of AMS and shows substantial interindividual differences during the first hours at simulated altitude.

ACUTE MOUNTAIN SICKNESS (AMS) may develop in subjects who rapidly ascend to altitudes above 2,500 m (7). During a sojourn at high altitude, cerebral blood flow (CBF) increases, probably because the stimulating effect of hypoxemia dominates the flow-depressant effect of hypocapnia, which results from hyperventilation (9, 12, 15, 27, 29). Most studies evaluating the pathogenetic role of CBF in AMS were performed within 12–24 h after arrival at high altitude (3, 9, 12, 15, 21, 23, 27, 29), although AMS develops within the first 6–12 h (11, 29). CBF alterations occurring before and during the development of AMS, and their association with this altitude illness, have not yet been studied.

Incipient hydrostatic edema of the brain, resulting from greater fluid leakage, has been postulated as the cause of the cerebral features of AMS (17). The leakage is assumed to be related to high hydrostatic pressure, resulting from hypoxemic vasodilatation and increased filtration through altered blood-brain capillaries. Hydrostatic pressure of cerebral capillaries might be further augmented by arterial blood pressure increases during exercise and by the cold (30).

The purpose of the present study was to compare relative changes in CBF velocity assessed by transcranial Doppler (TCD) sonography with the development of AMS in healthy volunteers during a 6-h decompression to a simulated altitude of 4,559 m.

MATERIALS AND METHODS

Subjects. Ten healthy white male volunteers, aged 20–24 (mean 22 yr) yr and living at altitudes below 500 m, were examined in a decompression chamber. No subject was exposed to altitudes higher than 3,500 m or had suffered from AMS. With the exception of subject 4, who spent 5 h at an altitude of 2,700 m 26 days before the present study, no subject was exposed to altitudes higher than 1,000 m within the 2 mo immediately before this study. Written informed consent was obtained, and our study protocol was reviewed and approved by the Ethical Committee of the University Hospital (Zürich).

Study design. Baseline examinations were performed at an altitude of 490 m [barometric pressure, 721 ± 6 (SD) mmHg; temperature, 20.4 ± 0.6°C]. They consisted of the evaluation of CBF velocity by means of TCD assessment of peak mean flow velocities in the right middle cerebral artery (V̇MCA), completion of an environmental symptom questionnaire (ESQ) (26), monitoring of arterial O2 saturation (SaO2), and measurement of blood pressure and heart rate.

During the subsequent decompression to 4,559 m (barometric pressure, 428 mmHg; temperature, 21.2 ± 0.7°C) that lasted for 13 min, as well as the first 12 min at simulated altitude (SA1), V̇MCA measurements were continued. MCA velocimetry was repeated for 12 min after 3 (SA2) and 6 h (SA3) at simulated altitude. Blood pressure, heart rate, and SaO2 measurements were repeated after decompression, and at the beginning as well as at the end of SA1, SA2, and SA3. ESQ testing was repeated after termination of SA1, SA2, and SA3. The median time for recompression to low altitude was 20 min (range 14–48 min).

TCD examinations. V̇MCA was measured by means of a TCD device (TC2–64B, EME, Überlingen, Germany) equipped with a 2-MHz probe. Through the temporal window the optimum strength and clarity of the right MCA signal at insonated depths of 50–55 mm was found. The monitoring probe (Trans-cran FP 2 monitoring, EME) was fixed with a headband and detached after SA1, SA2, and SA3. Both the exact position of the monitoring probe with respect to a line joining the intertragal incision with the lateral angle of the eye and the depth of insonation were carefully noted for each subject. The rationale was to maintain identical insonation angles and depths for V̇MCA measurements at SA1 and SA3. V̇MCA values calculated by the machine every 8 s, the 4 min before and during decompression, as well as during SA1, SA2,
and SA3 were noted. In each subject, the relative changes in \( V_{MCA} \) occurring during decompression, SA1, SA2, and SA3 were calculated, defining the average \( V_{MCA} \) obtained during the 4 min before decompression as 100%. All TCD studies were performed by the same examiner (R. W. Baumgartner). The subjects were relaxed in a supine position, with their eyes closed. Attention was paid to provide a calm environment.

Assessment of signs and symptoms of AMS. The ESQ was translated into German and used as described previously (2). Subjects were considered to suffer from AMS when the AMS-cerebral (AMS-C) score was \( \geq 70 \) in at least one examination at simulated altitude.

\( Sa_O_2 \) measurements. \( Sa_O_2 \) measurements were performed by using a pulse oximeter attached to an earlobe (Biox 3700, Ohmeda, Boulder, CO).

Statistical analysis. Testing according to Lilliefors indicated that the following variables were not normally distributed at baseline: \% \( V_{MCA} \), AMS-C score, \( Sa_O_2 \), and systolic and diastolic blood pressures (25). Therefore, changes from baseline were compared by nonparametric analysis of variance according to Friedman, followed by post hoc testing according to Wilcoxon and Wilcox in the case of overall significance. The relationship of various variables obtained after decompression with the corresponding values of \% \( V_{MCA} \) were determined by Pearson correlation analysis. Because all except for the above-mentioned baseline variables were normally distributed, we report mean values and SDs unless otherwise stated. \( P < 0.05 \) was considered significant.

RESULTS

Average \% \( V_{MCA} \) did not change with simulated altitude (\( P = 0.46 \); Table 1). During SA2 and SA3, \% \( V_{MCA} \) increased in three subjects, but remained unchanged or decreased in seven (Table 2, Fig. 1). The AMS-C score, \( Sa_O_2 \), blood pressure, and heart rate showed no difference when subjects with and without increased \% \( V_{MCA} \) were compared at SA2 and SA3 (Fig. 2). AMS-C scores increased significantly over time (\( P < 0.001 \)). Compared with baseline values, this increase was significant at SA2 (\( P < 0.05 \)) and at SA3 (\( P < 0.01 \)). Correspondingly, three subjects had AMS at SA1, seven at SA2, and eight at SA3.

\( Sa_O_2 \) decreased over time at simulated altitude (\( P < 0.001 \)). The decrease remained essentially unchanged at simulated altitude during the whole stay and was significant for SA1 (\( P < 0.05 \)), SA2 (\( P < 0.01 \)), and SA3 (\( P < 0.05 \)) compared with baseline values.

Blood pressure remained unchanged from baseline. Heart rate increased over time at simulated altitude (\( P < 0.001 \)). The increase was significant for SA3 compared with baseline values (\( P < 0.01 \)).

DISCUSSION

CBF showed no correlation with the AMS-C score in this study. Furthermore, there was no difference in

### Table 1. Mean MCA flow velocity, acute mountain sickness-cerebral score, arterial O2 saturation, heart rate, and arterial blood pressure before and during decompression to 4,559 m

<table>
<thead>
<tr>
<th>Altitude (m)</th>
<th>( V_{MCA} ) (cm/s)</th>
<th>Mean MCA-C Score</th>
<th>Mean ( Sa_O_2 ) (%)</th>
<th>Mean Heart Rate (beats/min)</th>
<th>Mean Arterial Blood Pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ht, m</td>
<td>Time, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>490</td>
<td>0</td>
<td>69 ± 15</td>
<td>100</td>
<td>0.16 ± 0.14</td>
<td>95 ± 1</td>
</tr>
<tr>
<td>4,559</td>
<td>13–25</td>
<td>74 ± 18</td>
<td>100</td>
<td>0.44 ± 0.31</td>
<td>76 ± 4*</td>
</tr>
<tr>
<td>4,559</td>
<td>180–192</td>
<td>72 ± 14</td>
<td>109 ± 23</td>
<td>1.11 ± 0.88*</td>
<td>71 ± 6</td>
</tr>
<tr>
<td>4,559</td>
<td>360–372</td>
<td>70 ± 9</td>
<td>109 ± 22</td>
<td>1.43 ± 1.03†</td>
<td>75 ± 5§</td>
</tr>
<tr>
<td>P ANOVA (Friedman)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD; \( n = 10 \) subjects. MCA, middle cerebral artery; \( V_{MCA} \), mean flow MCA velocity; AMS-C, acute mountain sickness-cerebral; \( Sa_O_2 \), arterial O2 saturation. *\( P < 0.05 \), †\( P < 0.01 \) compared with baseline values (Wilcoxon and Wilcox).

### Table 2. Individual MCA flow velocities, AMS-C scores, arterial O2 saturations, heart rate, and arterial blood pressures at simulated altitude (4,559 m)

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>( V_{MCA} ), %Baseline*</th>
<th>AMS-C Score</th>
<th>( Sa_O_2 )</th>
<th>Heart Rate, beats/min</th>
<th>Systolic/Diastolic Arterial Blood Pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SA1</td>
<td>SA2</td>
<td>SA3</td>
<td>SA1</td>
<td>SA2</td>
</tr>
<tr>
<td>1</td>
<td>105 ± 7</td>
<td>141 ± 4</td>
<td>143 ± 2</td>
<td>0.35</td>
<td>0.19</td>
</tr>
<tr>
<td>2</td>
<td>113 ± 2</td>
<td>83 ± 8</td>
<td>99 ± 2</td>
<td>0.71</td>
<td>2.06</td>
</tr>
<tr>
<td>3</td>
<td>97 ± 3</td>
<td>107 ± 3</td>
<td>109 ± 2</td>
<td>0.77</td>
<td>2.34</td>
</tr>
<tr>
<td>4</td>
<td>106 ± 3</td>
<td>70 ± 3</td>
<td>70 ± 3</td>
<td>0.09</td>
<td>0.83</td>
</tr>
<tr>
<td>5</td>
<td>107 ± 3</td>
<td>140 ± 3</td>
<td>131 ± 3</td>
<td>0.45</td>
<td>0.78</td>
</tr>
<tr>
<td>6</td>
<td>115 ± 5</td>
<td>107 ± 3</td>
<td>79 ± 7</td>
<td>0.45</td>
<td>0.83</td>
</tr>
<tr>
<td>7</td>
<td>120 ± 6</td>
<td>97 ± 4</td>
<td>95 ± 5</td>
<td>0.98</td>
<td>1.90</td>
</tr>
<tr>
<td>8</td>
<td>100 ± 4</td>
<td>142 ± 3</td>
<td>141 ± 4</td>
<td>0.23</td>
<td>0.19</td>
</tr>
<tr>
<td>9</td>
<td>109 ± 3</td>
<td>109 ± 3</td>
<td>112 ± 3</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>10</td>
<td>107 ± 6</td>
<td>91 ± 3</td>
<td>87 ± 4</td>
<td>0.35</td>
<td>1.95</td>
</tr>
</tbody>
</table>

Correlation with corresponding \( V_{MCA} \) 0.38 * -0.55 0.10 -0.12 -0.16 -0.57 0.42 -0.24 -0.68† 0.21/−0.44 0.32/0.22 -0.05/−0.26

\( SA_1 \), \( SA_2 \), and \( SA_3 \): 13–25, 180–192, 360–372 min at simulated altitude. *Means ± SD of 6 velocity measurements performed at \( SA_1 \), \( SA_2 \), and \( SA_3 \), which are shown in Figs. 1 and 2. †\( P < 0.05 \).
AMS-C scores in a comparison of subjects with and without raised CBF at SA2 and SA3. These findings are in accordance with the results of several therapeutic trials reporting successful treatment of AMS despite completely different reactions of CBF (2, 8, 10, 15, 23). CBF increases of 22% were observed after oral administration of 1.5 g acetazolamide (15); CBF rose by 25% (10) or remained unchanged (8) after 3% CO2 was added in ambient air (10), whereas O2 administration (33%) caused CBF to drop 20% (2). In the above-cited trials (2, 8, 10, 15, 23), arterial PO2, SaO2, or both increased during different treatments, indicating that these changes are more important than alterations of CBF in the pathogenesis of AMS. This notion is also supported by the observation that headache, the leading symptom of AMS, is not related to blood flow velocity measured in the internal carotid artery (23).

Although the statistical power of this study is lowered by the small sample size, the present findings and the results of previous studies (2, 8, 10, 15, 23) suggest that CBF alterations occurring before and during the development as well as during successful therapy of AMS are probably not relevant in the pathogenesis of this altitude illness.

Three subjects fulfilled the diagnostic criteria of AMS at SA1 and seven subjects at SA2, although most authors assume that AMS develops within 6–12 h of exposure to high altitude (11, 16, 29). No subject fulfilling the criteria of AMS at SA1 recovered at SA2 or SA3, and no subject who fulfilled the criteria of AMS at SA2 recovered at SA3. The temperature in the decompression chamber was normal, and the subjects spent most of the time in either the supine or the sitting position, were adequately hydrated, had normal arterial blood pressures, and showed no signs and symptoms of agoraphobia. Thus it is very unlikely that other diseases that may cause AMS-like signs and symptoms, such as cold, exhaustion, dehydration, hypotension, and agoraphobia, were present. Our data suggest that in some individuals AMS may already be detected by the AMS-C score within the first 3 h at simulated altitude.

The variation in CBF at simulated altitude was evaluated by repetitive assessment of relative changes in \( V_{MCA} \). Careful measures to minimize changes in insonation angles and depths, as well as restriction of observation to one examiner, have provided reliable intraobserver reproducibility for repeat \( V_{MCA} \) measurements (19, 31). TCD velocity measurements performed during alterations in arterial P\(_{CO2}\) (P\(_{aCO2}\)) and arterial P\(_{O2}\) are reliable, because several human studies have shown that only the diameter of cerebral resistance vessels changes and that the diameter of the insonated MCA remains essentially unchanged (6, 13, 22). Ringelstein et al. (24) reported a highly significant linear correlation \( r = 0.96 \) when comparing CO\(_2\)-induced relative changes in \( V_{MCA} \) measured by TCD with relative changes in CBF measured by the xenon-133-inhalation technique. Maeda et al. (18) found a high correlation coefficient of \( r = 0.95 \) by comparing relative changes in \( V_{MCA} \) measured by TCD with relative changes in flow in the internal carotid artery measured by an electromagnetic flow probe during carotid endarterectomies. Therefore, we assume that the diameter of the insonated MCA did not change significantly during hypoxic hypocapnia. Consequently, relative changes in \( V_{MCA} \) reflected flow alterations in this artery, which provides ∼80% of all blood supplied to the cerebral hemisphere (1).

CBF responses to simulated altitude in the present study showed substantial differences among diverse subjects, ranging from increases of 48% to decreases of 32%. Consequently, average CBF remained unchanged at simulated altitude. These findings are in accordance with ultrasonic data reported in the extracranial internal carotid and vertebral arteries by Huang et al. (12) and Reeves et al. (23). They found normal flow velocities caused by large interindividual differences, ranging from an increase of 52% to a decrease of 30% 2–4 h after an exposure to altitudes between 4,300 and 4,800 m. These data (12, 23) and ours suggest that, during the first hours at hypobaric hypoxia, CBF may decrease, remain unchanged, or increase, independent of the development of AMS. In contrast, several authors have reported increases in CBF of between 20 and 27% in subjects 12–24 h after their arrival at altitudes ranging between 3,475 and 4,559 m (3, 12, 15, 21).

The cause of the different CBF responses observed in our subjects at SA2 and SA3 is difficult to explain. Changes in blood pressure are an unlikely cause because all subjects had normal values. Animal (14, 20) and human (28) studies indicate that CBF rises with decreasing SaO2. However, SaO2 values showed no correlation with CBF and were identical in a comparison of subjects with and without increased CBF. The level of P\(_{aCO2}\) has an important effect on cerebral resistance vessels and CBF and is essentially determined by the amount of hyperventilation occurring during the first 6 h at hypobaric hypoxia. Although the SaO2 values were identical in subjects with and without raised CBF, it is possible that differences in ventilation caused...
Fig. 2. Peak mean $\nabla_{\text{MCA}}$ expressed as %baseline and corresponding acute mountain sickness-cerebral (AMS-C) after 13–25 (SA1; A), 180–192 (SA2; B), and 360–372 min (SA3; C) of decompression to 4,559 m.
distinct $P_{acO2}$ values and CBF changes. Fencl et al. (5) have demonstrated that cerebral vessels in humans with stable metabolic alkalosis fail to constrict in response to a sustained hypocapnic stimulus, presumably because of a resetting of $HCO_3^-$ concentrations in the cerebrospinal fluid (4). Thus only subjects with increased CBF may have already “reset” cerebral vasoreactivity.

Compared with our own field studies (2, 3), which evaluated CBF changes in and the development of AMS, we have demonstrated that cerebral vessels in humans are capable because of a resetting of $HCO_3^-$ response to a sustained hypocapnic stimulus, presumably because of a resetting of $HCO_3^-$ concentrations in the cerebrospinal fluid (4). Thus only subjects with increased CBF may have already “reset” cerebral vasoreactivity.

In conclusion, we have shown that CBF changes occurring before and during the development of AMS revealed no correlation with AMS-C scores, suggesting that CBF is not relevant in the pathogenesis of AMS. In addition, our data indicate that CBF changes show substantial interindividual differences during the first hours at simulated altitude.

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Received 29 September 1998; accepted in final form 30 December 1998.

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